An approach to the management of Delirium in the Intensive Care Unit

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The speaker has no conflict of interest to disclose.

Objectives

• Recognize the difference between pain/anxiety and delirium in the ICU
• Describe the implementation of a screening tool (ie CAM-ICU) at the bedside for daily use
• Select pharmacotherapy (ie typical vs atypical antipsychotic) for a patient with delirium in the ICU

Audience Response Question #1

• Which of the following is most frequently associated with delirium in the ICU?
  A. Family presence
  B. Intravenous analgesia/sedation
  C. Use of soft-restraints
  D. Fever
Patient Case

RJ is a 75 year old male who has been intubated secondary to respiratory distress from CAP.
- He has been intubated for 4 days and has episodes where he is visually agitated and then non-responsive.
- PMH: depression and COPD (secondary to smoking).
- RJ has required multiple doses of IVP fentanyl for pain and was started on a lorazepam infusion 2 days prior for anxiety.
- In addition, he has required vasopressors secondary to hypotension from septic shock.

Delirium

- Define: A disturbance of consciousness with inattention combined with changes in cognition over a brief period of time (hours to days).
  - Imbalance: ↑ Dopamine and ↓ Acetylcholine
- Delirium is predictive of a 3-fold higher rate of re-intubation and increased length of stay.
- Increased 3 fold risk of six-month mortality.
- Consequences of delirium after discharge.
- Sepsis Associated Delirium (SAD).

- Consensus to abandon the terms ICU psychosis, septic encephalopathy, and ICU syndrome.
- Three categories:
  - Hyperactive
    - Agitation, restlessness, and attempting to remove catheters and/or ET tube
    - Improved prognosis
  - Hypoactive
    - Withdrawal, flat affect, decreased responsiveness
    - Poor prognosis
  - Mixed

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Delirium

- Who should be monitored?
  - Patients on mechanical ventilation
  - Patients requiring physical restraints
- Development of a consistent method of screening patients
- Evaluation of the risk factors for delirium
- Initiate prompt treatment *(Pharmacological and Non-pharmacological)*

Delirium Assessment

- Six instruments identified with supporting literature:
  - Cognitive Test for Delirium (CTD)
  - Confusion Assessment Method-ICU (CAM-ICU) used with RASS scale
  - Intensive Care Delirium Screening Checklist (ICDSC) used with SAS scale
  - NEECHAM Scale
  - Delirium Detection Score (DDS)

Audience Response Question #2

- Which of the following is the gold standard for diagnosis of delirium in the ICU?
  A. DSM-IV
  B. CAM-ICU
  C. ICD-SC
  D. Unknown
**CAM-ICU method**

- **Acute Onset or fluctuating course**
  - Evidence of an acute change
- **Inattention**
  - Difficulty focusing
- **Disorganized thinking**
  - Evidence of incoherent thinking after response to questions and to follow commands
- **Altered level of consciousness**
  - Alert, vigilant, lethargic, stupor, or coma


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

and

**2. Inattention**

and

**3. Disorganized Thinking** or **4. Altered level of consciousness**

= Delirium


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**Barriers to Delirium Assessment**

- Evaluation Tool (6 methods used globally)
- Comprehension of the importance of recognition
  - 2001 survey revealed only 40% routinely screen
- Delirium assessment and patient outcome
- Clinician time constraints
- Communication between the clinicians (Physician, Nurse, and Pharmacist)
- Lack of literature in surgical population
- Inability to evaluate in the highly sedated patient
- Responsibility and accountability of screening


Approach to Delirium in the ICU

- Incidence of delirium in the ICU is approximately 83%
- Delirium defined by the following:
  - Acute change in mental status
  - Disorganized thinking
  - Altered level of consciousness
- Assessment of Delirium (Grade B)
  - CAM-ICU Protocol (Average time 2 minutes)
  - Average onset of after 48 hours of MV and duration of about 4 to 5 days


Risk Factors Associated with Delirium

- Preexisting risk factors (Baseline)
  - Dementia
  - Chronic illness
  - Depression
  - Smoking
  - Alcoholism
  - Severity of illness on admission
  - Advanced age

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Risk Factors (cont)

