"Sedation, Agitation, and Delirium in the ICU"

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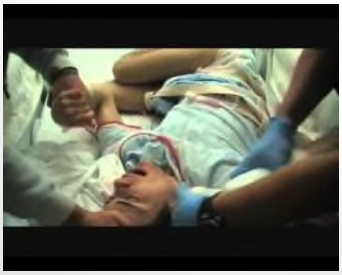
Objectives

- Understand the precipitating factors for agitation, anxiety, and delirium
- Discuss current guidelines and practices
- Review pain, sedation and delirium scales
- Gain a basic understanding of the neurotransmitters involved in agitation, anxiety, and delirium
- Understand the mechanism of action of benzodiazepines, propofol, and dexmedetomidine
- Understand typical and atypical anti-psychotics

The Patient



Definitions

- Sedation: Induction of a relaxed state
- Agitation: Excessive, purposeless cognitive and motor activity or restlessness, usually associated with a state of tension or anxiety
- Anxiety: An abnormal and overwhelming sense of apprehension and fear
- Delirium[1]: Disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period of time (hours to days) and fluctuates over time

Etiologies of Anxiety/Agitation

- Hypoxia
- Pain
- Withdrawal
- Sleep alteration
- Delirium
- Traumatic brain injury
- Medications
- Electrolyte abnormalities
- Endocrinopathies
- Hepatic encephalopathy
- Uremia
- Infection
- Mental health diagnosis

Delirium[1-3]

- Clinical manifestations:

Hypoactive	Hyperactive
Decreased responsiveness Withdrawal Apathy	Hallucinations Combativeness Restlessness

- Pathophysiology:
  - ? Cholinergic deficiency and dopamine excess
- Prevalence: Up to 80% of the ICU population
- Under-assessed and misdiagnosed as depression, dementia or part of critical illness
- Significance:
  - > LOS, increased mortality, and increased costs
  - Long-term cognitive decline after discharge

Delirium Risk Factors Mnemonic[1]

DELIRIUM (S)

- **D** Drugs, Drugs, Drugs
- **E** Eyes, ears (poor hearing, vision loss)
- **L** Low 02 states (MI, ARDS, PE, CHF, COPD)
- **I** Infection
- **R** Retention (of urine or stool), Restraints
- **I** Ictal
- **U** Underhydration/Undernutrition
- **M** Metabolic
- **(S)** Subdural, Sleep deprivation

Goals of Therapy

- Prevent harm to the patient and others
- Avoid toxicity
- Alleviate discomfort
- Improve oxygenation

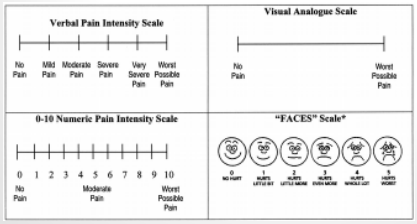
SCCM Guidelines[4]

- Published in 2002
- Recognizes patients exhibit agitated behavior due to inadequate pain management
- Algorithmic process for therapy
- Assessment with reliable and reproducible scales for pain, agitation and delirium
- Treat based on scores/patient report
- Does not advocate continuous infusions

SCCM Guidelines – 2012 Updates[5]

- Implementation of GRADE system
- Patient centered, NOT medication specifics
- Advocates:
  - Routine assessment
  - Awakening trials (sedation interruption)
  - Improving mobility
  - Pain management first
  - Lighter sedation preferred over deeper sedation
- Multidisciplinary approach encouraged

Pain Scales



CAM-ICU Delirium Scale

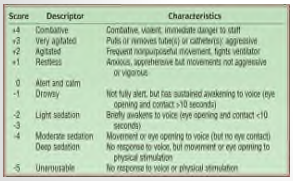
Table 7. The confusion assessment method for the diagnosis of delirium in the ICU (CAM-ICU) (182, 185)

