Palliative Care Interdisciplinary Curriculum

A Joint Initiative of the Palliative Medicine Faculty & Staff of

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Agitated Delirium
Latest in Symptom Management

Frank D Ferris, MD, FAAHPM, FAACE
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- St. Mary’s Hospital Foundation
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- Tri-County Health Network
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Objectives

• Management
  Potentially reversible
  Irreversible
  Pediatrics
  ICU
How long would you like to enjoy delirium?
Management...
Clarifying Delirium Management: Practical, Evidenced-Based, Expert Recommendations for Clinical Practice

Scott A. Irwin, MD, PhD, Rosene D. Pirrello, BPharm, RPh, Jeremy M. Hirst, MD, Gary T. Buckholz, MD, and Frank D. Ferris, MD, FAAHPM, FAACE

Abstract

Delirium is highly prevalent in those with serious or advanced medical illnesses. It is associated with many adverse consequences, including significant patient, family, and health care provider distress. This article suggests a novel approach to delirium assessment and management and provides useful, practical guidance for clinicians based on a complete review of the existing literature and the expert clinical opinion of the authors and their colleagues, derived from over a decade of collective bedside experience. Comprehensive assessment includes careful description of observed symptoms, signs, and behaviors; and an understanding of the patient’s situation, including primary diagnosis, associated comorbidities, functional status, and prognosis. The importance of incorporating goals of care for the patient and family is discussed. The concepts of potential reversibility versus irreversible delirium and delirium subtype are proffered, with a description of how diagnostic and management strategies follow from these concepts. Pharmacological interventions that provide rapid, effective, and safe relief are presented. Employing both pharmacological and nonpharmacological interventions, including patient and family education, improves symptoms and relieves patient and family distress, whether the delirium is reversible or irreversible, hyperactive or hypoactive. All interventions can be provided in any setting of care, including patients’ homes.
General Principles

- Manage based on:
  - Potential reversibility
  - Goals of care
- Ensure safety
- Address environment

*American Psychiatric Association (1999)*
*Am J Psychiatry 156: 1 Cook IA (2004)*
Delirium Management Decision Tree

Context & Reasonable Goals of Care

- Potentially Reversible
- Irreversible

- Dying
- Goals of care
- Treatment of cause unsuccessful
<table>
<thead>
<tr>
<th>Neurological Failure</th>
<th>Cardiac Failure</th>
<th>Renal Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered level of consciousness</td>
<td>Tachycardia / hypotension</td>
<td>Oliguria / anuria</td>
</tr>
<tr>
<td>Abnormal breathing patterns</td>
<td>Cyanosis</td>
<td></td>
</tr>
<tr>
<td>Loss of swallow / gag</td>
<td>Peripheral cooling</td>
<td></td>
</tr>
<tr>
<td>Oral / tracheal secretions</td>
<td>Venous pooling / mottling</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Is Patient Actively Dying?**

Signs of the dying process:
Two Roads to Death

USUAL ROAD
Hypoactive Delirium

Confused → Tremulous → Hallucinations → Mumbling → Myoclonic Jerks → Seizures → Semicomatose → Comatose → Dead

DIFFICULT ROAD
Hyperactive Delirium

Sick → Restless → Sleepy → Lethargic → Obtunded → Dead
Potentially Reversible…
Treat the Causes…
Treat the Causes

• Diagnostic workup
• Consider treatment
  Benefits
  Risks
  Burdens
• Time-limited therapeutic trials
  Time to treat
  Objective outcome measures
Treat the Experience...
# Prevention of Delirium...

852 patients age > 70 admitted to medicine service

<table>
<thead>
<tr>
<th>Target</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orientation</strong></td>
<td>Introduce care team / daily schedule each shift, oriented 1 – 3x / day</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td>Cognitive stimulation 3x / day</td>
</tr>
<tr>
<td><strong>Mobility</strong></td>
<td>Ambulate / range of motion 3x / day</td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
<td>Non-pharmacological sleep protocol</td>
</tr>
<tr>
<td><strong>Sensory aids</strong></td>
<td>Glasses, hearing aids</td>
</tr>
<tr>
<td><strong>Dehydration</strong></td>
<td>Rehydrate as needed</td>
</tr>
</tbody>
</table>
...Prevention of Delirium

