Advanced Management of Alcohol Withdrawal

Case-Based, Evidence-Informed Solutions

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ASAM Annual Conference 2026

PCSS Medications for Alcohol Use Disorder — Providers Clinical Support System

Learning Objectives

- Analyze complex patient presentations using validated assessment tools to guide risk stratification and individualized treatment planning.
- Apply pharmacologic and supportive care strategies to the management of severe and resistant alcohol withdrawal syndrome (AWS) in hospital or ICU settings.
- Select appropriate treatment strategies to overcome challenges with complex patient cases of AWS.

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Disclosures

- Tessa Steel, MD, MPH - *No Disclosures*
- Melissa Weimer, DO, MCR, DFASAM - *No Disclosures*
- Ryan JJ Buckley, MD, MPH - *No Disclosures*

No medications are FDA-approved for treating AWS; as such, we will be discussing off-label use of medications

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What is PCSS-MAUD?

- Aims to increase healthcare professionals' capacity to identify, prevent, and treat alcohol use disorder

- Provides free training, education, and consultative services
  - Live webinars and case-based discussions
  - Mini videos
  - Online modules
  - Digital resources (e.g., infographics, factsheets, toolkits)
  - Enduring trainings
  - Mentoring
  - Consultative services

www.pcss-maud.org

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Session Agenda

1. Overview, Screening, and Diagnosing Severe and Resistant AWS
2. Complex AWS Treatment Approaches
   - *Branching Case Scenario*
   - *Time for audience questions & comments throughout*
3. Key Takeaways & Q&A

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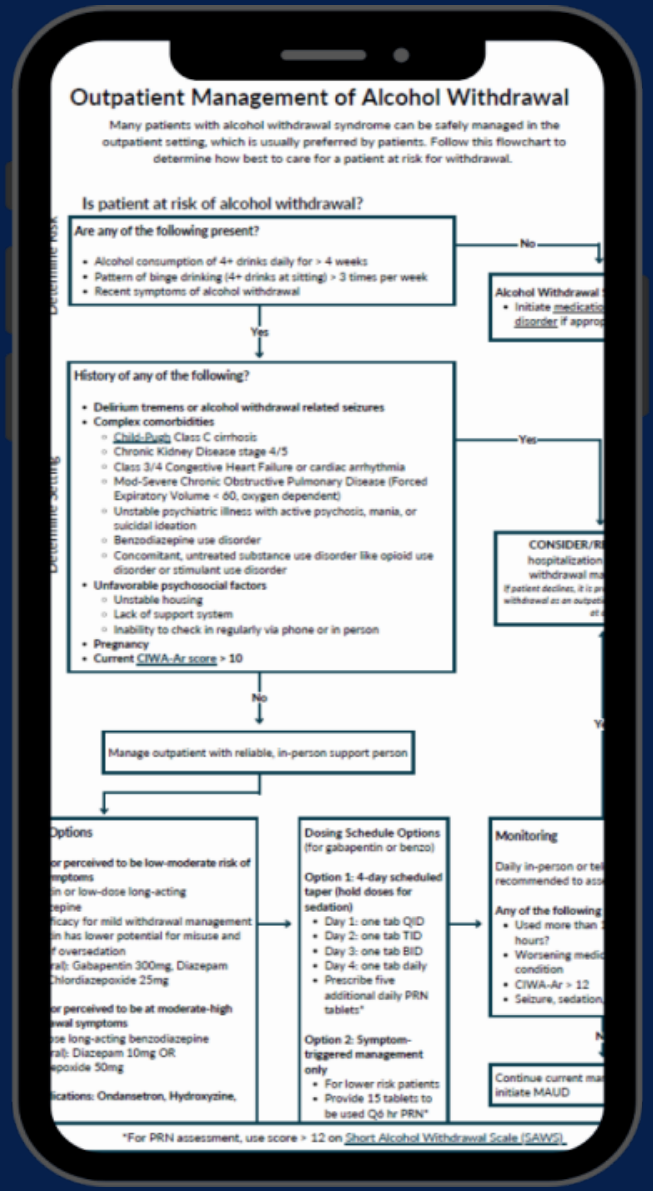
Accompanying Handouts

- Treatment of Severe and Complicated Alcohol Withdrawal Syndrome (PCSS-MAUD Digital Resource)
- Outpatient Management of Alcohol Withdrawal (PCSS-MAUD Digital Resource)
- Yale New Haven Health System Phenobarbital Guidance
- Flow Diagram of Pre- and Post-phenobarbital Orderset
- Session Slides



Download handouts from the conference App!

Wolpaw BJ, Oren H, Quinnan-Hostein L, et al. Hospital-Wide Implementation, Clinical Outcomes, and Safety of Phenobarbital for Alcohol Withdrawal. JAMA Netw Open. 2025;8(8):e2528694. doi:10.1001/jamanetworkopen.2025.28694

1. Overview, Screening, & Diagnosing Severe and Resistant AWS

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Alcohol withdrawal syndrome

- **Alcohol withdrawal syndrome (AWS)** can occur after an individual **suddenly stops or significantly reduces** their alcohol consumption

- **More than 50%** of individuals with a history of AUD exhibit symptoms of AWS

- **5-20%** of patients will have severe AWS

Cleveland Clinic. *Alcohol withdrawal*. January 25, 2024. Accessed October 29, 2024. https://my.clevelandclinic.org/health/diseases/alcohol-withdrawal

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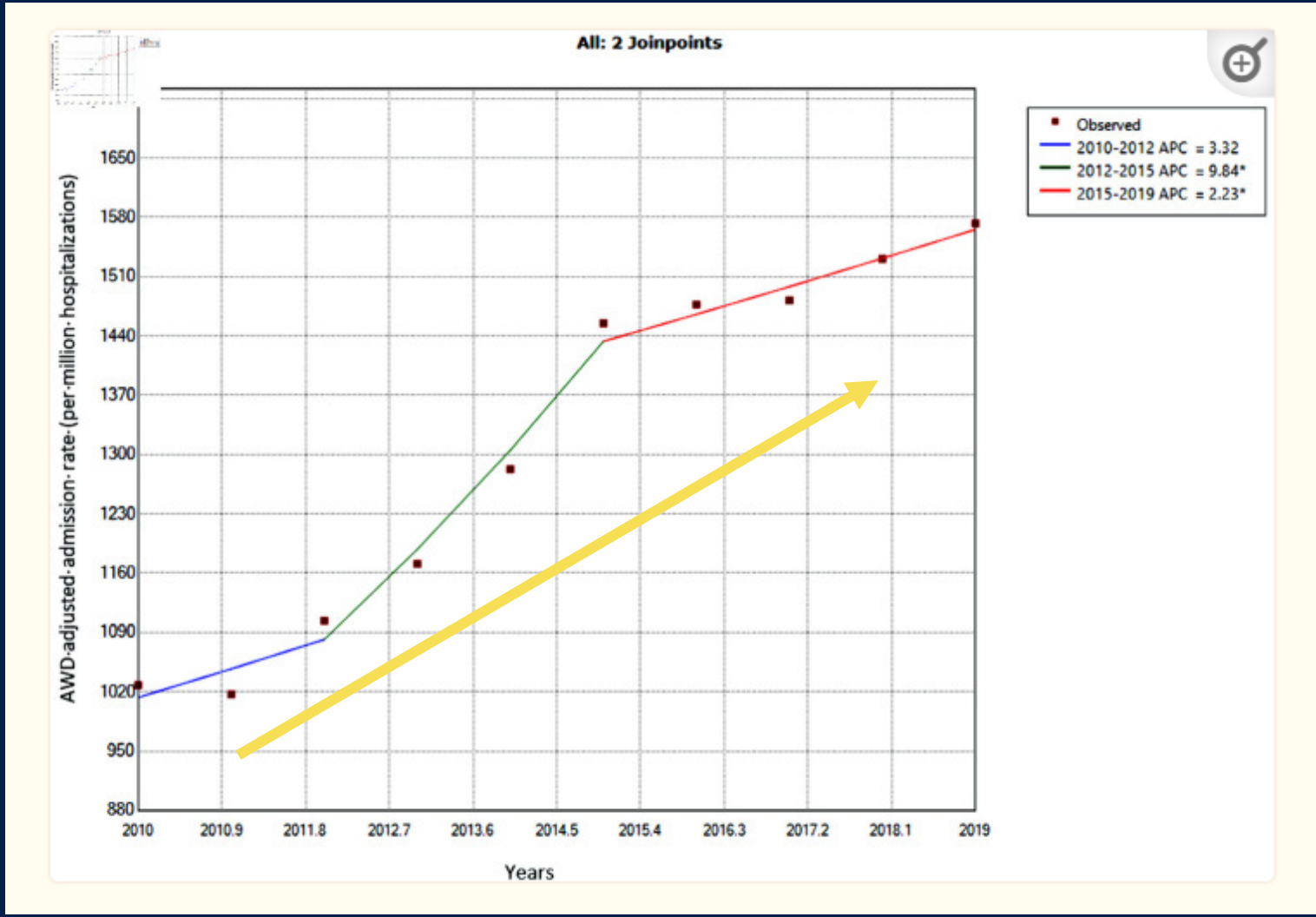
Trends in Alcohol Withdrawal Related Delirium, 2010-2019



