Definitely, Maybe: The Role of Antipsychotics in Children and Adults with ICU Delirium

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Professor, University of Oklahoma College of Pharmacy

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Disclosures

• Under guidelines established by the Accreditation Council for Pharmacy Education, disclosure must be made regarding financial relationships with commercial interests within the last 12 months.
• I have no relevant financial relationships or affiliations with commercial interests to disclose.
• Dr. Pete Johnson does not have any relevant financial relationships or affiliations with commercial interests to disclose.
• I will be referring to medications used for non-FDA labeled indications.
Learning Objectives

At the completion of this activity, pharmacists will be able to:

1. Identify risk factors for intensive care unit (ICU) delirium in children and adults
2. Recognize pediatric and adult scoring tools for delirium
3. List non-pharmacologic and pharmacologic treatment options for prevention of ICU delirium
4. State the role of antipsychotics in the treatment of ICU delirium
5. Outline a monitoring plan for patients receiving antipsychotics for ICU delirium

Overview

1. Background
2. Delirium scoring tools
3. Non-pharmacologic management
4. Antipsychotics
   a) Overview
   b) Prevention
   c) Treatment
   d) Adverse effects and monitoring
5. Other pharmacologic options
6. Conclusions
Pre-Assessment Question 1

RT is a 42 year old female admitted to the MICU for septic shock. She was extubated and remains on vancomycin and piperacillin/tazobactam. On hospital day 4, her ICSDC score is 5 due to inattention, disorientation, disorganized speech, sleep disturbances, and symptom fluctuation.

What pharmacologic treatment would you recommend?
A. Initiate IV haloperidol
B. Initiate enteral olanzapine
C. Initiate enteral risperidone
D. No pharmacologic treatment

Pre-Assessment Question 2

AB is an 8 month old male admitted to the PICU following cardiothoracic surgery. He remains mechanically ventilated and on multiple continuous infusion sedatives including hydromorphone, midazolam, and dexmedetomidine. On post-operative day 24, he develops agitation concerning for hyperactive delirium.

What pharmacologic treatment would you recommend?
A. Initiate IV haloperidol
B. Increase midazolam infusion rate
C. Initiate enteral quetiapine
D. No pharmacologic treatment
1. Background

Definition of Delirium

• Diagnostic and Statistical Manual of Mental Disorders (DSM-5)
  – Acute onset of disturbance in attention, awareness, and cognition
  – Fluctuates in severity
  – Consequence of another medical condition

• 3 types of delirium
  – Hypoactive (e.g., inattention, confusion, sedation, apathy)
  – Hyperactive (e.g., agitation, hallucinations, delusions, restlessness)
  – Mixed

Intensive Care Unit (ICU) Delirium

- Prevalence
  - Adults: 20 - 84%
  - Pediatrics: 12 - 65%
- Onset (median)
  - Adults: 2 days
  - Pediatrics: 1 - 3 days
- Duration (median)
  - Adults: 3 days
  - Pediatrics: 2 days

Klein PM, et al. BMJ. 2014;349:g6652. doi:10.1136/bmj.g6652.

Distribution of ICU Delirium Types

- Adults
  - Hypoactive
  - Mixed
  - Hyperactive

- Pediatrics
  - Hyperactive

Outcomes Associated with ICU Delirium

- ↑ mortality
- ↑ ICU and hospital length of stay
- ↑ duration of mechanical ventilation
- ↑ self-extubation and catheter removal
- Long-term cognitive impairment
- ↑ healthcare costs


Pathophysiology of Delirium

- Complex with many possible pathways
- Predisposition + precipitating factor
- Hypotheses
  - Neuroinflammatory
  - Neurotransmitter
  - Oxidative stress

Risk Factors for ICU Delirium: Adult

**Non-Modifiable**
- Increased age
- Dementia
- Prior coma
- Surgery or trauma before ICU admission
- Increased APACHE score
- Increased ASA score
- History of hypertension
- Admission due to neurologic illness

**Modifiable**
- Benzodiazepine use
- Blood transfusions
- Use of psychoactive medications (e.g., antipsychotics, anticonvulsants)

**Non-Modifiable**
- Age ≤ 2 years
- Development delay
- High severity of illness
- Pre-existing medical conditions
- Prior coma
- Mechanical ventilation
- Increased length of stay
- Decreased albumin
- Cardiac bypass surgery

