Ketamine and Dexmedetomidine: Not Just a Back Up Plan

Cristian Merchan Pharm.D., BCCCP
Clinical pharmacy manager, Critical Care and Emergency Medicine
NYU Langone Tisch Hospital
Objectives

• Review the PK/PD of ketamine and dexmedetomidine
• Recognize and manage adverse drug reactions from ketamine and dexmedetomidine
• Describe the benefits and risk of continuous infusion of ketamine and dexmedetomidine in critically ill patients
• Analyze the recent literature evaluating the use of ketamine and dexmedetomidine for ICU sedation, acute agitation, and alcohol withdrawal
# Analgosedation

- Society of Critical Care Medicine (SCCM) recommends analgesia first sedation with light sedation goals for most critically ill patients (2B recommendation)
- Analgesia first sedation + sedative if needed

## Advantages

- Decrease overall exposure to sedatives
- Associated with shorter durations of:
  - Mechanical ventilation
  - ICU LOS and cost
- Avoid potential sedative related ADR:
  - Death (e.g., PRIS)
  - Delirium
  - Metabolic acidosis
  - Hemodynamic derangement

## Disadvantages

- Respiratory depression
- Reduced GI motility
- Pain recurrence and withdrawal upon analgesic discontinuation
- Opioid induced hyperalgesia
- Immunosuppression

Barr et al. Crit Care Med 2013
Analgesedation is not for everybody

Many patients will require sedative supplementation (18-70%)

- Alcohol/drug withdrawal & drug intoxication
- Neuromuscular blockade
- Elevated intracranial pressure
- Status epilepticus
- ECMO

Barr et al. Crit Care Med. 2013
What is the ideal sedative agent

**Sedative properties**

- Fast ON/OFF effects
- No accumulation of active metabolites
- Limited hemodynamic derangements
- Increase patient comfort and safety
- Improves tolerance with mechanical ventilation

**Decrease**

- Duration of mechanical ventilation
- Length of ICU stay

Brown EN et al. NEJM. 2010
Current non-benzodiazepine options available

Propofol
Dexmedetomidine
Ketamine
Ketamine: Mechanism of Action

CNS
- Noncompetitive antagonist of NMDA receptors in the brain + spinal cord
- Reduces the frequency and mean opening time of the Ca\textsubscript{2} channel + prevents Ca\textsubscript{2} influx
- Anti-inflammatory properties: Inhibits NF-kB, TNF-alpha, + IL-6
- Very weak agonist for the delta + mu opioid receptors
- Naloxone has no effect in reversing ketamine effects

Cardiovascular
- Directly stimulates the CNS to release catecholaamines
- Inhibits neuronal and extra-neuronal uptake of catecholamines
- Results in a 10-30\% increase in SBP and HR
- Response attenuated with dexmedetomidine
- Negative inotrope

Pulmonary
- Does not suppress normal upper airway protective reflexes (coughing, sneezing and swallowing)
- Inhibits effect on muscarinic receptors \rightarrow increase in bronchial secretion and mucus formation
- Preserves pulmonary hypoxic vasoconstriction and has minimal effects on PVR
- Stimulates Beta 2 receptors \rightarrow bronchodilation (dose dependent)

**Ketamine: Pharmacokinetics**

**Absorption**
- Oral: 17-24%
  - Onset: 30min
- IM: 93%
  - Onset: 3-4 min
- Intranasal: 45%
  - Onset: 10 min

**Distribution**
- VD: 2-3L/kg
- Alpha half life: 2-4 min
- Beta half life: 2-4 h
- Protein binding: 10-30%

**Metabolism**
- 80% is N-demethylated to norketamine
  - CYP 3A, 2B6 and 2C9 responsible for N-demethylation

**Elimination**
- Metabolites are excreted in bile and urine after glucuronidation
- Renal excretion: 4% as unchanged drug

