The goal of this discussion will be to review the literature published since the PAD guidelines were released and formulate an approach to individualized patient treatment for pain, agitation, and delirium in the adult patient in the intensive care unit.

I have no financial disclosures to make regarding the contents of this presentation.

**OBJECTIVES**

- Describe “Early Goal Directed Sedation”.
- Compare analgosedation to standard sedation approaches.
- Explain the approach to prevention and treatment of delirium.
- Review atypical antipsychotics and list common adverse reactions to these agents seen while treating delirium.
- Identify bedside issues with implementation of an effective program for PAD.

**Early Goal Directed Sedation (EGDS)**

- Early implementation after intubation
- Goal directed to target LIGHT sedation (RASS -2 to 1)
- Use of dexmedetomidine as the primary sedative
- Minimizes use of benzodiazepines

**Analgosedation**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Decreased ventilation time</td>
<td>- Potential delirium</td>
</tr>
<tr>
<td>- Decreased ventilator time</td>
<td>- Recall (unpleasant events)</td>
</tr>
<tr>
<td>- Decreased ICU LOS</td>
<td>- Nightmares / hallucinations</td>
</tr>
<tr>
<td>- Use less “hypnotics”</td>
<td>- Immunosuppression</td>
</tr>
<tr>
<td>- Less sedation</td>
<td>- Withdrawal</td>
</tr>
<tr>
<td>- Less ADRx</td>
<td>- Hyperalgesia</td>
</tr>
</tbody>
</table>

- Majority of trials used remifentanil

Devabhatkhuri S et al Ann Pharmacother 2012
The ability to reliably assess pain is foundational for effective treatment. Critically ill patients may be unable to self-report pain. The ability to reliably assess pain is foundational for effective treatment.

**Subjective**
- Body movements
- Muscle tension
- Facial expressions
- Muscular relaxation
- Mood changes
- Respiratory depression
- Bowel regimen for constipation may be necessary

**Objective**
- Arousal
- Nausea, vomiting & constipation
- Rash
- Tachycardia
- Orthostatic hypotension
- Bradycardia

**Behavioral**
- Change in activities
- Change in vocalizations
- Change in level of consciousness

**Emergency**
- Changes in vital signs
- Changes in mental status
- Changes in behavior

**Assess ALL PATIENTS for any TYPE of pain**

**Opioid related side effects**
- Nausea
- Vomiting
- Constipation

**Adverse Effects**
- Respiratory depression
- Sedation
- Urinary retention
- Hypotension
- Hypertension
- Tachycardia
- Bradycardia

**NSAIDs**
- Ibuprofen (Motrin)
- Naproxen (Naprosyn)
- Ketorolac (Toradol)

**Behavioral Pain Scale (BPS)**
- Sedation (often desirable)
- Amount of opioids or eliminate need for IV opioids

**Use non-opioid analgesics to:**
- Reduce the need for IV opioids
- Reduce sedation
- Reduce respiratory depression

**Use a validated and reliable pain scale:**
- Behavioral Pain Scale (BPS)
- Critical Care Patient Observation Tool (CPOT)
- Facial expressions
- Body movements
- Muscle tension
- Compliance with ventilator