**Modifiable**
- Medications
  - Benzodiazepines
  - Anticholinergics
  - Opioids
  - Vasopressors
- Immobilization
- Restraints

*APACHE = Acute Physiology and Chronic Health Evaluation
ASA = American Society of Anesthesiologists*
2. Delirium Scoring Tools

Validated ICU Delirium Scoring Tools

<table>
<thead>
<tr>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Intensive Care Delirium Screening Checklist (ICDSC)</td>
<td>2. Pediatric Confusion Assessment Method (pCAM-ICU)</td>
</tr>
<tr>
<td></td>
<td>3. Preschool Confusion Assessment Method (psCAM-ICU)</td>
</tr>
</tbody>
</table>
## Adult Scoring Tools

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)</th>
<th>Intensive Care Delirium Screening Checklist (ICDSC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basis of assessment</td>
<td>Patient interaction and clinical observation</td>
<td>Clinical observation</td>
</tr>
<tr>
<td>Number of items</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Score range</td>
<td>N/A</td>
<td>0 - 8</td>
</tr>
<tr>
<td>Score indicating delirium</td>
<td>Positive for features 1, 2, and 3 or 4</td>
<td>≥ 4</td>
</tr>
</tbody>
</table>


### CAM-ICU

<table>
<thead>
<tr>
<th>Feature</th>
<th>Question / Activity</th>
<th>Positive Result</th>
<th>Required for Delirium</th>
</tr>
</thead>
</table>
| 1. Alteration / fluctuation in mental status | • Is the patient’s mental status different than his/her baseline?  
• Has the patient had any fluctuation in mental status in the past 24 hours as evidence by fluctuation on a sedation scale (e.g., RASS, GSC) or previous delirium assessment? | Yes to either question | Yes |
| 2. Inattention | • “I am going to read you a series of 10 letters. Whenever you hear the letter A, squeeze my hand”  
• “SAVEAHAART”, “CASABLANCA”, “ABADABAAY” | > 2 errors | Yes |
| 3. Altered level of consciousness | • Richmond Agitation-Sedation Scale (RASS) score  
• Riker Sedation-Agitation Scale (SAS) score | RASS ≠ 0 OR SAS ≠ 4 | Either Feature 3 OR Feature 4 must be positive |
| 4. Disorganized thinking | • Yes/No questions (Will a stone float on water? Are there fish in the sea? Does 1 pound weigh more than 2 pounds? Can you use a hammer to pound a nail?)  
• Commands (Hold up this many fingers. Now do the same with the other hand.) | > 1 error | |

### ICDSC

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered level of</td>
<td>• Exaggerated response to normal stimulation (SAS 5 - 7, RASS +1 to +4)</td>
<td>Score 1 point per category if patient meets any of the criteria listed</td>
</tr>
<tr>
<td>consciousness</td>
<td>• Response to mild or moderate stimulation (SAS = 3, RASS -1 to -3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* If SAS 1 - 2 or RASS -4 to -5, stop assessment</td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>• Difficulty in following commands</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Easily distracted by external stimuli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Difficulty in shifting focus</td>
<td></td>
</tr>
<tr>
<td>Disorientation</td>
<td>Mistake in either time, place, or person</td>
<td></td>
</tr>
<tr>
<td>Hallucinations or</td>
<td>• Equivocal evidence of hallucinations or a behavior due to hallucinations</td>
<td></td>
</tr>
<tr>
<td>delusions</td>
<td>• Delusions or gross impairment of reality testing</td>
<td></td>
</tr>
<tr>
<td>Psychomotor agitation or</td>
<td>• Hyperactivity requiring the use of additional sedative drugs or restraints</td>
<td></td>
</tr>
<tr>
<td>retardation</td>
<td>• Hypoactive or clinically noticeable psychomotor slowing or retardation</td>
<td></td>
</tr>
<tr>
<td>Inappropriate speech or</td>
<td>• Inappropriate, disorganized, or incoherent speech</td>
<td>Score ≥ 4 indicates delirium</td>
</tr>
<tr>
<td>mood</td>
<td>• Inappropriate mood related to events or situation</td>
<td></td>
</tr>
<tr>
<td>Sleep / wake cycle</td>
<td>• Sleeping &lt; 4 hours at night</td>
<td></td>
</tr>
<tr>
<td>disturbances</td>
<td>• Waking frequently at night (without stimulation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sleeping ≥ 4 hours during day</td>
<td></td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td>• Fluctuation of any of the above categories over 24 hours</td>
<td></td>
</tr>
</tbody>
</table>


