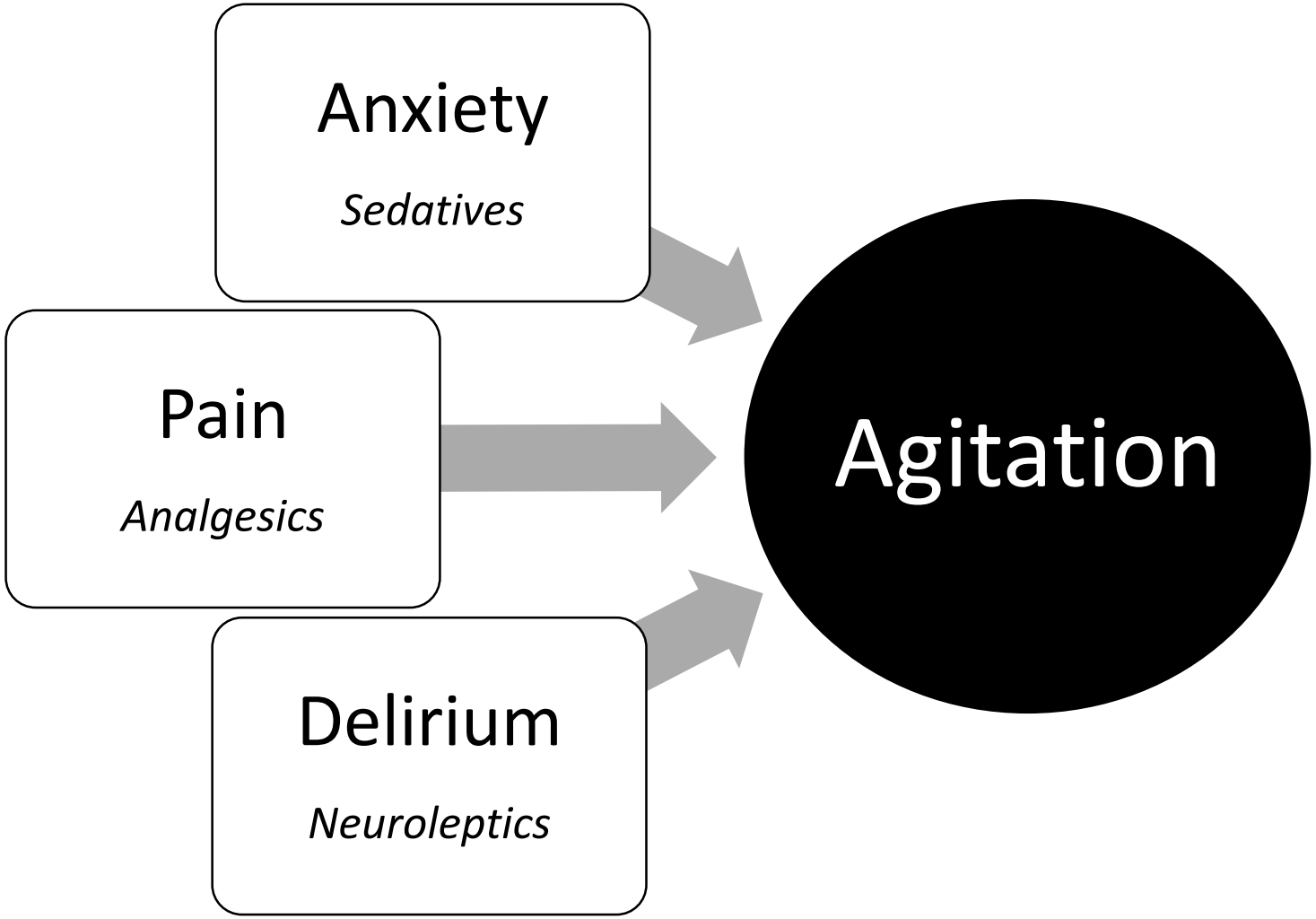
Sedation in the ICU

Andrew Straznitskas, PharmD, BCCCP

Clinical Pharmacist, Medical ICU

NYC H+H/Bellevue

Contributors to ICU Agitation



Methods to Identify Delirium

- Intensive Care Delirium Screening Checklist (ICDSC)
  - Identify presence or absence of delirium
  - Score ≥ 4: + delirium
- Identify patients who may benefit from antipsychotics
- Minimize unnecessary treatment