• In the treatment group
  Fewer episodes of delirium
    62 vs. 90 (9.9 % vs. 15 %, p = 0.03)
  Shorter duration
    105 vs. 161 days (p = 0.02)

• Followup showed up to an
  89 % reduction of risk of delirium

NON-PHARMACOLOGICAL INTERVENTIONS

- Frequent orientation/orientation board
- Cognitive exercises
- Dim lighting
- Natural daylight
- Sensory aides, e.g., glasses/hearing aides
- Familiar objects/pictures
- Limit sensory over-stimulation
- Consistent caregivers
- Relaxation techniques
- Daily routine
- Sleep hygiene
- Range of motion or physical activity
- Constant companions or family visitation
- Leisure activities
- Limit immobilization, e.g., catheters, IV’s, restraints
Pharmacological Management

No medication is US FDA approved for the treatment of delirium

Until 2016, no published double-blind, randomized, placebo controlled trials

No consensus among oncologists, geriatricians, psychiatrists, or palliative medicine specialists

Potentially Reversible, Hyperactive

- Context & Reasonable Goals of Care
  - Potentially Reversible
    - Hyperactive
      - Treat Cause
      - Treat Experience Antipsychotics
## Antipsychotic Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Anti-agitation</th>
<th>Sedation</th>
<th>Amnesia</th>
<th>Muscle relaxation</th>
<th>Anti-convulsant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Risperidone</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

The American Geriatrics Society 2012 Beers Criteria Update Expert Panel

Potentially inappropriate medications (PIMs) continue to be prescribed and used as first-line treatment for the most vulnerable of older adults, despite evidence of poor outcomes from the use of PIMs in older adults. PIMs now form an integral part of policy and practice and are incorporated into several quality measures. The specific aim of this project was to update the previous Beers Criteria using a comprehensive, systematic review and grading of the evidence on drug-related problems and adverse drug events (ADEs) in older adults. This was accomplished through the support of the American Geriatrics Society (AGS) and the work of an interdisciplinary panel of 11 experts in geriatric care and pharmacotherapy who applied a modified Delphi method to the systematic review and grading to reach consensus on the updated 2012 AGS Beers Criteria. Fifty-three medications or medication classes encompass the final updated Criteria, which are divided into three categories: potentially inappropriate medications and classes to avoid in older adults, potentially inappropriate medications and classes to use with caution in older adults, and potentially inappropriate medications and classes to consider in older adults.

Previously, the Beers Criteria were used to identify and reduce the use of medications that may harm older adults and improve outcomes. Estimates from past studies in ambulatory and long-term care settings found that 27% of adverse drug events (ADEs) in primary care and 42% of ADEs in long-term care were preventable, with most problems occurring at the ordering and monitoring stages of care. In a study of the 2000/2001 Medical Expenditure Panel Survey, the total estimated healthcare expenditures related to the use of potentially inappropriate medications (PIMs) was $7.2 billion.

Avoiding the use of inappropriate and high-risk drugs is an important, simple, and effective strategy in reducing medication-related problems and ADEs in older adults. Methods to address medication-related problems and ADEs in older adults include implicit and explicit criteria. Explicit criteria can identify high-risk drugs using a list of PIMs that have been identified through expert panel review as having an unfavorable balance of risks and benefits by themselves and considering alternative treatments available. A list of PIMs was developed and published by Beers and colleagues for nursing home residents in 1991 and subsequently expanded and modified in 1997, 2002, and 2007.

The 2012 AGS Beers Criteria are intended to serve as a tool to help clinicians make informed decisions about potential drug-related problems and adverse drug events in older adults. The criteria are intended to be used in a thoughtful and intentional manner, taking into account the specific needs and characteristics of individual patients.
1st Line Pharmacological Treatment

Double-blind RCT of 30 AIDS patients

- **Haloperidol**: 0.4 - 3.6 mg daily, n = 11 vs
- **Chlorpromazine**: 10 - 80 mg daily, n = 13 vs
- **Lorazepam**: 0.5 - 10 mg daily, n = 6

Haloperidol = chlorpromazine >> lorazepam

Lorazepam stopped early due to adverse events

Haloperidol & chlorpromazine minimal side effects

PEARL

• Use 1st generation antipsychotics
• Do Not Use Benzodiazepines

Not first-line treatment
Increase confusion, disinhibition, falls

Necessary for alcohol & sedative withdrawal

APA Practice Guidelines 2004

American Psychiatric Association (1999)

