PainWeek®

# Sedated and Elated: Treatment Tactics for Refractory Agitation

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# Disclosure

- Dr. Krichbaum has nothing to disclose
- Dr. Miransky has nothing to disclose

# Learning Objectives

- Define diagnostic and monitoring tools for agitation, delirium, and sedation
- Propose rational pharmacologic management for a patient with refractory agitation
- Describe the process of monitoring, weaning, and deprescribing of medications in the refractory agitation patient

# Pretest Question #1

- Which of the following is a validated tool for assessing agitation in an ICU patient?
  A. CPOT
  B. CAM-ICU
  C. PAIN-AD
  D. Palliative performance score

# Pretest Question #2

- GM is 28 YO male intubated in ICU after being involved in motor vehicle accident. He is receiving propofol 50mcg/kg/min and fentanyl 200mcg/hour. He is currently breathing over the ventilator, moving in bed, and has a positive CAM-ICU score. Patient is believed to be presenting with signs of agitated delirium during sedation vacations. If the patient's agitation is managed, he is a candidate for extubation. What would be an appropriate order of medication escalation to treat this patient's refractory agitation?
  A. haloperidol, valproic acid, lithium
  B. dexmedetomidine, midazolam, haloperidol
  C. dexmedetomidine, midazolam, ketamine
  D. phenobarbital, lorazepam, morphine

# Pretest Question #3

- Which of the following medications require serum drug level monitoring?
  A. Risperidone
  B. Dexmedetomidine
  C. Midazolam
  D. Valproic acid

# Background

- Agitation and anxiety occur frequently in critically ill patients and are associated with adverse clinical outcomes including:
  - Longer ICU stay
  - Longer duration of mechanical ventilation
  - Higher rate of self-extubation
  - More frequent infections and surgical interventions
- Behavioral manifestations are similar to pain and delirium and are distressing for patients, families, and healthcare providers




Burk, R. S., Grap, M. J., Munro, C. L., Schubert, C. M., & Sessler, C. N. (2014). Predictors of agitation in critically ill adults. *Am. J. Crit Care*, *23*(5), 414-423
Aubanel, S., et al. (2020). Therapeutic options for agitation in the intensive care unit. *Anaesth. Crit. Care Pain Med.* 639-646

# Epidemiology

- Agitation occurs in 42-71% of critically ill patients
- Terminal agitation is estimated at 59% for hospice patients
- Risk Factors
  - Pain
  - Delirium
  - Mechanical ventilation
  - Sepsis
  - Use of psychotropic drugs
  - Chronic alcohol intoxication

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Aubanel, S., et al. (2020). Therapeutic options for agitation in the intensive care unit. *Anaesth. Crit. Care Pain Med.* 639-646
Hosie, A., Agar, M., Lobb, E., Davidson, P.M and Phillips, J. (2017). Improving delirium recognition and assessment for people receiving inpatient palliative care: a mixed methods meta-synthesis. *Int. J. Nurs. Stud.* 75(1), PP. 123-127

Pain, Sedation, Agitation/Delirium

# Diagnostic and Monitoring Tools

# Pain: ICU

- Behavioral Pain Scale (BPS)
- Critical-Care Pain Observation Tool (CPOT)
- Valid and reliable behavioral pain scales
- Medical, postoperative, or trauma (except for brain injury) adult ICU patients
  - Unable to self-report
  - Intact motor function
  - Observable behaviors
- Extubated patients
  - Behavioral Pain Scale-Nonintubated (BPS-NI) or CPOT

## Critical Care Pain Observation Tool

| Indicator | Description | Score | |
|---|---|---|---|
| Facial expression | No muscular tension observed | Relaxed, neutral | 0 |
| | Presence of frowning, brow lowering, orbit tightening, and levator contraction | Tense | 1 |
| | All of the above facial movements plus eyelid tightly closed | Grimacing | 2 |
| Body movements | Does not move at all (does not necessarily mean absence of pain) | Absence of movements | 0 |
| | Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements | Protection | 1 |
| | Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed | Restlessness | 2 |
| Muscle tension Evaluation by passive flexion and extension of upper extremities | No resistance to passive movements | Relaxed | 0 |
| | Resistance to passive movements | Tense, rigid | 1 |
| | Strong resistance to passive movements, inability to complete them | Very tense or rigid | 2 |
| Compliance with the ventilator (intubated patients) | Alarms not activated, easy ventilation | Tolerating ventilator or movement | 0 |
| | Alarms stop spontaneously | Coughing but tolerating | 1 |
| | Asynchrony: blocking ventilation, alarms frequently activated | Fighting ventilator | 2 |
| OR | | | |
| Vocalization (extubated patients) | Talking in normal tone or no sound | Talking in normal tone or no sound | 0 |
| | Sighing, moaning | Sighing, moaning | 1 |
| | Crying out, sobbing | Crying out, sobbing | 2 |



Barr, J., et al. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit. Care Med.*, *41*(1), 263-306.

