Delirium in the Critically-Ill Patient: The Pharmacist’s Role in Identification, Prevention, and Treatment

Presented as a Breakfast Symposium at the 45th ASHP Midyear Clinical Meeting and Exhibition

Tuesday, December 7, 2010
Anaheim, California
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Delirium in the Critically-Ill Patient: The Pharmacist’s Role in Identification, Prevention, and Treatment

A G E N D A

6:15 a.m. – 6:45 a.m. Breakfast Buffet

6:45 a.m. – 6:50 a.m. Welcome and Introduction
John W. Devlin, Pharm.D., BCPS, FCCM, FCCP
Activity Chair

6:50 a.m. – 7:10 a.m. Recognizing and Preventing Delirium in the Intensive Care Unit (ICU)
Robert MacLaren, Pharm.D., FCCM, FCCP

7:10 a.m. – 7:35 a.m. State-of-the-Art Treatment of Delirium in the ICU
John W. Devlin, Pharm.D., BCPS, FCCM, FCCP

7:35 a.m. – 7:45 a.m. Closing Remarks and Discussion
All Faculty

F A C U L T Y

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Clinical Pharmacist, Medical ICU
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Associate Professor, School of Pharmacy
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University of Colorado Hospital
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Aurora, Colorado
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John W. Devlin, Pharm.D., BCPS, FCCM, FCCP, Chair
Dr. Devlin declares that he has received research grant support from Hospira.

Robert MacLaren, Pharm.D., FCCM, FCCP
Dr. MacLaren declares that he has received research grant support from Hospira.

Kristi N. Hofer, Pharm.D.
Dr. Hofer declares that she has no relationships pertinent to this activity.
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ACTIVITY OVERVIEW

Delirium occurs frequently in critically ill patients and is an independent predictor of adverse outcome. Therefore, delirium prevention, identification, and optimal treatment are essential components of intensive care unit (ICU) practice. Pharmacists have an important role to play in implementing strategies known to reduce the incidence of delirium, leading delirium screening efforts, and managing delirium should it occur.

In this educational activity, faculty will provide an overview of the risk factors and clinical sequelae of delirium in patients in the ICU. Strategies to boost the recognition of delirium by pharmacists will be discussed. Emphasis will be placed on the relationship between sedation choice and level of sedation achieved, and the prevention of delirium will be highlighted. Key points from the medical literature describing the provision of safe and effective pharmacotherapy for critically ill patients who develop delirium will be presented.

ACTIVITY OBJECTIVES

At the conclusion of this knowledge-based educational activity, participants should be able to

- Describe the clinical significance of delirium in patients in the ICU.
- Describe how to incorporate the use of delirium screening tools into daily practice.
- Identify reversible risk factors for delirium in critically ill patients and develop practice strategies to minimize the exposure of patients to these risk factors.
- Develop an evidence-based treatment plan for delirium in a critically ill patient.
- Describe safety concerns related to the treatment of delirium in the critically ill patient.
Delirium in the Critically-Ill Patient: The Pharmacist’s Role in Identification, Prevention, and Treatment

CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity #204-000-10-479-L01P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP Learning Center at http://ce.ashp.org following the activity.

Complete instructions for receiving your statement of continuing pharmacy education online are on the next page. Be sure to record the six-digit session code announced during the activity.

Available soon at http://ashpmedia.org/symposia/delirium

So that this educational activity can be shared with a wider audience, a Web-based version of it is being developed. Encourage your pharmacist colleagues who were unable to attend the Midyear to look for this free online educational activity beginning in March 2011.
Instructions for Processing CPE online at http://ce.ashp.org

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http://ce.ashp.org

1. Log in to the ASHP Learning Center using your e-mail address and password.
   
   If you have not logged in to the new ASHP Learning Center (launched August 2008) and are not a member of ASHP, you will need to set up an account by clicking on “Become a user” and following the instructions.

2. Once logged in to the site, click on “Process Meeting CE.”

3. If you are a registered attendee at the ASHP Midyear Clinical Meeting, click on the start button to the right of ASHP Midyear Clinical Meeting 2010.

   If you are not registered to attend the ASHP Midyear Clinical Meeting, click on the start link to the right of the activity title. If this activity title does not appear in your meeting list, enter the 5-digit activity code in the box above the list and click submit. The activity code for this activity is 10479. Click register again when prompted. When you receive the “thank you for registering” message, click continue. This step will bring you back to your meeting list. Click on the start link to the right of the activity title. Do not click on “remove"or you will not be able to process CE for this activity.

4. Click on the click here link to view sessions associated with the day of the activity.
   
   This activity was held on Tuesday, December 7, 2010.

5. Enter the session code (e.g., A12345 and note that the letter is case sensitive) which was announced during the activity, and select the number of hours equal to your participation in the activity.

6. Click submit to receive the attestation page.

7. Confirm your participation and click submit.

8. New this year, complete the overall Midyear evaluation and click the “finish” button. You will then be able to view and print your transcript.

<table>
<thead>
<tr>
<th>Date of Activity</th>
<th>Activity Code</th>
<th>Session Code (announced during the live activity)</th>
<th>CPE credit hours</th>
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<tr>
<td>Tuesday, December 7, 2010</td>
<td>10479</td>
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Delirium in the Critically-Ill Patient: The Pharmacist’s Role in Identification, Prevention, and Treatment
Robert MacLaren, Pharm.D., FCCM, FCCP
Clinical Pharmacist, Medical ICU
University of Colorado Hospital
Associate Professor, School of Pharmacy
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Aurora, Colorado

Robert MacLaren, Pharm.D., FCCM, FCCP, is Associate Professor in the Department of Clinical Pharmacy at the University of Colorado Denver School of Pharmacy in Aurora, Colorado. In addition, he is a clinical pharmacist in the medical intensive care unit at the University of Colorado Hospital, which is also located on the Anschutz Medical Campus in Aurora. Dr. MacLaren serves as co-director of the critical care residency at the University of Colorado.

