Pediatric Delirium: Typical or Atypical?

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Pharmacy Grand Rounds
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Objectives

• Discuss current literature available for the use of antipsychotics in pediatric delirium

• Explain the pharmacology of different antipsychotics used for treatment of delirium

• Identify appropriate treatment strategies based on patient factors and potential adverse effects
The Basics
Delirium: Definition

- Disturbance of consciousness and cognition that develops acutely with a fluctuating course of mental status, inattention, and an impaired ability to receive, process, store, or recall information directly triggered by a general medical condition, *substance intoxication or withdrawal*, *exposure to a toxin*, or *is due to multiple etiologies*

- Psychosis
- ICU syndrome
- Acute confusional state
- Encephalopathy
- Acute brain failure
- “Sun-downing”
Delirium: Incidence

- 30-80% of critically ill adults
- 20-30% of critically ill children
  - 75% of PICU patients are <3 years old
  - 50% are < 1 year old

## Delirium: Causes

<table>
<thead>
<tr>
<th>I</th>
<th>Infection</th>
<th>Encephalitis, meningitis, UTI, pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>Withdrawal</td>
<td>Alcohol, barbiturates, benzodiazepines</td>
</tr>
<tr>
<td>A</td>
<td>Acute metabolic</td>
<td>Electrolyte imbalance, hepatic or renal failure</td>
</tr>
<tr>
<td>T</td>
<td>Trauma</td>
<td>Head injury, postoperative</td>
</tr>
<tr>
<td>C</td>
<td>CNS Pathology</td>
<td>Stroke, hemorrhage, tumor, seizures</td>
</tr>
<tr>
<td>H</td>
<td>Hypoxia</td>
<td>Anemia, cardiac failure, pulmonary embolus</td>
</tr>
<tr>
<td>D</td>
<td>Deficiencies</td>
<td>Vitamin B12, thiamine, folic acid</td>
</tr>
<tr>
<td>E</td>
<td>Endocrinopathies</td>
<td>Thyroid, glucose, parathyroid, adrenal</td>
</tr>
<tr>
<td>A</td>
<td>Acute vascular</td>
<td>Shock, vasculitis, hypertensive encephalopathy</td>
</tr>
<tr>
<td>T</td>
<td>Toxic or drugs</td>
<td>Toxins, anaesthetics, anticholinergics, opioids, etc</td>
</tr>
<tr>
<td>H</td>
<td>Heavy metals</td>
<td>Arsenic, lead, mercury</td>
</tr>
</tbody>
</table>

Delirium: Clinical Presentation

Neuropsychiatric Symptoms

Adults & Children
- Impaired alertness, waxing/waning mental status, sleep-wake disturbances, disorientation, and inattention

Children
- Purposeless actions, labile affect, inconsolability

Delirium: Subtypes

- Hyperactive
- Hypoactive
- Mixed
- Emergence

Delirium: Subtypes

Hyperactive

- Restlessness
- Agitation
- Emotional labiality, inconsolability
- Delusions/Hallucinations
- Autonomic dysregulation

- $\uparrow$ dopamine
- $\downarrow$ acetylcholine

Hypoactive

- Apathy
- Decreased responsiveness
- Withdrawal
- Little spontaneous movement

- $\downarrow$ dopamine
- $\uparrow$ acetylcholine or GABA$_{\alpha}$

Delirium: Recognition Tools

- Pediatric Confusion Assessment Method (pCAM-ICU)
  - Adapted from CAM-ICU
  - Age: >5 years
  - psCAM-ICU
- Cornell Assessment for Pediatric Delirium (CAPD)
  - Adapted from Pediatric Anesthesia Emergence Delirium (PAED)
  - Age: 0-21 years

Costs of Delirium

- Increased length of hospital stay
- Higher $$ to patient and hospital
- Increased time on mechanical ventilation
- Delusional memories
- High morbidity and mortality

Q1: If confronted with the need for pharmacological treatment for delirium, which drug would be your first choice?