- Precipitating risk factors (Admission or iatrogenic)
  - Hypoxia
  - Metabolic/Electrolyte imbalance
  - Sleep deficits
  - Heart failure
  - Sepsis
  - Withdrawal syndrome
  - Hyperthermia
  - Medications (benzodiazepines, opioid, propofol)

Lorazepam is an independent risk factor for transitioning to delirium in the ICU

Patient Case (cont)
- What would be a tool used to identify delirium for a patient in the ICU?
- What are the risk factors associated with RJ's delirium?
  - Modifiable vs non-modifiable

Non-Pharmacological Treatment
- Repeated reorientation of patients
- Repetitive cognitive exercises
- Sleep protocol
- Early mobilization
- Range-of-motion exercises
- Removal of catheters
- Re-evaluation of physical restraints
- Minimization of external noise (pagers, phones, etc)
Pharmacologic Prevention

- Optimization of quantity and quality of sedation and analgesia
  - Sedation and analgesia protocol for patients on mechanical ventilation
  - Daily interruption of sedation/analgesia
  - Integration of a sedation and analgesia scale
- Initiation of recommended antipsychotics
  - Haloperidol (SCCM recommendation)
  - Aripiprazole, olanzapine, quetiapine, and ziprasidone

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Pharmacologic Prevention

- Dexmedetomidine
  - \(\alpha_2\) receptor antagonistic activity
  - Inhibition the release of NE
  - Activity of histamine, orexin, GABA, and serotonin
  - Non-significant trend toward lower incidence of delirium in a small study of 41 patients
    - Fentanyl + Midazolam, Propofol, and Dexmedetomidine
    - Awaiting larger, multi-center controlled results


Treatment Principles

RISK

BENEFIT

NOTE: Underlying Co-morbidities, Hepatic function, Renal function, Cardiovascular status, and iatrogenic Etiologies, Severity of Illness
Typical Antipsychotic

- MOA: Action on the mesolimbic and mesofrontal regions of the brain
  - Binding to D₁ and D₂, 5-HT₂ (serotonin), H₁ (histamine), and alpha adrenergic receptors
  - Blockade of D₁ receptor: EPS (dyskinesias)
  - Blockade of alpha adrenergic receptor: tachycardia, impotence, dizziness, and hypotension
  - Blockade of H₁: sedation and weight gain


Mechanism of Action: Typical Antipsychotic (Haloperidol)

Atypical Antipsychotic

- Action on the mesolimbic and mesofrontal regions of the brain
- Examples: risperidone, ziprasidone, olanzapine, and quetiapine
- MOA:
  - Action on D₂, 5-HT₂ (serotonin), alpha adrenergic receptors
  - Agents have little or no affinity for D₁
  - No effect on the H₁ (histamine) receptor
  - Inhibition of alpha adrenergic receptors: tachycardia, impotence, dizziness, and hypotension

Mechanism of Action: Atypical Antipsychotic

- Haloperidol is a butyrophenone with an onset of 30 to 60 min and lasts for 4 to 8 hr
- Dose 2mg every 2 to 4 hours or 5 mg IV or Oral every 12 hours (Grade C)
- ADR’s- Higher dosing: QT-interval prolongation (4%)
- Monitoring (Grade B)
  - Extrapyramidal symptoms (EPS)
  - Neuroleptic malignant syndrome (NMS)
  - Action on the mesolimbic and mesofrontal regions of the brain (ie risperidone, ziprasidone, olanzapine, and quetiapine)
  - Action on D2, 5-HT2 (serotonin), alpha adrenergic receptors with minimal affinity for D1
  - No effect on the H1 (histamine) receptor
  - Inhibition of alpha receptors: tachycardia, impotence, dizziness, and hypotension

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
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<tbody>
<tr>
<td>• Dose: 5mg IVP every 12 hours results in: 60% D2 receptor blockade</td>
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<tr>
<td>• Lower initial dosing in elderly (1 mg IVP)</td>
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<tr>
<td>• Caution in patients with extensive cardiac history and/or already on antiarrhythmics</td>
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<tr>
<td>• Discontinue if QTc exceeds 450 msec</td>
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<tr>
<td>• Monitoring for ADR’s (lower dosing in elderly)</td>
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<tr>
<td>• Olanzapine- 2.5 to 5mg once/day (Max 20mg)</td>
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<tr>
<td>• Quetiapine- 25mg once or twice/day and titrated by 25mg/dose every 2 days (Max 200mg)</td>
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<tr>
<td>• Risperidone- 0.5mg/day and titrated every 2 to 3 days (max 2.5mg)</td>
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Audience Response Question #3