Laswi, et al. *Gastroenterology Res.* 2022

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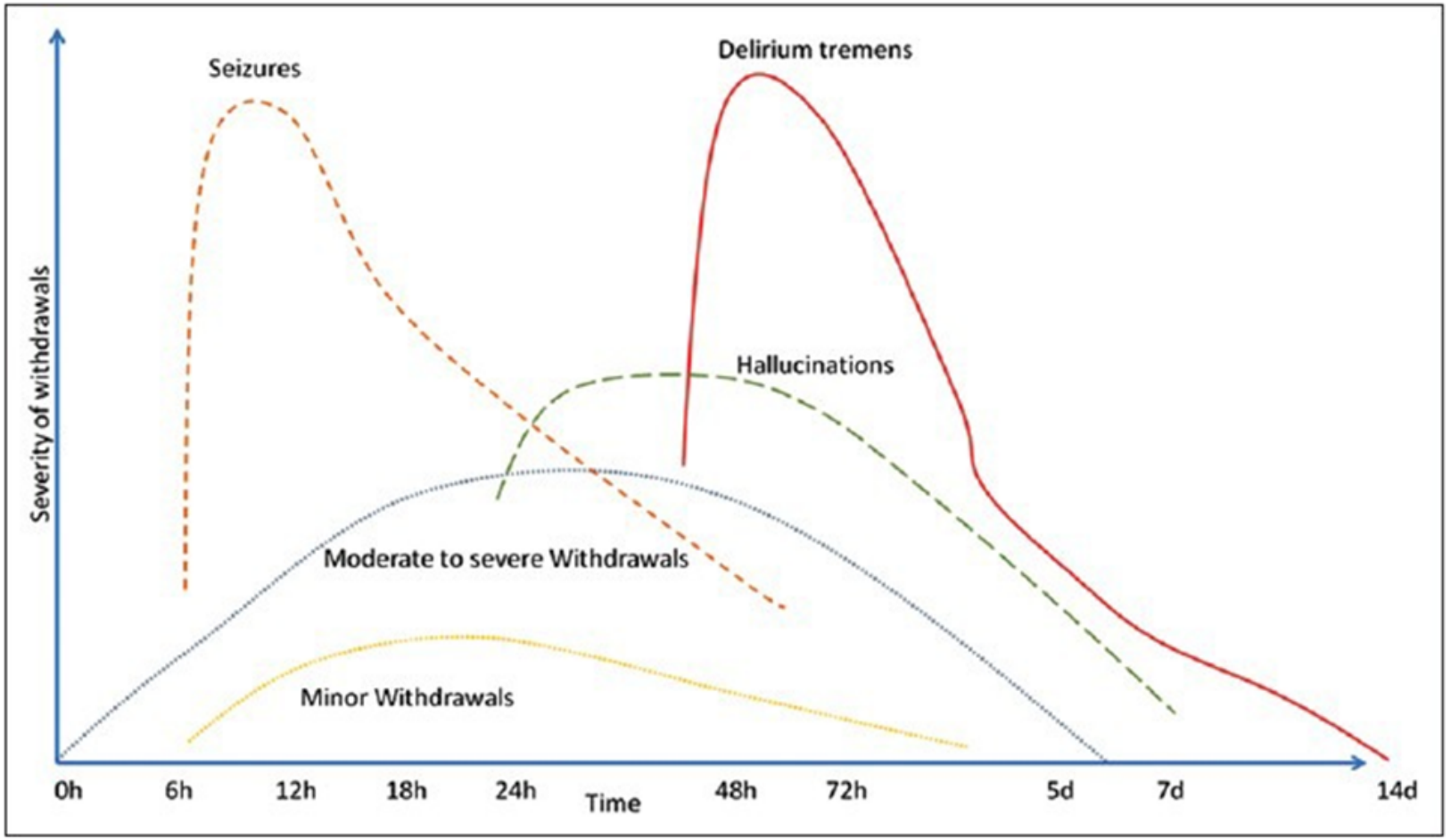
Alcohol Withdrawal Syndrome Continuum



Haber NL, et al. *Guidelines for the Treatment of Alcohol Problems.* 2009.

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Alcohol withdrawal syndrome neuroadaptations

Hyperexcitation: ↓GABA, ↑Glutamate

MINOR WITHDRAWAL	SEIZURE	HALLUCINATIONS	DELIRIUM TREMENS
6 – 36 *hrs from last drink*	6 – 48hrs (early as 2hrs)	12 – 48 hrs	48 – 96hrs
		👎 Dopamine	👍 Norepinephrine
Normal mental status	Generalized tonic clonic	Normal mental status	Disorientation, Agitation
Tremor	Usually singular	Vital signs normal.	Hallucinations
Mild anxiety	May be series of Sz over short period of time	Usually visual.	↑Autonomic activity tachycardia febrile, diaphoresis hypertension
Headache	If recurrent seizures think other cause, and get CT / LP.	Can be auditory, or tactile	Resp Acidosis → ↑pH → Resp Alkalosis
Diaphoresis	Treat with Benzos	Resolves in <48hrs, before DTs start	Lasts 5 – 7 days
Palpitation	If untreated, 1/3 → DT		5% Mortality
Anorexia			
GI upset			
Insomina			

"GABA debt" symptoms

Also involved: other monoamines like serotonin, HPA neuroendocrine axis, neuropeptides like CRF, NPY, endogenous opioids, and Ion channels

https://pmc.ncbi.nlm.nih.gov/articles/PMC6943828/

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Who is at risk for alcohol withdrawal?

- Alcohol consumption of 4+ drinks daily for > 4 weeks
- Pattern of binge drinking (4+ drinks in 1 sitting) > 3 times a week
- Prior symptoms of alcohol withdrawal → *"Have you ever gotten the shakes when you stop drinking?"*
- Prediction of Alcohol Withdrawal Severity Scale **(PAWSS)**
  - Prior episodes of withdrawal?
  - Prior withdrawal seizures?
  - Prior delirium tremens or "DTs"?
  - Prior engagement in inpatient treatment or alcoholics anonymous?
  - Black-outs?
  - Combine alcohol with other downers?
  - Use of other drugs?

+4 = LR 174 !