Feature	Assessment Variables
1. Acute Onset of mental status changes or Fluctuating Course	Is there evidence of an acute change in mental status from the baseline? Did the (abnormal) behavior fluctuate during the past 24 hours, i.e., tend to come and go or increase and decrease in severity? Did the sedation scale (e.g., SAS or MASS) or coma scale (GCS) fluctuate in the past 24 hours?*
2. Inattention	Did the patient have difficulty focusing attention? Is there a reduced ability to maintain and shift attention? How does the patient perform on Screening Examination (ASE)? (i.e., Visual component ASE tests the patient's ability to pay attention via recall of 10 pictures; auditory component ASE tests attention via having patient squeeze hands or nod whenever the letter "A" is called in a random letter sequence)
3. Disorganized thinking	If the patient is already extubated from the ventilator, determine whether or not the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject. For those still on the ventilator, can the patient answer the following 4 questions correctly? 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Was the patient able to follow questions and commands throughout the assessment? 1. "Are you having any unclear thinking?" 2. "Hold up this many fingers" (examiner holds two fingers in front of patient) 3. "Now do the same thing with the other hand." (not repeating the number of fingers)
4. Altered level of consciousness (any level of consciousness other than alert (e.g., vigilant, lethargic, stupor, or coma)	Alert: normal, spontaneously fully aware of environment, interacts appropriately Vigilant: hyperalert Lethargic: drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subjects lapse back into the unresponsive state. Coma: unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer, so that the interview is impossible even with maximal prodding

Patients are diagnosed with delirium if they have both Features 1 and 2 and either Feature 3 or 4.

*SAS = Sedation-Analgesia Scale, MASS = Motor Activity Assessment Scale, GCS = Glasgow Coma Scale.

Sedation Scales



Score	Descriptor	Characteristics
+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact >10 seconds)
-2	Light sedation	Briefly awakens to voice (eye opening and contact <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

Score	Defined	Description
1	Dangerous agitation	Pulling at endotracheal tube, trying to strike at staff, thrashing side to side
2	Very agitated	Does not calm despite frequent verbal commands, biting ETT
3	Agitated	Anxious or mildly agitated, attempting to sit
4	Calm and cooperative	Calm, awakens easily, follows commands
5	Sedated	Difficult to arouse, awakens to verbal stimuli, follows simple commands
6	Very sedated	Arouse to physical stimuli, but does not communicate spontaneously
7	Unarousable	Minimal or no response to noxious stimuli

Richmond Analgesia Sedation Scale (RASS)

Riker Sedation and Analgesia Scale (SAS)

Robinson, BRH. et al JTrauma. 2008;65:517-526

- Pain, agitation, and delirium therapy algorithm
- Scales used:
  - Pain visual/objective assessment scale (VAS/OPAS)
  - RASS
  - CAM-ICU
- Analgesia vs. sedation
- Bolus dosing vs. continuous infusion
- Delirium managed primarily with antipsychotics
- Minimization of benzodiazepine therapy
- ↓ ventilator days, ↓hospital LOS

Daily Sedation Interruptions

- Kress, JP, Pohlman AS, et al. NEJM. 2000; 342:1471-1477:
  - Sedative and opioid stopped until patient restless
  - ↓ MV by 2.4 days, ICU LOS ↓ 3.5 days
  - Decreased diagnostic testing
  - No difference in complications
- Mehta, S, Burry, L, et al. JAMA. 2012:1-8.
  - Interruptions in patients with light sedation
  - No change in MV, ICU LOS, or delirium
  - Higher nursing workload

Current Practice Recommendations

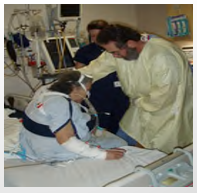
- Pain assessment and treatment
- Agitation assessment and treatment
- Delirium assessment and treatment
- Withdrawal prevention and treatment
- Sleep-wake cycle (circadian rhythm) re-institution
- Daily sedation interruptions
- Targeting lighter sedation

Therapeutic manipulations

- Environmental
- Physical
- Pharmacologic

Non-pharmacological

- Environmental:
  - Lights ON
  - Television/radio ON
  - Stimulation
  - Return to normal ADL/circadian rhythm
- Physical
  - Early mobility
  - Range of motion exercises
  - Decrease use of restraints