**References**
Ketamine dosing by indication and route of administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissociative sedation</td>
<td>IV</td>
<td>1.5–2 mg/kg</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>4–5 mg/kg</td>
</tr>
<tr>
<td>Brief sedation—rapid administration &lt;5 s</td>
<td>IV</td>
<td>0.5–0.8 mg/kg</td>
</tr>
<tr>
<td>Analgesia</td>
<td>IV</td>
<td>0.2–0.75 mg/kg</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>1–3 mg/kg</td>
</tr>
<tr>
<td></td>
<td>IN</td>
<td>0.5–1 mg/kg</td>
</tr>
<tr>
<td>Induction of rapid sequence intubation</td>
<td>IV</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Moderate to severe asthma</td>
<td>IV</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Pharmacologic restraint</td>
<td>IM</td>
<td>4–5 mg/kg</td>
</tr>
</tbody>
</table>

Dexmedetomidine: Mechanism of Action

CNS
- Hypnotic effect of DEX ↓ neuronal firing in the locus ceruleus + activity in the ascending noradrenergic pathway (via alpha-2A)
  - ↓ noradrenergic output from the locus ceruleus allows for increased firing of inhibitory neurons which further inhibit the locus ceruleus
- Analgesic effect:
  - Activation of both α2-C and α2-A, in the neurons of the superficial dorsal horn directly ↓ pain transmission
  - Reduce the release of substance P, and glutamate

Cardiovascular
- DEX can significantly↑ SBP when plasma conc. ↑ from 0.5 to 3.2 ng/ml.
  - Correlate with the rate of IV infusion and plasma concentration
  - At serum conc. greater than 1 mcg/l, the BP changes from a mild decrease from baseline to an elevation

Keating GM et al. Drugs. 2015
Tomassoni AJ. Crit Care toxicology. 2017
Dexmedetomidine: Pharmacokinetics

**Absorption**
- IV: 100%
  - Onset: 15-20 min
- Intranasal: 82%
  - Onset: 30-45 min

**Distribution**
- VD: 109-223 L
- Distribution half life: 6 min
- Elimination half life: 2.2-3.7 h
- Protein binding: 94%

**Metabolism**
- 34% Direct N-glucuronidation by UGT2B10 + UGT1A4
- Hydroxylation of CYP2A6
- No active metabolites

**Elimination**
- Metabolites excreted renally (95%) and fecally (4%)
- Less than 1% is excreted unchanged

Keating GM et al. Drugs. 2015
Tomassoni AJ. Crit Care Toxicology. 2017
# Comparison of Adverse Effects of Sedatives

<table>
<thead>
<tr>
<th>Dexmedetomidine</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bradycardia: up to 30% decrease from baseline</td>
<td>• Emergence reactions: 5-25%</td>
</tr>
<tr>
<td>- Incidence: 1-42%</td>
<td>• Crying, Agitation, delirium, dysphoria, nightmares, and hallucinations</td>
</tr>
<tr>
<td>• Increase risk with AVN blockers, hypovolemia</td>
<td>• Vomiting 5-15%</td>
</tr>
<tr>
<td>• Hypotension: 13-68%</td>
<td>- Increased when given IM, IV at doses &gt;2.5mg/kg</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>- Can be treated with BDZ or ondansetron</td>
</tr>
<tr>
<td>• Increase risk: larger doses + rapid IV push</td>
<td>• Laryngospasm</td>
</tr>
<tr>
<td>• Dry mouth</td>
<td>- Appears to be idiosyncratic</td>
</tr>
<tr>
<td>• Fever: up to 10%</td>
<td>• Increase in ICP</td>
</tr>
<tr>
<td></td>
<td>- Only in patients with structural barriers to normal CSF flow (ex: hydrocephalus)</td>
</tr>
<tr>
<td></td>
<td>• Hyper-salivation</td>
</tr>
<tr>
<td></td>
<td>• Hypertonicity and Random movements</td>
</tr>
<tr>
<td></td>
<td>• involuntary, rhythmic muscle contractions involving the arms and legs</td>
</tr>
</tbody>
</table>

Keating GM et al. Drugs. 2015
Tomassoni AJ. Crit Care toxicology. 2017
Question 1

For ketamine which dose would be classified as sub-dissociative

A. 2 mg/kg IM
B. 0.5 mg/kg IV
C. 1.2 mg/kg IV
D. 1.5 mg/kg IM
E. Both A and B
Clinical application of ketamine + dexmedetomidine