### Why NOT Benzodiazepines for Potentially Reversible Delirium

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Anti-agitation</th>
<th>Sedation</th>
<th>Amnesia</th>
<th>Muscle relaxation</th>
<th>Anti-convulsant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Midazolam</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Use Pharmacokinetics to Guide Dosing and Control Delirium Rapidly…
First Order Kinetics

For optimal efficacy & safety

• Titrate to effect or toxicity
  
  Start low
  
  Dose every $t_{C_{\text{max}}}$ PRN
  "Catch-up technique"

• Maintenance dosing, dose every $t_{1/2}$

• Steady state in $5 \times t_{1/2}$

• Elimination in $5 \times t_{1/2}$
Antipsychotic Kinetics

IV $t_{C_{max}} = 15$ minutes

SC, IM $t_{C_{max}} = 30$ minutes

PO, PR $t_{C_{max}} = 60$ minutes

$\frac{1}{2} \approx 24$ hours
# Medication Kinetics

## Antipsychotics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Time Cmax</th>
<th>Elimination $t_1/2$</th>
<th>Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine (sedating) aka Thorazine</td>
<td>PO: 1 hr SC/IM: 30 min IV: 15 min (6-15)</td>
<td>24 hrs (23-37)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Haloperidol (non-sedating) aka Haldol</td>
<td>PO: 1 hr SC/IM: 30 min IV: 15 min (6-15)</td>
<td>21 hrs (10-38)</td>
<td>2 mg</td>
</tr>
<tr>
<td>Olanzapine (sedating) aka Zyprexa</td>
<td>PO: 6 hrs IM: 30 min (15-45)</td>
<td>30 hrs (21-54)</td>
<td>4 mg</td>
</tr>
<tr>
<td>Prochlorperazine aka Compazine</td>
<td>PO/PR: 2 hrs (1.5-5)</td>
<td>8 hrs (6.8-9)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine (sedating) aka Seroquel</td>
<td>PO: 1.5 hrs</td>
<td>6 hrs</td>
<td>125 mg</td>
</tr>
<tr>
<td>Risperidone (non-sedating) aka Risperdal</td>
<td>PO: 1 hr (1-2) PO: 3 hrs Metabolites: 21-30 hrs</td>
<td>1 mg</td>
<td></td>
</tr>
</tbody>
</table>

### Notes
- * aka = also known as
- IR = Immediate Release
- ER = Extended Release
- † = † = essential medication as defined by WHO: World Health Organization
- SC dosing is preferable over IM dosing
- Avoid medications with short half-lives in patients with short life expectancy who may experience withdrawal when these medications are stopped at end of life

## Benzodiazepines

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Time Cmax</th>
<th>Elimination $t_1/2$</th>
<th>Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam aka Xanax</td>
<td>PO: 1 hr</td>
<td>11 hrs</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Clonazepam aka Klonopin</td>
<td>PO: 2 hrs (1-4) PR: 10-30 min</td>
<td>30 hrs (19-50)</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Diazepam aka Valium</td>
<td>PO: 1 hr (0.89-1.32) PR gel: 1.5 hrs IM: 1 hr IV: 8 min</td>
<td>45 hrs Metabolites: 30-100 hrs</td>
<td>5 mg</td>
</tr>
<tr>
<td>Lorazepam aka Ativan</td>
<td>PO: 1 hr SC/IM: 30 min</td>
<td>12 hrs Metabolites: 12-18 hrs</td>
<td>1 mg</td>
</tr>
<tr>
<td>Midazolam aka Versed</td>
<td>SC/IM: 30 min IV: 15 min (6-15)</td>
<td>2 hrs (1-3)</td>
<td></td>
</tr>
<tr>
<td>Oxazepam aka Serax</td>
<td>PO: 1 hr PO: 3 hrs Metabolites: 21-30 hrs</td>
<td>12 hrs (5-15)</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

### Benzodiazepines

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Time Cmax</th>
<th>Elimination $t_1/2$</th>
<th>Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem (non-benzo hypnotic) aka Ambien</td>
<td>PO: 1.6 hrs</td>
<td>2.5 hrs (1.5-7)</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