### Pediatric Scoring Tools

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cornell Assessment of Pediatric Delirium (CAPD)</th>
<th>Pediatric Confusion Assessment Method (pCAM-ICU)</th>
<th>Preschool Confusion Assessment Method (psCAM-ICU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages validated</td>
<td>0-21 years</td>
<td>Children &gt; 5 years</td>
<td>6 months – 5 years</td>
</tr>
<tr>
<td>Basis of assessment</td>
<td>Clinical observation</td>
<td>Patient interaction and clinical observation</td>
<td></td>
</tr>
<tr>
<td>Number of items</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Score range</td>
<td>0 - 32</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Score indicating delirium</td>
<td>≥ 9</td>
<td>Positive for features 1, 2, and 3 or 4</td>
<td>Positive for all 4 features</td>
</tr>
</tbody>
</table>

**CAPD**

- Score ≥ 9 indicates delirium
- If RASS score -4 or -5, do not use

<table>
<thead>
<tr>
<th>Feature</th>
<th>Question / Activity</th>
<th>Positive Result</th>
<th>Required for Delirium</th>
</tr>
</thead>
</table>
| 1. Acute change or fluctuation course of mental status | • Is there an acute change from mental status baseline?  
• Has the patient's mental status fluctuated during the past 24 hours? | Yes to either question | Yes |
| 2. Inattention | • “Squeeze my hand when I say A”  
• “ABADBADAY” | > 2 errors | Yes |
| 3. Altered level of consciousness | • Richmond Agitation-Sedation Scale (RASS) score | RASS ≠ 0 | Either Feature 3 OR Feature 4 must be positive |
| 4. Disorganized thinking | • Yes/No questions (Is sugar sweet? Is ice cream hot? Do birds fly? Is an ant bigger than an elephant?)  
• Commands (Hold up this many fingers. Now do the same with the other hand.) | > 1 error | |

**pCAM-ICU**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Question / Activity</th>
<th>Positive Result</th>
<th>Required for Delirium</th>
</tr>
</thead>
</table>
| 1. Acute change or fluctuation course of mental status | • Is there an acute change from mental status baseline?  
• Has the patient's mental status fluctuated during the past 24 hours? | Yes to either question | Yes |
| 2. Inattention | • “Squeeze my hand when I say A”  
• “ABADBADAY” | > 2 errors | Yes |
| 3. Altered level of consciousness | • Richmond Agitation-Sedation Scale (RASS) score | RASS ≠ 0 | Either Feature 3 OR Feature 4 must be positive |
| 4. Disorganized thinking | • Yes/No questions (Is sugar sweet? Is ice cream hot? Do birds fly? Is an ant bigger than an elephant?)  
• Commands (Hold up this many fingers. Now do the same with the other hand.) | > 1 error | |
# psCAM-ICU

<table>
<thead>
<tr>
<th>Feature</th>
<th>Question / Activity</th>
<th>Positive Result</th>
<th>Required for Delirium</th>
</tr>
</thead>
</table>
| 1. Acute change or fluctuating course of mental status | • Is there an acute change from mental status baseline?  
• Has the patient’s mental status fluctuated during the past 24 hours? | Yes to either question | Yes |
| 2. Inattention | • Show each picture to the patient. Slowly move it in front of their face to one side while verbally prompting them to look at the picture. Switch to the next picture. Repeat. (10 pictures)  
• Did the patient have difficulty keeping their eyes open? (Eyes closed or requiring voice to stimulate eye opening for majority of assessment?) | > 3 errors OR Difficulty keeping eyes open | Yes |
| 3. Altered level of consciousness | • Does the patient currently have an altered level of consciousness (i.e., not alert and calm)?                                               | Yes             | Yes                  |
| 4. Disorganized brain | • Does the patient have a sleep-wake cycle disturbance? (e.g., sleeps mostly during the day, does not awake easily to stimulation?)                       | Yes             | Yes |