After completing his undergraduate degree in pharmacy at the University of British Columbia in Vancouver, Canada, Dr. MacLaren earned his Doctor of Pharmacy degree at the University of Utah in Salt Lake City and completed a critical care specialty residency in Memphis at the University of Tennessee and Baptist Memorial Hospital. He worked for two years as a critical care specialist at the Queen Elizabeth II Health Sciences Centre in Halifax, Canada, before joining the faculty at the University of Colorado.

Dr. MacLaren is a fellow of the Society of Critical Care Medicine and the American College of Clinical Pharmacy. His clinical research interests include gastrointestinal motility dysfunction associated with critical illness and modes of providing patient comfort. He also conducts animal studies of acetaminophen toxicity and has been involved with outcomes research of pharmacologic therapies and the impact of pharmacists in the intensive care unit. He has authored several articles relating to the pharmacologic and nutritional therapies of critically ill patients and has been an invited speaker at national and international meetings.
Recognizing and Preventing Delirium in the ICU

Robert MacLaren, Pharm.D., FCCM, FCCP
Clinical Pharmacist, Medical ICU
Associate Professor, School of Pharmacy
University of Colorado Denver
Aurora, Colorado

Delirium Defined

- Disturbances of consciousness with reduced ability to focus or sustain attention
- Change in cognition (e.g., disorientation, memory impairment) or perceptual disturbances
- Acute onset (hours to days) and tends to fluctuate
- Exclusion of other causes


Case Study

- PN is 58-yr male admitted with COPD / pneumonia
- Currently receiving midazolam 2 mg/hr + frequent boluses and fentanyl 100 mcg/hr + occasional boluses
- RASS “sedation” score overnight ranges between -3 (moderate sedation) to +2 (agitated)
- Intermittently responsive to commands, oriented only to person despite frequent reminders, thought nurse was his wife

RASS = Richmond Agitation Sedation Scale
Which symptom indicates “delirium” in PN?

A. Fluctuating symptoms (varying RASS score and intermittently attentive)

B. Agitation (RASS score of +2 requiring boluses)

C. Inattention (only intermittently following commands)

D. Disorganized thinking (not oriented to place and thought the nurse was his wife)

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Survey: Symptoms Most Associated with Delirium

- Survey of 250 (55%) pharmacists practicing in clinical role in ICU ≥ 25% of their time in New England, TN and MI (n=457)


Cardinal Symptoms of Delirium and Coma

Delirium Assessment

- ICU incidence – 16% (less severely ill) to 89% (ventilated)
  - Variability due to assessment and training methods, frequency of assessment, ICU population (exclusion criteria), etc.
  - Types: hyperactive (<1.6%), hypoactive (43.5-64%), mixed (6-54.1%)

- Subjective assessments tools
  - Confusion Assessment Method (CAM-ICU)
  - Intensive Care Delirium Screening Checklist (ICDSC)
  - Cognitive Test for Delirium (CTD)
  - Neecham scale
  - Delirium Detection Score (DDS) from CIWA

Confusion Assessment Method (CAM-ICU)

1. Acute onset of mental status changes or a fluctuating course

and

2. Inattention

and

3. Altered level of consciousness

or

4. Disorganized thinking

= Delirium
CAM-ICU

Must have 1 and 2 and either 3 or 4:

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

2. Inattention (present if score ≤ 7/10)
   - SAVEAHAART

3. Disorganized thinking
   - Four yes/no questions (score each correct answer one point)
   - Command – hold up fingers (score 1 point if able to do with both hands)
   - Present if cumulative score ≤ 3

4. Altered level of consciousness
   - Use sedation score

Case of PN:
1. Fluctuating mental status = Yes
2. Inattention = Yes but difficult to assess
3. Disorganized thinking = Yes but difficult to assess
4. Altered level of consciousness = Yes

CAM-ICU positive… patient has delirium

Intensive Care Delirium Screening Checklist

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 during shift
- Score of 1-3 = Subsyndromal Delirium
- Score of ≥ 4 = Delirium

Case of PN:
1. Altered level of consciousness = Yes
2. Inattention = Yes
3. Disorientation = Yes
4. Hallucinations = Unknown or no
5. Psychomotor agitation or retardation = Yes
6. Inappropriate speech = Unknown or no
7. Sleep/wake cycle disturbances = Yes
8. Symptom fluctuation = Yes

ICDSC = 6… patient has delirium

Surveys of Delirium Screening

- Pharmacist survey
  - Delirium status frequently or always discussed: 50%
  - Delirium status screened ≥ 50% of the time: 18%
  - Pharmacist screened ≥ 1 patient for delirium: 32%
    - 64% screen for delirium in ≤ 10% of patients
    - Primary barrier to delirium screening
      - Lack of time = 34%
      - Perceived as a nursing role = 24%
      - Do not feel comfortable using screening tool = 13%

- Of 608 UK intensivists
  - 25% routinely screen but only 55% use an assessment tool
  - > 80% believe delirium prolongs ICU stay


### Assessment Leads to Rational Therapy

- Before vs. After analysis of CAM-ICU implementation

<table>
<thead>
<tr>
<th>Before (n=512)</th>
<th>During (n=589)</th>
<th>After (n=649)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 (10)</td>
<td>79 (13)</td>
<td>147 (23) *</td>
</tr>
<tr>
<td>Haloperidol dose per patient, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 (5-40)</td>
<td>12.5 (3-30)</td>
<td>6 (2-20) *</td>
</tr>
<tr>
<td>Haloperidol duration, days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (2-9)</td>
<td>3 (2-9)</td>
<td>3 (1-5) *</td>
</tr>
</tbody>
</table>


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### Keys to Boosting Delirium Screening in Your ICU

- 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
- Clinicians should be comfortable with “not being able to evaluate” some patients or some delirium 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


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### Keys to Boosting Delirium Screening in Your ICU

Pharmacists Can Screen for Delirium TOO!