Intensive Care Delirium Screening Checklist

Intensive Care Delirium Screening Checklist (ICDSC)	
Step 1. Altered Level of Consciousness	A. Exaggerated response to normal stimulation (RASS +1 or greater) **(1 point)** B. Normal wakefulness (RASS 0) **(0 points)** C. Response to mild or moderate stimulation (RASS -1 to -2) **(1 point)** D. Patient recently received sedative/analgesia and (RASS -1 to -2 **(0 points)** E. Response only to intense and repeated stimulation (e.g. loud voice and pain) (RASS -3 to -4) ***Stop Assessment*** F. No response (RASS -5) ***Stop Assessment*** **Based on primary caregiver assessment**
Step 2. Inattention (1 point, if any of the following abnormalities present)	A. Difficulty in following commands OR B. Easily distracted by external stimuli OR C. Difficulty in shifting focus **Does the patient follow you with their eyes?**
Step 3. Disorientation (1 point for any one obvious abnormality)	A. Mistake in either time, place or person **Does the patient recognize ICU caregivers who have cared for him/her and not recognize those who have not? What kind of place are you in?**
Step 4. Hallucinations OR Delusions (1 point for either)	A. Equivocal evidence of hallucinations or a behavior due to hallucinations; hallucination: perception of something that is not there with NO stimulus OR B. Delusions or gross impairment of reality testing; delusion: false belief that is fixed/unchanged **Any hallucinations now or over the past 24 hours? Are you afraid of the people or things around you? (Fear that is inappropriate to the clinical situation)**
Step 5. Psychomotor Agitation OR Retardation (1 point for either)	A. Hyperactivity requiring the use of additional sedative drugs OR restraints in order to control potential danger (e.g. pulling IV lines out or hitting staff) OR B. Hypoactive or clinically noticeable psychomotor slowing or retardation **Based on documentation and observation over shift by primary caregiver**
Step 6. Inappropriate Speech OR Mood (1 point for either)	A. Inappropriate, disorganized or incoherent speech OR B. Inappropriate mood related to events or situation **Is the patient apathetic to current clinical situation (i.e. lack of emotion)? Any gross abnormalities in speech or mood?** **Is the patient inappropriately demanding?**
Step 7. Sleep/Wake Cycle Disturbances (1 point for any one)	A. Sleeping less than four hours at night OR B. Waking frequently at night (do not include wakefulness initiated by medical staff or loud environment) OR C. Sleep greater than or equal to 4 hours during the day **Based on primary caregiver assessment**
Step 8. Symptom Fluctuation (1 point, if present)	A. Fluctuation of any of the above items (i.e. steps 1-7) over 24 hours (e.g. from one shift to another) **Based on primary caregiver assessment**

Common Sedatives Used in the ICU

	Mechanism of Action	Dosing	Pharmacokinetics	Adverse Effects
Propofol	GABA+ NMDA-	Bolus: 0.25-1 mg/kg Relative Max: 100 mg Infusion: 5-50 mcg/kg/min Max: 75 mcg/kg/min	Onset: < 1 minute Duration: < 10 minutes *May be slightly increased with prolonged infusions* Metabolism: Hepatic Risk for Accumulation: Minimal	Hypotension – Bradycardia – Respiratory Suppression Hypertriglyceridemia – Propofol Infusion Syndrome (PRIS) Green Urine (*Benign*) – Caloric Contribution (1.1 kcal/mL) Soy/Egg Allergy
Dexmedetomidine	Central α2 Agonist	Loading Dose: ***Not Recommended*** 1 mcg/kg over 10 min Infusion: 0.2-1 mcg/kg/hour Relative Max: 1.5 mcg/kg/hour	Onset (*without Loading Dose*): 20-30 minutes Duration: 30-60 minutes Metabolism: Hepatic Risk for Accumulation: Minimal	Bradycardia – Hypotension – No Respiratory Suppression Withdrawal following Prolonged Use (Role for Clonidine) Rare: Fever, HPA Suppression, Electrolyte Abnormalities
Midazolam	GABA+	Bolus: 2-4 mg Infusion: 1-10 mg/hr Consider Bolus with Initiation and Dose Increases	Onset (*Bolus*): 2-5 minutes Duration (*single dose*): 1-2 hours *Can be significantly longer (days-weeks) with prolonged infusion* Metabolism: Hepatic w/ Active Renal Metabolite Risk for Accumulation: Very High	Hemodynamically Neutral – Respiratory Suppression Delirium – Prolonged Sedation Withdrawal following Prolonged Use
Lorazepam	GABA+	Bolus: 2-4 mg Infusion: 1-10 mg/hr Consider Bolus with Initiation and Dose Increases	Onset (*Bolus*): 5-10 minutes Duration (*single dose*): 2-4 hours *Can be significantly longer (days-weeks) with prolonged infusion* Metabolism: Glucuronidation Risk for Accumulation: High	Hemodynamically Neutral – Respiratory Suppression Delirium – Prolonged Sedation Withdrawal following Prolonged Use Propylene Glycol Toxicity
Ketamine	NMDA-	*Subanesthetic (Analgesic)* Bolus: 0.1-0.3 mg/kg Infusion: 0.1-0.3 mg/kg/hr *Dissociative Sedation* Bolus: 0.5-1 mg/kg Infusion: 0.5-1.5 mg/kg/hr	Onset (*Bolus*): < 1 minute Duration: 10-20 minutes *Recover from Sedation: 1-2 hours* Metabolism: Hepatic Risk for Accumulation: Minimal	Hypertension – Tachycardia (Contraindicated with Significant Cardiac Disease) No Direct Respiratory Suppression Emergence Reaction/Acute Psychosis – Nystagmus Secretions (Oral/Ocular)
Fentanyl	Opioid	Bolus: 50-100 mcg Infusion: 25-200 mcg/kg Consider Bolus with Initiation and Dose Increases	Onset (*Bolus*): < 1 minute Duration (*single dose*): 1-2 hours *Can be significantly longer (days) with prolonged infusion* Metabolism: Hepatic Risk for Accumulation: Moderate-High	Hemodynamically Neutral – Respiratory Suppression Withdrawal following Prolonged Use Constipation/Ileus Start Bowel Regimen (Miralax+Senna) with Infusion Deescalate as Appropriate