See card 46 for Medication Information Sources

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NB: These PCIC Reference Guidelines do not replace careful clinical judgment specific to each patient / family situation. PCIC is a collaborative effort of OhioHealth, The Ohio State University Wexner Medical Center, and Nationwide Children's Hospital in Columbus, Ohio, USA. Copyright © Frank D Ferris 2013-2017. All rights reserved. Permission to reproduce any or all of these PCIC Reference Guidelines is granted for non-commercial educational purposes only, provided that the attribution statement and copyright are displayed. To reproduce for all other purposes, contact Frank D. Ferris, Palliative & Hospice Care, OhioHealth, +1-614-533-6299. V7, 2017
Sample Orders for Agitation

**Haloperidol** – 1 mg SC q 30 min PRN

- If 3 doses not effective, call MD
- Do not exceed **100 mg in 24 hr**
  - Schedule today’s PRNs tomorrow
    - 1 or 2 x / day + same PRN schedule

**Chlorpromazine** – 50 mg SC q 30 min PRN

- If 3 doses not effective, call MD
- Do not exceed **2000 mg in 24 hr**
  - Schedule today’s PRNs tomorrow
    - 1 or 2 x / day + same PRN schedule
Haloperidol

Typical Daily Doses

- Nausea 0.5 – 2.0 mg
- Delirium 2 – 10 mg
- Schizophrenia 5 – 50 mg

Risks

- Q-T Interval prolongation
- Parkinsonism

Potential Side Effects

Lower doses

- Akathisia
  “ants in your pants”

Higher doses

- Tardive dyskinesias
- Torticollis
2nd Generation Antipsychotics?

Haloperidol **EQUAL** to olanzapine and risperidone

1. haloperidol 1 - 28 mg daily  n = 45  vs  olanzapine  2.5 - 13.5 mg daily  n = 28
2. haloperidol 1.5 - 10 mg daily  n = 11  vs  olanzapine  5 - 15 mg daily  n = 11
3. haloperidol 1 - 3 mg daily  n = 12  vs  risperidone  0.5 - 2 mg daily  n = 12

Maintenance Dosing...
85 yo Woman

- Urinary tract infection, fever, Rx Cipro
- Mild delirium, w. confusion, agitation
  Rx Haloperidol 1mg IV x 3 doses in 1 hour
  ➔ settled, able to each lunch, communicate normally
- 24 hours later, afebrile, no confusion or agitation
- Use haloperidol PRN if symptoms return
Plasma Concentration

Half-Life ( $t_{\frac{1}{2}}$ )

Haloperidol

$t_{\frac{1}{2}} = 21$ hours

1.5 mg remains

3 mg

0

21

Time ( hours )
75 yo Man

- Heart failure, atrial fibrillation
- Major cerebral infarct
- Moderate ongoing delirium, w. confusion, agitation

Rx Haloperidol 2mg SC x 3 doses + 4mg x 1 dose in 2 hour ➔ settled

- Next days, mild agitation continues
- Maintenance haloperidol…
Haloperidol
$t_{\frac{1}{2}} = 21$ hours
5 mg remains

$+5$ mg maintenance
Management of Severe Agitation...
When is Agitation an Emergency?

- Aggression to property, hostile verbal behavior
- Irritability, intimidation
- Mood lability, loud speech
- Motor restlessness, purposeless movements
- Uncooperative, intense staring

Allen et al. Treatment of Behavioral Emergencies
Expert Consensus, 2001
Hierarchy of Treatments

1. Seclusion and / or Restraint (Always)
2. Emergency Medication (Usually)
3. Show of Force (Sometimes)
4. Voluntary Medication (Rarely)
5. Verbal Intervention (Sometimes)
6. Verbal Intervention (Rarely)
55 yo Man

- Lung cancer, bone, liver mets
- Found to have pneumonia
- Onset of severe agitation, wanting to take off his clothes, striking out at staff
- At risk of harming self / others

Will NEVER be any clinical trials
Severe Agitation...