Sequelae of Delirium

During the ICU/Hospital Stay
- Increased mortality
- 3x greater re-intubation rate
- Average 10 additional days in hospital
- Higher costs of care

After Hospital Discharge
- Increased mortality
- Development of dementia
- Long-term cognitive impairment
- Requirement for care in chronic care facility
- Decreased functional status at 6 months


Duration of Delirium Affects Mortality

Kaplan-Meier survival curve for 1-year mortality post-ICU admission, P < 0.001


Subsyndromal Delirium and Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>No delirium (ND)</th>
<th>Subsyndromal Delirium (SD)</th>
<th>Clinical Delirium (CD)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Mortality</td>
<td>2.4%</td>
<td>10.6%</td>
<td>15.9%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>2.5 d</td>
<td>5.2 d</td>
<td>10.8 d</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>31.7 d</td>
<td>40.9 d</td>
<td>36.4 d</td>
<td></td>
</tr>
<tr>
<td>Severity of illness</td>
<td>12.9</td>
<td>16.7</td>
<td>18.6</td>
<td></td>
</tr>
</tbody>
</table>

Delirium based on ICDSC (subsyndromal = 1-3, delirium ≥ 4). *Pair wise comparison.
Case Study

- PN is 58-yr male admitted with COPD/pneumonia
- Currently receiving midazolam 2 mg/hr + frequent boluses and fentanyl 100 mcg/hr + occasional boluses
- RASS "sedation" score overnight ranges between -3 (moderate sedation) to +2 (agitated)
- Intermittently responsive to commands, oriented only to person despite frequent reminders, thought nurse was his wife

What interventions may prevent/treat PN’s delirium?
- Early mobilization
- Minimize sedation
- Protocol-guided analgesia/ sedation
- Daily awakenings
- Neuroleptics

Patient Factors
- Increased age
- Alcohol use
- Male gender
- Living alone
- Smoking
- Renal disease

Environment
- Admission via ED or through transfer
- Isolation
- No clock
- No daylight
- No visitors
- Noise
- Use of physical restraints

Delirium: Pathophysiologic Factors

What to THINK When Delirium Is Present

- **Toxic situations**
  - CHF, shock, dehydration
  - Deliriogenic meds (Tight Titration)
  - New organ failure (e.g., liver, kidney)
- **Hypoxemia**, also, consider giving Haloperidol or other antipsychotics?
- **Infection/sepsis (nosocomial), Immobilization**
- **Nonpharmacologic interventions**
  - Hearing aids, glasses, reorient, sleep protocols, music, noise control, ambulation
- **K+ or electrolyte problems**


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**Early Mobilization**

**Trial Design**

- 104 sedated patients with daily interruption
  - Early exercise and mobilization (PT & OT; intervention; n = 49)
  - PT & OT as ordered by the primary care team (control; n = 55)
- **Primary endpoint**: number of patients returning to independent functional status at hospital discharge
  - Ability to perform 6 activities of daily living
  - Ability to walk independently
- **Secondary endpoints**
  - Duration of delirium during first 28 days of hospital stay
  - Ventilator-free days during first 28 days of hospital stay


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**Early Mobilization Protocol: Results**

Return to independent functional status at discharge
- 59% in intervention group
- 35% in control group ($P=0.02$)

**Mobilization = Less Delirium**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (n = 49)</th>
<th>Control (n = 55)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU/Hosp. Delirium (days)</td>
<td>2</td>
<td>4</td>
<td>0.03</td>
</tr>
<tr>
<td>Time in ICU with Delirium</td>
<td>33%</td>
<td>57%</td>
<td>0.02</td>
</tr>
<tr>
<td>Time in Hosp. with Delirium</td>
<td>28%</td>
<td>41%</td>
<td>0.01</td>
</tr>
</tbody>
</table>


**ICU Sedation: The Balancing Act**

- **Patient Comfort and Ventilatory Optimization**
  - Under sedation
    - Device removal
    - Ineffective mechanical ventilation
    - Initiation of ventilator-based sedation
    - Myocardial or cerebral ischemia
    - Decreased family satisfaction with care
    - Delirium likely
  - Oversedation
    - Prolonged mechanical ventilation
    - Increased length of stay
    - Increased risk of complications
    - Increased risk of nosocomial infections
    - Increased diagnostic testing
    - Inability to evaluate for delirium but at risk for delirium


**Use of Sedatives**

- Over Time
- Over Duration of Ventilation

Medications as Risk Factors

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>1.2 (1.1-1.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.7 (0.9-3.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.2 (1.0-1.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.1 (0.9-1.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.2 (0.9-1.7)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Lorazepam Dose, mg


Survey: Medications Frequently or Always Associated with Delirium

Daily Awakenings

- Randomized study of 150 medical ICU patients comparing propofol and midazolam sedation by continuous infusion vs. daily interruption.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Awakening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation, days</td>
<td>7.3 (3.4-16.1)</td>
<td>4.9 (2.5-8.6)*</td>
</tr>
<tr>
<td>LOS, ICU days</td>
<td>9.9 (4.7-17.9)</td>
<td>6.4 (3.9-12)*</td>
</tr>
<tr>
<td>LOS, hospital days</td>
<td>16.9 (8.5-26.6)</td>
<td>13.3 (7.3-20)</td>
</tr>
<tr>
<td>Neurologic tests, n</td>
<td>16</td>
<td>6*</td>
</tr>
<tr>
<td>ICU complications</td>
<td>6.2%</td>
<td>2.8%*</td>
</tr>
<tr>
<td></td>
<td>32%</td>
<td>0%*</td>
</tr>
</tbody>
</table>

* p < 0.05

- Time to daily awakening was 1.2 hr for prop. and 5.3 hr for mid.

