TREATING POST-OPERATIVE DELIRIUM

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Disclosures

- The author of this presentation does not have financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
Objectives

- Compare and contrast the pharmacologic agents available for the treatment of delirium
- Review the data supporting antipsychotics for the treatment of delirium
DSM-IV Criteria for Delirium

- Disturbance of consciousness with reduced ability to focus, sustain, or shift attention
- Change in cognition or development of a perceptual disturbance
- The disturbance develops in a short period of time and fluctuates during the course of the day

American Psychiatric Association: Delirium, Dementia, and Amnestic and Other Cognitive Disorders, in DSM IV ©2010.
Clinical Features

- **Cognitive decline**
  - Memory impairment, disorientation, language

- **Perceptual disturbances**
  - Misinterpretations, illusions, hallucinations
  - Visual, auditory, tactile, gustatory, and olfactory

- **Sleep disturbances**
  - Daytime sleepiness, nighttime agitation, sleep-wake cycle disturbances

- **Emotional disturbances**
  - Anxiety, fear, depression, anger, euphoria
  - Rapid shifts from one emotional state to another

## Differentiating Delirium

<table>
<thead>
<tr>
<th>Features</th>
<th>Delirium</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
</tr>
<tr>
<td>Course</td>
<td>Fluctuating</td>
<td>Progressive</td>
</tr>
<tr>
<td>Duration</td>
<td>Days to weeks</td>
<td>Months to years</td>
</tr>
<tr>
<td>Consciousness</td>
<td>Altered</td>
<td>Clear</td>
</tr>
<tr>
<td>Attention</td>
<td>Impaired</td>
<td>Normal</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Usually</td>
<td>Rarely</td>
</tr>
</tbody>
</table>

Delirium Subtypes

- Hyperactive (agitated, hyperalert)
  - Hallucinations, delusions, agitation, disorientation
- Hypoactive (lethargic, hypoalert)
  - Confusion, sedation
- Mixed delirium
  - Alternating features of hyper- and hypoactive delirium

- Cognitive impairment exists with both motor subtypes

Prevalence

- 15-60% medical/surgical inpatients
- 10-50% in postoperative patients
- 30-80% in ICU patients

- *Varies depending on patient population, instrument used, and frequency of screening*

Consequences of Delirium

- Failed or premature extubation
- Increased length of ICU and hospital stay
- Increased costs of hospital care
- Increased likelihood of dementia and permanent cognitive impairment
- Development of delirium in the ICU shown to be a predictor of increased mortality

# Risk Factors

<table>
<thead>
<tr>
<th>Predisposing</th>
<th>Precipitating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Restraints</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Catheters</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Pain</td>
</tr>
<tr>
<td>Alcoholism/Tobacco use</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Creatinine &gt;2 mg/dL</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Severity of illness</td>
<td>Sleep deprivation</td>
</tr>
</tbody>
</table>

### Prevention of Delirium

<table>
<thead>
<tr>
<th>Targeted Risk Factor and Eligible Patients</th>
<th>Standardized Intervention Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Impairment</td>
<td>Board with names of care-team members and day’s schedule Cognitively stimulating activities</td>
</tr>
<tr>
<td>Sleep Deprivation</td>
<td>At bedtime warm drink, relaxation tapes or music, and back massage Unit-wide noise-reduction strategies and schedule adjustments to allow sleep</td>
</tr>
<tr>
<td>Immobility</td>
<td>Ambulation or active range-of-motion exercises, minimal use of immobilizing equipment</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>Visual aids (glasses) and adaptive equipment</td>
</tr>
<tr>
<td>Hearing Impairment</td>
<td>Portable amplifying devices, earwax disimpaction</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Early recognition and volume repletion</td>
</tr>
</tbody>
</table>

Prevention of Delirium

Objective: Evaluate effectiveness of a multicomponent strategy for the prevention of delirium

Population: 852 patients ≥70 years admitted to general-medicine service

Standardized protocol for management of delirium risk factors

<table>
<thead>
<tr>
<th>Results</th>
<th>Intervention</th>
<th>Usual-Care</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium incidence</td>
<td>9.9%</td>
<td>15%</td>
<td>0.02</td>
</tr>
<tr>
<td># of days with delirium</td>
<td>105</td>
<td>161</td>
<td>0.02</td>
</tr>
<tr>
<td># of episodes</td>
<td>62</td>
<td>90</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Conclusions: The risk-factor intervention strategy resulted in significant reductions in the number and duration of episodes of delirium.

