Choice of Analgesia and Sedation
KEY REFERENCES: Laying the Foundation for C of the ABCDEF bundle

- Pandharipande P. *(Loraz.-delir. risk factor)* **Anesthesiology.** 2006;104:21-6.
- Pandharipande P. *(MENDS-Outcomes)* **Crit Care.** 2010;14:R38.
Session Objective

Construct a safe and effective medication regimen for the management of pain and agitation in critically ill adults, consistent with ICU PAD Guidelines recommendations.
All ICU patients should be routinely assessed for:

- **Pain** (Likert self-report, or BPS/CPOT non-self-report)
- **Agitation/depth of sedation** (RASS/SAS)
- **Delirium** (CAM-ICU/ICDSC)

Important factors influence the choice and dose of analgesia and sedative medications.

Non-pharmacologic strategies play an important role when managing pain and agitation.

Use of opioids:

- IV opioids should be considered first-line analgesics for the treatment of non-neuropathic pain. (+1C)
- All IV opioids are equally effective when titrated to similar pain scores. (C)

Use of non-opioid analgesics:

- Non-opioid analgesics should be considered to decrease the amount of opioids administered and to decrease opioid-induced adverse effects. (+2C)

Use of both opioid and non-opioid analgesics:

- For invasive and potentially painful procedures, analgesics with or without non-pharmacologic therapy may be administered pre-procedurally. (+2C)
  - Recommended prior to chest tube removal. (+1C)

- For neuropathic pain, enterally administered gabapentin or carbamazepine should be considered, in addition to IV opioids. (+1A)

Optimizing Opioid Regimens

• Is pain acute (e.g. procedural), persistent, or both?
  ➢ IV bolus versus scheduled IV bolus/infusion

• Route of administration (IV versus oral/enteral)
  ➢ Faster onset with IV administration
  ➢ Longer duration with oral/enteral administration but a functioning gut is needed

• Hemodynamic instability
  ➢ Avoid morphine

Optimizing Opioid Regimens (contd.)

- Opioid tolerance may occur after only 2 days of continuous IV opioid therapy
- Think about multimodal analgesic options in a patient with persistent pain when opioid therapy has been maximized
- There is little role for transdermal or PCA opioid therapy in critically ill patients, particularly for patients with acute or changing pain levels
- Avoid morphine in patients with renal insufficiency

# General Approach To Treating Acute Pain in the ICU

<table>
<thead>
<tr>
<th>Situation</th>
<th>Preferred Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pain</td>
<td>Fentanyl IVP until pain resolves</td>
</tr>
<tr>
<td>Acute pain that persists/recurs</td>
<td>Fentanyl infusion plus fentanyl IVP for breakthrough</td>
</tr>
<tr>
<td>Acute pain in chronic opioid user?</td>
<td>Account for previous opioid use when using IV opioid (may consider ketamine)</td>
</tr>
<tr>
<td>Planned transition out of ICU and patient on IV opioid infusion</td>
<td>Start scheduled oral/enteral opioid therapy (e.g., oxycodone) plus intermittent IV opioid (e.g., IVP or PCA)</td>
</tr>
</tbody>
</table>
Avoid deep sedation/coma:

- Sedative medications should be titrated to maintain lighter levels of sedation, unless clinically contraindicated. (+1B)
- Use daily awakening or a titrated sedation strategy to maintain patient wakefulness. (1B)

Choice of sedative:

- Non-benzodiazepines may be preferred over benzodiazepines to improve clinical outcomes in mechanically ventilated ICU patients. (+2B)

Reduction in sedation requirements:

- Use of an analgesia-first (i.e., analog-sedation) strategy is recommended in mechanically ventilated patients. (+ 2B)

Properties of the Ideal Sedative

• Rapid onset and rapid offset
• Predictable dose-response relationship
• Ease of administration
• Lack of drug accumulation
• Few side effects
• Minimal drug interactions
• Cost-effectiveness
• Promotion of natural sleep

Clinical Effects of Sedatives and Opioids

<table>
<thead>
<tr>
<th></th>
<th>Benzodiazepines</th>
<th>Propofol</th>
<th>Opioids</th>
<th>Alpha-2 agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedation</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Alleviation of anxiety</strong></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>Analgesic properties</strong></td>
<td></td>
<td></td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Preservation of arousability</strong></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>Suppression of respiratory drive</strong></td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Reduction of delirium prevalence</strong></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td><strong>Disruption of sleep</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