Scheduled Intermittent Lorazepam vs. Propofol with Daily Interruption in MICU Patients

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam n = 64</th>
<th>Propofol n = 68</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator days</td>
<td>8.4</td>
<td>5.8</td>
<td>0.04</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>10.4</td>
<td>8.3</td>
<td>0.20</td>
</tr>
<tr>
<td>APACHE II</td>
<td>22.9</td>
<td>20.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Daily sedation dose</td>
<td>11.5 mg</td>
<td>24.4 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Morphine dose (mg/day)</td>
<td>10.7</td>
<td>31.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of haloperidol</td>
<td>12%</td>
<td>9%</td>
<td>0.80</td>
</tr>
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</table>


ABC Trial: Main Outcomes

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>SBT, n=168</th>
<th>SAT+SBT, n=168</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free days</td>
<td>12</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>Successful extubation</td>
<td>7.0</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU discharge</td>
<td>13</td>
<td>9</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>19</td>
<td>15</td>
<td>0.04</td>
</tr>
<tr>
<td>Death at 1 year, n (%)</td>
<td>97 (58%)</td>
<td>74 (44%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Days of brain dysfunction</td>
<td>3.0</td>
<td>2.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Delirium</td>
<td>2.0</td>
<td>2.0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

ABC Trial = Awakening and Breathing Controlled Trial
SBT = spontaneous breathing trial
SAT = spontaneous awakening trial
* Median [interquartile range] except as noted
† SBT compared with SAT+SBT


Barriers to Daily Sedation Interruption (Survey of 904 SCCM members)

Clinicians preferring propofol were more likely use daily interruption than those preferring benzodiazepines (55% vs. 40% , P < 0.0001)

**Analgesedation**

- 140 critically-ill adult patients undergoing mechanical ventilation in single center
- Randomized, open-label trial
  - Both groups received bolus morphine (2.5 or 5 mg)
  - Group 1: No sedation (n = 70) - morphine prn
  - Group 2: Sedation (propofol for 48 hr, midazolam thereafter) with daily interruption until awake (n = 70, control group)
- Patients receiving no sedation had
  - More days without ventilation (13.8 vs. 9.6 days, P = 0.03)
  - Shorter stay in ICU (HR 1.86, P = 0.03)
  - Shorter stay in hospital (HR 3.57, P = 0.004)
  - More agitated delirium (N = 11, 20% vs. N = 4, 7%, P = 0.04)
- No differences found in
  - Accidental extubations
  - Need for CT or MRI
  - Ventilator-associated pneumonia


**Dexmedetomidine**

- R, DB study of dexmedetomidine (Dex) vs. lorazepam (Lor) infusion ≤120 hours in 106 MICU/S ICU patients
- Dex (n=52) Lor (n=51)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dex, median mg/kg/hr (mg/hr)</th>
<th>Lor, median mg/kg/hr (mg/hr)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>dose, median mg/kg/hr (mg/hr)</td>
<td>0.74 (0.39-1.04)</td>
<td>3 (2.3-4)</td>
<td></td>
</tr>
<tr>
<td>duration of treatment, median days</td>
<td>5 (2-8)</td>
<td>4 (2-6)</td>
<td></td>
</tr>
<tr>
<td>Delirium prevalence, n (%)</td>
<td>41 (79)</td>
<td>42 (82)</td>
<td>0.65</td>
</tr>
<tr>
<td>Confusion prevalence, n (%)</td>
<td>33 (63)</td>
<td>47 (94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delirium-free days</td>
<td>7 (1-10)</td>
<td>3 (1-8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Confusion-free days</td>
<td>9 (5-11)</td>
<td>7 (1-10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Median fentanyl (mg/day)</td>
<td>575 (140-2206)</td>
<td>150 (0-902)</td>
<td>0.008</td>
</tr>
<tr>
<td>18-day mortality in each subgroup, n</td>
<td>5 (16%)</td>
<td>13 (41%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

No differences in duration of mechanical ventilation, ICU stay, mortality, ADRs.
Hospital cost $22,500 higher with dexmedetomidine.


**MENDS Delirium: All Patients**

- Higher lorazepam concentrations predicted delirium (OR 13.2; 1.4-120.1)

**Dexmedetomidine**

- R, DB study of Dex vs. midazolam in 366 MICU patients ≥ 24 hr

<table>
<thead>
<tr>
<th></th>
<th>Dex (n=244)</th>
<th>Mid (n=122)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, mean mcg/kg/hr or mg/kg/hour</td>
<td>0.83 ± 0.37</td>
<td>0.02-0.1 ± 0.028</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration of treatment, median days</td>
<td>3.5 (2-5.2)</td>
<td>4.1 (2.8-6.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Goal Sedation [% of time]</td>
<td>77.3</td>
<td>75.1</td>
<td></td>
</tr>
<tr>
<td>Delirium [% patients]</td>
<td>54</td>
<td>77</td>
<td>0.0004</td>
</tr>
<tr>
<td>Mechanical ventilation, median days</td>
<td>3.7 (5.1-6)</td>
<td>5.6 (6.6-5.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Infections [% patients]</td>
<td>10-2</td>
<td>10.7</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU Stay, median days</td>
<td>5.9 (5-7-7.2)</td>
<td>7.6 (6.7-9.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypotonus/bradycardia [% patients]</td>
<td>56/42</td>
<td>56/10</td>
<td>NS/&lt;0.001</td>
</tr>
</tbody>
</table>

No differences in mortality or other ADRs.