# Sedation: ICU

- Richmond Agitation and Sedation Scale (RASS)
- Riker Sedation-Agitation Scale (SAS)
- Valid and reliable

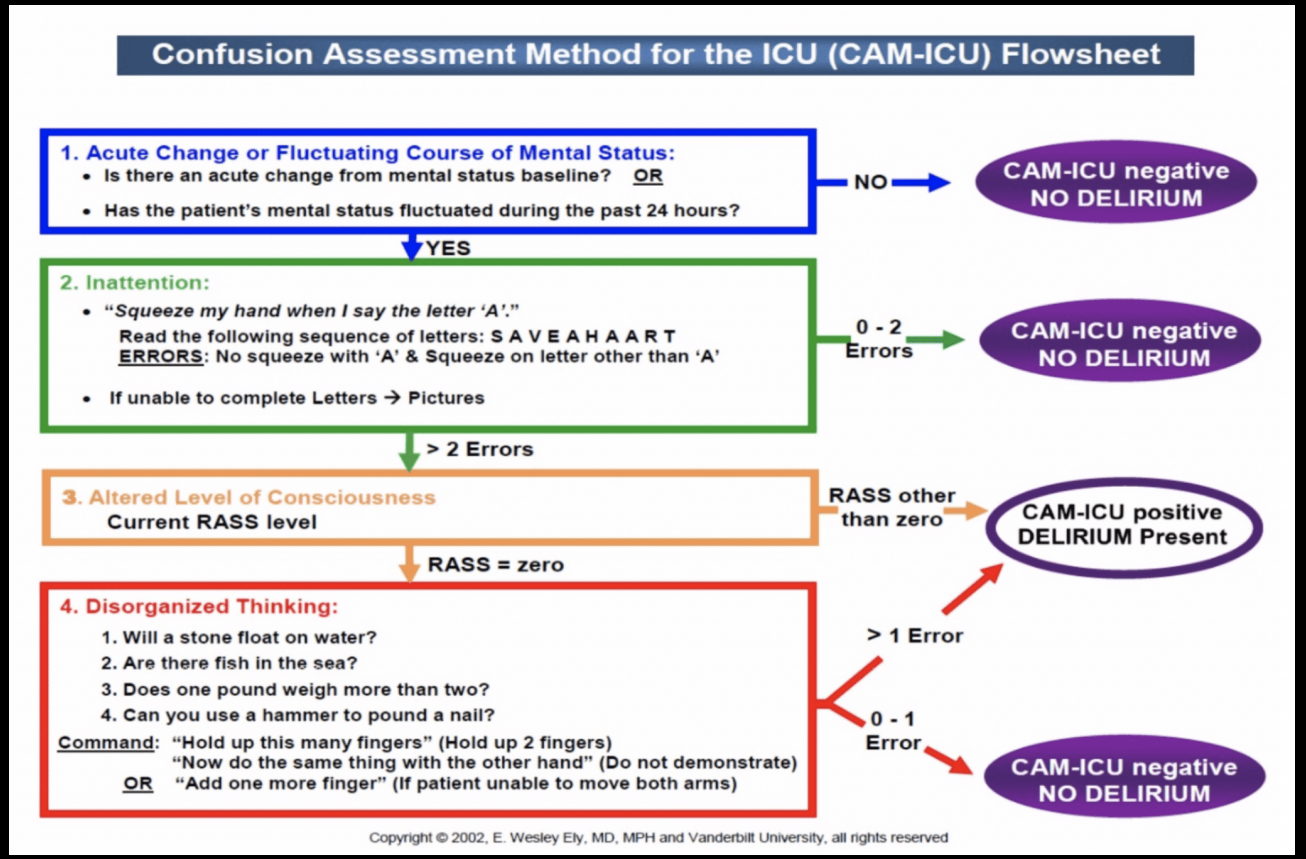
| RASS (Richmond Agitation Sedation Scale) | | |
|---|---|---|
| 4 | Combative | Overtly combative, violent, immediate danger to staff |
| 3 | Very agitated | Pulls or removes tubes or catheters; aggressive |
| 2 | Agitated | Frequent non-purposeful mvmt, fights ventilator |
| 1 | Restless | Anxious but movements not aggressive or vigorous |
| 0 | Alert and calm | |
| -1 | Drowsy | Sustained awakening to voice (≥10sec) |
| -2 | Light sedation | Briefly awakens with eye contact to voice (<10 sec) |
| -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 | Cannot be aroused | No response to voice or physical stimulation |

| Score | Category | Description |
|---|---|---|
| 7 | Dangerous agitation | Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side |
| 6 | Very agitated | Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting endotracheal tube |
| 5 | Agitated | Anxious or mildly agitated, attempting to sit up, calms down on verbal instructions |
| 4 | Calm, cooperative | Calm, easily arousable, follows commands |
| 3 | Sedated | Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands |
| 2 | Very sedated | Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously |
| 1 | Unarousable | Minimal or no response to noxious stimuli, does not communicate or follow commands |

Barr, J., et al. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit. Care Med.*, *41*(1), 263-306.
Devlin, J. W., et al. (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit. Care Med. 46*(9), e825-e873.

# Delirium: ICU

- Confusion Assessment Method for ICU (CAM-ICU)
- Intensive Care Delirium Screening Checklist (ICDSC)
- Valid and reliable






Barr, J., et al. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit. Care Med. 41*(1), 263-306.

