Alcohol Withdrawal & Treatment of Alcohol Use Disorder

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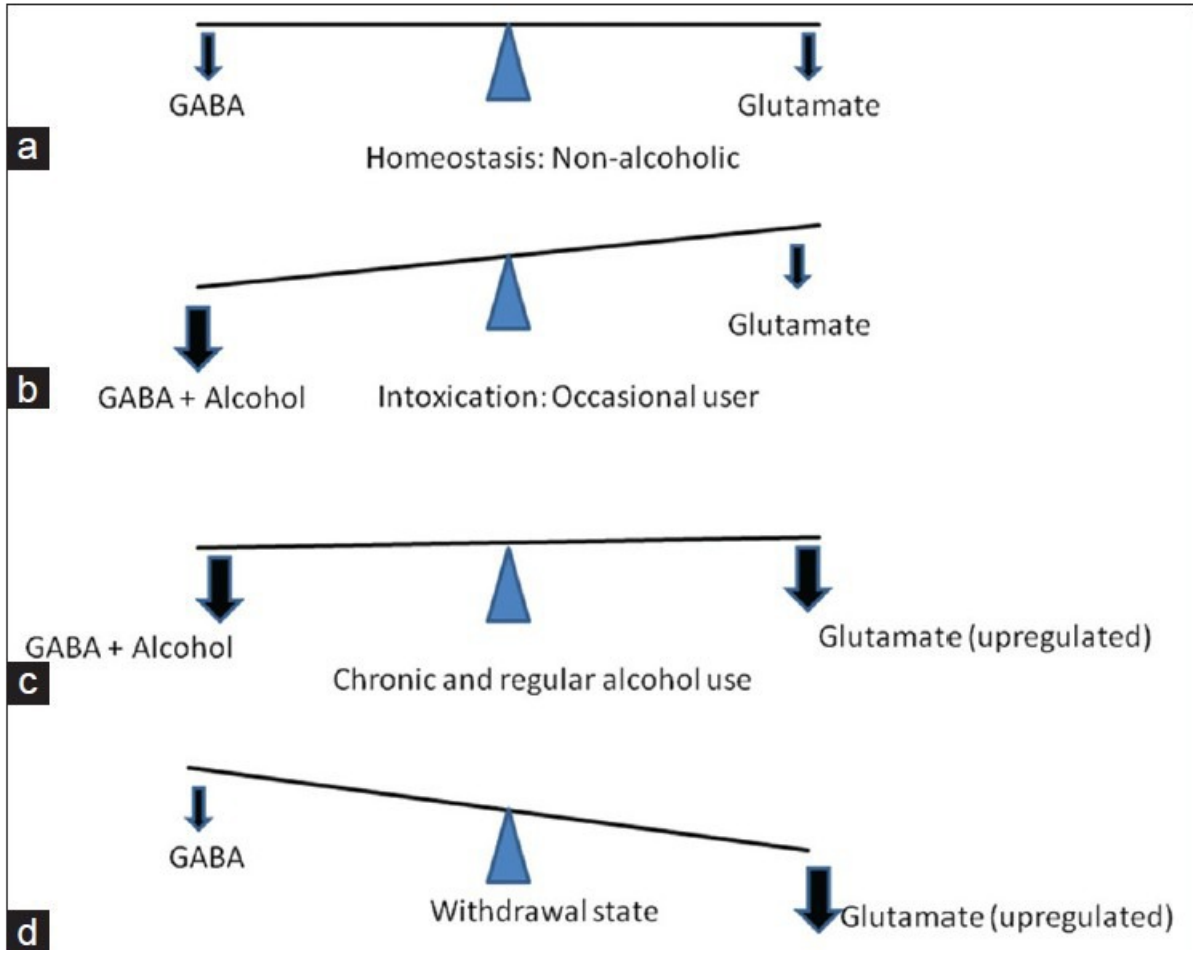
Disclosures