- Which of the following is first-line therapy for delirium in the ICU?
  A. high dose haloperidol
  B. quetiapine
  C. sertraline
  D. chloral hydrate

Patient Case (cont)

- What type of pharmacotherapy would you select for RJ?
  - Typical vs atypical antipsychotic
  - Rationale for therapy selected

Summary of Delirium in the ICU

- Evaluation and monitoring for delirium in the ICU
- Multidisciplinary discussion on each patient
- Identification of risk factors for delirium
- Review of sedation and analgesia requirements and protocol adherence for mechanically ventilated patients
- Consider risk and benefit profile for each patient when selecting therapy (i.e., Typical versus Atypical Antipsychotic)
- Website: http://www.icudelirium.org

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Atypical Antipsychotics

- Adverse effects similar Cardiovascular effects for both classes of agents (haloperidol vs others)
  - Aripiprazole, Olanzapine, Quetiapine, and Ziprasidone
- Endocrine effects from olanzapine (blood sugar and lipids)
- Inhibition of dopamine and affecting NE, serotonin, histamine, and acetylcholine (Ach)
- Addressing other areas of CNS activity in hypoactive and/or mixed delirium


Haloperidol Use Associated with Decreased Mortality

- **Objective**: Determine whether haloperidol is associated with decreased mortality in patients requiring MV
- **Methods**: Retrospective analysis of 989 patients who had received haloperidol within 2 days of intubation
- **Results**:
  - Reduction of mortality in haloperidol group versus control (20.5% vs 36%, \( p=0.004 \))

Olanzapine versus Haloperidol

- Prospective, randomized trial
- Small study population of 73 patients (over 1,000 screened)
- 45 patients in Haloperidol group versus 28 patients in Olanzapine group
- Mean APACHE II score 12 +/- 7
- Average age greater than 60 years
- Delirium diagnosis via ICU Delirium Screening Checklist (ICU-SCD)


Olanzapine versus Haloperidol

- Methods:
  - Haloperidol 2.5 to 5 mg oral/enteral every 8 hours
  - Olanzapine 5mg oral/enteral daily
  - Lower starting doses in Elderly
    - Haloperidol 0.5 to 1mg
    - Olanzapine 2.5mg

- Results:
  - Similar decrease in delirium index
  - Decreased amounts of benzodiazepines in both groups
  - Similar outcomes, decreased extrapyramidal side effects


Quetiapine vs placebo for delirium

- Objective: Evaluate efficacy and safety of quetiapine vs placebo for delirium in the ICU
- Methods: Prospective, randomized, double-blind, placebo-controlled study
  - N=36 patients with ICDM score of greater than 4
  - Tolerating enteral nutrition
  - Quetiapine 50mg every 12 hours (Increase quetiapine every 24 hours (50-100 to 150 to 200mg every 12 hours) or placebo

Quetiapine vs placebo for delirium

• Results:
  – N=18 in each group
  – Quetiapine associated with faster resolution of delirium (1 day [IQR 0.5 to 3] vs 4.5 days [IQR 2-7], p=0.001)
  – Less SAS scores > 5 from 6 hrs [IQR 0-38] vs 36 hours [IQR 11-66], p=0.02
  – No difference in LOS and mortality

• Conclusion:
  – Improved cognitive function
  – Re-evaluation of pilot data to larger trial to evaluate LOS and mortality

Post Test Questions

1. Which of the following below describes a patient who may have delirium in the ICU?
   a. Hypoactive
   b. Hyperactive
   c. Mixed
   d. All of the above

2. Which of the following is a barrier to the implementation of a delirium screening tool in the ICU?
   a. Communication
   b. Reimbursement by Medicare / Medicaid
   c. Time of RN shift
   d. Lack of family presence at bedside

3. Which of the following is an adverse drug event that can be avoided by the use of atypical antipsychotics?
   a. Sedation
   b. Dyskinesias
   c. QTc prolongation
   d. Extravasation