**Monitor for**
- Sedation
- Hypotension
- Bradycardia
- Respiratory depression

**Agent**
- Analgesic and antipyretic effects
- Selective COX-2 inhibitor
- Metabolites with different effects

**Oral options**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Equivalent Dose</th>
<th>Dosing</th>
<th>Half-life</th>
<th>Metabolism</th>
<th>Adverse Effects</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>30 mg</td>
<td>15-60 mg every 4-6 h</td>
<td>2.5-3 h</td>
<td>N-demethylation/Demethylation</td>
<td>Active metabolites</td>
<td>Active metabolites</td>
</tr>
<tr>
<td>Oxycodone (OxyContin)</td>
<td>20 mg</td>
<td>5-15 mg every 4-6 h (IR)</td>
<td>3-4.5 h</td>
<td>CYP 2D6, 2E1</td>
<td>Active metabolites</td>
<td>Active metabolites</td>
</tr>
<tr>
<td>Hydrocodone (Norco, Lorcet, Vicodin)</td>
<td>30 mg</td>
<td>2.5-10 mg hydrocodone every 4-6 h</td>
<td>3-4.5 h</td>
<td>CYP 2D6, 2E1</td>
<td>Active metabolites</td>
<td>Active metabolites</td>
</tr>
<tr>
<td>Methadone</td>
<td>N/A</td>
<td>10-60 mg every 6-12 h</td>
<td>15-60 h</td>
<td>CYP 3A4, 2D6, 2E1, 1A2</td>
<td>Active metabolites</td>
<td>Monitor at emergence of acetaminophen</td>
</tr>
</tbody>
</table>

**Comment**
- Alert for increased respiratory depression when used with synthetic opioids
- Use with caution and close monitoring
- Use with intolerance to opioids

**PAIN ASSESSMENT**
- If unable to self-report - Use a validated and reliable pain scale
- Behavioral Pain Scale (BPS)
- Critical Care Patient Observation Tool (CPOT)
- Facial expressions
- Body movements
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**ADVERSE EFFECTS**
- Respiratory depression
- Sedation
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- Bradycardia

**COMPARISON**
- OPIOID
- NON OPIOID ANALGESICS

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**ADVERSE EFFECTS**
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- Sedation
- Urinary retention
- Hypotension
- Hypertension
- Tachycardia
- Bradycardia
Non-opioid analgesia

**NSAIDs**

<table>
<thead>
<tr>
<th>Drug, route</th>
<th>Dosing</th>
<th>Time to Onset</th>
<th>Half-life</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac (Toradol) PO, IM, IV</td>
<td>15-30 mg q 6 h (MAX 5 days)</td>
<td>10 min</td>
<td>2 - 6 h</td>
<td>Hydroxylation, conjugation, renal excretion</td>
</tr>
<tr>
<td>Ibuprofen (Motrin) PO, IV</td>
<td>400 - 800 mg q 4 h (MAX 2.4 g/day)</td>
<td>PO 25 min</td>
<td>PO 1.8 - 2.5 h</td>
<td>IV 2.2 - 2.4 h</td>
</tr>
</tbody>
</table>

**Benzodiazepines**

<table>
<thead>
<tr>
<th>Drug, route</th>
<th>Onset after IV Loading Dose</th>
<th>Half-life</th>
<th>Initial Dosing-Intermittent</th>
<th>Initial Dosing-Continuous Infusion</th>
<th>Titratin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (Versed) IV, IM, PO</td>
<td>2 - 5 min</td>
<td>2 - 11 h</td>
<td>2 - 4 mg q 0.5 - 2 h</td>
<td>2 - 4 mg/h (bolus before gt)</td>
<td>Adjust by 1 - 2 mg/h, q30 min, bolus with each rate increase</td>
</tr>
<tr>
<td>Lorazepam (Ativan) IV, IM, PO</td>
<td>15 - 20 min</td>
<td>8 - 15 h</td>
<td>1 - 2 mg q 2 - 6 h</td>
<td>1 - 2 mg/h (bolus before gt)</td>
<td>Adjust by 1 mg/h, q30 min: give bolus dose with each rate increase</td>
</tr>
</tbody>
</table>

**Neuropathic pain**

<table>
<thead>
<tr>
<th>Drug, route</th>
<th>Dosing</th>
<th>Time to onset</th>
<th>Half-life</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin (Neurontin) PO</td>
<td>Initial: 100mg BID</td>
<td>5 - 25 mg PO 3 - 4 times daily</td>
<td>8 - 15 h</td>
<td>1 - 2 mg/q 2 - 6 h (bolus before gt)</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Initial: 100 - 200 q 4 - 6 hr</td>
<td>1 - 2 mg q 2 - 6 h</td>
<td>1 - 2 mg/h (bolus before gt)</td>
<td>Adjust by 1 mg/h, q30 min: give bolus dose with each rate increase</td>
</tr>
</tbody>
</table>