No financial relationships to disclose

Learning objectives

- Understand clinical criteria for deciding on inpatient vs outpatient therapy for patients desiring medically supervised alcohol withdrawal
- Review inpatient and outpatient medication regimens for alcohol withdrawal, including phenobarbital, benzodiazepines and adjunctive medications
- Understand the evidence supporting the use of medications to treat alcohol use disorder and the clinical considerations in medication selection

Pathophysiology

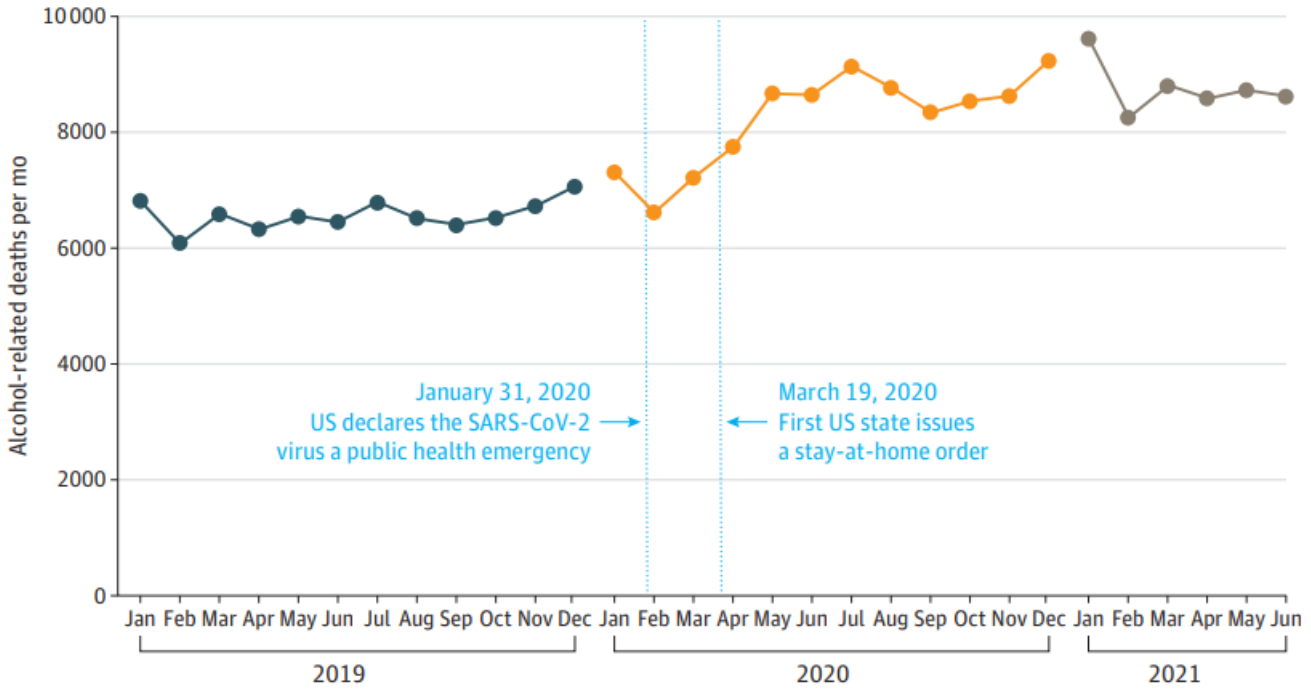


Alcohol Use & Use Disorder: Burden of Disease

- **Worldwide 5.1% of all deaths** are attributable to alcohol
- **In the United States 140,000 deaths** attributable to excessive drinking (premature deaths due to motor vehicle crashes, poisoning, suicide and cumulative health effects over time) per year
- **In Montana** excessive drinking results in **390 deaths**, representing 11,331 years of potential life lost in Montana per year
- **Montana hospitals** charged a total of $189 million dollars for alcohol-related hospitalizations and emergency department visits per year
- **During the pandemic**, deaths attributable to alcohol increased 25% between 2019-2020, where previously had been increasing by approximately 2.2% per year between 1999-2017

