

## 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.




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## 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




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## 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




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## 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




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## 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 ↓ Ach**

- 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)

Ebersoldt M, et al. *Intensive Care Med.* 2007

Pun B and Ely W. *Chest.* 2007

Skrabik Y. *Crit Care Clin.* 2009




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## Delirium

- 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**

Pun B and Ely W. *Chest.* 2007

Skrabik Y. *Crit Care Clin.* 2009




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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*)




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## Delirium Assessment

- Six instruments identified with supporting literature:
  - Cognitive Teat 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)

Delvin JW, et al. *Intensive Care Med.* 2007




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## Audience Response Question #2

- Which of the following is the gold standard for diagnosis of delirium in the ICU?
  - DSM-IV
  - CAM-ICU
  - ICD-SC
  - Unknown




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### 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

Ely W, et al. *JAMA*. 2001




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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

Pun, B. T. et al. *Chest* 2007;132:624-636




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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

Delvin JW, et al. *Intensive Care Med*. 2007

Skröbik Y. *Crit Care Clin*. 2009




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## 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

SCCM Guidelines for Sedation/Analgesia. *Crit Care Med.* 2002




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## Risk Factors Associated with Delirium

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

Pun B and Ely W. *Chest.* 2007




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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*)

Pun B and Ely W. *Chest.* 2007 and Skrobik Y. *Crit Care Clin.* 2009




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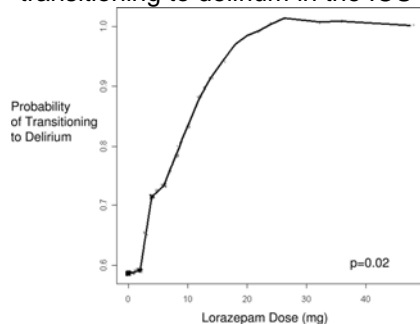
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### Lorazepam is an independent risk factor for transitioning to delirium in the ICU



Pun B and Ely W. *Chest*. 2007




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### 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




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### 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 (*paggers, phones, etc*)

Pun B and Ely W. *Chest*. 2007




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## 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

Pun B and Ely W. *Chest*. 2007




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## Pharmacologic Prevention

- Dexmedetomidine
  - A<sub>2</sub> 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

Szumita PM, et al. *Am J Health-Syst Pharm*. 2007




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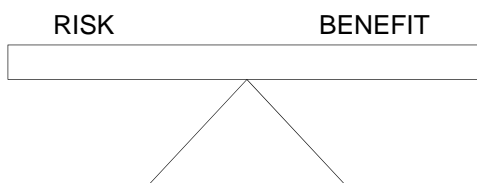
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## Treatment Principles



**NOTE:** Underlying Co-morbidities, Hepatic function, Renal function, Cardiovascular status, and Iatrogenic Etiologies, Severity of Illness




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## Typical Antipsychotic

- **MOA:** Action on the mesolimbic and mesofrontal regions of the brain
  - Binding to  $D_1$  and  $D_2$ ,  $5-HT_2$  (serotonin),  $H_1$  (histamine), and  $\alpha$  adrenergic receptors
  - Blockade of  $D_1$  receptor: EPS (dyskinesias)
  - Blockade of  $\alpha$  adrenergic receptor: tachycardia, impotence, dizziness, and hypotension
  - Blockade of  $H_1$ : sedation and weight gain

Katzung B. Basic and Clinical Pharmacology 11<sup>th</sup> edition. 2009




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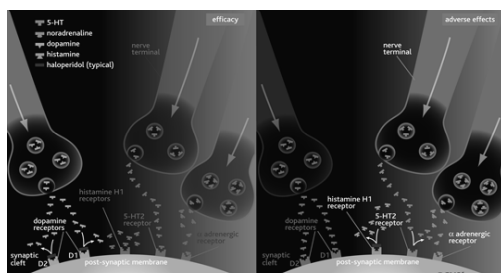
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## Mechanism of Action: Typical Antipsychotic (Haloperidol)




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## Atypical Antipsychotic

- Action on the mesolimbic and mesofrontal regions of the brain
- Examples: risperidone, ziprasidone, olanzapine, and quetiapine
- **MOA:**
  - Action on  $D_2$ ,  $5-HT_2$  (serotonin),  $\alpha$  adrenergic receptors
  - Agents have little or no affinity for  $D_1$
  - No effect on the  $H_1$  (histamine) receptor
  - Inhibition of  $\alpha$  adrenergic receptors: tachycardia, impotence, dizziness, and hypotension