Non-Pharmacologic Modalities

- Reduce or eliminate exacerbating factors
- Reorient patients
- Provide environmental stimulation
- Reduce sensory impairments
- Create familiar environment

*Reassurance and information concerning delirium may reduce fear or demoralization*
PHARMACOTHERAPY
Pharmacotherapy

**Typical Antipsychotics**
- High Potency
  - Haloperidol (Haldol®)
  - Droperidol (Inapsine®)
- Low Potency
  - Chlorpromazine (Thorazine®)
  - Thioridazine (Mellaril®)

**Atypical Antipsychotics**
- Quetiapine (Seroquel®)
- Olanzapine (Zyprexa®)
- Risperidone (Risperdal®)
- Aripiprazole (Abilify®)
- Ziprasidone (Geodon®)
Haloperidol (Haldol®)

- Most frequently used antipsychotic for delirium
- MOA: Butyrophenone, high potency dopamine-2 receptor antagonist
- Administration: PO, IM, or IV
- Society of Critical Care Medicine guidelines recommend as drug of choice
Haloperidol Pharmacokinetics

- 60-70% oral bioavailability
- Tmax: 2-6 hours PO, 20 min IM
- Metabolism: glucuronidation and CYP3A4
  - No active metabolites
- Half-life (elimination): 18 hours
Haloperidol Side Effects

- Extrapyramidal symptoms (EPS)
- Less anticholinergic effects, sedation and hypotension than low potency antipsychotics
- Neuroleptic Malignant Syndrome (NMS)
- QTc prolongation
  - Torsades de pointes
    - Incidence ranges from 0.004% to 0.04%
    - Associated with higher IV doses (>35mg/day)
  - Monitor baseline EKG and q1-2 days while on therapy
  - QTc interval > 450 msec or >25% over baseline may warrant reduction or discontinuation

Haloperidol Dosing

- Haloperidol 1-2mg Q2-4h prn
  - (Elderly: 0.25-0.5mg q4h prn)

OR

- Haloperidol 2-10 mg IVP q30min, then 25% of loading dose q6h

Atypical Antipsychotics

- D2 receptor antagonists
  and
- 5HT receptor antagonists
## Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine</th>
<th>Olanzapine</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>Rapid</td>
<td>IM: Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td></td>
<td>PO: Well absorbed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>83%</td>
<td>93%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP 3A4</td>
<td>CYP1A2, CYP2D6, Glucuronidation</td>
<td>CYP2D6</td>
</tr>
<tr>
<td><strong>Active Metabolite(s)</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>6</td>
<td>21-54</td>
<td>20</td>
</tr>
<tr>
<td><strong>T-max (h)</strong></td>
<td>1.5</td>
<td>IM: 0.25-0.75; PO: 6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Urine (73%); Feces (20%)</td>
<td>Urine (57%); Feces (30%)</td>
<td>Urine (70%); Feces (40%)</td>
</tr>
</tbody>
</table>
## Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Quetiapine</th>
<th>Olanzapine</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>PO- IR</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>PO- ER</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>ODT tablets</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Oral Solution</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>IM Injection (acute)</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>IM ER Injection (chronic)</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>Quetiapine</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Extrapyramidal Symptoms</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sedation</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>QTc Prolongation</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
SUPPORTING DATA
Are Antipsychotics Beneficial?

- **Intervention:** Haloperidol 5mg, ziprasidone 40mg, or placebo q6h up to 14 days

<table>
<thead>
<tr>
<th>Results</th>
<th>Haloperidol</th>
<th>Ziprasidone</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium/coma-free days</td>
<td>14</td>
<td>15</td>
<td>12.5</td>
<td>0.66</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>7.8</td>
<td>12</td>
<td>12.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>13.8</td>
<td>13.5</td>
<td>15.4</td>
<td>0.68</td>
</tr>
<tr>
<td>21-Day Mortality (%)</td>
<td>11</td>
<td>13</td>
<td>17</td>
<td>0.81</td>
</tr>
<tr>
<td>EPS Score</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.56</td>
</tr>
</tbody>
</table>

- **Conclusion:** Antipsychotics did not reduce the duration of delirium or increase adverse outcomes.