# Pain Assessment in Advanced Dementia (PAIN-AD)

- 5 indicators rated 0,1,2 similar to CPOT
- Reliable pain assessment for patients with advanced dementia
- May also be helpful in assessing pain in any patient with cognitive impairment

# Pharmacologic Management

# Guideline Recommendations for Pain

- Multimodal analgesia approach to pain management in perioperative setting to reduce use of opioids
  - Names acetaminophen, ketamine, lidocaine, neuropathic agents, and nonsteroidal anti-inflammatory drugs (NSAIDs) as having been evaluated in critically ill adults with the aim of sparing opioid use and improving analgesic effectiveness
- We are in support of the *judicious* use of opioids as part of a multi-modal analgesic regimen




Devlin, J. W., et al. (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Critical care medicine*, *46*(9), e825-e873.

# Guideline Recommendations for Sedation/Agitation

- Suggest using light sedation (vs deep sedation) in critically ill, mechanically ventilated adults
  - Nonbenzodiazepine sedatives (propofol or dexmedetomidine) are preferable to benzodiazepine sedatives in critically ill, mechanically ventilated adults due to improved short-term outcomes such as length of stay, duration of mechanical ventilation, and delirium
- Suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults
- Duration of sedation
  - If sedated for more than a few days, then prefer benzodiazepines as part of plan because propofol is not recommended for extended administration
  - Benzodiazepines have anxiolytic, anticonvulsant, and amnestic properties




Devlin, J. W., et al. (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit. Care Med. 46*(9), e825-e873.

# Guideline Recommendation for Delirium

- Suggest not using antipsychotics, dexmedetomidine, statins, or ketamine to prevent delirium in all critically ill adults (conditional recommendation, very low to low quality of evidence).
- Suggest not routinely using antipsychotics or statins to treat delirium (conditional recommendation, low quality of evidence)

- We prefer using antipsychotics at lowest effective doses for management of delirium




Devlin, J. W., et al. (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit. Care Med. 46*(9), e825-e873.

# Propofol

- MOA: Lipophilic, anesthetic, presumed to work through $GABA_A$ receptor agonism
- Usual maintenance dose: 5 to 50 mcg/kg/minute
- Side Effects: hypotension, burning/pain at injection site, involuntary body movements, apnea, hypertriglyceridemia, respiratory acidosis during weaning, propofol-related infusion syndromes
- Has amnestic properties



Propofol. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021.
Sahinovic, M. M., Struys, M. M., & Absalom, A. R. (2018). Clinical pharmacokinetics and pharmacodynamics of propofol. *Clin Pharmacokinet*, *57*(12), 1539-1558

# Dexmedetomidine

- MOA: Selective alpha$_2$-adrenergic agonist with anesthetic and sedative properties
- Dosing: IV continuous infusion: 0.2 to 1.5 mcg/kg/hour
- Side effects: bradycardia, hypotension, delirium, hypertension with loading dose, loss of airway reflexes
- Should not be used if deep sedation is required
- Shorter time on mechanical ventilation and decreased incidence of delirium vs benzodiazepines
  - Possible decreased incidence of delirium vs propofol
- Does not provide adequate and reliable amnesia (benzodiazepines or propofol preferred)



Devlin, J. W., et al. (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit. Care Med. 46*(9), e825-e873.
Barr, J., et al. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit. Care Med. 41*(1), 263-306.
Dexmedetomidine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021

# Benzodiazepines

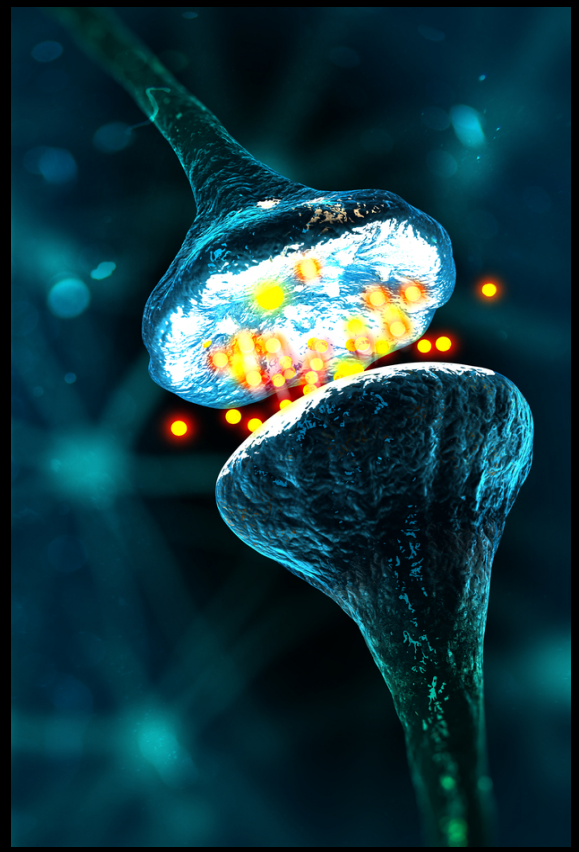
- MOA: Binds to benzodiazepine receptor on $GABA_A$ receptor to increase frequency of channel opening
- IV formulations:
  - Midazolam
    - Onset: 1-5 minutes
    - $T_{1/2}$: ~3 hours
  - Lorazepam
    - Onset: 15-20 minutes
    - $T_{1/2}$: ~14 hours
    - Long term/high-dose continuous IV can accumulate propylene glycol causing toxicity
  - Diazepam
    - Onset: 1 minute
    - $T_{1/2}$: 33-45 hours (also has active metabolites)