Sedation
- General ICU patients
- Acute Brain injury patients

Treatment of acute agitation

Utility in alcohol withdrawal
## Evidence for dexmedetomidine in ICU sedation

<table>
<thead>
<tr>
<th>Study Name + Comparator</th>
<th>N</th>
<th>% Time at target sedation range</th>
<th>Dex median (IQR) dose (mcg/kg/h) + duration</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MIDEX (2012)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEX: 0.2-1.4 mcg/kg/h</td>
<td>249</td>
<td>60.7</td>
<td>NO LD MD: 0.45 (0.27-0.76) Duration: 42h</td>
<td>Median time to extubation 101h v 147h*</td>
</tr>
<tr>
<td>MID: 0.03-0.2 mg/kg/h</td>
<td>251</td>
<td>56.6</td>
<td></td>
<td>Median duration of ICU stay 211h v 243h</td>
</tr>
<tr>
<td><strong>PRODEX (2012)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEX: 0.2-1.4 mcg/kg/h</td>
<td>251</td>
<td>64.6</td>
<td>NO LD MD: 0.93 (0.67-1.2) Duration: 42h</td>
<td>Median time to extubation 69h vs 93h*</td>
</tr>
<tr>
<td>PRO: 0.3-4.0 mg/kg/h</td>
<td>247</td>
<td>64.7</td>
<td></td>
<td>Median duration of ICU stay 164h v 185h</td>
</tr>
<tr>
<td><strong>SEDCOM (2009)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEX: 0.2-1.4 mcg/kg/h</td>
<td>244</td>
<td>77.3</td>
<td>LD: 1 mcg/kg (only in 8%) MD: 0.83 (0.46–1.20) Duration: 84h</td>
<td>Median time to extubation 3.7 days v 5.6 days*</td>
</tr>
<tr>
<td>MID: 0.02-.01 mg/kg/h</td>
<td>122</td>
<td>75.1</td>
<td></td>
<td>Median duration of ICU stay 5.9 days v 7.6 days</td>
</tr>
</tbody>
</table>

Dex: dexmedetomidine, PRO: propofol, MID: midazolam

*Significant difference
## Does literature support the use of ketamine in ICU

<table>
<thead>
<tr>
<th>Author (year) and study design</th>
<th>Patients</th>
<th>Ketamine dosing (mg/kg/h) Regimen</th>
<th>Comparator regimen</th>
<th>Primary Outcomes</th>
<th>Significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillou et al. (2003) Prospective, single center, double-blind RCT (n=93)</td>
<td>Major abdominal surgery and mechanically ventilated in SICU</td>
<td>Ketamine + Morpine PCA Bolus: 0.5 mg/kg Initial: 0.12 for 24 h, then 0.06 mg/kg/hr for the following 24 h</td>
<td>Morphine via PCA + placebo LD: 2mg MD: 1mg q7min</td>
<td>Morphine Consumption at 48 h 80 (+/-37) v 58 (+/-35) mg (P &lt; 0.05)</td>
<td>No difference • Hallucinations • Pain scores • Ramsay sedation scores</td>
</tr>
<tr>
<td>Umunna et al (2015) Single center retrospective (n=30)</td>
<td>Mechanically intubated &gt; 24 h</td>
<td>No bolus given Initial: 0.5 Median: 2 Range: 0.5-4 Duration: 59.6 h</td>
<td>None</td>
<td>Incidence of ADR 4/30 switched agents due to ADR • 2/4: Afib • 2/4: Agitation</td>
<td>Average MAAS: 1.9 • 50% also on fentanyl infusions</td>
</tr>
<tr>
<td>Groetzinger et al (2015) Single center retrospective (n=43)</td>
<td>Mechanically intubated &gt; 6 h</td>
<td>Used as an adjunct Initial: 0.16 Median: 0.44 Range: 0.05-2 Duration: 86.4 h</td>
<td>None</td>
<td>Goal SAS score achieved in 69% of pts</td>
<td>Once initiated • 60% of pts had 1 sedative ↓ or DC</td>
</tr>
<tr>
<td>Buchheit et al (2017) Single center retrospective (n=40)</td>
<td>Mechanically ventilated in SICU</td>
<td>No bolus Initial: 0.3 Median: 0.3 Range: 0.06-0.3 Duration: 46 h</td>
<td>Morphine:6.6 mg/h Propofol:150 mg/h</td>
<td>The Morphine infusion rate at 24 h after ketamine initiation 0 (0-3.3) v. 6.6 (3.3-10) mg/h (P &lt; .001)</td>
<td>Once initiated • 55% of pts had opioid infusions DC within 24 h • No difference in RASS</td>
</tr>
</tbody>
</table>
Sedation in Acute Brain Injuries
Rationale for using sedation in patients with acute brain injury