If imminent risk of harm to self or others

Haloperidol 2 - 5 mg
+ Diphenhydramine* 50 - 100 mg x 1
( protects against EPS & adds sedation )

± Lorazepam 1 - 2 mg ( or Midazolam )

In same syringe, mix very slowly in order

Lorazepam ► Haloperidol ► Diphenhydramine
Severe Agitation Alternatives…

Chlorpromazine 50 - 100 mg SC

Increase dose by 50 mg once every
Time to Maximum Concentration (t_{Cmax}) until controlled

Up to 2 gm / day

If SC administration painful, e.g., burning, consider IV infusion with dexamethasone

Likely don’t need diphenhydramine

± Lorazepam
...Severe Agitation Alternatives

Olanzapine 5 - 10 mg IM
- May repeat x 1 in 2 hr
- May repeat x 1 again 4 hr later
- Up to 30 mg / day (Expensive)

Ziprasidone 10 - 20 mg IM
- May repeat 10 mg every 2 hr
- May repeat 20 mg every 4 hr
- Up to 40 mg / day (Expensive)
New Evidence...
Potentially Reversible, Hyperactive

- Potentially Reversible
  - Context & Reasonable Goals of Care

- Hyperactive
  - Treat Cause
  - Treat Experience Antipsychotics?
Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial

Meera R. Agar, PhD; Peter G. Lawlor, MB; Stephen Quinn, PhD; Brian Draper, MD; Gideon A. Caplan, MBBS; Debra Rowett, BPharm; Christine Sanderson, MPH; Janet Hardy, MD; Brian Le, MBBS; Simon Eckermann, PhD; Nicola McCaffrey, PhD; Linda Devilee, MBus; Belinda Fazekas, BN; Mark Hill, PhD; David C Currow, PhD

**IMPORTANCE** Antipsychotics are widely used for distressing symptoms of delirium, but efficacy has not been established in placebo-controlled trials in palliative care.

**OBJECTIVE** To determine efficacy of risperidone or haloperidol relative to placebo in relieving target symptoms of delirium associated with distress among patients receiving palliative care.

**DESIGN, SETTING, AND PARTICIPANTS** A double-blind, parallel-arm, dose-titrated randomized clinical trial was conducted at 11 Australian inpatient hospice or hospital palliative care services between August 13, 2008, and April 2, 2014, among participants with life-limiting illness, delirium, and a delirium symptoms score (sum of Nursing Delirium Screening Scale behavioral, communication, and perceptual items) of 1 or more.

**INTERVENTIONS** Age-adjusted titrated doses of oral risperidone, haloperidol, or placebo solution were administered every 12 hours for 72 hours, based on symptoms of delirium.
Risperidone, Haloperidol or Placebo...

- Double blind, randomized control trial
  
  Placebo = best nursing care; non-pharmacological Rx

- 11 Australian inpatient hospice or hospital palliative care services

- 6 years

- 247 participants

  Mean age 74.9; 34 % women; 88.3 % cancer
...82 Risperidone, 81 Haloperidol or 84 Placebo...

- **Delirium symptom scores**
  - Risperidone > placebo, \( p = 0.02 \)
  - Haloperidol > placebo, \( p = 0.009 \)

- **Extrapyramidal side effects**
  - Risperidone > placebo, \( p = 0.03 \)
  - Haloperidol > placebo, \( p = 0.01 \)

- **Overall survival**
  - Risperidone \( \approx \) placebo, \( p = 0.14 \)
  - Haloperidol < placebo, \( p = 0.003 \)
Potentially Reversible, Hyperactive

Potentially Reversible

Hyperactive

Treat Cause

Treat Experience

Antipsychotics

Context & Reasonable Goals of Care
...Risperidone, Haloperidol or Placebo Recommendations from the Australian Group

- Treat underlying cause
- Best nursing care
- Non-pharmacological Rx
- Avoid anti-psychotic medications
- For severe agitation / risk of harm
  Rx benzodiazepines to settle patient
Pediatric Delirium: Treatment…

Treatment is similar to adults:

- When able, treat underlying cause of delirium
- Environmental measures
  - Familiar objects and people at bedside
  - Frequent re-orientation
  - Establish and maintain daily routine
Pediatric Delirium: Treatment

- Re-regulate sleep-wake cycle
- Decrease deliriogenic medications when able
- Use of psychotropic medications if needed
ICU Delirium
Jennica Johns
ICU Delirium is Common

In a multicenter international study:
- Prevalence of delirium = 32.3% \(^{(8)}\)
- Incidence of delirium = 45% - 87% \(^{(8)}\)