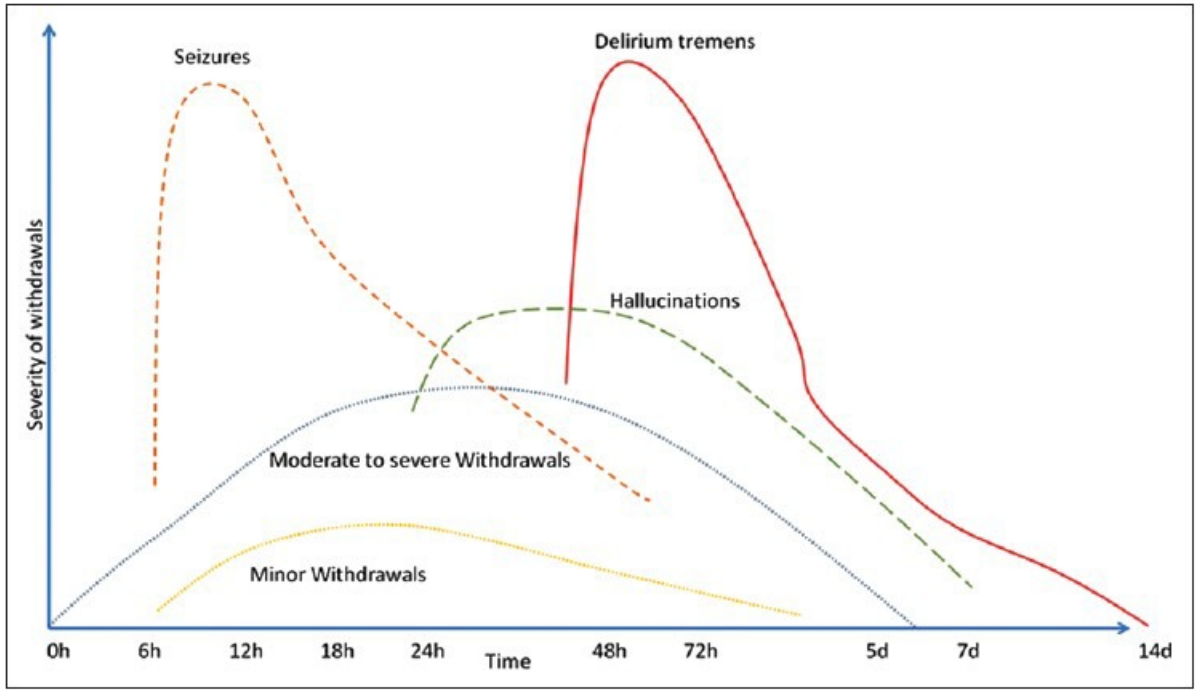
Alcohol Use & Use Disorder: Burden of Disease