Katzung B. Basic and Clinical Pharmacology 11<sup>th</sup> edition. 2009




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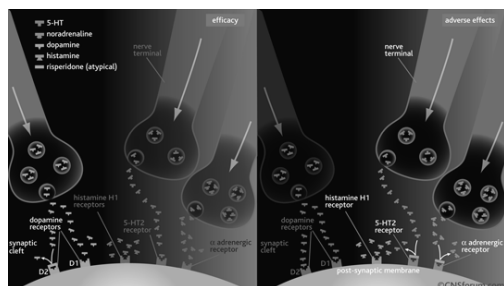
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## Mechanism of Action: Atypical Antipsychotic



Typical	Atypical
<ul style="list-style-type: none"> <li>Haloperidol is a butyrophenone with an onset of 30 to 60 min and lasts for 4 to 8 hr</li> <li>Dose 2mg every 2 to 4 hours or 5 mg IV or Oral every 12 hours (<i>Grade C</i>)</li> <li>ADR's- Higher dosing: QT-interval prolongation (4%)</li> <li>Monitoring (<i>Grade B</i>) <ul style="list-style-type: none"> <li>Extrapyramidal symptoms (EPS)</li> <li>Neuroleptic malignant syndrome (NMS)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Action on the mesolimbic and mesofrontal regions of the brain (<i>ie risperidone, ziprasidone, olanzapine, and quetiapine</i>)</li> <li>Action on D2, 5-HT2 (serotonin), alpha adrenergic receptors with minimal affinity for D1</li> <li>No effect on the H1 (histamine) receptor</li> <li>Inhibition of alpha receptors: tachycardia, impotence, dizziness, and hypotension</li> </ul>

Typical	Atypical
<ul style="list-style-type: none"> <li><u>Dose</u>: 5mg IVP every 12 hours results in: 60% D2 receptor blockade</li> <li>Lower initial dosing in elderly (<i>1 mg IVP</i>)</li> <li><u>Caution</u> in patients with extensive cardiac history and/or already on antiarrhythmics</li> <li>Discontinue if QTc exceeds 450 msec</li> </ul>	<ul style="list-style-type: none"> <li>Monitoring for ADR's (<i>lower dosing in elderly</i>)</li> <li><u>Olanzapine</u>- 2.5 to 5mg once/day (Max 20mg)</li> <li><u>Quetiapine</u>- 25mg once or twice/day and titrated by 25mg/dose every 2 days (Max 200mg)</li> <li><u>Risperidone</u>- 0.5mg/day and titrated every 2 to 3 days (max 2.5mg)</li> </ul>

### 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




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### Patient Case *(cont)*

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




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### 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 (*ie Typical versus Atypical Antipsychotic*)
- Website: <http://www.icudelirium.org>

Pun B and Ely W. *Chest*. 2007




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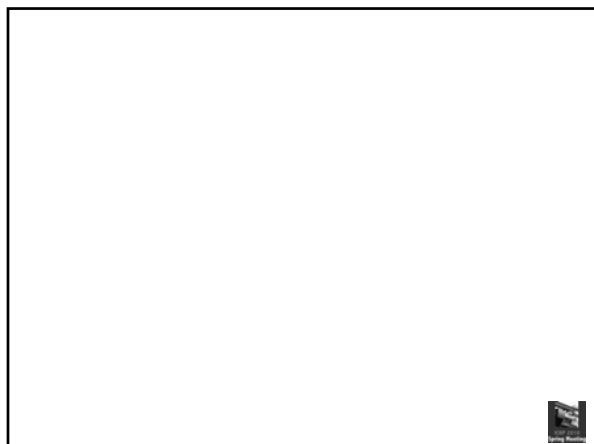
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### Atypical Antipsychotics

- 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

Rea R, et al. *Pharmacotherapy*. 2007




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### 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%,  $p=0.004$ )

Milbrandt E, et al. *Crit Care Med*. 2005




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## 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)

Skrobik YK, et al. *Intensive Care Med.* 2004




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## 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

Skrobik YK, et al. *Intensive Care Med.* 2004




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## 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

Devlin JW, et al. *Crit Care Med.* 2010




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## 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  $\geq 5$  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

Devlin JW, et al. *Crit Care Med.* 2010



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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