*Median ICU associated costs $9,676 ($2,314-17,045) lower with dexmedetomidine.*


---

**Reduced Delirium Prevalence with Dexmedetomidine vs. Midazolam**

**SEDCOM**

![](image1)


---

**Dexmedetomidine**

- R, DB study of Dex vs. propofol in 85 MICU/SICU patients with daily awakening

<table>
<thead>
<tr>
<th></th>
<th>Dex (n=41)</th>
<th>Mid/Propofol (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, median mcg/kg/hr</td>
<td>0.8 (0.3-1.4)</td>
<td>0.8 (0.4-1.6)</td>
<td>0.87 (0.4-1.6) / 0.867 (0.4-1.6)</td>
</tr>
<tr>
<td>Duration of treatment, median hours</td>
<td>40 (3-108)</td>
<td>40 (3-108)</td>
<td></td>
</tr>
<tr>
<td>Sedation [% patients]</td>
<td>Goal = Calm</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Goal = Deep</td>
<td>82</td>
<td>82</td>
<td>0.006</td>
</tr>
<tr>
<td>Delirium, n (%)</td>
<td>12/21</td>
<td>12/21</td>
<td>0.02</td>
</tr>
<tr>
<td>Mechanical ventilation, median hrs</td>
<td>77.2 (17-5-338.8)</td>
<td>110.6 (20-1.675)</td>
<td>0.025</td>
</tr>
<tr>
<td>Cardiovascular SOFA &gt; 2 [% patients on day 2]</td>
<td>77.5</td>
<td>56.1</td>
<td>0.026</td>
</tr>
<tr>
<td>Cumulative fentanyl [median mg]</td>
<td>1.5 (0.1-20)</td>
<td>1.6 (0.1-9)</td>
<td></td>
</tr>
</tbody>
</table>

No differences in duration of ICU stay, mortality, ADRs.

Better nursing assessments of communication in Dex group.

Pharmacist-Driven Sedation Protocol

- 156 MICU patients prescribed continuous sedation
- Protocol encouraged analgesia followed by benzodiazepine use
- Before/after design evaluating impact of pharmacist promoting protocol on at least a daily basis

<table>
<thead>
<tr>
<th>Protocol (86)</th>
<th>Control (72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hourly cost, $ Canadian</td>
<td>5.68 ± 4.27</td>
</tr>
<tr>
<td>Goal sedation (% time sedated)</td>
<td>29.6</td>
</tr>
<tr>
<td>Agitated delirium (% time sedated)</td>
<td>11</td>
</tr>
<tr>
<td>Pain (% of time sedated)</td>
<td>5.9</td>
</tr>
</tbody>
</table>

* p < 0.01.


Sedation Protocol that Incorporates Delirium

- 1133 mixed ICU patients with >24 hours stay
- Protocol encouraged intermittent analgesia and benzodiazepine administration with music therapy (99%)
- Before/after design evaluating impact of using the protocol

<table>
<thead>
<tr>
<th>Protocol (561)</th>
<th>Control (572)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median daily doses, mg Morphine</td>
<td>9.3</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.77</td>
</tr>
<tr>
<td>Delirium, %</td>
<td></td>
</tr>
<tr>
<td>ICDSC</td>
<td>34.2%</td>
</tr>
<tr>
<td>Subsyndromal</td>
<td>24.6%</td>
</tr>
<tr>
<td>ICDSC = 0</td>
<td>41.2%</td>
</tr>
<tr>
<td>Coma</td>
<td>8.7%</td>
</tr>
<tr>
<td>Antipsychotics used</td>
<td>19.7%</td>
</tr>
<tr>
<td>Duration of therapies, days</td>
<td></td>
</tr>
<tr>
<td>Ventilation</td>
<td>5.9 ± 6.6</td>
</tr>
<tr>
<td>ICU</td>
<td>5.4 ± 6.3</td>
</tr>
<tr>
<td>Return home, %</td>
<td>74.8%</td>
</tr>
</tbody>
</table>

* p < 0.001


Keys to Minimizing Delirium in Your ICU

- Implement nonpharmacologic options early and assess regularly
  - Frequent re-orientation, sleep protocols, early mobilization, exercises (ROM), removal of devices, return assisted living devices, disimpaction, hydration, pain protocol, minimize noise
- Minimize pharmacologic risk factors
  - Limit amount of sedation administered, minimize use of medications known to be delirogenic, electrolyte repletion
  - Use sedation protocols with daily awakenings.

Keys to Minimizing Delirium in Your ICU

Pharmacists Frequently Manage Pharmacologic and Nonpharmacologic Therapies

But the Prevention, Recognition, and Treatment of Delirium Requires a Multimodal Approach
Delirium in the Critically-Ill Patient: The Pharmacist’s Role in Identification, Prevention, and Treatment

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Clinical Pharmacist, Medical ICU
Tufts Medical Center
Associate Professor, School of Pharmacy
Northeastern University
Adjunct Associate Professor, School of Medicine
Tufts University
Boston, Massachusetts

John W. Devlin, Pharm.D., BCPS, FCCM, FCCP, is Associate Professor of Pharmacy at Northeastern University and Adjunct Associate Professor of Medicine at Tufts University. In addition, he is a clinical pharmacist in the medical intensive care unit at Tufts Medical Center in Boston, Massachusetts. Dr. Devlin serves as the director of the critical care fellowship at Northeastern University and Tufts Medical Center.

Dr. Devlin earned his Bachelor of Science in pharmacy and his Doctor of Pharmacy degrees at the University of Toronto in Ontario, Canada. He completed a pharmacy practice residency at London Health Sciences Centre in London, Ontario, and a critical care pharmacy fellowship at Henry Ford Hospital in Detroit, Michigan. He is also a board certified pharmacotherapy specialist.