**Special Considerations**

- Benzodiazepines
- Propofol
- Dexmedetomidine

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Onset</th>
<th>Half-Life</th>
<th>Initial Dosing-Intermittent</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam (Valium) IV, PR, PO</td>
<td>2 - 5 min</td>
<td>20 - 120 h</td>
<td>0.03 - 0.1 mg/kg IV q 0.5 - 1 h</td>
<td>Rapid onset, Metabolites can prolong duration with repeated doses, Accumulation - avoid continuous dosing</td>
</tr>
<tr>
<td>Alprazolam (Xanax) PO</td>
<td>1 - 2 h</td>
<td>12 - 15 h</td>
<td>Start at 0.25 - 0.5 mg PO TID</td>
<td>Anxiety and panic disorders</td>
</tr>
<tr>
<td>Clonazepam (Klonopin) PO</td>
<td>0.5 - 4 h</td>
<td>20 - 60 h</td>
<td>0.5 - 2 mg PO 3 - 4 times daily</td>
<td>Anxiety, Alcohol withdrawal</td>
</tr>
</tbody>
</table>

**Adverse effects**

- **Midazolam**: ↓ BP
- **Lorazepam**: ↓ BP
- **Diazepam**: Pain, phlebitis at injection site

**Special Considerations**

- **Midazolam**: Intermittent dosing preferred, Active metabolite prolongs sedation, especially in patients with renal failure, CYP 450 w more drug interactions
- **Lorazepam**: Intermittent dosing preferred, No active metabolites
- **Diazepam**: Active metabolite, extremely long half life, Short duration of effect, Infusion requires large volume
**PRECAUTIONS: BENZO’S**

- Hypotension upon initiation
- Caution if hemodynamically unstable
- Withdrawal
- Autonomic instability, altered perception, paresthesias, headaches, tremors, and seizures
- Taper off benzodiazepines if high doses or > 7 days of use
- Avoid use of flumazenil (BZD antagonist) for reversal of withdrawal

**DEXMEDETOMIDINE (PRECEDEX®)**

- Central, selective alpha-2 agonist
- Immediate onset, short duration (6 minutes)
- Has sedative, anxiolytic & analgesic effects but less amnesia
- May facilitate decreasing doses of analgesics, other sedatives
- Hepatic elimination, no dose adjustments for renal dysfunction

**Propofol**

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory depression</td>
<td>Rapid onset / offset</td>
</tr>
<tr>
<td>Hypotension / bradycardia</td>
<td>Requires a dedicated IV line</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Drug incompatibility</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Change tubing every 12 hours</td>
</tr>
<tr>
<td>Propofol-related Infusion Syndrome (PRIS)</td>
<td></td>
</tr>
</tbody>
</table>

**Dexmedetomidine**

<table>
<thead>
<tr>
<th>Onset</th>
<th>Half-Life</th>
<th>Initial Dosing</th>
<th>Initial Dosing-Continuous Infusion</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>1.6 - 3 h</td>
<td>NA</td>
<td>0.2 – 1.5 mcg/kg/h do not bolus</td>
<td>Adjust by 0.1 mcg/kg/h q15 min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Dose range listed in product labeling differs from that in literature</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>- No bolus</td>
</tr>
<tr>
<td>Tachyphylaxis</td>
<td>- Higher doses</td>
</tr>
<tr>
<td>Minimal respiratory depression</td>
<td>- &gt; 24h administration</td>
</tr>
<tr>
<td>Loss of airway reflexes</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

**MONITORING DEPTH OF SEDATION**

- Richmond Agitation Sedation Scale (RASS) and the Sedation Agitation Scale (SAS) are the most valid and reliable tools assessing sedation
- More precise dosing
- Reduced use of sedatives & analgesics
- Shorter duration of mechanical ventilation
- Reduced need for vasopressors
- Reduced incidence of over-sedation

**AGITATION**

- Agitation and anxiety occur frequently in critically ill patients
- Anxiety: absence of a sense of well-being, exaggerated feelings of fear, nervousness, or apprehension
- Agitation: combination of anxiety and increased motor activity