Midazolam. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Lorazepam. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Diazepam. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021

# Refractory Agitation

# Neurotransmitters

- Excitatory
  - –Glutamate
  - –Serotonin
  - –Norepinephrine
  - –Epinephrine
  - –Dopamine
  - –Histamine
  - –Acetylcholine
  - –Orexin A and B



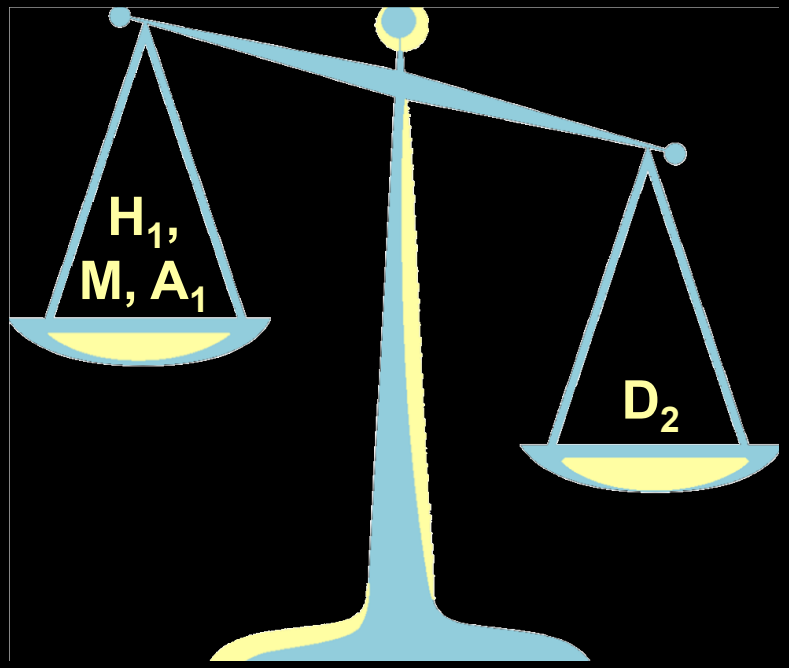
- Inhibitory
  - –GABA
  - –Glycine

- Neuronal Excitability
  - –Sodium channels
  - –Potassium channels
  - –Calcium channels

# Antipsychotics – 1st Generation/Typicals

- Dopamine-2 receptor antagonists
- Antagonize alpha-1, histamine-1, and muscarinic receptors

| Receptor Potency | Chlorpromazine | Haloperidol |
|---|---|---|
| Dopamine-2 | Low | High |
| Histamine-1 | High | Low |
| Muscarinic | High | Low |
| $Alpha_1$ | High | Low |
| Equivalent Doses | 100mg | 2mg |






Chlorpromazine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Haloperidol. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021

# FGAs/Typicals – Side effects

- Low dopamine potency results in more:
  - Sedation
  - Anticholinergic effects
  - Orthostasis
- High dopamine potency results in more:
  - Extra Pyramidal Symptoms (EPS)
- Seizures: phenothiazines, haloperidol
- Hyperprolactinemia
- Blood dyscrasias
- QTc prolongation
- Boxed Warnings:
  - Elderly pts w/dementia related psychosis treated w/antipsychotics are at increased risk of death
  - Additional boxed warnings - drug specific



Chlorpromazine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Haloperidol. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021

# Haloperidol

- Dose: 2-10mg IM/IV
  - Dose-dependent Qt prolongation with IV doses >2mg
  - Doses > 20mg/day have **not** been shown to be superior to lower doses
- Contraindications – Parkinson's disease, dementia w/ Lewy bodies
- $T_{1/2}$:
  - IM: 20 hours
  - IV: 14-26 hours
  - PO: 14-37 hours



Haloperidol. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021

# Chlorpromazine

- Dose: 25 to 50 mg single dose as a slow IV infusion (maximum rate: 1 mg/minute)
- Contraindications – hypersensitivity to phenothiazines
- $T_{1/2}$: ~30 hours



Chlorpromazine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021

# Antipsychotics – 2nd Generation/Atypicals

| Pines | Dones | 2 Pips | And a rip |
|---|---|---|---|
| • Clozapine<br>• Olanzapine<br>• Quetiapine<br>• Asenapine | • Risperidone<br>• Paliperidone<br>• Ziprasidone<br>• Lurasidone<br>• Iloperidone | • Aripiprazole<br>• Brexpiprazole | • Cariprazine |



Stahl, S. M. (2013). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (4th ed.). Cambridge University Press.

# SGAs/Atypicals – Side effects

| Pines | Dones | 2 Pips | And a rip |
|---|---|---|---|
| • Metabolic<br>• Sedation<br>• Anticholinergic | • EPS<br>• Hyperprolactinemia<br>• Qt Prolongation | • Akathisia<br>• Headache<br>• Insomnia | • Akathisia<br>• Headache<br>• Insomnia |

Boxed warning (ALL): elderly pts w/dementia related psychosis treated w/antipsychotics are at increased risk of death
Additional Boxed warnings - drug specific



Stahl, S. M. (2013). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (4th ed.). Cambridge University Press.