Pharmacological

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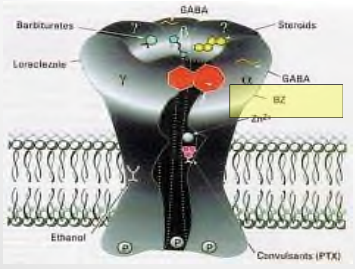
Neurotransmitters

Neurotransmitter	Affects	Associated Diseases
Norepinephrine (NE)	Arousal, wakefulness, learning, memory, and mood	
Serotonin (5-HT)	Sleep, dreaming, mood, eating, and pain Decreased in aggressive behavior	Depression (↓)
Dopamine (DA)	Movement, motivation and reward, and pleasure	Schizophrenia (↑) Parkinson's (↓)
Acetylcholine (Ach)	Arousal, attention, memory, motivation, and muscle action	Alzheimer's (↓)
GABA	Primary inhibitory neurotransmitter, sedation	Severe anxiety (↓)

GABA Receptor



Picking the Right Medication

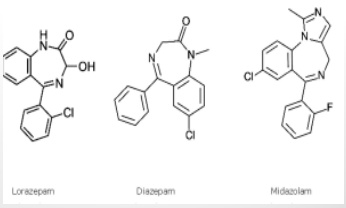
- Assessment
  - Pain
  - Agitation
  - Delirium
  - Withdrawal
- Tolerance
- Toxicity
- Drug interactions
- Onset and duration
- Reversibility
- Route
  - PO, IM, IV

Pharmacologic Modalities

- Benzodiazepines
- Propofol (Diprivan)
- Dexmedetomidine (Precedex)
- Antipsychotics
  - Typical (Haloperidol)
  - Atypical (Risperdal, Seroquel, Zyprexa, Geodon)

Benzodiazepines (BZD)

- Pharmacology
  - Binds to BZD site on GABA to enhance GABA mediated inhibition and decreased neuronal excitability
- Effects
  - Anxiolysis
  - Sedation
  - Amnesia
  - Skeletal muscle relaxation



Benzodiazepines (BZD)

Drug	Usual Dose	Onset	Duration	Metabolism Excretion	Side effects
Midazolam	**PRN**: 1-5 mg IV q1-4hrs **Drip**: 1-10 mg/hr	2-5 min	2-6 hrs	**M:** Hepatic, active metabolite **E:** Renal	Accumulation of metabolite, unpredictable clearance after long infusions
Lorazepam	**PRN**: 1-5 mg IV q1-4hrs **Drip**: 1-10 mg/hr	5-20 min (avg. 10-15 min)	8-15 hrs	**M**: Hepatic, NO active metabolite **E**: Renal	Propylene glycol toxicity with prolonged infusion → ATN, acidosis
Diazepam	**PRN**: 2-10 mg IV q4-6hrs *Rectal available	Instant	T½ = 20-50 hrs, Metabolite = 50-100 hrs	**M:** Hepatic, active metabolites **E**: Renal	Propylene glycol toxicity with IV long-term use

Why BZD may not be ideal…

- Deeper sedation is achieved
  - Desirable in some circumstances (paralytics)
- Increases risk for delirium
- Increased ventilator days when compared to other sedatives
- Active metabolites and long duration of therapy

Propofol

- Uses:
  - Sedation
  - Anesthesia
  - Refractory status epilepticus
  - Elevated ICP
- Pharmacology
  - True mechanism is poorly understood
  - Differs from BZD and barbiturates
  - GABA agonist, decreased glutamate activity, NMDA antagonism

Propofol

- Dose:
  - Loading: 0.25-1 mg/kg
  - Infusion: 1-80 mcg/kg/min
- Onset: ~ 30 seconds
- T½: 1-3 minutes
- Lipid 10% emulsion carrier
  - 1.1 kcal/ml
- Metabolism: Hepatic
- Excretion: Urine and feces