## 3. Non-Pharmacologic Management
Non-Pharmacologic Management of Delirium

- “Multi-component, non-pharmacologic intervention”

- ABCDE(F) Bundle
  - Awakening and Breathing Coordination, Delirium monitoring /management, Early mobility, Family engagement
  - Outcomes
    - ↓ delirium
    - ↓ mortality
    - ↑ coma and delirium free ICU days

4a. Antipsychotics: Overview

Antipsychotics for ICU Delirium

- No agents with FDA-labeled indication for prevention or treatment of ICU delirium
- 2018 Pain, Agitation / Sedation, Delirium, and Sleep Disruption in Adult Patients in the ICU (PADIS) Guidelines
  - Antipsychotics **NOT** recommended for prevention of ICU delirium
  - Antipsychotics **NOT routinely** recommended for treatment of ICU delirium
- Pediatric guidelines from the Society of Critical Care Medicine (SCCM) expected in 2020

# Use of Antipsychotics for Adult ICU Delirium

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study Period</th>
<th>Total Sample Size</th>
<th>Incidence of Delirium</th>
<th>Antipsychotic Exposure</th>
<th>Haloperidol</th>
<th>Second-Generation Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swan et al. 2012</td>
<td>2010</td>
<td>164,996</td>
<td>6.1% (n=10,034)</td>
<td>38.7%</td>
<td>30.0%</td>
<td>25.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Olanzapine: 12.7% Risperidone: 5.0%</td>
</tr>
<tr>
<td>Collet et al. 2018</td>
<td>2016</td>
<td>1,260</td>
<td>25% (n=314)</td>
<td>-</td>
<td>46.2%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quetiapine: 19% Olanzapine: 9%</td>
</tr>
</tbody>
</table>


## Antipsychotics: Dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adult Dosing Range</th>
<th>Pediatric Dosing Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.5 - 10 mg every 6-8 hours</td>
<td>0.003 - 0.278 mg/kg/dose every 6-8 hours</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5 - 200 mg every 12 hours</td>
<td>0.43 - 2.8 mg/kg/dose every 8 hours</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5 - 20 mg daily</td>
<td>0.625 - 60 mg daily or divided BID</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5 - 8 mg daily or divided BID</td>
<td>0.1 - 2 mg daily or divided BID</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>2.5 - 40 mg every 12 hours</td>
<td>-</td>
</tr>
</tbody>
</table>

### Antipsychotics: Immediate Release Formulations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tablets or Capsules</th>
<th>Oral Solution</th>
<th>IV</th>
<th>IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Tablets: 0.5, 1, 2, 5, 10, 20 mg</td>
<td>2 mg/mL</td>
<td>5 mg/mL (lactate)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>IR tablets: 25, 50, 100, 200, 300, 400 mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>IR tablets: 2, 5, 7.5, 10, 15, 20 mg Orally disintegrating tablets: 5, 10, 15, 20 mg</td>
<td>-</td>
<td>-</td>
<td>10 mg</td>
</tr>
<tr>
<td>Risperidone</td>
<td>IR and orally disintegrating tablets: 0.25, 0.5, 1, 2, 3, 4 mg</td>
<td>1 mg/mL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Capsules: 20, 40, 60, 80 mg</td>
<td>-</td>
<td>-</td>
<td>20 mg (mesylate)</td>
</tr>
</tbody>
</table>

### 4b. Antipsychotics: Prevention
Efficacy of Antipsychotics for Prevention of ICU Delirium: Adults

- Systematic reviews and meta-analyses of haloperidol or second-generation antipsychotics compared to placebo
  - ICU or hospital length of stay: no significant differences
  - Mortality: no significant differences
  - Delirium incidence
    - Haloperidol: no significant differences
    - Second-generation antipsychotics: decreased in post-surgical patients

- Conclusion: routine use of antipsychotics for the prevention of delirium in adults **NOT** supported by the literature