Propofol

- Pharmacologic Class: Sedative Hypnotic
- Mechanism of Action:
  - Stimulates GABA mediated sedation
  - NMDA receptor antagonism
- Dosing:
  - Bolus: 0.25-1 mg/kg
    - Relative Max: 100 mg
  - Infusion: 5-50 mcg/kg/min
    - Max: 75 mcg/kg/min

Propofol

- Pharmacokinetics
  - Onset: < 1 minute
  - Duration: < 10 minutes
    - *May be slightly increased with prolonged infusions*
  - Metabolism: Hepatic
  - Risk for Accumulation: Minimal

- Adverse Effects
  - **Hypotension**
  - Bradycardia
  - Respiratory Suppression
  - Hypertriglyceridemia
  - Propofol Infusion Syndrome (PRIS)
  - Green Urine (Benign)
  - Caloric Contribution (1.1 kcal/mL)
  - Soy/Egg Allergy

Dexmedetomidine

- Pharmacologic Class: Central α-adrenergic agonist
- Mechanism of Action:
  - α-adrenergic agonist in the locus ceruleus of the brain stem
  - Decreased central sympathetic output
  - Increased activity of inhibitory neurons.
  - α-adrenergic agonist in the dorsal horn of the spinal cord (analgesia)
- Dosing
  - Loading Dose:
    - Not recommended; can cause significant bradycardia
    - 1 mcg/kg over 10 min
  - Infusion: 0.2-1 mcg/kg/hour
    - Relative Max: 1.5 mcg/kg/hour

Dexmedetomidine

- Pharmacokinetics
  - Onset (*without Loading Dose*): 20-30 minutes
  - Duration: 30-60 minutes
  - Metabolism: Hepatic
  - Risk for Accumulation: Minimal
- Adverse Effects
  - **Bradycardia**
  - Hypotension
  - No Respiratory Suppression
  - Withdrawal following Prolonged Use
    - Role for Clonidine
  - Rare:
    - Fever
    - HPA Suppression
    - Electrolyte Abnormalities

Midazolam & Lorazepam

- Pharmacologic Class: Benzodiazepine
- Mechanism of Action:
  - Stimulates GABA mediated sedation
- Dosing:
  - Bolus: 2-4 mg
  - Infusion: 1-10 mg/hr
    - Consider Bolus with Initiation and Dose Increases
  - Lorazepam 1 mg ≈ Midazolam 2 mg
    - Dose conversion of minimal clinical significance with prolonged infusion

Midazolam & Lorazepam

- Pharmacokinetics
  - Onset (*Bolus*):
    - Midazolam: 2-5 minutes
    - Lorazepam: 5-10 minutes
  - Duration (*single dose*)*:*
    - Midazolam: 1-2 hours
    - Lorazepam: 2-4 hours
    - *Can be significantly longer (days-weeks) with prolonged infusion*
  - Metabolism:
    - Midazolam: Hepatic w/ Active Renal Metabolite
    - Lorazepam: Glucuronidation
  - Risk for Accumulation: Very High
- Adverse Effects
  - Hemodynamically Neutral
  - Respiratory Suppression
  - Delirium
  - Prolonged Sedation
  - Withdrawal following Prolonged Use
  - Propylene Glycol Toxicity (Lorazepam)