## Adverse Effects of Sedatives and Opioids

<table>
<thead>
<tr>
<th></th>
<th>Benzodiazepines</th>
<th>Propofol</th>
<th>Opioids</th>
<th>Alpha-2 agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prolonged emergence</strong></td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory depression</strong></td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>Bradycardia</strong></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Dose-related toxicity</strong></td>
<td><strong>Lorazepam:</strong> propylene glycol accumulation often seen with high doses</td>
<td>↑ TG¹ level → ↑ risk for acute pancreatitis</td>
<td>↑ PRIS² (dose ≥ 60 μg/kg/min)</td>
<td>None</td>
</tr>
</tbody>
</table>

¹TG = triglyceride, ²PRIS = propofol-related infusion syndrome

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Acquisition Costs for Sedatives and Opioids*

- Fentanyl, 100 mcg/hr = $24
- Hydromorphone, 2 mg/hr = $19
- Dexmedetomidine, 1.4 mcg/kg/hr
  - Using vial (generic) = $209
- Midazolam, 5 mg/hr = $52
- Propofol, 60 mcg/kg/min = $63

*Based on the daily acquisition cost for a 70 kg patient at Tufts Medical Center as of August 1, 2015
Analgo-Sedation Strategies

- Addressing pain and discomfort first before administering sedatives.
- Utilization of one drug for two purposes:
  - Pain relief and sedation
- Usually accomplished with an opioid.
Analgo-Sedation

Benefits

• Reduces pain and discomfort, which are common causes of agitation
• Avoids potential sedative-related adverse events:
  ➢ Delirium
  ➢ Hemodynamic instability
  ➢ Metabolic acidosis (lorazepam)
  ➢ Immunomodulation
  ➢ Death (PRIS)

Limitations

• May interfere with respiratory drive, gastric motility, nutrition
• Potential for opioid withdrawal
• ICU LOS, ventilator time, delirium, VAP, mortality, and cost of care are not consistently reduced
• Rigorously evaluated only in European ICUs

Scheduled Intermittent IV Lorazepam versus Propofol with Daily Interruption in Medical ICU Patients

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam (N = 64)</th>
<th>Propofol (N = 68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of MV (days)</strong></td>
<td>8.4 (4.6 to 14.7)</td>
<td>5.8 (3.5 to 10.3)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>ICU LOS (days)</strong></td>
<td>10.4 (6.7 to 16.8)</td>
<td>8.3 (5.2 to 15.2)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

MENDS Trial: Dexmedetomidine versus Lorazepam Sedation

• Study Design:
  • Double-blind, randomized, controlled trial of mechanically ventilated medical and surgical ICU patients (N = 106)

• Results:
  • Dexmedetomidine sedation:
    🗿 more days alive without delirium or coma than with lorazepam ($P = 0.01$)
    🗿 lower prevalence of coma ($P < 0.001$) than with lorazepam ($P = 0.01$)
    🗿 more time spent within sedation goals than with lorazepam ($P = 0.04$)
  • No differences in 28-day mortality and delirium-free days
  • Incidence of bradycardia and hypotension were similar

MENDS Trial: Daily Risk of Delirium

Delirious Patients (%)

Day

1 2 3 4 5 6

P=0.02

Lorazepam
Dexmedetomidine

Pandharipande P. Crit Care. 2010;14:R38.
SEDCOM Trial: Dexmedetomidine vs Midazolam Sedation

• Study Design:
  ➢ Double-blind, randomized, multicenter trial comparing long-term (> 24 hr) dexmedetomidine (n = 244) with midazolam (n = 122)

• Results:
  ➢ No difference between groups in percentage of time patients were in targeted sedation range ($P = 0.18$)
  ➢ Lower delirium prevalence in the dexmedetomidine group ($P < 0.001$)
  ➢ Shorter sedation duration in the dexmedetomidine group ($P = 0.01$)
  ➢ Shorter time to extubation in the dexmedetomidine group ($P = 0.01$)

SEDCOM Trial: Daily Risk of Delirium

Delirious Patients (%)

Enrollment Day 1 2 3 4 5 6

Day 1

Dexmedetomidine
Midazolam

Risk of Developing Delirium With Benzodiazepine Use

• A cohort study (N = 198) investigated whether analgesia and sedative medications increased the risk of ICU pts. developing delirium.