# Parenteral Antipsychotics for unreliable GI tract

- Chlorpromazine IM/IV(off-label)
- Haloperidol lactate IM/IV(off-label)
  - Onset of action: 3-20 minutes
  - $T_{1/2}$: 14-26 hours
- Ziprasidone IM/IV(off-label)
  - Onset of action: 15-30 minutes
  - $T_{1/2}$: 2-5 hours
- Olanzapine IM/IV(off-label)
  - Onset of action: 5-15 minutes
  - $T_{1/2}$: 21 to 54 hours



Girard, T. D., et al. (2018). Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med*, *379*(26), 2506-2516.
Khorassani, F., & Saad, M. (2019). Intravenous olanzapine for the management of agitation: review of the literature. *Ann Pharmacother*, *53*(8), 853-859.

# Olanzapine

- MOA: Potent $5HT_{2A}$, $5HT_{2C}$, $D_{1-4}$, $H_1$, $A_1$ antagonist
  - Moderate antagonism $5HT_3$ and $M_{1-5}$
- Initial dose (agitation): 1.25-10mg PO/IM/IV Q4H
- Max dose: 30mg/day
- Weight gain, dyslipidemia, insulin resistance, sedation, and anticholinergic effects
  - Reports of diabetic ketoacidosis
  - EPS is dose dependent
- Severe Drug-Drug Interaction: parenteral olanzapine and parenteral benzodiazepines
- $T_{1/2}$: 21-54 hours



Olanzapine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Stahl, S. M. (2013). Antipsychotic agents. In: *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (4th ed.). Cambridge University Press.

# Quetiapine

- MOA: $D_2$ and $5HT_{2A}$ antagonist
  - Very potent $H_1$ antagonist, moderate $M_1$ and $M_3$ antagonist
  - Active metabolite (norquetiapine) is a NE reuptake inhibitor and $5HT_{2C}$ antagonist
- Initial dose (agitation): 25mg IR
- Max dose: 800mg/day
- Drug of choice for psychosis in Parkinson's
- ADRs: Weight gain, dyslipidemia, insulin resistance, sedation, anticholinergic effects, orthostasis
- $T_{1/2}$: ~6 hours (parent), 12 hours (norquetiapine)




Quetiapine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Stahl, S. M. (2013). Antipsychotic agents. In: *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (4th ed.). Cambridge University Press.

# Risperidone

- MOA: Potent $D_{2-4}$ and $5HT_{2A}$ antagonist
  - Potent $A_1$ and $A_{2C}$ antagonist
  - Modest $H_1$ antagonist, No muscarinic activity
- Dosage forms: tablet, oral solution, ODT
- Initial dose (agitation): 0.25mg-2mg
- Max oral dose 8mg/day
- Atypical, but at higher doses acts more like a typical
- ADRs:
  - EPS, hyperprolactinemia with doses >6mg/d
  - Cerebrovascular incidents (TIA, stroke) esp. in the elderly
  - Orthostasis and reflex tachycardia
  - Usually little QT prolongation, except in overdose situations
- Metabolized by CYP2D6 to 9-hydroxyrisperidone (active)
- $T_{1/2}$: ~20 hours



Risperidone. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Stahl, S. M. (2013). Antipsychotic agents. In: *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (4th ed.). Cambridge University Press.

# Ziprasidone

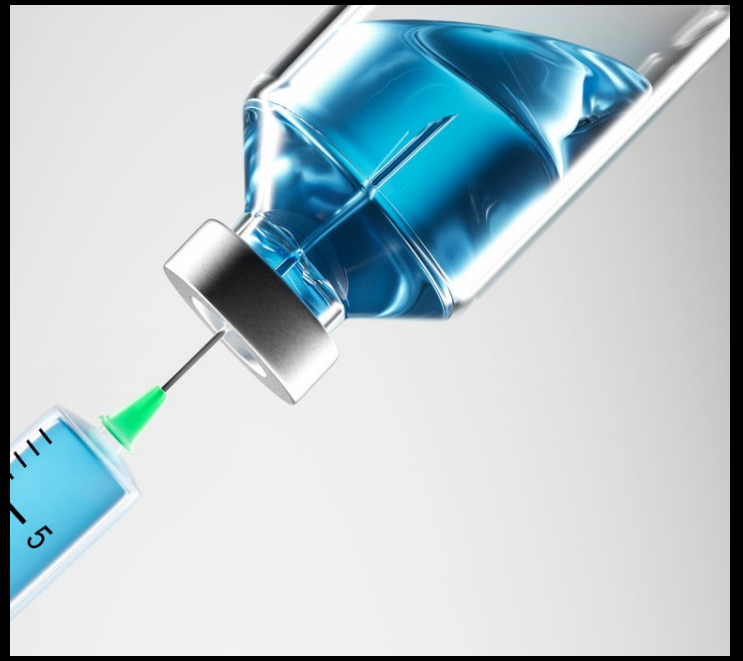
- MOA: Potent $D_{2-3}$ and $5HT_{2A}$, $5HT_{1D}$ antagonist, Partial agonist at $5HT_{1A}$,
  - Modest antagonism $5HT_{2C}$ and $5HT_{1D}$
  - Minimal histamine or alpha activity, No muscarinic activity
- Dosage forms: Capsule, IM (cannot be used via enteral tubes)
- Dose (agitation):
  - 10mg IM Q2 hours OR 20mg q 4 hours
    - Max dose: 40mg/day
  - 20-40mg PO Q12H
    - Oral should be administered twice daily with food ($\geq$500 cal)
    - Max dose: 80mg/day
- ADRs: sedation, EPS, dizziness
  - Rare but serious ADRs: Dose dependent QTc prolongation, Drug reaction w/ Eosinophilia and Systemic Symptoms (DRESS)
- $T_{1/2}$: 7 hours (PO), 2-5 hours (IM)