Figure. Monthly Alcohol-Related Deaths Among People 16 Years and Older



Timeline

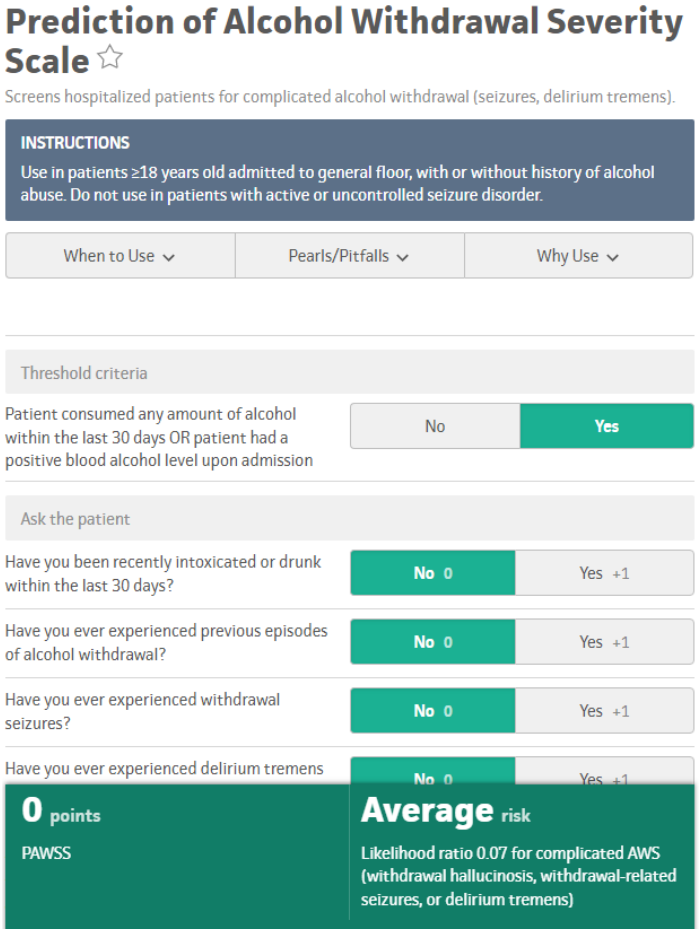
- 5% of patients will have DTs
- Delirium Tremens is defined by abnormal vital signs/autonomic instability, agitation and diaphoresis



Inpatient vs outpatient

PAWSS Score

- Binary – a score of 4 or more is considered positive, a score less than 4 is considered negative
  - Positive scores are associated with a likelihood ratio of 174 for complicated alcohol withdrawal
- Caveat: intended to risk stratify **hospitalized** patients but somewhat useful if negative
- Patients with a negative PAWSS score **might** be eligible for outpatient management