• Lorazepam (OR 1.2, \( P = 0.003 \)) is an independent risk factor for daily transition to delirium.

MIDEX-PRODEX Trials: Dexmedetomidine vs. Midazolam or Propofol

• Two-phase, three multicenter RCTs:
  • MIDEX trial: Dexmedetomidine vs. midazolam sedation
    ➢ **Shorter time to extubation** (4.2 vs. 6.1 days, \( P = 0.01 \)) with dexmedetomidine than with midazolam.
    ➢ **Shorter duration of mechanical ventilation** (5.1 vs. 6.8 days, \( P = 0.03 \))
  • PRODEX trial: Dexmedetomidine vs. propofol sedation
    ➢ **Shorter time to extubation** with dexmedetomidine vs. propofol (2.9 vs. 3.9 days, \( P = 0.04 \))
    ➢ No difference in duration of mechanical ventilation (\( P = 0.24 \))
• Dexmedetomidine equal to midazolam in maintaining light to moderate sedation
• More adverse effects associated with dexmedetomidine
• Patients receiving dexmedetomidine aroused easier, were cooperative, and better able to report pain.

Non-Benzodiazepine Sedative Medications are Associated with Better ICU Outcomes

Systematic review and meta-analysis of 6 RCTs comparing benzodiazepine vs. non-benzodiazepine ICU sedation regimens:

• ↓ ICU LOS (6 studies)
  ➢ Difference of 1.6 days, \( P = 0.0007 \)

• ↓ duration of mechanical ventilation (4 studies)
  ➢ Difference of 1.9 days, \( P < 0.00001 \)

• Similar delirium prevalence and short-term mortality.

Fraser G. Crit Care Med. 2013; 41:S30-8
## Pharmacologic Management of Acute Agitation

<table>
<thead>
<tr>
<th>Situation</th>
<th>Preferred Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation and pain</td>
<td>Fentanyl until agitation resolves</td>
</tr>
<tr>
<td>Acute agitation in a patient who requires deep sedation</td>
<td>Continue opioid, add propofol infusion plus midazolam IVP for breakthrough agitation</td>
</tr>
<tr>
<td>Acute agitation in a non-intubated patient</td>
<td>Low-dose intermittent IV opioid, midazolam or haloperidol OR dexmedetomidine infusion</td>
</tr>
</tbody>
</table>
Conclusions

• Treat pain first before considering sedative therapy.
• Not all mechanically ventilated ICU patients need to be started on IV opioid and/or sedation infusions following intubation.
• Use IV bolus doses liberally before starting or increasing opioid or sedative IV infusions.
• Maximize strategies to avoid the use of continuous IV infusions of benzodiazepines:
  1. Optimize the use of IV opioids for pain management.
  2. If lighter sedation is required, consider dexmedetomidine.
  3. If deep sedation is required, consider propofol.
Conclusions (cont)

• The interdisciplinary ICU team should re-evaluate, at least daily, the appropriateness and the continued need for ALL pharmacologic interventions that have been initiated for treating pain and agitation!
Additional slides
Risk of Transitioning to Delirium With Benzodiazepine Use

• Two cohort studies investigated whether analgesia and sedative medications increase the risk of transition to delirium.

• Both lorazepam (OR 1.2, \( P = 0.003 \)) and midazolam (OR 1.04, \( P < 0.001 \)) are independent risk factors for daily transition to delirium.

Zaal I. *Intens Care Med*. 2015 (under review)
# Comparison of Common IV Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Equi-Analgesic Dose (mg)</th>
<th>Onset (min)</th>
<th>Half-Life</th>
<th>Metabolic Pathway</th>
<th>Active Metabolite</th>
<th>Intermittent Dosing (starting)</th>
<th>IV Infusion Rate (starting)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Fentanyl    | 0.1                      | 1-2         | 2-4 hr    | N-dealkylation     | None             | 0.3 – 0.5 mcg/kg IV q 0.5-1 hr | 0.7 – 10 mcg/kg/hr         | - Fastest onset
- Synthetic therefore minimal hypotension
- Accumulation with hepatic failure and in patients with ESRD
- Muscle rigidity |
| Hyromorphone| 1.5                      | 5-15        | 2-3 hr    | Glucuronidation    | None             | 0.5 – 1.0 mg IV q1-2 hr       | 0.5 – 3 mg/hr              | - Slower onset but longer duration of action (vs. fentanyl)
- Opioid of choice in patients with ESRD |
| Morphine    | 10                       | 5-10        | 3-4 hr    | Glucuronidation    | 6- and 3-Glucuroni de | 2 – 4 mg Q 1-2 hr               | 2 – 10 mg/hr              | - Accumulation with renal/hepatic disease
- Histamine |
Effective ICU Pain Control: Not Just Opioids