Wood E, Albarqouni L, Tkachuk S, et al. Will this hospitalized patient develop severe alcohol withdrawal syndrome?: The rational clinical examination systematic review. *JAMA*. 2018;320(8):825-833. doi:10.1001/jama.2018.10574

Maldonado JR, Sher Y, Ashouri JF, et al. The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): Systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol*. 2014;48(4):375-390. doi:10.1016/j.alcohol.2014.01.004

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Predicting AWS Risk Profile

- Most powerful predictor = history → prior withdrawal experience
- But what if history is unavailable? → need objective clues next

EXAM FINDINGS	LABORATORY DATA	COMORBIDITIES

Fight-or-flight signs
• Cardiac: tachycardia, hypertension
• Neuro: agitation, hyper-alertness, confused, delirium
• General: tremor, diaphoresis
	Evidence of organ toxicity
	• Elevated ethanol level >250
	• liver toxicity: ↑ AST:ALT ratio
	• bone marrow suppression: ↑ MCV, pancytopenia
	• malnutrition – drinking, not eating
	  • ↓ BUN
	  • ↓ Na, ↓ K, ↓ Mg, ↓ phos
	  • ↑ AG d/t starvation ketosis
		Things that ignite stress response
		• Sepsis: twice as likely & double the mortality
		• Trauma: esp. burns & long bone fractures
		• hepatitis
		• pancreatitis

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Definitions

Severe Alcohol Withdrawal Syndrome (SAWS)	Complicated alcohol withdrawal syndrome	Refractory (or Resistant) Alcohol Withdrawal Syndrome	Refractory Alcohol Withdrawal Syndrome + *another withdrawal or medical illness*
• CIWA >15, impending delirium, agitation	• Development of alcohol withdrawal-related seizure or delirium	• Severe or complicated AWS despite high dose of benzo or phenobarbital	• Severe or complicated AWS despite high dose of benzo or phenobarbital • Additional diagnostic criteria met

ASAM Clinical Practice Guideline, *JAM* 2020

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2. Complex AWS Treatment Approaches

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Case (Part 1)

- 53-year-old man
- Alcohol-associated liver disease (Child-Pugh B), HFrEF (EF 45%), insulin-dependent diabetes
- Divorced, unstable housing; lives with support animal (“Chip”)
- Reports ~1 liter vodka + several beers daily
- Blood alcohol level: 455 mg/dL
- Prior hospitalization for alcohol withdrawal; possible prior seizure (uncertain)
- Recent gait instability
- Subjective fevers and malaise and increased shortness of breath

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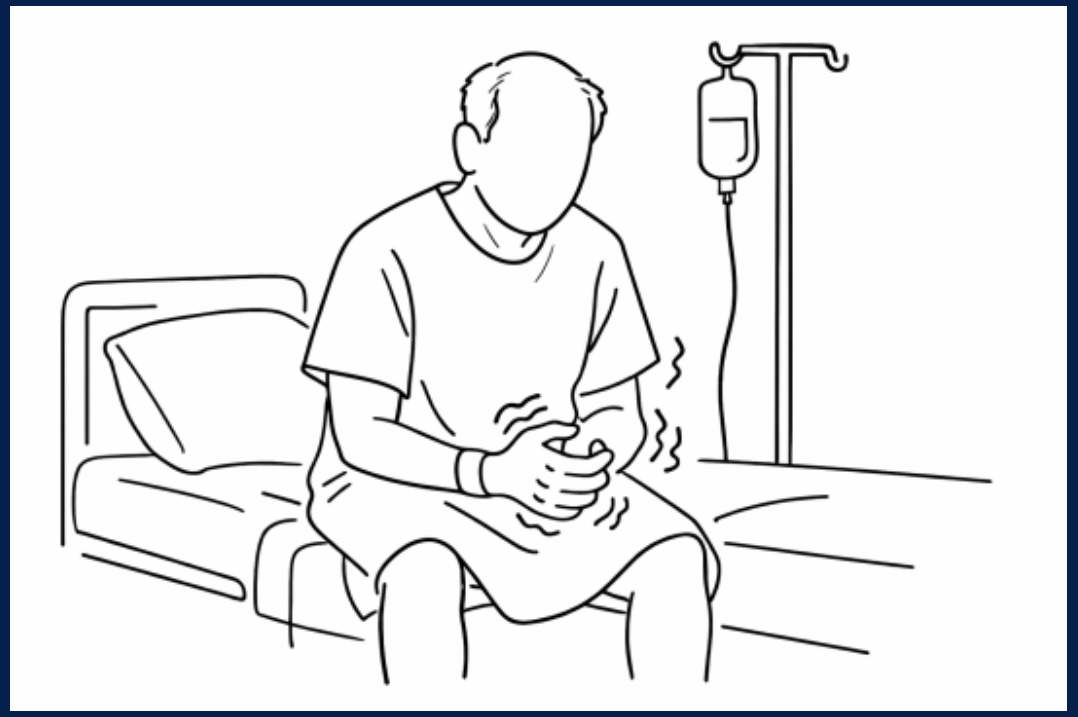
Case 1 (Part 1)

- 16 hours after presentation.....
- BP 180/100, HR 130
- Anion gap 18
- AST/ALT 250/100
- T bili 2.5
- Otherwise normal vitals and labs
- Alert and oriented
- "Ruddy" appearance, unsteady on his feet, and extremely tremulous
- Supplemental O2, subtle CXR abnormality that is read as pulmonary edema and retrocardiac opacity

- CIWA-Ar is 25



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Is the CIWA-AR result accurate?

- Delirium
- Encephalopathy
- Severe underlying anxiety
- Concomitant substance withdrawal
- Baseline tremor
- Patient and assessor's experience with the test

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Treatment Options

Two options:

1. Phenobarbital
2. Frontloading benzodiazepines

Wolpaw BJ, et al. *JAMA Netw Open.* 2025;8(8):e2528694. The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. *J Addict Med*. 2020 May/Jun;14(3S Suppl 1):1-72. .

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1 Phenobarbital

Different mechanism of action

Long half life

Fast onset

Multiple admin routes

Medication interactions

"Tricky" therapeutic window

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1 Proposed Phenobarbital Indications

- History of severe AWS or DTs
- History of AWS and success with phenobarbital in the past
- Concomitant benzodiazepine withdrawal
- Patient with traumatic injury
- Patient with delirium
- History of resistant alcohol withdrawal
  - Severe alcohol withdrawal syndrome despite receiving high doses of benzodiazepines (>150mg diazepam or >30mg lorazepam in first few hours of treatment)

- *Precautions*: decompensated liver disease (safety of BZDs vs phenobarbital uncertain), acute liver failure, diagnosis is not clear

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1 Phenobarbital Mechanism of Action

- Binds to GABA receptors at alpha subunit
- Increases duration of bursts of GABA-mediated chloride channels without increasing the frequency of bursts
  - Ethanol binds the delta subunit of GABA
  - Benzos binds at alpha subunit of GABA and increase frequency of bursts
- Additionally, decreases glutamate via NMDA, AMPA, and kainite receptors

- *Due to overlapping mechanism of action, do not recommend benzos + phenobarbital*
  - Phenobarbital monotherapy approach- Several small retrospective/prospective studies have mixed outcomes, however, a recent JAMA QI study showed improve outcomes when using the 10-15 mg/kg IV loading dose.