- Decrease ICP
  - Reduce cerebral metabolic rate
  - Decreases cerebral blood flow
  - Reduce pain and agitation prevents ICP surge
  - Improves tolerance of the endotracheal tube
  - Reduces coughing,
    - Avoids ↑ in intrathoracic pressure
    - Reduce jugular venous outflow
  - Prevents 2nd injury from mass depolarization of neurons and lesion expansion

- Improving cerebral tolerance to ischemia
- Reduction of intracranial volume

Fundamental problems associated with sedation in acute brain injury

- Continued benzodiazepine use
  - Leads to tolerance and tachyphylaxis
  - Increased incidence of delirium

- Propofol at higher doses or longer duration increases risk of
  - Arterial hypotension
  - Hypertriglyceridemia
  - Propofol infusion syndrome (PRIS)

- Daily sedation breaks are not sufficiently safe in this patient group
Ketamine does not increase intracranial pressure compared with opioids

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuous infusion</th>
<th>Bolus dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>104</td>
<td>63</td>
</tr>
<tr>
<td>Study design</td>
<td>Four prospective RCTs</td>
<td>2 prospective single arm trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 prospective case control</td>
</tr>
<tr>
<td>Pt description</td>
<td>All patients were classified as severe TBI, with GCS of 8 or less, and all being ventilated + sedated with midazolam</td>
<td></td>
</tr>
<tr>
<td>Dosing range</td>
<td>2.5-6.2 mg/kg/h</td>
<td>1-5 mg/kg</td>
</tr>
<tr>
<td>Duration range</td>
<td>1 – 6 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No difference in ICP control</td>
<td>Reduction in ICP with ketamine bolus</td>
</tr>
<tr>
<td></td>
<td>No ICP fluctuations</td>
<td>Sustained effect when used preemptively for stimulating procedures</td>
</tr>
</tbody>
</table>

Gillman LM et al. Neurocrit Care. 2014

### ICP

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ketamine Mean</th>
<th>SD</th>
<th>Total</th>
<th>opioids Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourgoin 2003</td>
<td>19</td>
<td>8.4</td>
<td>12</td>
<td>15</td>
<td>6.8</td>
<td>13</td>
<td>16.8%</td>
<td>4.00</td>
<td>[-2.02, 10.02]</td>
</tr>
<tr>
<td>Bourgoin 2005</td>
<td>14.6</td>
<td>8.3</td>
<td>15</td>
<td>18.7</td>
<td>6.8</td>
<td>15</td>
<td>17.9%</td>
<td>-4.10</td>
<td>[-9.53, 1.33]</td>
</tr>
<tr>
<td>Kolenda 1996</td>
<td>12</td>
<td>2.2</td>
<td>17</td>
<td>13</td>
<td>1.2</td>
<td>18</td>
<td>24.5%</td>
<td>-1.00</td>
<td>[-2.18, 0.18]</td>
</tr>
<tr>
<td>Michalczyk 2013</td>
<td>27</td>
<td>7</td>
<td>39</td>
<td>17</td>
<td>6</td>
<td>10</td>
<td>20.0%</td>
<td>10.00</td>
<td>[5.68, 14.32]</td>
</tr>
<tr>
<td>Schmittner 2007</td>
<td>15.9</td>
<td>5.9</td>
<td>12</td>
<td>14.7</td>
<td>3.4</td>
<td>12</td>
<td>20.9%</td>
<td>1.20</td>
<td>[-2.60, 5.00]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>95</td>
<td>68</td>
<td></td>
<td></td>
<td>100.0%</td>
<td></td>
<td>1.94</td>
<td>[-2.35, 6.23]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 19.15; Chi² = 27.54, df = 4 (P < 0.0001); I² = 85%
Test for overall effect: Z = 0.89 (P = 0.38)
Dexmedetomidine use in acute brain injury