A. Haloperidol
B. Olanzapine
C. Quetiapine
D. Risperidone
E. Ziprasidone
F. None of the above
Treatment
Non-Pharmacological Management

- **Ultimate goal:** “Normal” routine
  - Reassurance and reorientation
    - Repeat frequently
  - Calendars, clocks
  - Pictures of people and objects
  - Familiar toys, music, blankets
  - Lighting, noise
  - Early mobilization, avoiding restraints
  - Psychiatry consult

Individualization

Antipsychotic adverse effects

Untreated delirium
Pharmacologic Management

Historically: Haloperidol

Atypicals → Olanzapine, quetiapine, risperidone, ziprasidone

Optimal therapy???
Why Antipsychotics?

- Established clinical efficacy
- Decreased symptoms and severity
- Shorter time to clinical improvement
- Decreased need for other medications
- Can assist in weaning off of other medications

**Haloperidol: Oldie but Goodie?**

- Most studied
- Only IV agent that can be administered safely
- Relatively less sedation than other agents
- Blocks dopamine

- Significant cardiac effects may be more common in children <12
- Extrapyramidal symptoms (EPS), dystonia, akathisia, and hyperpyrexia

## Antipsychotic Summary

<table>
<thead>
<tr>
<th>MOA</th>
<th>Haloperidol</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>α1</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>H1</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>ACh</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Available Formulations
- Haloperidol: Tablet, IV, IM, suspension
- Olanzapine: Tablet, ODT, IM
- Quetiapine: Tablet
- Risperidone: Tablet, ODT, liquid
- Ziprasidone: Capsule, IM

### Renal
- No adjustment

### Hepatic
- No adjustment

### Drug-Drug Interactions
- Haloperidol: CYP2D6 & CYP3A4
- Olanzapine: CYP1A2
- Quetiapine: CYP 3A4
- Risperidone: CYP2D6, P-glycoprotein
- Ziprasidone: Minor

### Child-Pugh C

### Hepatic
- Use IM with caution

### Renal
- No adjustment

- <30mL/min

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Q2: Haloperidol’s main mechanism of action is:

A. Serotonin agonist
B. Serotonin antagonist
C. Dopamine antagonist
D. Dopamine agonist
E. None of the above
Adverse Effects
Antipsychotic Adverse Effects

- CNS: akathisia, sedation, lower seizure threshold, laryngeal spasm, neuroleptic malignant syndrome (NMS)

- Metabolic: metabolic syndrome, obesity, hyperglycemia, elevated cholesterol, increased risk for DM Type 2, ASCVD

Cardiovascular Effect

♥ Less frequent in children and adolescents

♥ Tachycardia, hypotension

♥ Arrhythmia, usually caused by prolongation of the QTc
   ♥ Risk for ventricular dysrhythmias, torsades de pointes, and sudden cardiac death

♥ Monitoring: Baseline EKG, potassium, magnesium, QTc
   ♥ Consider cessation:
      ♥ QTc >500 or >30 from baseline
      ♥ New T-wave abnormalities
      ♥ Bradycardia
# Summary Table of Adverse Effects

<table>
<thead>
<tr>
<th>Anti-Cholinergic</th>
<th>EPS</th>
<th>NMS</th>
<th>Orthostasis</th>
<th>QTc</th>
<th>Sedation</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>♥</td>
<td>(40)</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>♥</td>
<td>(10)</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>♥</td>
<td>(6.4)</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>♥</td>
<td>(14.5)</td>
<td>++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>♥</td>
<td>(20.6)</td>
<td>++</td>
</tr>
</tbody>
</table>

+++ → greater than 30% (except for NMS in haloperidol just is – rare but highest risk since highest potency antipsychotic

++→>10%

<10%

Current Literature
# Atypical Antipsychotic Medications to Control Symptoms of Delirium in Children and Adolescents (2012)