Wolpaw BJ, Oren H, Quinnan-Hostein L, et al. Hospital-Wide Implementation, Clinical Outcomes, and Safety of Phenobarbital for Alcohol Withdrawal. JAMA Netw Open. 2025;8(8):e2528694. doi:10.1001/jamanetworkopen.2025.28694

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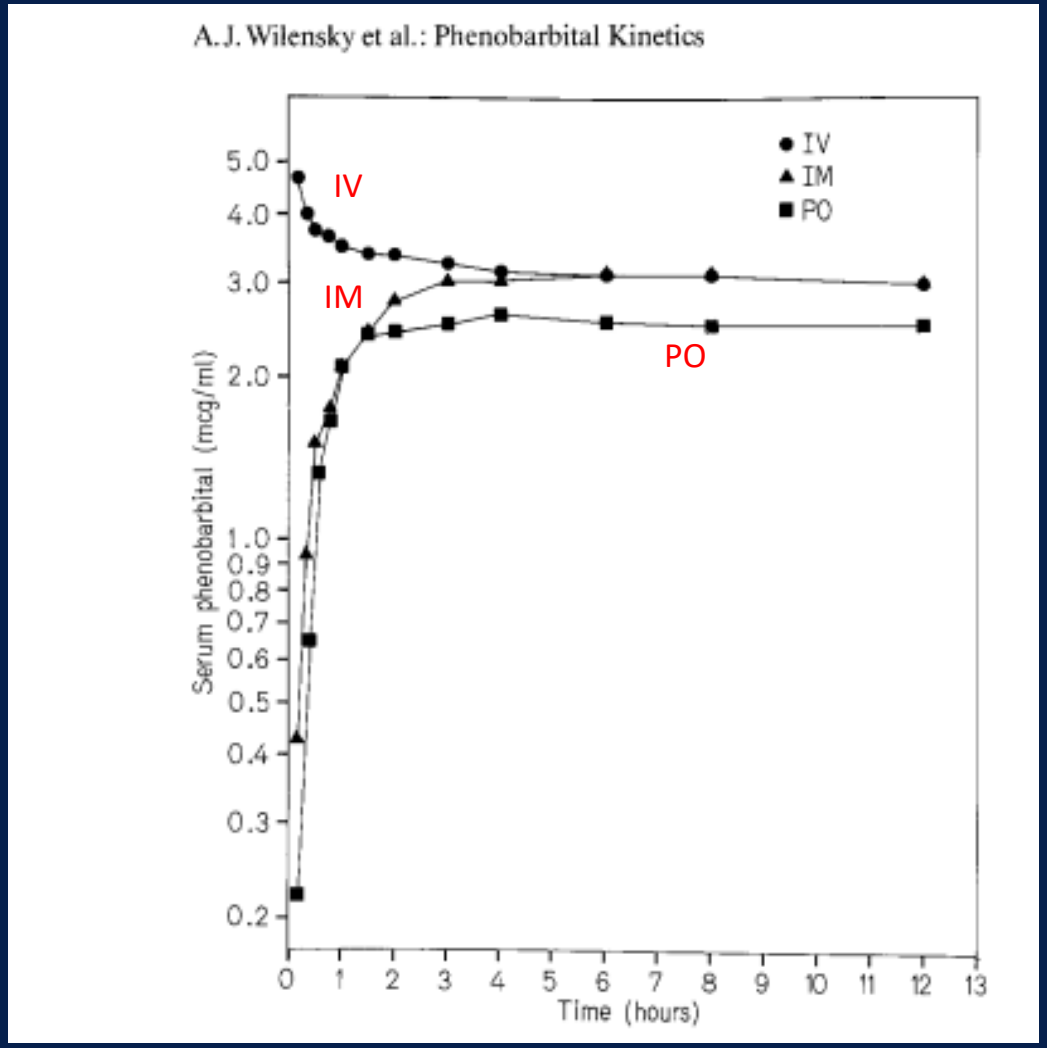
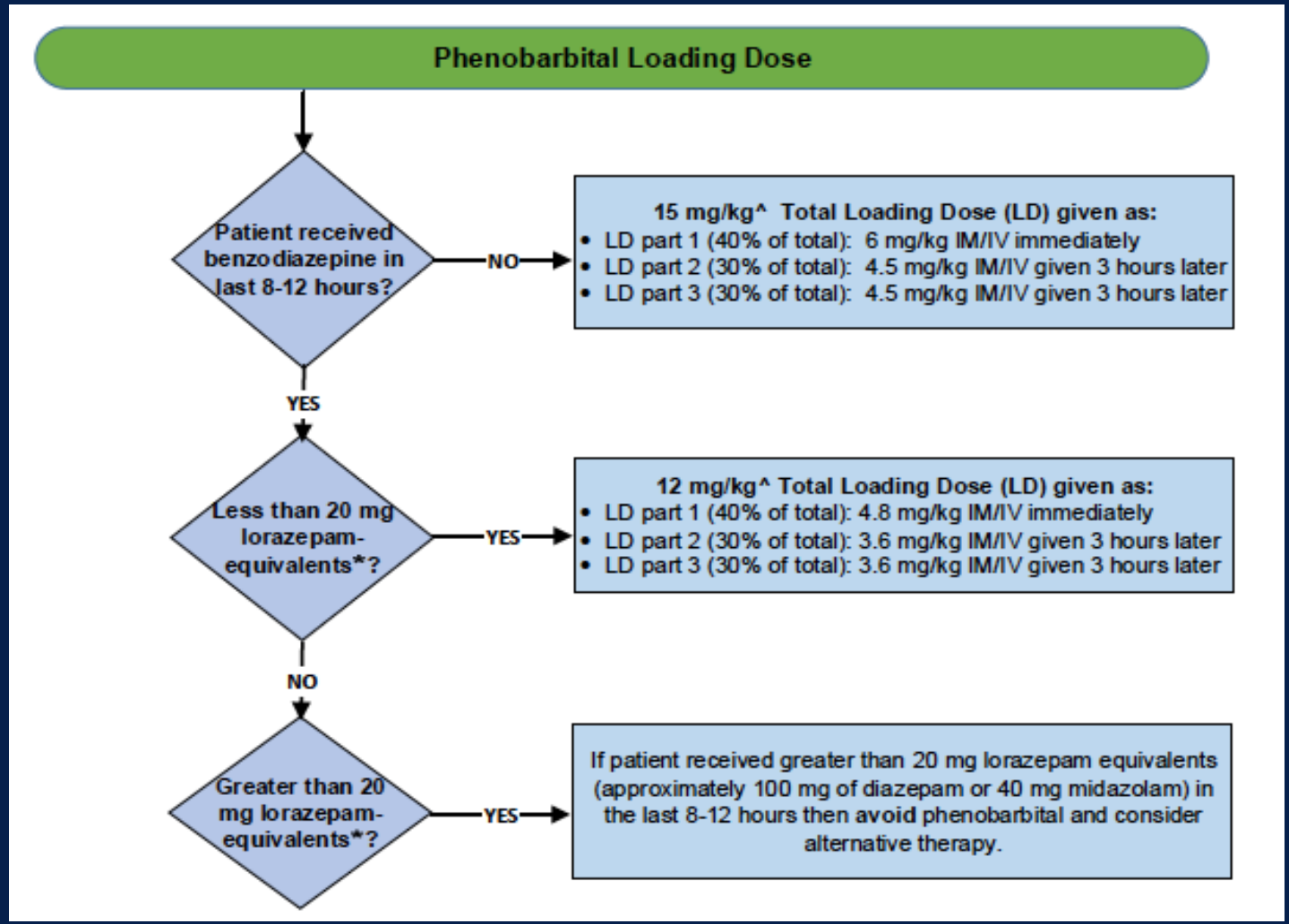
1 Phenobarbital Pharmacokinetics

When to Consider IV vs IM		
	IV	IM
Onset	5 minutes	1 hour
Peak	15 minutes	2-8 hours
Bioavailability	100%	100%
Other	Consider Institutional Culture Consider Patient Comfort and Trust	



1 Phenobarbital Loading

- 12-15mg/kg load followed by taper
  - Additional dosing guided by symptoms
  - Taper maintains levels over course of treatment



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2 Alternative Treatment: Frontloading Benzodiazepines

- Diazepam 10mg PO or IV (lorazepam 2mg)
  - Assess response after 30 min - 1 hour
  - If CIWA >10
- Give Diazepam 20mg PO or IV (Ativan 4mg)
  - Assess response after 30 min - 1 hour
  - If CIWA >10
- Give another Diazepam 20mg PO or IV (Ativan 4mg)
  - Repeat as needed until CIWA <10

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Case (Part 2)

- **Clinical Status:** Patient worsening despite ongoing treatment.
- **Mental Status / Behavior:**
  - Nonverbal; shouting incoherently; swatting at unseen objects
  - Severely agitated and disoriented ×3, Requires multiple staff for safety and restraint
- **Physical Exam / Symptoms:**
  - Diaphoretic
  - Coarse bilateral tremor
  - Productive cough reported by nursing
- **Vital Signs / Respiratory Status:**
  - T 101.1°F | BP 165/100 mmHg | HR 132 bpm | RR 28 breaths/min
  - SpO_2 92%, Initially on 2 L NC → now requires 4 L NC for hypoxemia
  - WBC 17.5 K/μL with left shift
- **Severity Assessment:**
  - mMINDS score: 28
  - Consistent with severe alcohol withdrawal syndrome (SAWS)

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CIWA vs BAWS vs SEWS vs mMINDS?!