Dr. Devlin is a fellow of the Society of Critical Care Medicine and the American College of Clinical Pharmacy. He has published more than 80 peer-reviewed papers and textbook chapters and presented more than 80 research abstracts, primarily in the field of critical care pharmacotherapy. He is a member of the editorial board of Critical Care Medicine and Pharmacotherapy. Dr. Devlin’s federally-funded research program is primarily focused on the detection and treatment of delirium in the intensive care unit and the use and assessment of sedation in the critically ill.
State-of-the-Art Treatment of Delirium in the ICU

John W. Devlin, Pharm.D., FCCP, FCCM
Clinical Pharmacist, Medical ICU
Associate Professor, School of Pharmacy
Northeastern University
Adjunct Associate Professor, School of Medicine
Tufts University
Boston, Massachusetts

Mechanisms for ICU Delirium are Numerous and Complex

- Antipsychotic medications are often the pharmacologic treatment of choice.
  (Grade I = recommended with substantial clinical confidence)
- Haloperidol can be initiated at 1-2 mg every 2-4 hr, with titration to higher doses for patients who continue to be agitated. For patients who require multiple boluses, continuous infusion may be useful.
- Some physicians have used the newer (atypical) antipsychotics.

- Haloperidol is the preferred agent for the treatment of delirium in critically-ill patients.
  (Grade C recommendation)

Haloperidol

- MOA: dopamine antagonist
- High potency antipsychotic
- Does not suppress respiratory drive
- Wealth of clinical experience
- Inclusion in SCCM practice guidelines

- Adverse Effects
  - QTc: Max daily IV dose of 40 mg/day
    - >500 msec or 60 msec increase above baseline
  - EPS: rarely seen in ICU likely b/c of widespread IV use
  - Neuroleptic malignant syndrome
  - Tardive dyskinesia


Haloperidol is Associated with Lower Mortality

![Graph showing probability of survival over days since initiation of haloperidol or no haloperidol treatment.](image)


Antipsychotic Pharmacology

![Graphs showing pharmacology of antipsychotics including haloperidol, quetiapine, and risperidone.](image)


27
Atypical Antipsychotics

- Receptor adherence is variable between agents
- Safety advantages vs. conventional antipsychotics
- Data suggest equal efficacy
- Possible limitations
  - No IV formulations available
  - Little published experience in ICU patients
  - Troublesome reports of adverse events but most associated with prolonged use in non-delirium pts


Safety Advantages of Atypical vs. Conventional Antipsychotics

- Decreased extrapyramidal effects
- Little effect on the QTc interval (except ziprasidone)
- Less hypotension/fewer orthostatic effects
- Less likely to cause neuroleptic malignant syndrome
- Unlikely to cause laryngeal dystonia
- Lower mortality when used in the elderly to treat agitation related to dementia


Use of Atypical Antipsychotic Therapy is Increasing

<table>
<thead>
<tr>
<th>Year</th>
<th>Antipsychotics</th>
<th>Benztropine</th>
<th>Prom dol</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>454</td>
<td>603</td>
<td>34</td>
</tr>
<tr>
<td>2007</td>
<td>592</td>
<td>522</td>
<td>31</td>
</tr>
</tbody>
</table>

What is the first-line pharmacologic treatment option for ICU patients with delirium at your institution?

A. Atypical antipsychotic (e.g., quetiapine)
B. Benzodiazepine (e.g., lorazepam)
C. Dexmedetomidine
D. Haloperidol

Survey: First-Choice Delirium Treatment Options
- Delirium should always be managed with a medication: 85%
- Use ≥ 2 medications to treat delirium: 68%

Survey: Treatment Patterns

<table>
<thead>
<tr>
<th>Medication</th>
<th>Frequently or always used in a patient with agitated delirium (%)</th>
<th>Published RCT demonstrating benefit (%)</th>
<th>Labeled by the FDA for delirium treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>87</td>
<td>42</td>
<td>34</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>59</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>47</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Midazolam</td>
<td>32</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>26</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>25</td>
<td>33</td>
<td>8</td>
</tr>
</tbody>
</table>
Few Prospective, Randomized Trials Have Evaluated Antipsychotic Therapy for Delirium Treatment in the ICU

- Pubmed search
  - 1960 – December 2009
  - Antipsychotic
    - Haloperidol, olanzapine, quetiapine, risperidone, ziprasidone
  - Delirium
  - Critical care
  - Limited to prospective, randomized trials

- Results: 3 trials

Modifying the Incidence of Delirium (MIND) Trial

- Design: Double-blind, placebo-controlled, randomized trial
- Setting: 6 tertiary medical centers
- Patients: Mechanically-ventilated adults with an abnormal level of consciousness or who were receiving continuous sedatives/analgesics
  Note: Patients had brain dysfunction but only 49% had delirium at baseline
- Intervention:
  - Haloperidol (5 mg po/ngt q6h) vs. ziprasidone (40 mg po/ngt q6h) vs. placebo (po/ngt q6h) for a maximum of 14 days
  - Dose interval increased if CAM-ICU negative
  - Could give IM if NPO up to max 8 doses
  - Overdose: ↓ dose frequency when RASS ≥ 2 levels above target (after holding sedation therapy)
  - If delirium recurred after d/c of study drug, restarted at last effective dose (and weaned again as per above)
- Primary outcome:
  - Number of days patient alive without delirium or coma during the 21-day study period
    - Delirium = + CAM-ICU
    - Coma = RASS ≤ 4 (i.e., responsive to physical but not verbal stimulation) or RASS ≤ 5 (i.e., not responsive to either)

MIND Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Haloperidol, n = 35</th>
<th>Ziprasidone, n = 30</th>
<th>Placebo, n = 36</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium/coma-free days</td>
<td>14.0</td>
<td>15.0</td>
<td>12.5</td>
<td>0.66</td>
</tr>
<tr>
<td>Delirium days</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0.93</td>
</tr>
<tr>
<td>Resolution of delirium on study drug, n (%)</td>
<td>24 (85)</td>
<td>23 (77)</td>
<td>21 (58)</td>
<td>0.28</td>
</tr>
<tr>
<td>Coma days</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.90</td>
</tr>
<tr>
<td>% of days accurately sedated</td>
<td>90</td>
<td>84</td>
<td>71</td>
<td>0.91</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>7.8</td>
<td>12.0</td>
<td>12.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>11.7</td>
<td>9.6</td>
<td>7.3</td>
<td>0.70</td>
</tr>
<tr>
<td>Hospital</td>
<td>13.8</td>
<td>13.5</td>
<td>15.4</td>
<td>0.68</td>
</tr>
<tr>
<td>21-day mortality, n (%)</td>
<td>4 (11)</td>
<td>4 (13)</td>
<td>6 (17)</td>
<td>0.91</td>
</tr>
<tr>
<td>Average extrapyramidal symptoms score</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Is there evidence from randomized-controlled studies in the ICU that supports the use of haloperidol for the treatment of delirium in the critically ill?