Ziprasidone. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Stahl, S. M. (2013). Antipsychotic agents. In: *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (4th ed.). Cambridge University Press.

# Ketamine

- MOA: NMDA receptor antagonist
- Dosing (Mechanically ventilated ICU analgesia/sedation/agitation):
  - 0.1-0.5 mg/kg IVP x 1 followed by 0.2-0.5 mg/kg/hour continuous infusion
- ADRs: Psychomimetic effects, confusion, delirium, hallucinations, blurred vision, blood pressure and heart rate increase
- Relative Contraindications: Unstable cardiovascular disease, such as angina, heart failure or malignant hypertension, history of cerebrovascular disease, increased ocular pressure, known or suspected schizophrenia, porphyria
- $T_{1/2}$: 2.5 hours

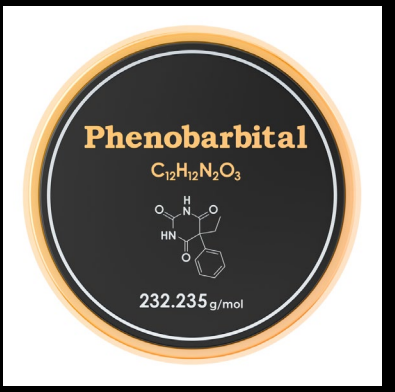




Ketamine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021

# Phenobarbital

- MOA: Binds to $GABA_A$ subunit increasing length of time chloride ion channels stay open and blocks AMPA/kainite glutamate receptors
  - Depresses the sensory cortex and motor activity, alters cerebellar function, produces drowsiness, sedation, and hypnosis
  - High doses directly open channels
    - Benzodiazepines increase frequency but cannot activate in the absence of GABA
- Dosing (sedation): 30 to 120 mg IV or IM/day in 2 to 3 divided doses
- Max: 400 mg/day
- ADRs: drowsiness, confusion, bradycardia, hypotension, dose-dependent reduction in REM sleep, Stevens-Johnson syndrome, hematologic effects
- Strong CYP3A4 inducer, metabolized by CYP2C9
- $T_{1/2}$: 53-118 hours






Phenobarbital. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021
Löscher, W., & Rogawski, M. A. (2012). How theories evolved concerning the mechanism of action of barbiturates. *Epilepsia*, *53*, 12-25.

# General Monitoring

- Vital signs
- Weight
- FBG
- $O_2$ saturation (ketamine)
- Complete Blood Counts
  - With differential (phenobarbital)
- Comprehensive Metabolic Panel
- Pregnancy
- Lipid panel
- ECG and serum $K^+$
- Abnormal involuntary movement or agitation
- Signs of hyperprolactinemia
- Signs and symptoms of Neuroleptic Malignant Syndrome
  - Mental status changes, fever, muscle rigidity, and/or autonomic instability



Ketamine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021; Phenobarbital. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021; Haloperidol. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021; Olanzapine. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021; Risperidone. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Accessed July 13, 2021

# Valproic Acid (VPA)

- MOA:
  - Inhibits glutamate binding to AMPA
  - Increases GABA concentration in the plasma and CNS
    - Increase GABA synthesis by enhancing glutamic acid decarboxylase (converts glutamate to GABA)
    - Inhibits GABA transaminase
    - Enhances the action of GABA at the GABAA receptor
  - Dopamine
    - Increase DA in prefrontal and hippocampus
    - Decrease DA in striatum
  - Normalizes sodium and calcium channels
  - Anti-inflammatory and Anti-oxidant properties

Valproic Acid and Derivatives. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021
Sher, Y., et al. (2015). Valproic acid for treatment of hyperactive or mixed delirium: rationale and literature review. *Psychosomatics*, *56*(6), 615-625.
Gagnon, D. J., et al. (2017). Repurposing valproate, enteral clonidine, and phenobarbital for comfort in adult ICU patients: a literature review with practical considerations. *Pharmacotherapy. 37*(10), 1309-1321.