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<table>
<thead>
<tr>
<th>Publication</th>
<th>Sample Size</th>
<th>Population</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al. 1999</td>
<td>78</td>
<td>Elderly patients admitted to the ICU after gastrointestinal surgery</td>
<td>Decreased incidence of delirium</td>
<td>Changes in practice since publication</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No significant adverse effects</td>
<td>Limited information provided</td>
</tr>
<tr>
<td>Wang et al. 2012</td>
<td>457</td>
<td>Adults ≥ 65 years admitted to the ICU after non-cardiac surgery</td>
<td>Decreased incidence of delirium</td>
<td>Median ICU stay: 21 vs. 23 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased time to onset of delirium</td>
<td>Median APACHE II score: &lt; 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased hospital length of stay</td>
<td>Continuous infusion haloperidol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased delirium free days</td>
<td></td>
</tr>
</tbody>
</table>
Second-Generation Antipsychotics for Post-Operative ICU Delirium

- Meta-analysis: decreased delirium incidence vs. placebo (RR 0.26, CI 0.26-0.50)
- Overall incidence of delirium in these trials: 11 - 31%
- Hakim et al. 2012: risperidone
  - Population: 101 adults ≥ 65 years with subsyndromal delirium after cardiac surgery
  - 5% of patients received open-label haloperidol
- Prakanrattana et al. 2007: risperidone
  - Population: 126 adults ≥ 40 years undergoing elective cardiac surgery


Antipsychotics for Prevention of ICU Delirium: Pediatrics

Currently no published studies available
Summary: Antipsychotics for Prevention of Delirium

• Most adult literature does NOT support the use of antipsychotics for prevention of ICU delirium

• Second-generation antipsychotics may be beneficial in preventing post-operative ICU delirium in older adults

• No data to support use in children

4c. Antipsychotics: Treatment
Efficacy of Antipsychotics for Treatment of ICU Delirium: Adults

- Systematic review and meta-analysis of haloperidol or second-generation antipsychotics vs. placebo
  - Delirium duration
  - Hospital length of stay
  - Mortality
  - Sedation

- Landmark trial: MIND-USA (2018)

MIND-USA Trial: Methods

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, double-blind, placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>To determine the effects of haloperidol and ziprasidone on delirium during critical illness</td>
</tr>
<tr>
<td>Population</td>
<td>Adults treated for delirium in the medical or surgical ICU</td>
</tr>
</tbody>
</table>
| Intervention         | 3 treatment groups
  - Haloperidol 2.5 mg IV q12h*  
  - Ziprasidone 5 mg IV q12h*  
  - Placebo  
  *Doses were reduced 50% in patients ≥ 70 years |
| Doses titrated to maximum doses of haloperidol 20 mg/day and ziprasidone 40 mg/day |
| Duration             | 14 days or until ICU discharge |
| Outcomes             | Primary outcome: days alive without delirium or coma |
|                      | Secondary outcomes: duration of delirium, 30-day survival, 90-day survival, time to freedom from mechanical ventilation, time to ICU discharge, time to hospital discharge, time to ICU readmission |

MIND-USA Trial: Results

**Demographics**
- Sample size: 566
  - Median age: 60 years
  - Hypoactive delirium at randomization: 89%
  - Median number of days from ICU admission to randomization: 2.36 days
  - Most common diagnoses: acute respiratory distress syndrome, sepsis, airway protection

**Treatment**
- Mean daily doses
  - Haloperidol: 11.0 ± 4.7 mg
  - Ziprasidone: 20.0 ± 9.4 mg
- Open-label antipsychotic use: 21%
- Adherence to ABCDE bundle: 88%

**Primary and Secondary Outcomes**
- Median number of days alive without delirium or coma (placebo, haloperidol, ziprasidone): 8.5, 7.9, 8.7 (p=0.26)
- No significant differences in any secondary outcomes

**Safety**
- QT prolongation: more common with ziprasidone

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MIND-USA Trial: Conclusions

- **Authors’ conclusion**: haloperidol or ziprasidone use does not affect duration of delirium in critically ill adults
- **Limitations**
  - 89% of patients presented with hypoactive delirium
  - 21% of patients received open-label antipsychotics
- **Unanswered questions**
  - Role of haloperidol and ziprasidone for hyperactive delirium
  - Role of other antipsychotics in treatment of delirium
Summary: Treatment of ICU Delirium in Adults

- Literature does NOT support the use of antipsychotics for treatment of ICU delirium

- Caveats
  - Most trials allowed open-label antipsychotic use
  - **Short-term** antipsychotic use may be beneficial for certain patients with **hyperactive** delirium