Yet we still believe it is frequently *underdiagnosed* \(^{(1)}\)
Morbidity Associated with ICU Delirium

Increased risk of short term and long-term and cognitive dysfunction (1, 8, 17)

- 9-Fold higher incidence of cognitive impairment at discharge (17)

- One study noted 70% had cognitive impairment at 1-year follow-up (8)
Mortality Associated with ICU Delirium

Increased 30 day all-cause mortality

- 39% for those with 3 days or more of delirium \(^{(18)}\)

3.2-fold increase in 6-month mortality \(^{(17)}\)

Each additional day an ICU patient spent in delirium was associated with a 10% increased risk of death \(^{(17)}\)
## Common Medications for ICU Delirium

<table>
<thead>
<tr>
<th>Medication</th>
<th>Onset of Action</th>
<th>Tmax Response</th>
<th>Sedation</th>
<th>Of Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haldol</td>
<td>1 hour (PO) 2-5 min (IV)</td>
<td>4-7 days</td>
<td>Doses &gt;2mg</td>
<td>Avoid in LBD and Parkinsons</td>
</tr>
<tr>
<td>Thorazine</td>
<td>30-60 min (PO) 15 min (IV)</td>
<td>5-14 days</td>
<td>Yes, significant</td>
<td>Avoid in ↓ BP or myelosuppressed Pts</td>
</tr>
<tr>
<td>Seroquel</td>
<td>1.5 hours (PO)</td>
<td>4-7 days</td>
<td>Yes, moderate</td>
<td>Preferred in Parkinsons</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1-3 hours (PO)</td>
<td>4-7 days</td>
<td>Yes, small</td>
<td>3mg/day is avg effective dose</td>
</tr>
<tr>
<td>Zyprexa</td>
<td>6 hours (PO)</td>
<td>3-7 days</td>
<td>Yes, moderate</td>
<td>Avoid in ↓ BP Least effect on QTc</td>
</tr>
<tr>
<td>Precedex</td>
<td>&lt;5 minutes</td>
<td>15-30 min</td>
<td>Yes</td>
<td>Avoid in ↓ BP or ↓ HR Can develop tolerance</td>
</tr>
</tbody>
</table>
Systematic Review of Prevention and Treatment of Delirium in ICU

Journal of Critical Care Medicine 2015

- 25 articles reviewed, all RCTs
- Only 1 study with reduced time to delirium resolution
  - Seroquel vs Placebo: 1 day vs. 4.5 days (n = 36)
- Only 1 study with reduced LOS in ICU
  - Precedex vs. Haldol gtt: 1.5 d vs 6.5 d (n=20)
    *Pilot Study
- No difference in mortality in any study
Any changes since that review?

Journal of Critical Care Medicine June 2017

Retrospective analysis of antipsychotic use for delirium in ICU \(^{(22)}\)

- **No difference** in time to resolution of delirium
- **No difference** LOS in ICU
- **No difference** in mortality
Where do we go from here?

SCCM published Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium

Meant to be a “road map” to treating ICU delirium based on available evidence

Reads more as what not to do… offers no pharmacologic suggestions for treatment
When I Think We Should Consider Medications…

Pt with delirium in ICU

Affecting medical management of other co-morbidities

- **Yes**
  - Is QTc prolonged
    - **Yes**
      - Continue to monitor and/or consider non-QTc prolonging alt
    - **No**
      - Choose agent based on SE profile and ROA

- **No**
  - Continue to monitor and use non-pharmacologic trx
Summary

ICU delirium is:

- Relatively common
- Associated with high morbidity (short and long term cognitive dysfunction)
- Associated with increased risk of mortality

There is **no evidence** to support anti-psychotic or Precedex use for treatment of delirium in the ICU, BUT we lack alternative treatment options at this time
Summary

• Treat underlying cause
• Best nursing care
• Non-pharmacological therapies
• If agitation remains mild to moderate, trial of lower dose anti-psychotics
• If agitation severe, with risk of harm, Lorazepam + Haloperidol + Benadryl
Delirium Management Decision Tree

Context & Reasonable Goals of Care

Potentially Reversible
- Hyperactive
  - Medical Rx
    - Successful
    - Unsuccessful
- Hypoactive
  - Medical Rx