Ketamine

- Pharmacologic Class: NMDA Antagonist
- Mechanism of Action:
  - NMDA receptor antagonism
  - Disrupts connection within cortico-limbic system
  - “Dissociative” sedation
  - Modulates pain pathways, decreasing hyperalgesia, allodynia, and opioid tolerance
- Dosing
  - *Subanesthetic (Analgesic)*
    - Bolus: 0.1-0.3 mg/kg
    - Infusion: 0.1-0.3 mg/kg/hr
  - *Dissociative Sedation*
    - Bolus: 0.5-1 mg/kg
    - Infusion: 0.5-1.5 mg/kg/hr

Ketamine

- Pharmacokinetics
  - Onset (*Bolus*): < 1 minute
  - Duration: 10-20 minutes
    - *Recovery from Sedation: 1-2 hours*
  - Metabolism: Hepatic
  - Risk for Accumulation: Minimal

- Adverse Effects
  - Hypertension/Tachycardia
    - Due to Catechol Release
    - Contraindicated with Significant Cardiac Disease
  - No Direct Respiratory Suppression
    - Bronchodilatory
    - Positional Respiratory Inhibition
    - Potential Laryngospasm
  - Emergence Reaction/Acute Psychosis
  - Nystagmus
  - Secretions (Oral/Ocular)

Fentanyl

- Pharmacologic Class: Opioid Analgesic
- Mechanism of Action:
  - Binds to opioid receptors throughout CNS, increasing pain threshold and altering pain signal reception
  - Action in the CNS respiratory center directly suppresses respiratory drive
- Dosing
  - Bolus: 50-100 mcg
  - Infusion: 25-200 mcg/hr
    - Consider Bolus with Initiation and Dose Increases

Fentanyl

- Pharmacokinetics
  - Onset (*Bolus*): < 1 minute
  - Duration (*single dose*)*:* 1-2 hours
    - *Can be significantly longer (days) with prolonged infusion*
  - Metabolism: Hepatic
  - Risk for Accumulation: Moderate-High
- Adverse Effects
  - Hemodynamically Neutral
  - Respiratory Suppression
  - Withdrawal following Prolonged Use
  - Constipation/Ileus
    - Start Bowel Regimen (Miralax+Senna) with Infusion
    - Deescalate as Appropriate

Monitoring Sedation in ICU

- Richmond Agitation-Sedation Scale (RASS)
- Important to titrate sedatives to objective measure of sedation
  - Must include goal in sedative order

Richmond Agitation-Sedation Scale		
Score	**Term**	**Description**
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes or catheters; aggressive
+2	Agitate	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive; vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice ≥ 10 seconds
-2	Light Sedation	Briefly awakens with eye contact to voice (< 10 seconds)
-3	Moderate Sedation	Movement or eye opening to voice but no eye contact
-4	Deep Sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Sedation Goals

- Significant benefit with lighter levels of sedation
  - Shortened duration of mechanical ventilation
  - Decreased ICU and hospital length of stay
  - Lower risk of delirium/long term cognitive impairment
- Exceptions: Patients with requirement for deeper levels of sedation
  - ARDS
  - Patients requiring paralytics
  - Refractory status epilepticus
  - ICP Elevation

RASS Score

Richmond Agitation-Sedation Scale		
Score	**Term**	**Description**
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes or catheters; aggressive
+2	Agitate	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive, vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice ≥ 10 seconds
-2	Light Sedation	Briefly awakens with eye contact to voice (< 10 seconds)
-3	Moderate Sedation	Movement or eye opening to voice but no eye contact
-4	Deep Sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Goal

Strategies to Achieve Sedation Goals

- Analgosedation
- Prioritize Bolus Doses for Acute Symptoms
  - Benzodiazepines
  - Opioids
- Daily Sedation Interruptions

Analgosedation

- Providing adequate pain control can minimize sedation requirement
  - Avoid adverse effects of sedation
  - Minimize duration of sedation recovery
- Importance of pain assessment and treatment

Prioritize Bolus Dosing for Acute Symptoms

- Important strategy when using benzodiazepines and opioids
- Bolus more effective for control of acute agitation
  - Starting infusion of midazolam at 2 mg/hr it will take 1 hour to give 2 mg
- Uptitration of infusion rate without giving bolus can lead to excessive infusion rates and prolonged sedation

Daily Sedation Interruptions

- Holding sedation until patient awakens
  - Pair with Spontaneous Breathing Trial
- Restart sedation at 50% previous dose
  - Allow patient to demonstrate they need ongoing sedation
- Allows for neurological/pain assessment
- Minimize sedation accumulation
- Has been shown to decrease duration of mechanical ventilation and LOS

Questions