Effect on ICP
- 3 studies (2 RCTs + 1 prospective control trial)
- 54 patients 85% of patients with TBI
- All patients had a baseline ICP < 20
- No difference in ICP as compared to placebo or propofol

Effect on CPP
- When compared to propofol
  - No difference in brain tissue oxygenation or lactate-to-pyruvate ratio
  - No difference in mean CPP during active drug infusion, during breaks in sedation for neurological examination

ADRs
- Total of 13 studies and 425 patients
- Hypotension: 6-46%
- Bradycardia: 5-41%
- No significant differences in adverse events between dexmedetomidine and propofol or midazolam

Tran A et al. Neurocrit Care. 2017
Question 2

Which of the following patients should avoid the use of ketamine

A. TBI patient with ICP: 25 on fentanyl 300mcg/hr and propofol a 80 mcg/kg/min
B. TBI patient with a known history of hydrocephalus and ICP 15
C. TBI patient in which an EGD will be performed
D. All of the above
# Summary of sedative effects on CNS

<table>
<thead>
<tr>
<th>Sedative</th>
<th>ICP</th>
<th>CPP</th>
<th>CBF</th>
<th>MAP</th>
<th>Seizure threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>Decreased or unchanged</td>
<td>Increased or unchanged</td>
<td>Decreased</td>
<td>Decreased</td>
<td>?</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Decreased or unchanged</td>
<td>Increased or unchanged</td>
<td>Increased or unchanged</td>
<td>Increased or unchanged</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Tran A et al. Neurocrit Care. 2017
Gillman LM et al. Neurocrit Care. 2014
Role Of Sedatives In Acute Agitation
Management of acute agitation in non-intubated patients

- Prevalence of acute agitated delirium = 25%

- Current problems with commonly utilized agents
  - Doses of haloperidol necessary to relieve agitation can be high
    - IV daily doses can range from 20 to 1540mg
    - Increases concerns for QTc prolongation, extrapyramidal symptoms, and NMS
    - Haloperidol failure rates range from 30-43%
  - Propofol and benzodiazepines utility is limited
    - Due to high risk of respiratory depression and possible intubation

Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients

Study design

- Nonrandomized controlled single center trial
- Nonintubated ICU patients with RASS 1-4, CAM-ICU + and ICDSC > 4

**Initial Titration (n=132)**
- Haloperidol 2.5-5mg q10-30min until RASS 0 to -2 or 30mg/day

**Responders (n=86, 65%)**
- Haloperidol infusion 0.5-1mg/hr titrated to RASS 0

**Nonresponders (n=46, 35%)**
- Dexmedetomidine 0.2-0.7 mcg/kg/hr titrated to RASS 0. After reaching goal RASS haloperidol infusion was tapered and DC

**Dexmedetomidine group**

- Mean RASS of 3.9
- Mean Dose of DEX: 0.47 (0.43-0.50) mcg/k/h
- More time at sedation goal (RASS 0 to -2)
  - (93 v 59%, p=0.0001)
- Lower rate of excessive sedation
  - (0 v 11.6%), p=0.01
- Less morphine administered
  - (0.1 v 0.6mg/kg/day p=0.0001)
- Decrease in ICU length of stay
  - (3.1 v 6.4 days) p=0.0001
- No difference in bradycardia + hypotension