Efficacy of Antipsychotics for Treatment of ICU Delirium: Pediatrics

- 13 studies (n=370)
- Agents used
  - Haloperidol (n=131)
  - Olanzapine (n=125)
  - Quetiapine: (n=82)
  - Risperidone: (n=34)
- Majority reported improvements in delirium symptoms
- Limitations
  - Mostly **retrospective**
  - Significant variability in dosing
  - Omission of important details (e.g., dosing, formulation, duration)
  - Only 5 studies used validated screening tools

Summary: Treatment of ICU Delirium in Pediatrics

- Limited data available
  - Mainly retrospective
  - Most data: haloperidol, olanzapine
- Consider antipsychotics for children who failed non-pharmacologic interventions
- Consider patient-specific factors (e.g., risk of QTc prolongation, age, weight)
- Dosage formulations may limit treatment options

4d. Antipsychotics: Adverse Effects and Monitoring
Atypical antipsychotics: Adverse Effects

<table>
<thead>
<tr>
<th>Short Term</th>
<th>Long Term</th>
<th>Abrupt Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• QTc prolongation</td>
<td>• Weight gain</td>
<td>• Dyskinesia</td>
</tr>
<tr>
<td>• Extrapyramidal symptoms</td>
<td>• Hyperlipidemia</td>
<td>• Psychosis</td>
</tr>
<tr>
<td>(e.g., dyskinesia, akathisia)</td>
<td>• Hyperglycemia</td>
<td>• Insomnia</td>
</tr>
<tr>
<td>• Neuroleptic malignant syndrome</td>
<td></td>
<td>• Cholinergic effects</td>
</tr>
<tr>
<td>• Anticholinergic effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g., dry mouth, constipation)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse Effects: Adults vs. Pediatrics

- Adult specific warnings / effects
  - Black box warning for increased mortality in patients ≥ 65 years
  - Higher rates of long-term institutional care
- Effects seen more frequently in pediatrics
  - Orthostatic hypotension
  - Drowsiness / over-sedation
  - Agitation
  - Metabolic effects (second-generation)
Adverse Effects: First vs. Second-Generation

- First-generation antipsychotics
  - ↑ extrapyramidal symptoms
- Second-generation antipsychotics
  - ↓ extrapyramidal symptoms
  - ↑ sedation
- Agent specific considerations
  - Orthostatic hypotension: more common with risperidone and quetiapine
  - Anticholinergic effects: more common with olanzapine and quetiapine
  - Quetiapine: treatment of choice for Parkinson’s disease

QT Prolongation

- All antipsychotics associated with ↑ risk of QT prolongation
- Definitions vary
  - Children: > 440 - 470 ms, or > 60 ms above baseline
  - Adults: > 450 ms (males), > 460 - 470 ms (females), or > 60 ms above baseline
- Surrogate marker for increased risk of torsades de pointes
- Less common in children


Risk Factors for QT Prolongation

- Electrolyte disturbances
  - Hypokalemia
  - Hypomagnesemia
  - Hypocalcemia
- Use of proarrhythmic / QT prolonging drugs
- Female sex
- Age ≥ 65 years
- Family history of QT prolongation
- Renal failure (GFR < 30 mL/min or hemodialysis)

- Stimulating conditions or medications (e.g., exercise, epinephrine)
- Cardiovascular disease
- Hypothyroidism
- Hypopituitarism
- Primary aldosteronism
- Sepsis
- Fever
- Hypothermia

---

**QT Prolongation: Agent Specific Risk**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Risk of Torsades de Pointes</th>
<th>Risk of Increased QT in Labeling</th>
<th>Risk of Torsades de Pointes in Labeling</th>
<th>QT Monitoring Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Known</td>
<td>Yes</td>
<td>Yes</td>
<td>IV haloperidol*</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Possible</td>
<td>Yes</td>
<td>No</td>
<td>Overdose</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Conditional</td>
<td>Yes</td>
<td>No</td>
<td>Diuretic use; overdose</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Conditional</td>
<td>Yes</td>
<td>No</td>
<td>Overdose</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Conditional</td>
<td>No</td>
<td>No</td>
<td>Overdose</td>
</tr>
</tbody>
</table>