# VPA – Adverse Effects

- GI: nausea, vomiting, diarrhea, dyspepsia
- CNS: sedation, tremor, dizziness
- Metabolic: weight gain
- Dermatologic: alopecia
- Hematologic: thrombocytopenia (dose related)
- Hepatic: increased LFTs
- Neurologic: ataxia, diplopia, dizziness, sedation, tremor
- Hyperammonemia/encephalopathy (idiosyncratic)
- Delayed hypersensitivity: toxic epidermal necrolysis, Stevens-Johnson Syndrome, DRESS
- Black Box Warnings:
  - Hepatotoxicity (idiosyncratic)
  - Pancreatitis
  - Teratogenic



Valproic Acid and Derivatives. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021

# VPA - Monitoring

- Serum Levels
  - Therapeutic range: 50-125 mcg/mL
  - Trough
  - Steady state reached after 3 days

- Metabolic
  - Weight
  - Glucose
  - Lipids

- CBC with platelets

- Pregnancy

- Liver function
  - Serum ammonia if symptoms

PAINWEEK

Valproic Acid and Derivatives. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021

# VPA – Dosing/Pharmacokinetics

- Dosage forms: IV, IR capsule, oral solution, DR and ER capsule/tablet
- Dosing:
  - 500-750 mg/day PO in 3-4 divided doses; titrate 250-500 mg/d every 1-3 days per clinical response and serum levels OR
  - 20-30mg/kg/day PO 3-4 divided doses or IV Q6H
  - PO:IV=1:1
    - ER is not equivalent
- Max Dose: 60mg/kg/day
- 80-90% protein bound (albumin)
  - Caution: hypoalbuminemia, uremia
- Extensive hepatic metabolism
- $T_{1/2}$: 9-19 hours



Valproic Acid and Derivatives. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021

# VPA – Drug Interactions

| Decrease VPA | Increase VPA | VPA Increases | Displaces VPA |
|---|---|---|---|
| Carbamazepine<br>Phenobarbital<br>Phenytoin<br>Carbapenems | Fluoxetine<br>Cimetidine<br>Erythromycin<br>Isoniazid | Propofol<br>Lamotrigine<br>Carbamazepine<br>Benzodiazepines<br>Warfarin<br>TCAs | ASA |



Valproic Acid and Derivatives. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021

# Lithium

- MOA:
  - –Enhances neuronal resilience, plasticity, proliferation
    - Reduces neuronal excitability
    - Enhances brain-derived neutropic factor
  - –Modulates serotonin and norepinephrine reuptake
  - –Inhibiting apoptotic glycogen synthase kinase activity
  - –After initial increase, reduces glutamate
  - –Modulates second messenger systems
  - –Decrease nitric oxide production
  - –Regulates intracellular calcium




Lithium. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021
Alda, M. (2015). Lithium in the treatment of bipolar disorder: pharmacology and pharmacogenetics. *Molecular psychiatry*, *20*(6), 661-670.

# Lithium Adverse Effects

- Teratogenicity: Ebestein's anomaly
  - Greatest risk during 1st trimester
- Endocrine: Hypo/hyperthyroidism, hyperparathyroidism, weight gain
- Hematologic: benign leukocytosis
- Cardiovascular: Abnormal T waves, Prolonged QTc (toxicity), bradyarrhythmia, AV block, unmasked Brugada syndrome
- Hyponatremia/hypokalemia
- Genitourinary: Polyuria, AKI, possible morphological changes, Nephrogenic Diabetes Insipidus
- Neurological: tremor, cognitive problems, sedation, fatigue
- GI: Nausea, vomiting, diarrhea
- Dermatologic: acne, psoriasis, rashes, alopecia



Lithium. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021

# Lithium-Monitoring

- **P**-Pregnancy
- **TH**-Thyroid
- **B**-Blood
- **E**-ECG
- **E**-Electrolytes
- **R**-Renal Function
- Serum levels
  - Therapeutic range: 0.6-1.2 mEq/L
  - Trough
  - Steady state reached after 5 days
  - Situations which increase the risk of toxicity
    - Sodium restriction, dehydration, vomiting/diarrhea, fever, drug-drug interactions



Lithium. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021

# Lithium – Dosing/Pharmacokinetics

- Dosage forms: tablet (carbonate),capsule (carbonate), 8mEq/5mL oral solution (citrate), ER tablet (carbonate)
- Dosing:
  - 300-900 mg/day PO in 2-3 divided doses; titrate 300-600mg every 1-5 days per clinical response and serum levels
  - 300mg carbonate ~ 5mL citrate
- No protein binding
- No metabolism, ~100 renal excretion
- $T_{1/2}$: 18-36 hours



Lithium. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021

# Lithium-Drug Interactions

- Decrease lithium
  - Mannitol
  - Caffeine
  - Theophylline
  - Loop diuretics
- Increase lithium
  - NSAIDs
  - ACEi/ARBs
  - Thiazide diuretics



Lithium. Lexi-Drugs. Lexicomp. https://online.lexi.com/ Last Accessed July 13, 2021

# Case #1

- **CC:** Apparent drug overdose
- **HPI**: EW, a 36-year-old obese male with an unknown past medical history was found apneic and unconscious. EMS administered a total of 6mg of naloxone in route to ED. He became combative and agitated upon arrival and then rapidly developed acute respiratory distress requiring emergent intubation. A right upper lobe pneumonia, sepsis and acute renal failure were identified.
- **Labs** (All normalized with time and treatment):
  - Temp: 101.7°F
  - WBC: 26K
  - Creatinine 3.4, AST: 763, ALT: 856, Lactic Acid 7.9
  - Urine Toxicology: Positive for benzodiazepines and cocaine. Not Positive For opioids*
  - QTc: 424ms
- Admitted to the ICU for continued treatment, pressors and ventilatory management