Tissue trauma causing release of inflammatory mediators (bradykinins, leukotrienes, prostaglandins, substance P, and histamine)

Opioids
- Local anesthetics
- Alpha-2 agonists
- NMDA antagonists
- Gabapentinoids

Brain
- Thalamus
- Spinothalamic tracts
- Descending modulation tract

Brain
- Epidural opioids
- Alpha-2 agonists

Spinal cord
- Dorsal horn
- Dorsal root ganlion

Peripheral nerve fibers
- Epidural or intrathecal blocks
- Local anesthetics

Peripheral nerve blocks
- Local anesthetics
- NSAIDS
- COX-II inhibitors

Surgery/Trauma
- Burns
- Malignancy
- Infection
- Tubes/lines/drains

Effective ICU Pain Control: Not Just Opioids
- Depth and quality of sedation should be routinely assessed (1B)
- Target the lightest possible level of sedation (1B)
- If pain is appropriately treated and/or if an analgo-sedation approach is used to manage agitation, continuous IV sedative therapy may not be required
- For patients requiring continuous IV sedation:
  - Use daily awakening or a protocolized approach to maintain patient wakefulness (1B)
  - Use a non-benzodiazepine (e.g., propofol or dexmedetomidine) rather than a benzodiazepine (e.g., lorazepam or midazolam)

Continuous IV Sedatives are Commonly Used During Mechanical Ventilation

Impact of a policy of reducing the use of continuous IV opioids and benzodiazepine infusions in ALI patients

<table>
<thead>
<tr>
<th></th>
<th>Before reduction in IV infusion use policy N = 120</th>
<th>After reduction in IV infusion use policy N = 82</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid infusion (%)</td>
<td>74</td>
<td>33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Benzodiazepine infusion (%)</td>
<td>70</td>
<td>22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median patient RASS</td>
<td>-4</td>
<td>-1.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Light sedation achieved (%) (RASS = -1 or O)</td>
<td>20</td>
<td>50</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Days spent in coma (%)</td>
<td>65</td>
<td>23</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Non-pharmacologic interventions are critical:
- Non-pharmacologic strategies play an important role when preventing and managing delirium (+1B)

Pharmacologic delirium prevention:
- We provide no recommendation for using a pharmacological delirium prevention protocol in adult ICU patients, as no compelling data demonstrate this reduces the incidence or duration of delirium in these patients (0, C)
- We do not suggest that either haloperidol or atypical antipsychotics be administered to prevent delirium (-2C)
- We provide no recommendation for the use of dexmedetomidine to prevent delirium in adult ICU patients, as there is no evidence regarding its effectiveness in these patients (0, C)

Pharmacologic delirium treatment:
- There is no published evidence that treatment with haloperidol reduces the duration of delirium (No Evidence)
- Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C)
- We suggest that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine (rather than benzodiazepine infusions) be administered for sedation to reduce the duration of delirium in these patients (+ 2B)
- We do not recommend administering rivastigmine to reduce the duration of delirium (-1B)

Why are Clinicians Often Quick to Administer a Medication to Prevent or Treat Delirium in the ICU?

• Medication-focused delirium reduction strategies are usually quick and easy to administer whereas non-medication strategies are more time-consuming/complex
• Ability to predict and recognize delirium remains limited in many ICU patients
• Assumption that agitation = delirium
  • Most delirium hypoactive
  • Agitation more likely related to uncontrolled pain or withdrawal states
• Reliance on mechanistic postulation rather than on rigorous RCT evidence when justifying pharmacologic intervention in patients at risk for or who have delirium
• Assumption that decades of use (e.g. antipsychotics) rather than rigorous RCT evidence represents a strong rationale to use