Quetiapine for ICU Delirium

- **Intervention**
  - Quetiapine 50mg q12H + Haloperidol IV 1-10 mg q2h prn
    - ↑ by 50mg q24h if >1 dose of haloperidol in previous 24 hrs
  - Placebo + Haloperidol IV 1-10 mg q2h prn

- **Drug continued until delirium resolution, therapy >10 days, or ICU discharge**

# Quetiapine for ICU Delirium

## Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Quetiapine (n = 18)</th>
<th>Placebo (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first resolution of delirium (d)</td>
<td>1</td>
<td>4.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of delirium (hr)</td>
<td>36</td>
<td>120</td>
<td>0.006</td>
</tr>
<tr>
<td>Agitation (Sedation-Agitation Scale score ≥5) (hr)</td>
<td>6</td>
<td>36</td>
<td>0.02</td>
</tr>
<tr>
<td>Days of haloperidol prn</td>
<td>3</td>
<td>4</td>
<td>0.05</td>
</tr>
<tr>
<td>Haloperidol doses (mg/day)</td>
<td>1.9</td>
<td>4.3</td>
<td>NS</td>
</tr>
<tr>
<td>More somnolence (%)</td>
<td>22</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>11</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>11</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>ICU length of stay (d)</td>
<td>16</td>
<td>16</td>
<td>NS</td>
</tr>
</tbody>
</table>

Risperidone vs Haloperidol

- Randomized to treatment x 7 days
  - Haloperidol PO 0.75 mg
  - Risperidone 0.5 mg BID
- Results (n = 28)
  - Delirium assessment scores decreased in each group
  - No difference in decrease of scores or frequency of response between groups
  - No clinically significant side effects
- Conclusions: Low dose haloperidol is as safe and efficacious as risperidone in the management of delirium

Olanzapine vs Haloperidol

- **Treatment**
  - Haloperidol PO 2.5–5 mg q8h (0.5-1 mg if >60 yo)
  - Olanzapine PO 5 mg daily (2.5 mg if >60 yo)
  - Subsequent titration based on clinical judgment
  - Rescue IV haloperidol allowed

- **Results (n = 73)**
  - No difference btwn groups in dose of rescue haloperidol
  - 13% haloperidol pts vs no olanzapine pts developed EPS

- **Conclusions:** Olanzapine is a safe alternative to haloperidol in critical care patients, and may be of interest when haloperidol is contraindicated.

Summary of Data

- Studies used different assessments, dosing, and rescue therapy
- No standardization of non-pharmacologic therapy
- Randomized trials provide support for treatment of delirium, however, superiority of specific agents remains controversial
Recommendations for Clinical Practice

- Selection of agent usually based on:
  - Clinical experience
  - Pharmacokinetic properties
  - Drug formulation
  - Formulary options
  - Adverse side effects
- **Haloperidol** is an appropriate agent for patients who are NPO and low risk of QT prolongation
- **Atypical antipsychotics** should be considered in patients who cannot tolerate haloperidol or those who have failed haloperidol
Risk factors for postoperative delirium?

**PREVENT delirium**
Monitor and minimize delirium risk factors

**RECOGNIZE delirium**
Assess frequently, understand risk factors, identify patients early on

**REVERSE delirium**
Correct reversible causes
Non-pharmacologic treatment

**TREAT delirium**
Optimize all non-pharmacologic options
Consider treatment with typical or atypical antipsychotics
Nurses can intervene by:

- Early identification of fluctuating mental status
- Recognition and reversal of environmental causes
- Familiarizing patient with surroundings including introduction to the patient care team
- Adjusting the timing of medications to improve sleep-wake cycles

Poor outcomes can be avoided with better recognition and earlier, more appropriate treatment
Misconceptions about Delirium

- “ICU delirium is common, so it’s ok”
- “I know what’s causing it, so no need to treat”
- “The patient looks agitated so treat with benzodiazepines”