DELIRIUM

- An acute brain dysfunction; a disturbance of consciousness and attention
- Can be hyperactive, hypoactive, or mixed
- Cardinal feature is inattention
- Underrecognized
- 60 – 80% prevalence of mechanically ventilated patients
- icudelirium.org

DELIRIUM OUTCOMES

- Delirium is strongly associated with ↑ mortality in adult patients
- Delirium is strongly associated with ↑ LOS in adults
- Delirium is moderately associated with development of post ICU cognitive impairment in adults

DELIRIUM RISK FACTORS

- Baseline risk factors associated with delirium
  - Pre-existing dementia
  - History of hypertension
  - History of alcoholism
  - Admission severity of illness
- Coma is an independent risk factor but linking a definitive relationship between subtypes of coma and delirium requires more study
- Opioids and delirium ⇒ Conflicting evidence

DELIRIUM RISK FACTORS

- Benzodiazepines may be a risk factor for delirium in adults
- Propofol and delirium ⇒ insufficient data
- Vented patients are at risk for delirium, use of dexmedetomidine may be associated with lower incidence compared to benzodiazepines

TYPES OF DELIRIUM

- Hypoactive: 55%
- Hyperactive: 15%
- Mixed: 30%

DETECTING & MONITORING DELIRIUM

- Routine monitoring for delirium in all adult patients
- Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable tools in adults
- Routine monitoring is feasible in practice
Prevention is the BEST treatment for delirium

- Treatment options
  - Non-pharmacologic
  - Pharmacologic
    - Antipsychotics
    - Atypical antipsychotics

DELIRIUM TREATMENT

- Little data that treatment with haloperidol reduces delirium
- Atypical antipsychotics may reduce the duration of delirium
- Do not use antipsychotics in patients at risk for torsades de pointes (history of long QT, patients with meds which if QT or patients with prior torsades de pointes)
- Dexmedetomidine instead of benzodiazepines be used for patients with delirium to reduce its duration

DELIRIUM PREVENTION

- Early mobilization should be performed whenever feasible to prevent delirium incidence
- No recommendation for use of pharmacologic agents to prevent delirium
- No recommendation for combined non-pharmacologic and pharmacologic agents to prevent delirium
- Neither haloperidol or antipsychotics prevent delirium
- No recommendation for prophylactic use of dexmedetomidine to prevent delirium

Antipsychotics Properties

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>DA, 5HT-1, H1</th>
<th>DA, 5HT-1 &amp; 2</th>
<th>DA, 5HT-1 &amp; 2, H2</th>
<th>DA, 5HT-1</th>
<th>DA, 5HT-1 &amp; H1</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>60</td>
</tr>
<tr>
<td>Clozapine</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>10 to 20</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>40 to 80</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>10 to 30</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>1.5 to 30</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>10 to 30</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>1.5 to 30</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3 to 6</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>4 to 8</td>
</tr>
<tr>
<td>Clozapine</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1.5 to 30</td>
</tr>
</tbody>
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Comparative Risk of Adverse Effects of Antipsychotic Medications

- Protocol design
  - PAD protocol, algorithms and guidelines
- Implementation of protocols
  - Use of assessment tools CONSISTENTLY
  - Documentation of assessment
  - Consistency from days to nights
GUIDELINE MANAGEMENT & IMPLEMENTATION
- Daily interruption or light target level of sedation be used
- Analgesia be implemented as first sedative
- Sleep should be promoted to protect the normal sleep cycle

GUIDELINE MANAGEMENT & IMPLEMENTATION
- Multidisciplinary team plus:
  - Provider education
  - Preprinted +/- computerized protocols and order forms
  - ICU rounds checklist be used to assess pain, agitation and delirium ROUTINELY

TAKE HOME POINTS
- Treat pain first
- Evaluate the pharmacology of agents to select optimal therapy to avoid delirium when possible
- Sedation: lighter is better than deeper
- Promote sleep
- Identify your goal and routinely reassess therapy
- Use a multi-disciplinary approach

QUESTIONS??