van den Boorgaard M. BMJ. 2012;344:e420.
<table>
<thead>
<tr>
<th>Medication-Related Delirium: Strategies to Reduce Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid polypharmacy/Ensure medication dosing is appropriate</td>
</tr>
<tr>
<td>Consider medication withdrawal as a cause for delirium symptoms</td>
</tr>
<tr>
<td>Avoid anticholinergic medications whenever possible</td>
</tr>
<tr>
<td>Avoid benzodiazepine medications whenever possible</td>
</tr>
<tr>
<td>Minimize use of non-benzodiazepine sleep medications</td>
</tr>
<tr>
<td>Use the lowest effective corticosteroid dose</td>
</tr>
<tr>
<td>Use the lowest effective opioid dose to control pain/maximize use of non-opioid analgesics</td>
</tr>
<tr>
<td>Avoid metoclopramide when possible</td>
</tr>
<tr>
<td>If delirium occurs in a patient receiving famotidine/ranitidine, switch to pantoprazole</td>
</tr>
<tr>
<td>If delirium occurs in a patient who is receiving levetiracetam (Keppra), consider other anticonvulsant options</td>
</tr>
<tr>
<td>Reassess need for continued antibiotic therapy</td>
</tr>
<tr>
<td>Monitor diuretic therapy for signs of dehydration and/or electrolyte abnormalities</td>
</tr>
<tr>
<td>Check a serum drug concentration if a medication is being administered when supratherapeutic concentrations might cause delirium-like symptoms</td>
</tr>
</tbody>
</table>
Before Administering a Medication to Either Prevent or Treat Delirium in the ICU:

1. Consider non-medications-related, reversible factors for delirium (e.g., hypoxemia, infection, electrolyte abnormalities)
2. STOP (or decrease the dose) of any medication (if possible) that may increase delirium risk
3. Mobilize patients (when possible)
4. Optimize non-pharmacologic interventions that may reduce delirium incidence and/or burden:
   - Hearing aids, glasses, reorientation, sleep protocols, music, noise control, family interaction

Kamdar B. Crit Care Med. 2013; CCM 2015
NICE Guidelines 2010
AGS Post Operative Delirium CPG 2015
## Comparison of Clinical Effects of Medications Commonly Used to Treat Delirium in the ICU

<table>
<thead>
<tr>
<th></th>
<th>Conventional Antipsychotics</th>
<th>Atypical Antipsychotic</th>
<th>Alpha-2 agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haloperidol</td>
<td>Olanzapine</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Sedative effects</td>
<td>XX</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>Dopamine-2 antagonism</td>
<td>XXX</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>Serotonergic effects</td>
<td>XXX</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IV availability</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc interval prolongation</td>
<td>XXX</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>Extrapyramidal effects</td>
<td>XX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## General Approach to Treating Delirium

<table>
<thead>
<tr>
<th>Situation</th>
<th>Preferred Intervention</th>
</tr>
</thead>
</table>
| Patient found to have delirium                                           | 1. Remove/reduce all modifiable risk factors (including medications) that could be causing/worsening delirium  
2. Implement non-pharmacologic interventions known to reduce delirium occurrence/duration (e.g. reorientation, ear plugs). |
| Patient has persistent delirium with agitation                            | 1. If agitation is mild, is not related to pain or benzodiazepine withdrawal and the QTc interval is ≤ 500 msec, then haloperidol, 1mg IV q6h (if patient NPO) and quetiapine 50mg PO/FT q12h (if patient eating/tolerating TF)  
2. If agitation is severe and is not related to pain or benzodiazepine withdrawal, then start a dexmedetomidine infusion  
Note: If patient on a benzodiazepine or propofol infusion – change to dexmedetomidine (if deep sedation is not required) |
| Patient has delirium, no agitation, but has bothersome delirium symptoms  | If the QTc interval is ≤ 500 msec initiate haloperidol 1mg IV q6h (if patient NPO) and quetiapine 50mg PO/FT q12h (if patient eating/tolerating TF)                                                                 |
| Patient has delirium but neither agitation nor bothersome delirum symptoms | No pharmacologic treatment is warranted                                                                                                                                                                                    |
| Patient has delirium, mild agitation and/or bothersome symptoms but has QTc interval ≥ 500 ms | If eating/tolerating TF then initiate risperidone 1mg PO/FT q12h or olanzapine 5mg PO/FT q12h.  
If the patient is NPO, consider initiating IV valproic acid (500mg IV x 1 then 100mg IV q6h) [can then transition to oral suspension] |
| Patient has delirium, severe agitation, but cannot tolerate dexmedetomidine | Initiate IV valproic acid 500mg x 1 then 100 mg IV q6h [can then transition to oral suspension] |