# Ketamine: acute agitation

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Single center, prospective observational study (n=98)</td>
<td>Single center, retrospective, observational study (n=78)</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>Acutely agitated adult pts in the ED Baseline agitation score: 4.2-4.8 (highly aroused + violent)</td>
<td>Acutely agitated mental health pts transported by critical care retrieval team Retrieval duration range: 175-187 min</td>
</tr>
<tr>
<td><strong>Ketamine</strong></td>
<td>N=24 18 pts: 0.87 mg/kg IV 6 pts: 2.97 mg/kg IM</td>
<td>N=28 Ketamine monotherapy: 63% Ketamine + propofol (15%) or BDZ (19%) Antipsychotic combinations: 8%</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Midazolam (n=19) 3mg IV (12), 2.3mg IM (4) Lorazepam (n=33) 1.9mg (28), 2.4mg IM (5) Haloperidol (n=14) 5.7mg IM (14) Combo: (n=10) 5mg IM haloperidol + Lorazepam 2mg</td>
<td>N=50 Propofol monotherapy: 26% Combo: 26% propofol + BDZ Ketamine monotherapy: 19% Antipsychotic combinations: 16%</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Agitation score &lt; 2 2: mildly aroused and pacing, 1: settled and 0: asleep</td>
<td>Compared intubation rates pre- and post ketamine protocol</td>
</tr>
<tr>
<td><strong>Ketamine group results</strong></td>
<td>• More pts were no longer agitated at 5, 10, + 15 mins vs other medications (p = 0.001, p ≤ 0.001, p = 0.032) • No difference in time to control agitation: (K:6.5 v M:15 v L:17.7 v H:13.4 v Combo:23.3, p=0.1) • Median SBP changes from +5 to +17 mm Hg + HR changes from 0 to +8 beats per minute • 8.7% of ketamine pts were intubated</td>
<td>• Dose: 0.25 - 0.5 mg/kg IV slow push or infusion of 1-2mg/kg/hour titrated to effect • 36.00% of pts intubated before v 7.14% after ketamine protocol • OR: 0.14, 95% CI (0.02–0.71, P &lt; 0.01) • Receiving psychiatric services did not report any adverse findings related to ketamine</td>
</tr>
</tbody>
</table>
Potential Adjunctive Agents Utilized in Alcohol Withdrawal
Options for Benzodiazepine-Refractory Alcohol Withdrawal?

• Refractory alcohol withdrawal
  • Received > 40 mg diazepam or equivalent in one hour
  • Received > 200 mg of diazepam or 40 mg of lorazepam during the first 3h without achieving sedation goals
• Down regulation of GABAA receptors and increase in excitatory neurotransmitters
• Multimodal Approach
  • Identify benzodiazepine failure
  • Adjunctive agents
    • Propofol
    • Dexmedetomidine
    • Phenobarbital
    • Ketamine

## Dexmedetomidine and Ketamine for AWS

<table>
<thead>
<tr>
<th>Author (year) and study design</th>
<th>Patients</th>
<th>Prior BDZ requirements (diazepam eq)</th>
<th>Intervention dosing regimen and duration</th>
<th>Comparator regimen</th>
<th>Change in BDZ requirement (diazepam eq)</th>
<th>Significant findings</th>
</tr>
</thead>
</table>
| Wong et al (2015) Retrospective single center N=23 | ICU pts + 75% had DTs | 170mg | Ketamine  
Time to start: 33.6 h  
Median dose: 0.2mg/kg/h  
Duration: 56 h | N/A | Change in 12 h  
- Median: −40.0 (−106.7, +21.7)  
Change in 24 h  
- Median: −13.3 (−86.7, +50.0) | • ICU LOS: 6.3 d  
Median duration of MV: 2.5 (2.4)d |
Time to start: 24 h  
Median dose: 0.5 mcg/kg/h  
Duration: 36 h | Symptom-triggered diazepam protocol | Change at 24 h  
- DEX decreased 20 v 40 p=0.001 | • ICU LOS: 2.1 d  
Higher rates of bradycardia (31 v 6%) p=0.03 |
| Mueller et al (2014) prospective double blind RCT N=24 | ICU pts req > 16mg of lorazepam + CIWA > 15 | 82mg in lorazepam equivalent | Dexmedetomidine  
Time to start: 24.5 h  
HD: 1.4 mcg/kg/h  
LD: 0.4 mcg/kg/hr  
Duration: 61 h | Symptom-triggered CIWA protocol with lorazepam | Change at 24 h  
- Median: −56.4 (-94.5 to −16.8) in lorazepam equivalent | ICU LOS: 4.7 d  
No difference between HD + LD Dex in lorazepam requirements |
Conclusion

• Ketamine and dexmedetomidine are increasingly being utilized in critically ill patients due to their unique advantages over more traditional sedatives
  • These agents have proven to lower opioid + BDZ requirements with minimal adverse effects
  • Should be incorporated into a multimodal analgesic approach to treat pain in critically ill patients requiring mechanical ventilation
• Evidence continues to accumulate but more research is needed in the critically ill population for alcohol withdrawal and acute agitation