# Case #1 – Hospital Course

- Sedation maintained with propofol 50 mcg/kg/min IV (RASS Goal: -3) and fentanyl 50mcg/hr IV (NVPS 0-3)
  - Also: Midazolam 2 mg IV Q2H PRN anxiety, haloperidol 5 mg IV Q4H PRN agitation
- Propofol transitioned to dexmedetomidine 1mcg/kg/hr IV, and extubated after 2 days
- Patient was awake and alert, but not following commands and had poor impulse control. Olanzapine and haloperidol trials were minimally effective, and midazolam was not helping with restlessness.
  - Initiated diazepam 5 mg IV Q8H
    - Patient continued to be impulsive, having bowel movements on the floor and manipulating his feces
  - Switched haloperidol to chlorpromazine 100 mg PO Q8H
    - Insufficient

# Case #1 – Hospital Course

- Initiated valproic acid 250 mg PO Q8H
  - Some improvement, but continued episodes of agitation, restlessness, and impulsivity likely secondary to hypoxia-induced neurological injury
- Initiated lithium 300 mg PO BID
- After 2 days, patient was stable enough to have his dexmedetomidine weaned off and transferred out of ICU
  - Lithium 300 mg PO Q12H
  - Valproic acid 250 mg PO Q8H
  - Diazepam 5 mg PO Q8H
  - Chlorpromazine 100 mg PO Q8H
- During remainder of hospital stay
  - Chlorpromazine tapered to DC, restarted olanzapine ODT 10 mg QHS, diazepam tapered to DC, valproic acid and lithium tapered to DC
- After a 19-day hospital stay, discharged to neurological rehab facility on olanzapine 10 mg PO QHS

# Weaning, Deprescribing

# Weaning/Deprescribing

- Considerations when weaning are:
  - $T_{1/2}$ of agents
  - Pt's clinical presentation as doses changed
  - Route of administration
  - Pt's renal/hepatic function
- Recommend tapering to discontinuation
  - Propofol
    - PRN benzo available
  - Dexmedetomidine
    - Consider rebound hypertension if abruptly D/C
  - Benzos if frequent daily administration
  - Antipsychotics
  - phenobarbital
  - VPA
  - Lithium

# Agitation without Delirium - ICU

- Ensure external causes are controlled
  - adequate pain control, empty bladder, no hypoxia, etc
- Dexmedetomidine (based on level of care)
- Add benzodiazepine (e.g. midazolam in ICU, clonazepam ODT outside ICU)
- Antipsychotic
  - Sedating antipsychotic (olanzapine, quetiapine, chlorpromazine)
  - Less sedating (risperidone, haloperidol, ziprasidone)
- Add valproic acid
- Add lithium

# Agitation with Delirium - ICU

- Mechanically ventilated patients: propofol or dexmedetomidine
- Ensure external causes are controlled
  - adequate pain control, empty bladder, no hypoxia, etc
- Antipsychotic
  - Less sedating (risperidone, haloperidol, ziprasidone) with benzodiazepine ± antihistaminergic/anticholinergic (e.g. diphenhydramine, benztropine)
  - OR
  - Sedating antipsychotic (olanzapine, quetiapine, chlorpromazine)
- Add ketamine if intubated AND no immediate extubation planned + benzo
- Add valproic acid
- Add lithium
- Add barbiturate for ventilated patients only
  - Consider if renal failure and tachyphylaxis with benzos

# Agitation in Non-ICU Palliative Patients

- Ensure external causes are controlled
  - adequate pain control, empty bladder, no hypoxia, etc
- Dexmedetomidine (if your facility allows)
- Add benzodiazepine (e.g. midazolam, clonazepam ODT, alprazolam)
- Antipsychotic (Dealer's choice)
  - Sedating antipsychotic (olanzapine, quetiapine, chlorpromazine)
  - Less sedating (risperidone, haloperidol, ziprasidone)
- Add valproic acid
- Add lithium

# Post Test Question #1

- Which of the following is a validated tool for assessing agitation in an ICU patient?
  A. CPOT
  B. CAM-ICU
  C. PAIN-AD
  D. Palliative performance score

# Post Test Question #2

- GM is 28 YO male intubated in ICU after being involved in motor vehicle accident. He is receiving propofol 50mcg/kg/min and fentanyl 200mcg/hour. He is currently breathing over the ventilator, moving in bed, and has a positive CAM-ICU score. Patient is believed to be presenting with signs of agitated delirium during sedation vacations. If the patient's agitation is managed, he is a candidate for extubation. What would be an appropriate order of medication escalation to treat this patient's refractory agitation?
  A. haloperidol, valproic acid, lithium
  B. dexmedetomidine, midazolam, haloperidol
  C. dexmedetomidine, midazolam, ketamine
  D. phenobarbital, lorazepam, morphine

# Post Test Question #3

- Which of the following medications require serum drug level monitoring?
  A. Risperidone
  B. Dexmedetomidine
  C. Midazolam
  D. Valproic acid

PAINWEEK®

# Sedated and Elated: Treatment Tactics for Refractory Agitation

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