No evidence from randomized, placebo-controlled studies that haloperidol improves outcomes in ICU patients

Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double blind, placebo-controlled pilot study

- Design: Double-blind, placebo-controlled, randomized trial
- Setting: 3 academic medical centers
- Intervention:
  - Quetiapine 50 mg PO/NGT twice daily titrated to a maximum of 200 mg twice daily vs. placebo
  - PRN IV haloperidol per protocol and encouraged in each group
  - Oversedation: hold study drug when SAS ≤ 2 (after holding sedation therapy)
- Primary outcome:
  - Time to first resolution of delirium (i.e., first 12-hr period when ICDSC ≤ 3)
**Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine (n=18)</th>
<th>Placebo (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.4 ± 14</td>
<td>63.6 ± 15.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>APACHE II (on admission to ICU)</td>
<td>19.7 ± 5.3</td>
<td>21.4 ± 9.2</td>
</tr>
<tr>
<td>Medical (%)</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>ICU days prior to enrollment</td>
<td>5 (2-8)</td>
<td>7 (3-11)</td>
</tr>
<tr>
<td>Intubated at study entry (%)</td>
<td>72</td>
<td>89</td>
</tr>
<tr>
<td>Sedation Agitation Scale (SAS) score at study entry (%)</td>
<td>3 or 4</td>
<td>72, 67</td>
</tr>
<tr>
<td>≥5</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>ICDSC score at study entry</td>
<td>5 (4-6)</td>
<td>5 (4-6)</td>
</tr>
</tbody>
</table>


**Time to First Resolution of Delirium**

Log-Rank

\[ P = 0.001 \]

Placebo

Quetiapine

Day During Study Drug Administration


**Clinical Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine (n=18)</th>
<th>Placebo (n=18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of study drug administration (hours)</td>
<td>102 (84-150)</td>
<td>166 (108-226)</td>
<td>0.04</td>
</tr>
<tr>
<td>Time in delirium (hours)</td>
<td>38 (12-87)</td>
<td>120 (50-195)</td>
<td>0.006</td>
</tr>
<tr>
<td>Time spent agitated (SAS ≥ 5) (hours)</td>
<td>0 (0-30)</td>
<td>38 (11-46)</td>
<td>0.02</td>
</tr>
<tr>
<td>Percent of time spent in delirium after ICU discharge</td>
<td>0 (0-5)</td>
<td>14 (0-47)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Subject placement after hospital discharge (%)

<table>
<thead>
<tr>
<th></th>
<th>Home / rehabilitation center</th>
<th>Chronic care facility / another acute care hospital / death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>89</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>44</td>
</tr>
</tbody>
</table>

\[ P = 0.06 \]

- Five episodes of somnolence and one episode of hypotension were observed that were possibly related to the administration of quetiapine.
- No episodes of EPS were experienced during the study drug period.
- The number of subjects with QTc prolongation as determined by a > 60 msec increase from baseline (39 vs. 44%, p=0.74), QTc > 500 msec (22 vs. 28%, p=1.0), or other CPMP definition (50 vs. 72%, p=0.31) was similar in the quetiapine and placebo groups.


32
Likelihood of Delirium Symptom Resolution (always or frequently) with Antipsychotic Therapy

Impact of Quetiapine on the Resolution of Individual Delirium Symptoms

Median ICDSC and individual delirium symptoms similar at study baseline

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Quetiapine</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>3</td>
<td>8</td>
<td>0.10</td>
</tr>
<tr>
<td>Disorientation</td>
<td>2</td>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td>4</td>
<td>14</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Time with each symptom (median [IQR])

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Quetiapine</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>47 (40-67) %</td>
<td>78 (63-100) %</td>
<td>0.02</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0 (0-37) %</td>
<td>28 (0-45) %</td>
<td>0.10</td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td>47 (14-87) %</td>
<td>80 (23-100) %</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Why did Patient Outcomes Improve in Quetiapine Study but not in MIND Study?

Many differences between the two studies

- Presence of delirium at study entry
- Presence of coma at study entry
- Inclusion of patients with active alcohol withdrawal
- Duration of ICU stay at study entry
- Method of antipsychotic discontinuation
- Use of haloperidol in placebo group
- Twofold difference in dose of atypical antipsychotic administered

5-HT2A serotonergic
α2-adrenergic
α1-adrenergic
D2 dopamine
H1-histaminic
S-HT2A serotonergic

Olanzapine vs. haloperidol for ICU Delirium

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine (N=28)</th>
<th>Haloperidol (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of rescue IV haloperidol (%)</td>
<td>36 (mostly day #1)</td>
<td>42 (mostly day #1)</td>
</tr>
<tr>
<td>Extrapyramidal Symptoms</td>
<td>None</td>
<td>6 pts with possible episodes but all rated very low on Simpson-Angus Scale</td>
</tr>
</tbody>
</table>
When antipsychotic therapy is considered for patient ≥ 65 yr, are patients with a history of dementia excluded (always/frequently)?