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>Describe the use of atypical antipsychotics in controlling symptoms of delirium in children/adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Retrospective chart review&lt;br&gt;Children’s Hospital Los Angeles (CHLA)&lt;br&gt;24 month period&lt;br&gt;Patients 1-18 years (~1/2 of patients &lt; 12, &gt;12)&lt;br&gt;Diagnosed with delirium; DRS-R-98&lt;br&gt;110 pediatric patients</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Olanzapine, risperidone, or quetiapine</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>DRS-R-98 score decreased significantly (p&lt;0.001) with antipsychotics without significant adverse side effects</td>
</tr>
</tbody>
</table>

## Mean Antipsychotic Dosages

<table>
<thead>
<tr>
<th>(mg)</th>
<th>Olanzapine (n=78)</th>
<th>Risperidone (n=13)</th>
<th>Quetiapine (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Daily Dose</td>
<td>4 (0.625-30)</td>
<td>0.6 (0.25-1)</td>
<td>30 (12.5-100)</td>
</tr>
<tr>
<td>Ending Daily Dose</td>
<td>5.4 (1.25-20)</td>
<td>0.7 (0.25-2)</td>
<td>70 (12.5-300)</td>
</tr>
<tr>
<td>Minimum Daily Dose</td>
<td>3 (0.625-5)</td>
<td>0.5 (0.15-1)</td>
<td>25 (12.5-50)</td>
</tr>
<tr>
<td>Maximum Daily Dose</td>
<td>10 (1.25-60)</td>
<td>1 (0.25-2)</td>
<td>75 (12.5-300)</td>
</tr>
<tr>
<td>Average Daily Dose</td>
<td>10 (1-52.5)</td>
<td>1.3 (0.375-4)</td>
<td>56 (12.5-125)</td>
</tr>
<tr>
<td>Usual Dosing</td>
<td>2.5-20</td>
<td>0.2-3</td>
<td>50-800</td>
</tr>
<tr>
<td>Days on Med</td>
<td>26.5 days (1-132, 178)</td>
<td>17.5 days (2-54)</td>
<td>35.1 days (1-108, 118)</td>
</tr>
</tbody>
</table>

Atypical Antipsychotic Medications to Control Symptoms of Delirium in Children and Adolescents

Discussion

- Causes: multifactorial; mainly infection or drug (opioids or benzodiazepines)
- Dosages were the highest when delirium was drug induced
- Length of treatment wasn’t significantly different ($p>0.3$)
- Not able to determine decreased DRS-R-98 scores was due to antipsychotic
- ODT and liquid formulations seemed to remove the need for IV
- No distinction between hypoactive, hyperactive, or mixed

Conclusion

- Atypical antipsychotic medications appear to be effective and safe
- Variability in starting doses
- Younger children should be started on the lower end of the range

Quetiapine as treatment for delirium in critically ill children: A case series (2013)

- CAPD screening tool
- Delirium improved in first 24 hours
- Successful treatment from infancy to adolescents

<table>
<thead>
<tr>
<th></th>
<th>Case 1 8 months</th>
<th>Case 2 3 years</th>
<th>Case 3 6 years</th>
<th>Case 4 14 years</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting daily dose</td>
<td>15mg* (1.7mg/kg)</td>
<td>25mg (2.1 mg/kg)</td>
<td>30mg* (1.6mg/kg)</td>
<td>50mg (1.3mg/kg)</td>
<td>15-50mg/day (1.7 mg/kg/day)</td>
</tr>
<tr>
<td>Max daily dose</td>
<td>20mg (2.2mg/kg)</td>
<td>100mg (8.3mg/kg)</td>
<td>100mg (5.3mg/kg)</td>
<td>137.5mg (3.6mg/kg)</td>
<td>20-137.5mg (3.6/mg/kg/day)</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>15 days; DC+taper</td>
<td>20 days; DC+taper</td>
<td>9 days</td>
<td>12 days</td>
<td>9-20 days</td>
</tr>
</tbody>
</table>