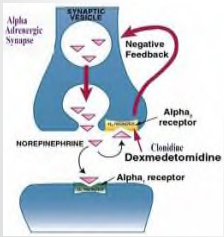
Propofol Adverse Effects

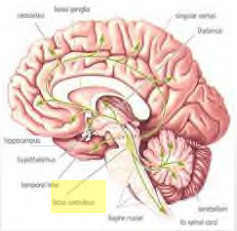
- Hypotension
- Bradycardia
- Hyperlipidemia
  - Monitor Triglycerides
- Propofol Related Infusion Syndrome
  - Elevated CPK
  - Cardiovascular collapse
  - Intractable metabolic acidosis
- Avoid if egg allergy

Dexmedetomidine

- Approved in 1999 for 24 hr infusion
- Pharmacology:
  - Central acting selective α_2-receptor agonist to reduce norepinephrine output
  - Sedative, anxiolytic, sympatholytic, and analgesic properties
  - Does not suppress respiratory drive
- Induces a state of arousable sedation
  - Deep sedation and amnesia not achieved
  - Not appropriate if on paralytics

Dexmedetomidine





Dexmedetomidine

- Analgesic Properties
  - α2 proposed to have nociceptive properties
  - Mediated by both spinal and supraspinal mechanisms
  - Opioid sparing effect
  - Does not meet total analgesia needs
- Less Delirium
  - α2a selectivity = minimal disruption of neurotransmitter pathways
  - Noradrenergic changes may decrease the development
  - Decreases opioid use
  - Light sedation promotes sleep-wake cycle

Pharmacokinetics

- Onset: Up to 30 minutes
- T½: ~ 1.5-2.5 hours
- Duration: ~ 4 hours

- Metabolism: Glucuronidation and hepatic enzymatic alteration to inactive metabolites
- Elimination: Renal
- Adverse effects:
  - Hypotension or reflex hypertension
  - Bradycardia (Avoid bolus dose)
  - Atrial fibrillation

Sedated or Delirious Yet? Comparing Agents…

- Dex vs. Midazolam or Propofol for Sedation During Prolonged MV
  - Dex had higher RASS scores (lighter sedation)
  - No change in LOS, ICU days, or mortality
  - Median duration of MV:
    - Dex 123 hrs vs. midazolam 164 hrs; P = .03
    - Dex 97 hrs vs. propofol 118 hours; not significant
- Cost of a drip:

Lorazepam	Midazolam	Propofol	Dexmedetomidine
$5	$9	$8	$68

Jakob SM, Ruokonen E, et al. JAMA. 2012; 307(11): 1151–1160.

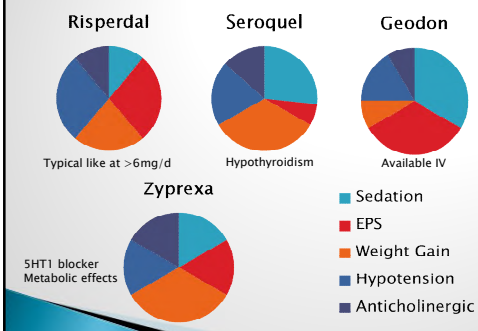
Anti-psychotics

- Uses:
  - Mental health (e.g. schizophrenia)
  - Acute aggression
  - Delirium
- Mechanism of Action:
  - Typical: Dopamine (D2) blocker
  - Atypical:D2 blocker, 5HT2 blocker
    - H1, muscarinic (Ach), α1 blocker
- Adverse effects:
  - Typical: Extrapyridamal disorders (EPS), hypotension, sedation, QT prolongation
  - Atypical: EPS, hypotension, sedation, anti-cholinergic s/e, weight gain, metabolic effects, QT prolongation

Commonly Used Anti-psychotics

- Typical
  - Haloperidol (Haldol)
    - PO, IV, IM, Long-acting IV
- Atypicals
  - Risperidone (Risperdal)
    - Long-acting IV
  - Quetiapine (Seroquel)
  - Olanzapine (Zyprexa)
  - Ziprasidone (Geodon)
    - Acute IV

Atypical AP Comparisons[12]



Take Home Points

- Delirium causes significant morbidity and mortality
- Lighter sedation should be targeted using validated scales
- Pain should be assessed and treated
- Newer pharmacological agents are alternatives to BZD for sedation
- Anti-psychotics may be used to treat delirium and reduce sedative use
  - Anti-psychotics are dirty drugs, monitor side effects

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Questions?