- CIWA-Ar and BAWS (Brief AWS) have significant limitations:
  - CIWA-Ar requires subjective self-reporting
  - BAWS less so, however, hasn't been validated in ICU populations
  - As withdrawal worsens, focus on objective findings like vitals
- Severity of Ethanol Withdrawal Scale (SEWS)
- Personal Takeaway - More important than which scoring tool → use standardized tool within each unit/institution
  - One retrospective cohort study
- Modified Minnesota Detoxification Scale (mMINDS) is validated in ICU patients
    - One retrospective found ICU nurses preferred mMINDS and found it easier to administer

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Modified Minnesota Detoxification Scale (mMINDS)

Pulse (beats per minute)
Diastolic blood pressure (mmHg)
Tremor
Sweat
Hallucinations
Agitation - *Assess with Richmond Agitation-Sedation Scall (RASS)*
Orientation
Delusions
Seizures

Calculate the score based on the real-time assessment of the patient

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Worsening SAWS (Beyond the PHB Load)

Summary of Receptor Targets-

- GABA Receptors:
  - IV Phenobarbital Continued (proposed maximum dose **25 mg/kg** IBW, can continue to dose 2 mg/kg IBW q3hrs) - *max dose varies by institution*
  - Monitor phenobarbital level <30
- Sympathetic Receptors: ("autonomic features")
  - Alpha - 2 adrenoreceptors (inhibit norepinephrine release)
    - Adjunctive Dexmedetomidine (Infusion) IV Infusion
  - Beta
    - *Generally avoid beta-antagonism, however, you will see it referenced*
- Dopamine D2 Receptors: ***("agitation/delirium")***
  - Anti-Psychotics (need to be mindful of QTc in the setting of metabolic derangements)
- NMDA Receptor:
  - Ketamine: NMDA receptor antagonist

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Before *Progressing* – A Consideration to Prevent Anchoring

- Am I treating "Phenobarbital *Refractory* SAWS?"

OR…

- Is there commitment intoxication/withdrawal/illness?
  - Sympathomimetic intoxication?
  - Opioid/Synthetic Opioid withdrawal?
  - Alpha-2 adrenergic withdrawal? (medetomidine/xylazine)
  - Traumatic/Medical Comorbid Illness

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Dexmedetomidine in Severe Alcohol Withdrawal

Role / Indications

- **Adjunct** to benzodiazepines for **severe or benzodiazepine-refractory AWS**
- Addresses **autonomic hyperactivity & anxiety**
- **Not** monotherapy (does **not** prevent seizures or delirium)
- Useful in **ICU** and **geriatrics** to limit respiratory depression

Mechanism

- Selective Central α2 Adrenergic-agonist → ↓ norepinephrine release
- May improve tachycardia, hypertension, tremor
- Provides cooperative, arousable sedation

No respiratory suppression; not an antiepileptic

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Dexmedetomidine in Severe Alcohol Withdrawal

- **Dosing (IV infusion)**
  - Typical: **0.4–0.7 µg/kg/hr**
  - Range: **0.2–1.4 µg/kg/hr**, titrated
  - Bolus generally avoided

- **Key Adverse Effects**
  - **Bradycardia** (dose-dependent; RR ~2.7) → monitor closely
  - **Hypotension** (variable)
  - **Contraindicated in heart block**

- **Clinical Impact**
  - **Benzodiazepine-sparing** (≈20–60% reduction in 24h)
  - **No clear reduction** in intubation risk
  - **ICU LOS benefit uncertain**

Fiore M, et al. *Pharmaceuticals (Basel).* 2024;17:1125

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Ketamine: Rationale & Potential Role

- **Proposed Mechanism**
  - In the setting of AWS, decreased GABA results in ↑ NMDA activity / (↑ glutamate-mediated excitotoxicity)
  - Ketamine is a NMDA receptor antagonist
  - May reduce need for escalating GABA-mediated sedation

- **Role / Indications**
  - Adjunct to benzodiazepines for severe, benzodiazepine-refractory AWS
  - Consider in ICU patients with delirium tremens
  - Not monotherapy; evidence still evolving

- **When to Consider**
  - Escalating benzodiazepine and/or phenobarbital doses with poor control
  - Delirium tremens despite standard therapy
  - Concern for respiratory depression with high-dose benzodiazepines/phenobarbital

Pizon et al. Crit Care Med. 2018;46(8):e768-e771.

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Ketamine for Severe Alcohol Withdrawal

- **Dosing (IV)**
  - Consider bolus: **0.3 mg/kg** (protocol-dependent)
  - Infusion: **0.15–0.3 mg/kg/hr**

- **Clinical Outcomes (**Really Limited Data)***
  - ↓ **Intubation risk** (OR ~0.14)
  - ↓ **ICU LOS** (~3 days)
  - **Benzodiazepine-sparing** (↓ requirements at 12–24 hrs)

- **Safety / Limitations**
  - Generally **well tolerated** at low doses
  - Rare oversedation; **no major adverse events** reported
  - Evidence limited by **small, heterogeneous studies**
  - **Prospective RCTs needed**

Pizon et al. *Crit Care Med.* 2018

Clinical Case (Part 3)

- Phenobarbital blood concentration is 22 µg/dL
- Persistent tachycardia and fever
- BP elevated, increasingly labile
- Lactate 3.2
- Procalcitonin elevated
- Given broad-spectrum antibiotics

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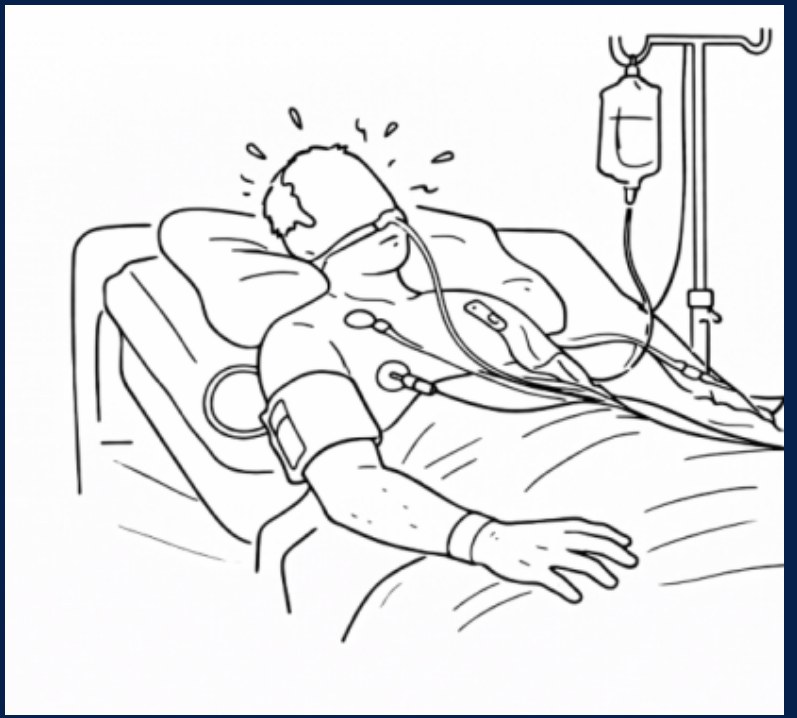
Clinical Case (Part 3)

- Headache reported
- Tonic-clonic seizure – resolved before medication
- Now somnolent with ongoing fever, tachycardia, and hypertension
- Lactate 11 in direct wake of seizure
- Already on dexmedetomidine and received "max phenobarbital"
- 2/2 blood cultures showing GPCs in pairs and chains
- Dexamethasone started for suspected meningitis