*Compounded liquid solution


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<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>Systematically evaluate the safety of short-term quetiapine use in pediatric patients for the purpose of treating ICU delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Retrospective Chart Review</td>
</tr>
<tr>
<td></td>
<td>Weill Cornell Center of New York Presbyterian Hospital</td>
</tr>
<tr>
<td></td>
<td>22 month period</td>
</tr>
<tr>
<td></td>
<td>Patients 2-20 years (median-4.5 years old), diagnosis of delirium; CAPD 50 patients</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Quetiapine</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Length of use, days 12 (4.5-22)</td>
</tr>
<tr>
<td></td>
<td>Dosage, mg/kg/day 1.3 (0.4-2.3)</td>
</tr>
<tr>
<td></td>
<td>Episodes of prolonged QTc 3</td>
</tr>
</tbody>
</table>

Evaluation of the Safety of Quetiapine in Treating Delirium in Critically Ill Children: A Retrospective Review

**Discussion**

- Largest systematic evaluation of the side effect profile in pediatrics
- Therapy initiation at Weill Cornell Center:
  - 1.5 mg/kg/day, divided in 3 doses
  - Extra 0.5 mg/kg for breakthrough agitation
  - Maximum dose is limited to 6mg/kg/day

**Conclusion**

- Quetiapine is a safe drug for short-term use with >2,400 doses used
- Administration is safe even in our youngest children
- Start patients on quetiapine 1.5mg/kg/day divided q8h
- Monitoring QTc is important, but increase may not be clinically significant

## Detection and Management of Delirium in the Neonatal Unit: A Case Series (2016)

<table>
<thead>
<tr>
<th>Description</th>
<th>Case 1 DOL 119</th>
<th>Case 2 DOL 77</th>
<th>Case 3 DOL 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consult</td>
<td>PICU and psych; CAPD</td>
<td>PICU and psych; CAPD</td>
<td>Psych; CAPD</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Hyperactive, inconsolable, poor attention, altered sleep wake cycle</td>
<td>Inconsolable, purposeless movements, insomnia, agitation</td>
<td>Agitation, restlessness, frequent flailing of arms and legs</td>
</tr>
<tr>
<td>Treatment</td>
<td>Quetiapine</td>
<td>Quetiapine</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Dose</td>
<td>1.5mg/kg/day - q 8hr - q 6h - titrated off</td>
<td>1.5mg/kg/day - q 8hr</td>
<td>1.5mg/kg/day - q 8hr - continued for 5 weeks</td>
</tr>
</tbody>
</table>

Patient weight: 2.5-4kg
Q3: 9 y/o boy (20kg) with mixed delirium and difficulty sleeping. All non-pharmacologic measures have been maximized. What would be the best drug therapy to start?

A. Haloperidol IV STAT 
B. Quetiapine 0.5mg/day prn 
C. Risperidone 3mg/kg/day 
D. Quetiapine 1.5mg/kg/day 
E. I wouldn’t start drug therapy
Future Research

- MIND-USA Trial
  - Multi-center, double-blind, randomized, placebo-controlled trial
  - 561 Adults
  - Haloperidol IV vs. Ziprasidone IV vs. placebo
  - Objective: define the role of antipsychotics in the management of delirium in vulnerable critically ill patients
  - Study completion: July 2019
Summary

• Hypoactive: avoid potent antipsychotics
• Hyperactive: haloperidol or quetiapine
• Renal and/or liver dysfunction: avoid risperidone
• Drug-Drug Interactions: ziprasidone
• IV: haloperidol
• Sedation: start at bedtime
• Daily dose = control symptoms
• Discontinue/taper: improved clinical status or SEs

SEs: side effects
Questions & Discussion
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