Outpatient management: the ideal situation

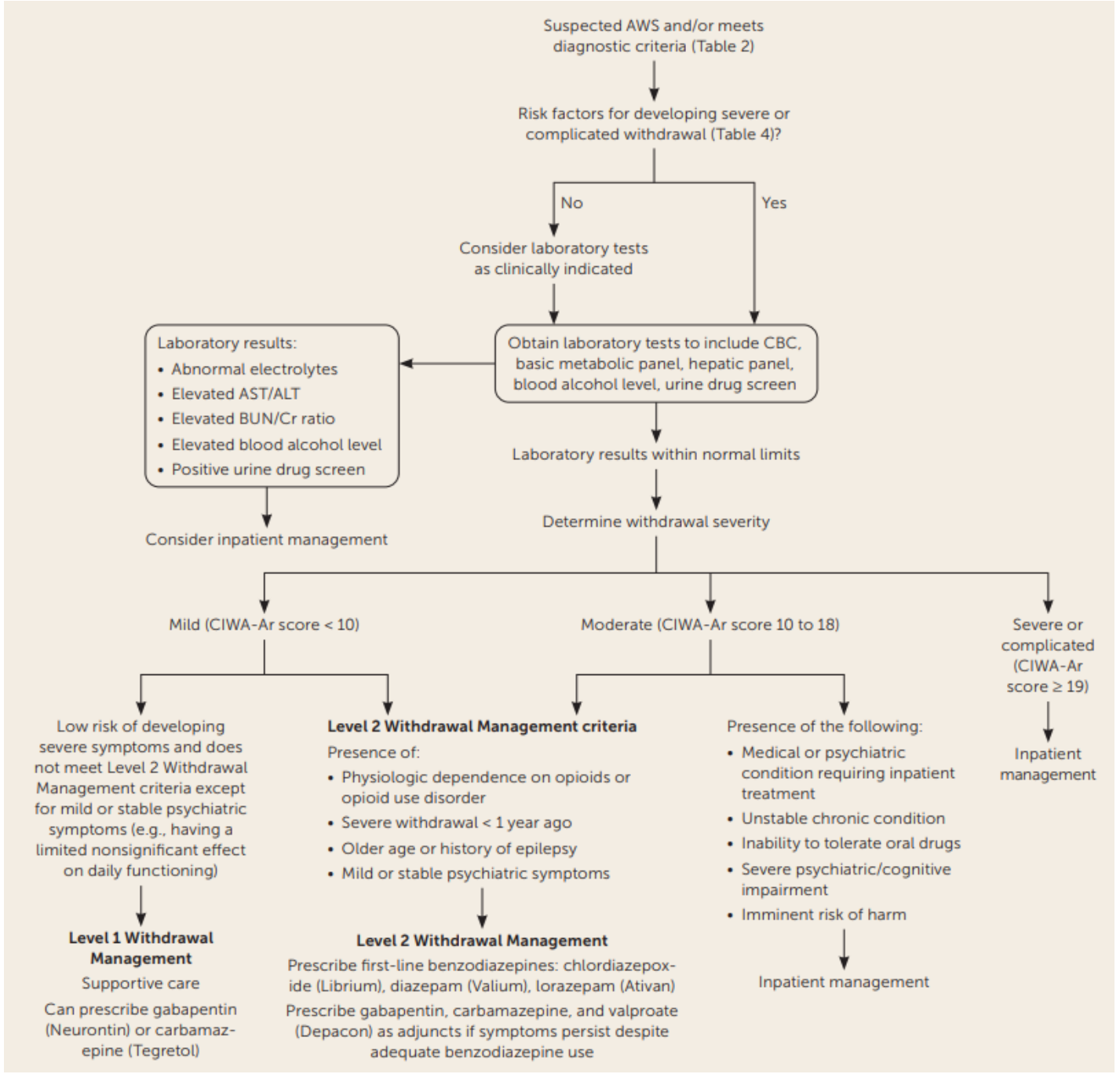
- Under age 65
- Able to come to the clinic regularly for check-ins with either PCP or nurse
- It's a Monday
- Reliable support person at home
- Stable housing
- No history of alcohol withdrawal seizures, DTs, ICU admission or prolonged hospitalization
- No active suicidal ideation
- No coronary artery disease, COPD, heart failure, insulin dependent DM, severe liver disease or other condition that might be exacerbated by the process of alcohol withdrawal
- No opioid or sedative-hypnotic dependence or use disorder history

Reminder: it’s ok to say “No”

Outpatient Management

- Ideally starting the process early in the week to allow for frequent re-assessment of the patient
- First visit with the patient and support person within 12-24 hours of the last drink
- See the patient daily or every other day to reassess symptoms, vitals and response to treatment
- Check labs: CMP, blood alcohol level, urine drug screen
- Provide clear ED precautions, overview of the expected symptoms
- Discuss a plan for sobriety after the acute withdrawal period
- Don’t forget: anti-emetics, thiamine, multivitamin

Outpatient Management



Outpatient Management: Low Risk (no benzodiazepines)

- **Who:** patients with mild withdrawal symptoms who are at minimal risk of developing severe/complicated alcohol withdrawal with low (< 10) CIWA scores
- Medication options:
  - Carbamazepine 600 to 800mg daily, tapered to 200mg – 400mg per day over 4-9 days
    - Why carbamazepine??? It's associated with decreased risk of return to heavy drinking!!
  - Gabapentin
    - 1200mg day 1 as loading dose
    - 300mg-600mg Q6H PRN withdrawal symptoms up to 1200mg daily
    - Taper to 300mg – 600mg daily over a week
    - Dosing for alcohol use disorder treatment is 300mg-600mg TID – most useful for prolonged withdrawal symptoms, less effective than naltrexone or acamprosate

Outpatient Management: Medium Risk (benzodiazepines)

- **Who:** patients with mild to moderate CIWA scores (10-18) or patients with mild CIWA scores and medical comorbidities or history of severe alcohol withdrawal