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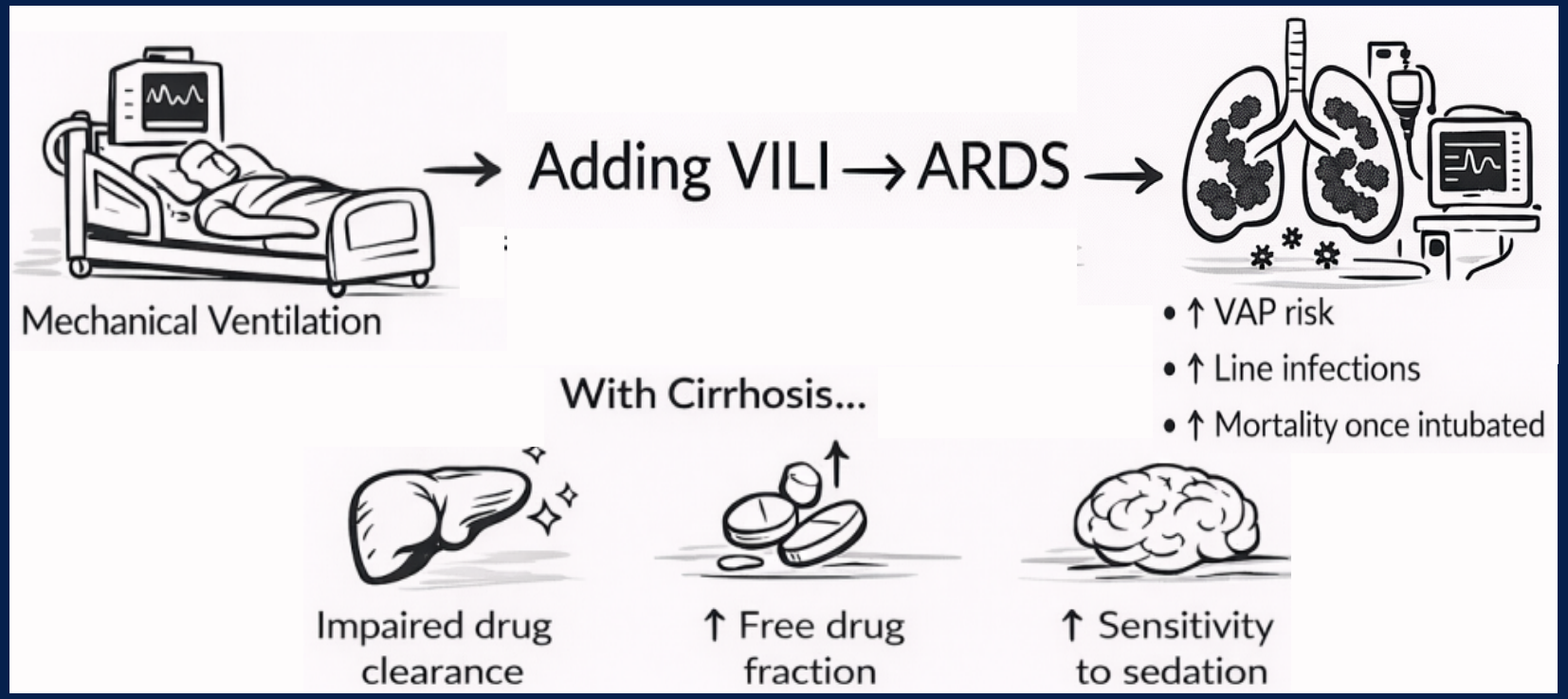
Should we intubate? No free lunch…

- Secondary infection risk
- Ventilator induced lung injury added to existing PNA
- Cirrhosis + Sedatives = Prolonged Ventilation



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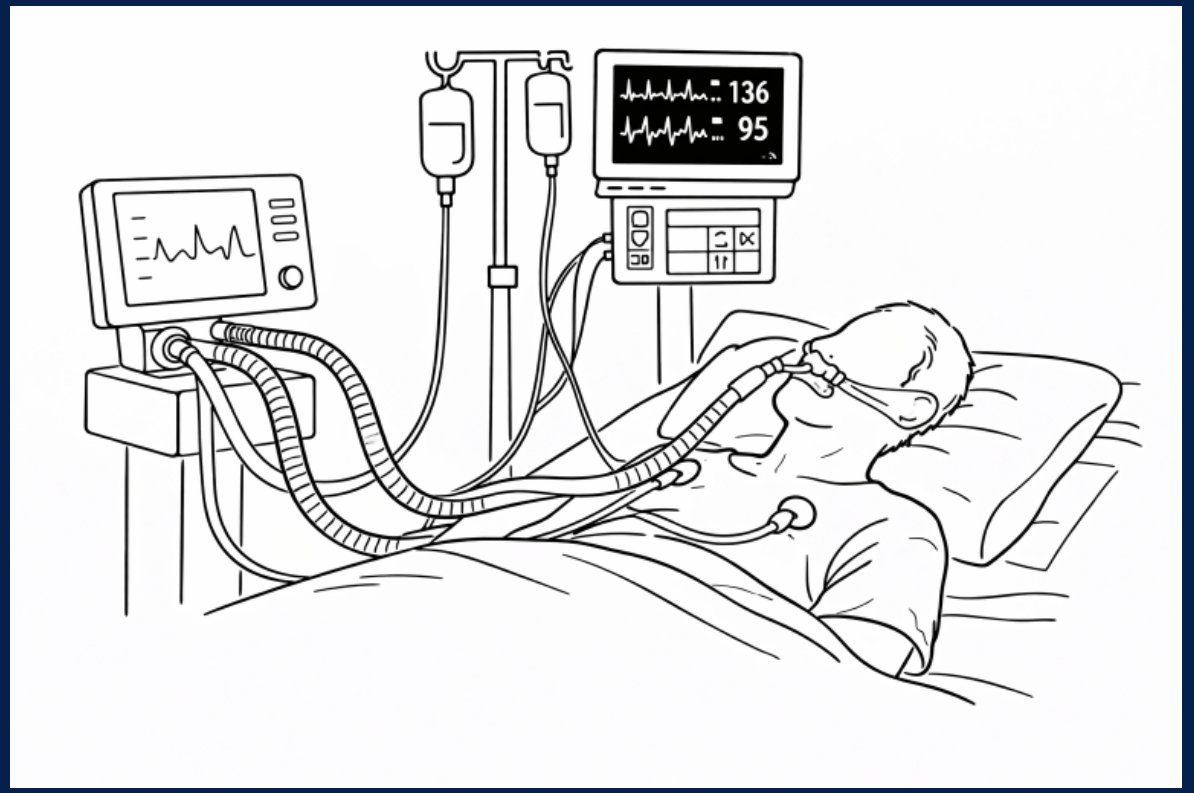
Clinical Case (Part 4)

Escalation

- Recurrent seizure
- Worsening encephalopathy—unresponsive
- Unreliable airway protection

Priorities Shift

- Achieve sustained cortical suppression
- Secure airway
- Facilitate lumbar puncture



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Alcohol Use Disorder & Disseminated Pneumococcal Infection

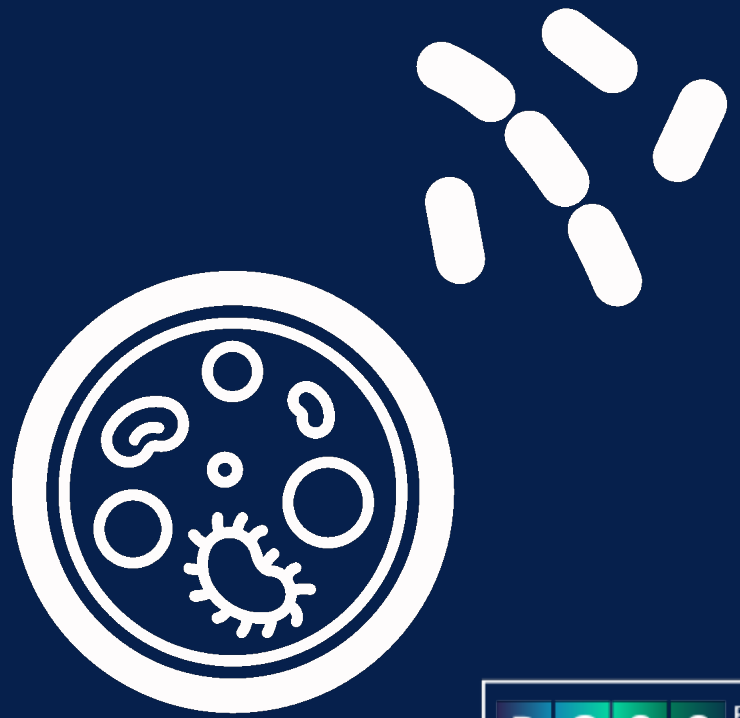
- AUD is an independent risk factor for invasive pneumococcal disease (IPD)
- Higher rates of bacteremia and meningitis
- Increased mortality once invasive infection occurs

Why?