Institutional protocol re: haloperidol use in the ICU

<table>
<thead>
<tr>
<th>Monitoring Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTC monitoring</td>
<td>82%</td>
</tr>
<tr>
<td>≥ once per day using ECG strip</td>
<td>80%</td>
</tr>
<tr>
<td>≥ twice per day using ECG strip</td>
<td>64%</td>
</tr>
<tr>
<td>≥ once per day using 12-lead ECG</td>
<td>44%</td>
</tr>
</tbody>
</table>

Haloperidol held or D/C when QTc

- ≥ 500 msec: 36%
- ≥ 550 msec: 28%
- ≥ 600 msec: 32%
- ≥ 60 msec above baseline: 15%

Methodologic Considerations for Studies Investigating Antipsychotic Therapy For Delirium Prevention or Treatment in the ICU

- Interventions shown to reduce delirium in the ICU are maximized.
- Patients with conditions know to mimic delirium are excluded.
- Underlying causes of delirium are reversed when possible prior to randomization.
- Use of a placebo arm that does not involve antipsychotic administration.
- Patient stratification based on the presence of positive versus negative delirium symptoms.
- Antipsychotic dosing strategy is based on formalized dose-response testing.
- Avoidance of a level of sedation where patient is unarousable.
- Adequate sample size to measure differences in standard ICU patient outcomes (e.g., duration of mechanical ventilation).
- Evaluation of post-ICU neurocognitive outcomes.

Dexmedetomidine vs. Haloperidol for the Treatment of Delirium

- Haloperidol: 0.5-2 mg/hr infusion to maintain RASS=0
- Dexmedetomidine: 0.2-0.7 mcg/kg/hr to maintain RASS=0

Haloperidol: 0.5-2 mg/hr infusion to maintain RASS=0

Dexmedetomidine: 0.2-0.7 mcg/kg/hr to maintain RASS=0

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Pharmacological Considerations When Treating Delirium

- Pharmacological therapy should be considered ONLY after underlying causes of delirium are reversed/treated.
- Pharmacological therapy generally should be reserved for patients with severe agitation that will affect patient/caregiver safety.
- The underlying cause(s) of the delirium may affect response to antipsychotic therapy.


Treatment of PN’s delirium:

1. Remove any reversible factors causing his delirium.
   - Change midazolam to dexmedetomidine if patient is hemodynamically stable.
2. If patient remains agitated, give haloperidol 1-2 mg IV q4-6h prn if QTc remains ≤ 500 msec and is not ≥ 60 msec above baseline.
3. If delirium persists 24 hr after #1 and #2 implemented, consider quetiapine 50 mg PO/NGT q12h.

Prophylactic Administration of Antipsychotic Therapy May Improve Outcome in Patients at High Risk for Delirium

- Elective hip surgery patients > 70 years randomized to haloperidol 0.5 mg po tid or placebo (start pre-op and then x 3 days)
  - Incidence of delirium (15.1 vs. 16.5%, p>0.05)
  - Delirium duration (5.4 vs. 11.8 days, p=0.001)
  - Hospital LOS (17.1 vs. 22 days, p<0.001)
- Patients undergoing CABG randomized to risperidone 1 mg SL x 1 or placebo post-op
  - Incidence of delirium (11.1 vs. 31.7%, p=0.009)

Cholinesterase Inhibitors

- Cardiac ICU: Delirium developed in 17 of 57 (30%) and 18 of 56 (32%) patients in the placebo and rivastigmine groups, respectively ($p = 0.8$).
  - No difference in mortality between groups.

- Dutch placebo-controlled, RCT intended to study 440 ICU patients found higher mortality (12 vs. 4 deaths) among patients receiving rivastigmine and more delirium in rivastigmine arm.


Conclusions

- No high quality data available to support the routine administration of haloperidol to ICU patients with delirium

- Pilot study data suggest that the addition of quetiapine to “as needed” haloperidol may improve delirium resolution and other patient outcomes

- Pilot study suggests that dexmedetomidine will resolve delirium faster than haloperidol

- Additional rigorous studies are needed to clarify the role of antipsychotics, dexmedetomidine, and other modalities in the treatment of delirium in the ICU
Delirium in the Critically-Ill Patient: The Pharmacist’s Role in Identification, Prevention, and Treatment

SELECTED REFERENCES


Delirium in the Critically-III Patient: The Pharmacist’s Role in Identification, Prevention, and Treatment


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DELIRIUM IN THE CRITICALLY-ILL PATIENT: THE PHARMACIST’S ROLE IN IDENTIFICATION, PREVENTION, AND TREATMENT

SELF-ASSESSMENT QUESTIONS

1. Which of the following is a key difference when comparing the use of the CAM-ICU and ICDSC for detecting delirium in the ICU?
   a. The CAM-ICU detects current symptoms while the ICDSC may assess symptoms over a nursing shift.
   b. The CAM-ICU only assesses the presence of delirium while the ICDSC may distinguish subsyndromal delirium from clinical delirium.
   c. Only the CAM-ICU has been validated for the assessment of delirium in the ICU.
   d. A and B.

2. Which of the following are key factors for the successful implementation of a delirium screening tool in the ICU?
   a. Didactic education regarding the use of a validated screening tool.
   b. Skill-based education regarding the application of a validated screening tool.
   c. Documentation and discussion of the screening tool results across disciplines.
   d. All of the above.

3. Early mobilization has been shown to...
   a. Reduce the duration of delirium.
   b. Increase functional status at hospital discharge.
   c. Reduce hospital mortality.
   d. A and B.

4. Which of the following antipsychotic-neurotransmitter effect pairing is most true?
   b. quetiapine: dopamine-1.
   c. ziprasidone: histamine.
   d. risperidone: serotonin.

5. Which of the following medications is labeled by the FDA for the treatment of delirium in the ICU?
   a. Dexmedetomidine.
   b. Quetiapine.
   c. Haloperidol.
   d. None of the above.

Answers
1. d
2. d
3. d
4. b
5. d