*IV haloperidol
- FDA warning for risk of QT prolongation and torsades de pointes
- Continuous ECG monitoring recommended
- Likely safe in patients receiving < 2 mg with no risk factors for QTc prolongation and a normal baseline QTc
Safety of Antipsychotics for ICU Delirium: Adults

- Meta-analyses: no significant differences in adverse effects
  - Extrapyramidal symptoms more common with haloperidol
  - Trend toward increased cardiac effects
- Patient-specific risk must be considered
  - Overall low rate of adverse effects
  - Higher risk patients excluded from many studies
- Monitoring recommended


Safety of Antipsychotics for ICU Delirium: Pediatrics

- Overall rate of adverse drug reactions: 6.2% (n=23)
  - Dystonia: 3.5% (n=13)
  - Extrapyramidal symptoms: 1% (n=4)
  - Hyperpyrexia ± neuromalignant syndrome: 1% (n=3)
  - QTc prolongation: 1% (n=3)
    - No torsades de pointes
  - Over-sedation: 0.5% (n=2)
- Agent specific rate of adverse drug reactions
  - Haloperidol: 14.5% (n=9)
    - One death due to hyperpyrexia associated with IV haloperidol
  - Quetiapine: 3.7% (n=3)
  - Olanzapine: 0.8% (n=1)
  - Risperidone: 0

Antipsychotics for ICU Delirium: Monitoring

<table>
<thead>
<tr>
<th>Monitoring Parameter</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes (e.g., potassium, magnesium)</td>
<td>Baseline and every 48-72 hours</td>
</tr>
<tr>
<td>Electrocardiogram (ECG)</td>
<td>Baseline and every 48-72 hours</td>
</tr>
<tr>
<td>Continuous ECG (i.e., telemetry)</td>
<td>• IV haloperidol: all patients</td>
</tr>
<tr>
<td></td>
<td>• Other agents: consider for patients at high risk of arrhythmias</td>
</tr>
<tr>
<td>Adverse effects (e.g., extrapyramidal symptoms, over-sedation, orthostatic hypotension)</td>
<td>• Short-term side effects: daily</td>
</tr>
<tr>
<td>Present or absence of delirium (using validated screening tools)</td>
<td>At least every 12 hours</td>
</tr>
</tbody>
</table>

Duration of Delirium Treatment

- **Adults**
  - Duration typically limited to < 1 month
  - Reasons for discontinuation
    - ICU discharge
    - Delirium-free for > 48 hours
- **Pediatrics**
  - Haloperidol: 3 - 22 days
  - Quetiapine: 1 - 108 days
  - Olanzapine: 1 - 151 days
  - Risperidone: 2 - 151 days
- **Discontinuing treatment**
  - **Tapering** recommended for prolonged course (> 10 days)

Continuation of Antipsychotics at Discharge

• In adult patients initiated on antipsychotics in the ICU
  – 23 - 84% were continued on antipsychotics at ICU discharge
    • Majority (64 - 68%) of continuation was inappropriate
  – 10 - 55% were continued on antipsychotics at hospital discharge

• Implementation of an antipsychotic discontinuation bundle can decrease continuation of antipsychotics at ICU and hospital discharge

Flurie RW, et al. Am J Health-Sys Pharm. 2015;72:

5. Other Pharmacologic Options
## Melatonin for Prevention of Delirium: Adults

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of Studies Included</th>
<th>Total Sample Size</th>
<th>Population</th>
<th>Significant Differences</th>
<th>No Significant Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng et al. 2019</td>
<td>16</td>
<td>1,634</td>
<td>Hospitalized adults</td>
<td>• Decreased ICU length of stay</td>
<td>• Incidence of delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Decreased ICU length of stay</td>
<td>• Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Mortality</td>
<td>• Need for sedatives</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Mortality</td>
<td>• Need for restraints</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Mortality</td>
<td>• Duration of mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Mortality</td>
<td>• Adverse effects</td>
</tr>
<tr>
<td>Zhang et al. 2019</td>
<td>8</td>
<td>409</td>
<td>Critically ill adults</td>
<td>• Decreased prevalence of delirium</td>
<td>• ICU mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Decreased ICU length of stay</td>
<td>• Trend toward longer sleep duration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Decreased ICU length of stay</td>
<td>• Trend toward decreased duration of mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Decreased nighttime awakenings</td>
<td></td>
</tr>
</tbody>
</table>