Irreversible
- Hyperactive
  - Medical Rx
- Hypoactive
  - Medical Rx
Irreversible Terminal, Hyperactive

- Signs of Active Dying
- Irreversible
- Hyperactive
  - Support
  - Treat Experience Benzodiazepines, Barbiturates, Propofol
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Anti-agitation</th>
<th>Sedation</th>
<th>Amnesia</th>
<th>Muscle relaxation</th>
<th>Anti-convulsant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Midazolam</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Opioids</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
</tr>
</tbody>
</table>
Sample Orders... For Agitation

With signs of the dying process:
Lorazepam – 1 mg PO q 60 min PRN

If 3 doses not effective, call MD

Do not exceed 40 mg in 24 hr

Schedule today’s PRNs tomorrow
3 x / day + same PRN schedule
Sample Orders... For Agitation

With signs of the dying process:

Midazolam – 0.2 mg / kg SC load

Then 0.1 mg / kg q 30 min x 2 PRN

Maintenance dose / hr =

25 % total dose to sedate

Consider alternative if need > 10 mg / hr
Are you Hastening Death?

- **Lethal Doses in Rats**
  - Lorazepam LD 50 = 4,500 mg / kg
  - Midazolam LD 50 = 215 mg / kg

- **Not concerned about**
  - Amnesia, confusion, restlessness
  - Hypotension
  - Respiratory depression

- **Nigel Sykes 2003**
  - Patients receiving sedation lived longer
When Benzodiazepines Fail

**Phenobarbital**

10 - 30 mg/kg IV/SC/PO/PR loading dose then 160 - 800 mg PO/PR tid or 10 - 100 mg/hrs IV/SC

**Propofol**

- Start 1 mg/kg/hr
- Titration in 0.5 mg/kg/hr steps within 15-30 min
- Max in palliative medicine literature 6 mg/kg/hr

*Lundström S, et al.*

*(2005) JPSM 30: 570*
Irreversible, Hyperactive

Goals of Care or Work-up / Treatment Unsuccessful

Irreversible

Hyperactive

Support

Treat Experience
Antipsychotics, Benzodiazepines, Barbiturates, Propofol
The Challenge
Reversible or Irreversible, Hypoactive

Hypoactive

Support

?
Treat the Experience…
In Dementia…
Agitation in Alzheimer’s / Vascular / Mixed Dementia

Optimize Existing (if currently prescribed) Medications:
- Acetyl-cholinesterase inhibitors: Donepezil: 10 mg PO qhs
- Rivastigmine: 9.5 mg/24 hr transdermal patch
- NMDA receptor antagonist (memantine: 10 mg PO q12hr)

First Choices:
- Trazodone: 50-100 mg q1hr prn. Max 600 mg/dose/24 hr. Schedule q8hr based on previous day’s prn need.
- Gabapentin: 100 mg q1hr prn. Schedule q8hr based on previous day’s prn need, max dose 3600 mg/d
- Propranolol: 5 mg q8hr, titrate by 5 mg tid to effect as tolerated, max dose: 320 mg/day
- Sertraline: 25 mg daily, titrate to effect by 25-50 mg q/wk. Max dose 200 mg.

Second Choices: Antipsychotics
- Haloperidol: 1 mg q30min SC prn (q60min PO). Max 10 mg/dose 100 mg/day
- Risperidone: 0.25 mg PO q1hr prn. Max 6 mg/day
- Chlorpromazine: 50mg SC q30min prn (q60min PO/PR). Max 200 mg/dose 2000 mg/day

Note: Use lower, slower titrations in the elderly, frail, demented patient as safety allows.
PEARL

• Treat agitation like a breakthrough symptom, e.g., pain

• Provide breakthrough (PRN) doses on the Time to maximum concentration ($T_{Cmax}$)

  • If 3 doses not effective, call MD (time-limited trials)

• Provide routine / maintenance doses once every Half-life ($t_{1/2}$)
Summary – It takes a team!

- Assess potential reversibility
- Treat the cause
- Use pharmacokinetics to guide dosing & treat the experience rapidly
Gandhi... You need to be the change you want to see in the world...
Palliative Care
Interdisciplinary Curriculum

A Joint Initiative of the
Palliative Medicine Faculty & Staff of

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