- Multifaceted immune dysfunction

Clinical Implications

- Lower threshold to evaluate for CNS infection



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Why Cortical Suppression Matters

- **Sustained cortical hyperexcitation is biologically injurious**:
  - NMDA-driven Ca^{2+} influx → oxidative/mitochondrial stress → neuronal death pathways
- **Bacterial meningitis amplifies this pathophysiology**:
  - Neuroinflammation + excitatory signaling → injury
- **↑ CSF glutamate in bacterial meningitis correlates with outcomes**, supporting the relevance of excitotoxicity

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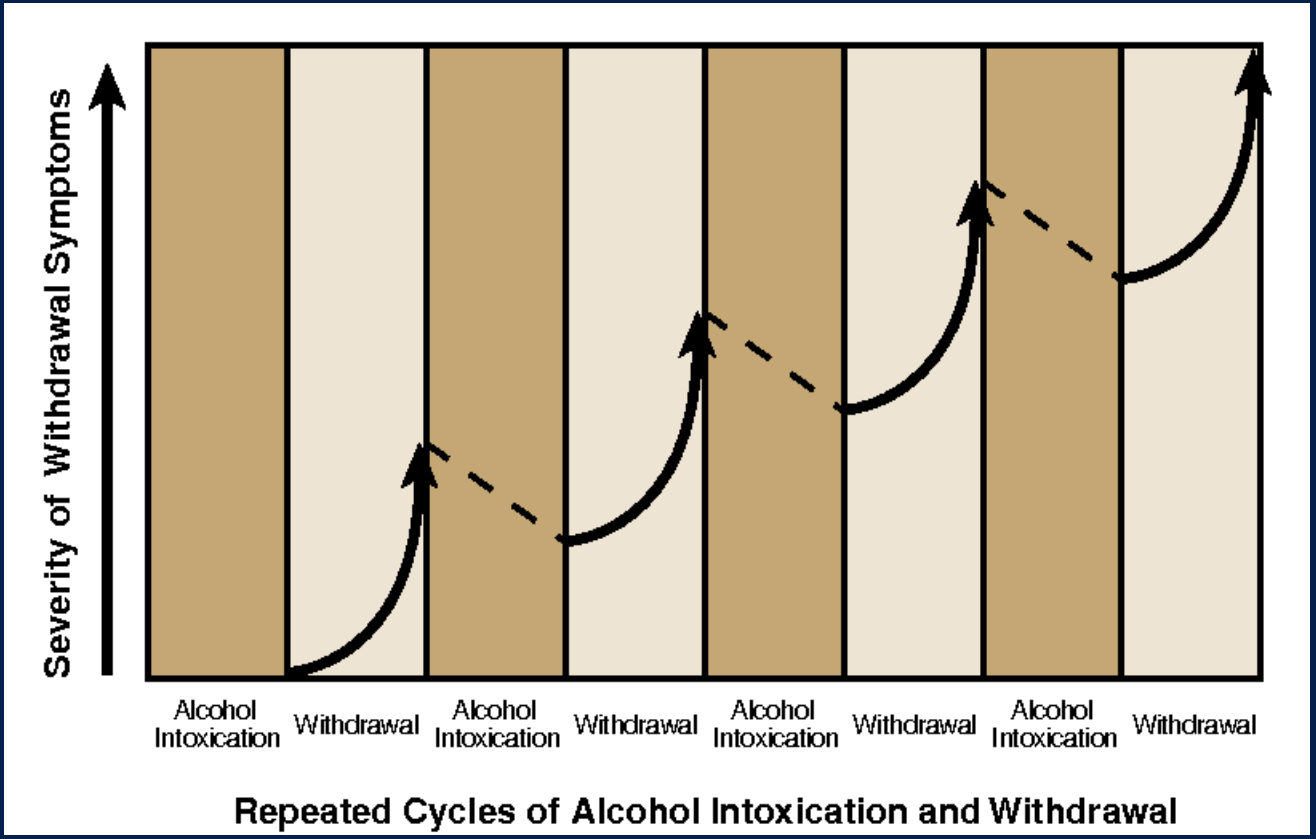
Kindling - Recurrent AWS is not benign



- Repeated withdrawal episodes → progressive NMDA upregulation
- Increased seizure susceptibility, greater risk of delirium tremens
- Associated with worse neurocognitive outcomes

Becker HC, Mulholland PJ. Neurochemical mechanisms of alcohol withdrawal. *Handb Clin Neurol*. 2014;125:133-156. doi:10.1016/B978-0-444-62619-6.00009-4

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Propofol in Severe AWS with Recurrent Seizure

Why now?

- Recurrent tonic-clonic seizure is evidence of ongoing brain hyperexcitation
- Encephalopathy with unreliable airway protection and concern for meningitis
- Need for sustained cortical suppression ("cortical" & "glutamate-mediated excitotoxicity”= same thing)

Mechanism

- Potent, TITRATABLE GABA-A agonist → enhances inhibitory tone
- Indirect NMDA attenuation → reduces excitatory transmission
- Rapid onset, short context-sensitive half-time, administered as continuous infusion

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Evidence for Propofol—AWS & Hyperexcitation

As Alcohol Withdrawal Treatment

- Evidence base: **5 retrospective ICU cohorts (N≈218)** + case series/case reports
- Signals: ↓ **benzodiazepine requirements**, but often ↑ **mechanical ventilation duration / ICU LOS** (confounding by indication likely)
- Propofol is typically used for **severe, benzodiazepine-refractory AWS** in **intubated** patients or used by some clinicians as primary treatment in patients intubated for other indications

As Treatment for Severe Brain Hyperexcitation (status epilepticus)

- In **refractory status epilepticus**, continuous infusion of **propofol** is standard ICU therapy
- Provides biologic/clinical precedent for **continuous, titratable cortical suppression**