## Melatonin for Prevention of Delirium: Pediatrics

Currently no published studies available
## Dexmedetomidine for ICU Delirium: Adults

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of Studies Included</th>
<th>Total Sample Size</th>
<th>Population</th>
<th>Significant Differences</th>
<th>No Significant Differences</th>
</tr>
</thead>
</table>
| Chen et al. 2015       | 7                          | 1,624             | Critically ill adults | • Decreased duration of mechanical ventilation  
• Decreased ICU length of stay  
• Increased risk of bradycardia | • Incidence of delirium  
• Mortality |
| Flukiger et al. 2018   | 25                         | 4,975             | Critically ill adults | • Decreased incidence of delirium  
• Increased risk of bradycardia and hypotension | • Mortality  
• 2 studies for treatment (vs. placebo and midazolam) indicated favorable results |


## Dexmedetomidine for Post-Operative Delirium: Adults

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of Studies Included</th>
<th>Total Sample Size</th>
<th>Population</th>
<th>Significant Differences</th>
<th>No Significant Differences</th>
</tr>
</thead>
</table>
| Liu et al. 2016        | 8                          | 969               | Adults undergoing cardiac surgery         | • Decreased incidence of delirium  
• Decreased length of intubation  
• Increased risk of bradycardia | • ICU length of stay  
• Hypotension  
• Atrial fibrillation |
| Zeng et al. 2019       | 6                          | 2,102             | Adults ≥ 65 years undergoing non-cardiac surgery | • Decreased incidence of delirium  
• Increased risk of bradycardia  
• Decreased risk of hypertension, stroke, and hypoxemia | • Mortality  
• Hypotension  
• Myocardial infarction |

# Dexmedetomidine for Delirium: Pediatrics

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of Studies Included</th>
<th>Total Sample Size</th>
<th>Population</th>
<th>Significant Differences</th>
<th>No Significant Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pickard et al. 2014</td>
<td>10</td>
<td>669</td>
<td>Children (0-16 years) receiving general anesthesia</td>
<td>• Decreased incidence of post-operative emergence delirium</td>
<td>• Recovery time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Decreased need for rescue analgesia</td>
<td>• Time to discharge</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Time to discharge</td>
<td>• Adverse effects</td>
</tr>
<tr>
<td>Pan et al. 2016</td>
<td>14</td>
<td>2,229</td>
<td>Children undergoing surgery for congenital heart disease</td>
<td>• Decreased incidence of agitation or delirium</td>
<td>• ICU or hospital length of stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Decreased need for rescue analgesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Shorter duration of mechanical ventilation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Increased risk of bradycardia and hypotension</td>
<td></td>
</tr>
</tbody>
</table>

6. Conclusions
Conclusions

• ICU delirium is common in critically ill children and adults
• Validated screening tools should be used to detect ICU delirium
• Non-pharmacologic interventions are recommended to prevent and manage delirium
• Antipsychotics are not routinely recommended for prevention or treatment of ICU delirium
• Antipsychotics can be considered for short-term use in children and adults with hyperactive delirium not responding to non-pharmacologic interventions
• Patients should be monitored for safety and efficacy during treatment

Post-Assessment Question 1

RT is a 42 year old female admitted to the MICU for septic shock. She was extubated and remains on vancomycin and piperacillin/tazobactam. On hospital day 4, her ICSDC score is 5 due to inattention, disorientation, disorganized speech, sleep disturbances, and symptom fluctuation.

What pharmacologic treatment would you recommend?
A. Initiate IV haloperidol
B. Initiate enteral olanzapine
C. Initiate enteral risperidone
D. No pharmacologic treatment
Post-Assessment Question 2

AB is an 8 month old male admitted to the PICU following cardiothoracic surgery. He remains mechanically ventilated and on multiple continuous infusion sedatives including hydromorphone, midazolam, and dexmedetomidine. On post-operative day 24, he develops agitation concerning for hyperactive delirium.

What pharmacologic treatment would you recommend?
A. Initiate IV haloperidol
B. Increase midazolam infusion rate
C. Initiate enteral quetiapine
D. No pharmacologic treatment

Definitely, Maybe: The Role of Antipsychotics in Children and Adults with ICU Delirium

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Professor, University of Oklahoma College of Pharmacy

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