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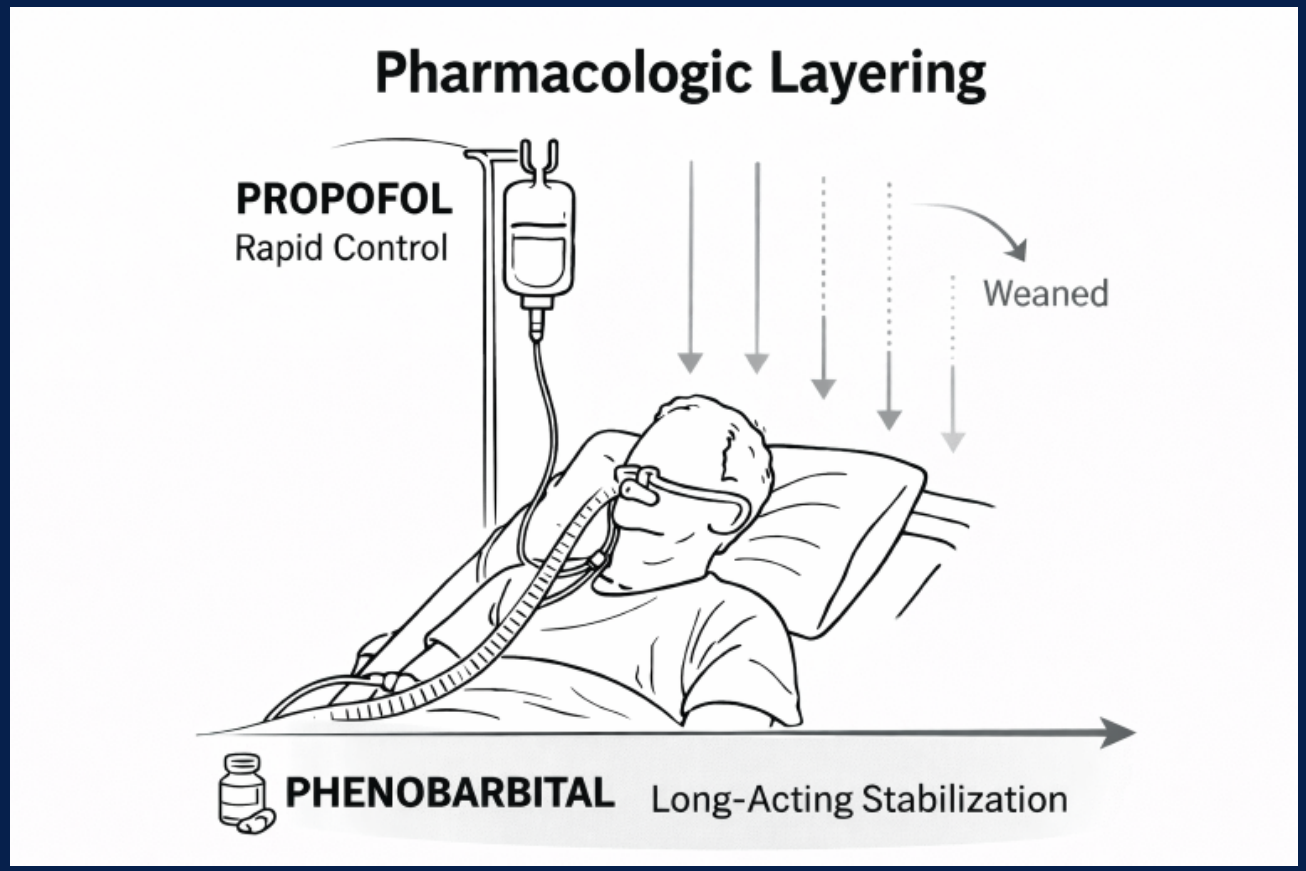
Clinical Case (Resolution)



- Pharmacologic layering
  - Phenobarbital maintained ~20 µg/dL (2 mg/kg BID) for sustained coverage
  - Propofol gradually weaned

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Medications for Alcohol Use Disorder

Clinical Case (Resolution)

- **Clinical stabilization**
  - Propofol infusion ×2 days → cortical suppression
  - BAL and LP → cultures *Strep. pneumoniae*
  - Broad-spectrum antibiotics → narrowed
- **Outcome**
  - No further seizures
  - Successfully extubated; oxygen weaned; out of bed
  - Transferred to acute care

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Key Takeaways

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RECAP – Pharmacologic Strategy in Severe / Complicated AWS

Phenobarbital

Long-acting stabilization

- GABA ↑
- Glutamate ↓
- Long half-life

Ketamine

Glutamate blockade

- NMDA antagonist
- Helps when GABA drugs insufficient
- Preserves respiratory drive

Dexmedetomidine

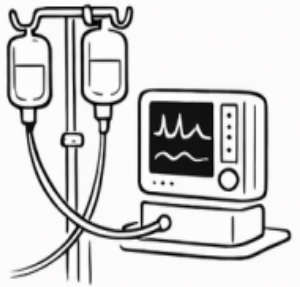
Autonomic control

- α2 agonist
- ↓ norepinephrine
- No respiratory depression

Propofol

Continuous cortical suppression

- Potent GABA-A agonist
- Titratable
- ICU / intubated patients



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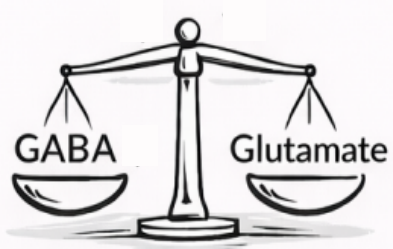
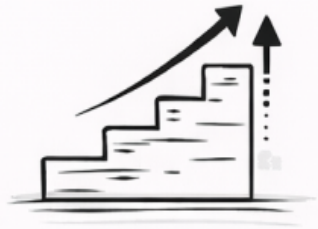
What Have We Learned?



Neurobiology

↓ GABA
↑ Glutamate
Hyperexcitation



Treatment evolves with severity

- Preserve respiratory drive when possible
- Escalate when needed

Kindling

- Progressive sensitization
- ↑ seizure risk

Severe AWS rarely occurs alone

- Treat comorbid illness

AWS stabilization ≠ AUD treatment

- Acute stabilization → Long-term recovery care → Recovery

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Questions?

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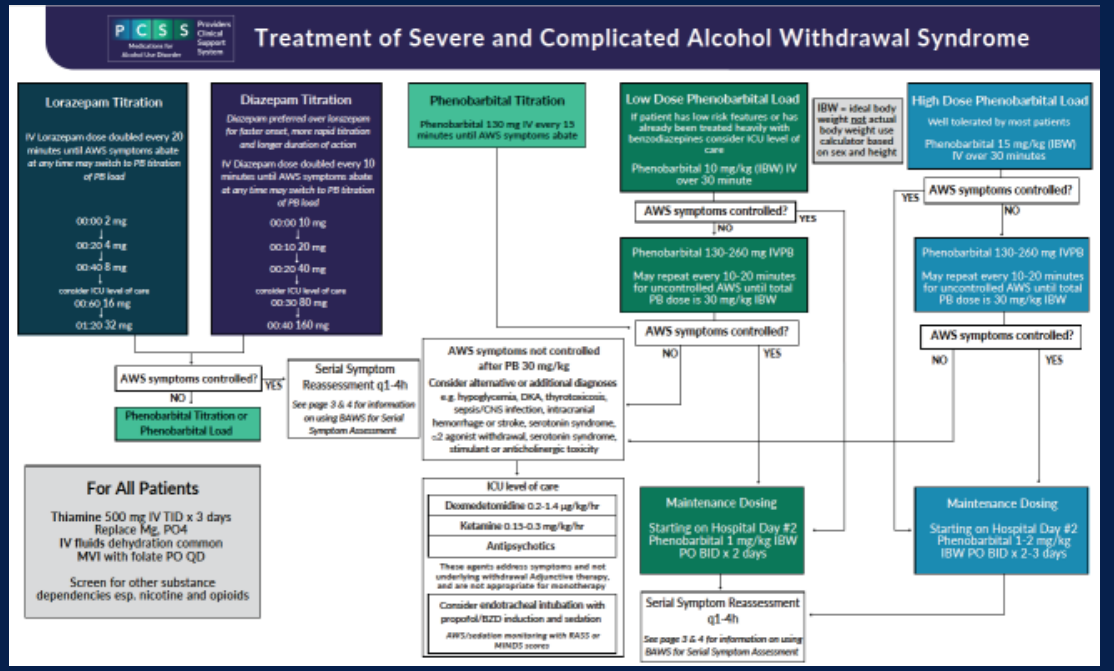
Further Learning

- Online module: Assessment and Management of Alcohol Withdrawal
- Digital Resource: Treatment of Severe and Complicated Alcohol Withdrawal Syndrome
- Digital Resource: Medications for Alcohol Use Disorder: Considerations for Patients with Comorbid Conditions
- Digital Resource: Outpatient Management of Alcohol Withdrawal
- Enduring Training: Who is at Risk of Alcohol Withdrawal? Management in Ambulatory Care



SCAN ME

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Medications for Alcohol Use Disorder

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Wrap-up

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