- **Benzodiazepines** are first-line therapy
  - **Short-acting** benzodiazepines in patients with liver disease or patients over 65
  - **Long-acting** benzodiazepines in most other patients
    - **Chlordiazepoxide** 50mg-100mg daily, divided BID or TID

- Supportive Medications
  - Carbamazepine 200mg Q8H
  - Clonidine 0.2mg daily for anxiety or autonomic hyperactivity
  - Gabapentin 400mg Q8H
  - Anti-emetics
  - Consider Valproate 300mg-500mg Q6H (avoid in patients with liver disease)

Inpatient management

Who: patients not meeting criteria for outpatient management, patients who have escalating withdrawal symptoms despite outpatient medication therapy, severe or complicated alcohol withdrawal

CIWA-Ar vs RASS

Richmond Agitation and Sedation Scale (RASS)		
+4	Combative	violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert & calm	
-1	Drowsy	Not fully alert, but has sustained awakening to *voice* (eye opening & contact ≥ 10 sec)
-2	Light sedation	Briefly awakens to *voice* (eye opening & contact < 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	Unarousable	No response to *voice or physical* stimulation

Clinical Insitutue Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

Patient:_____ Date: _____ Time: _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute:_____ Blood pressure:_____

NAUSEA AND VOMITING — Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TREMOR — Arms extended and fingers spread apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

PAROXYSMAL SWEATS — Observation.
0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

ANXIETY — Ask "Do you feel nervous?" Observation.
0 no anxiety, at ease
1 mild anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

AGITATION — Observation.
0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCES — Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.
0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning ornumbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

AUDITORY DISTURBANCES — Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

VISUAL DISTURBANCES — Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD — Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 no present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM — Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place/or person

Total CIWA-Ar Score

Alcohol

- ASAM Practice Guideline recommends against it
- That said, it is common practice, and reasonable to consider on and individualized patient basis when:
  - Patient has capacity to make medical decisions
  - The patient does not desire to stop drinking
  - Patient is able to take PO
  - No significant cirrhosis
  - Available on the hospital formulary

Phenobarbital Advantages Over Benzodiazepines

- Works on both GABA receptors to prolong opening of the ligand-gated channel and acts to down-regulate glutamate
- May be associated with less delirium
- More predictable pharmacodynamics
- Wider therapeutic index
- Ability to measure serum drug levels and correlate clinically
- Less risk of sedation at therapeutic doses

Evidence for Phenobarbital

Nisavic et al *Use of Phenobarbital in Alcohol Withdrawal Management*	Retrospective chart review of 562 alcohol withdrawal patients. Phenobarbital was associated with similar treatment outcomes and some patients in the benzodiazepine group had refractory symptoms that improved with transition to phenobarbital. Some possible decreased leaving AMA.
Tidwell et al *Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs CIWA-Ar protocol*	Retrospective cohort study of patients treated before (symptom triggered benzodiazepine therapy) and after implementation of a hospital phenobarbital protocol. Decreased ICU length of stay, hospital length of stay, less mechanical ventilation, less need for additional agents
Rosenson et al *Phenobarbital for Acute Alcohol Withdrawal: A prospective Randomized Double Blind Placebo Controlled Study*	Patients in the phenobarbital arm had decreased ICU admission and no increase in adverse outcomes.
Nelson et al *Benzodiazepines vs Barbituates for Alcohol Withdrawal: Analysis of 3 Different Treatment Protocols*	Retrospective study during a benzodiazepine shortage, patients were assigned to phenobarbital +/- lorazepam or diazepam. Similar outcomes across the three groups. No adverse outcomes.

Phenobarbital Pitfalls and Contraindications

- **Contraindications:**
  - Patient is truly allergic
  - Advanced cirrhosis w/ hepatic encephalopathy – potential for dose stacking and persistent coma
  - Chronic use of phenobarbital as an antiepileptic agent
  - Acute Intermittent Porphyria

- **Potential Pitfalls:**
  - Drug interactions – phenobarbital is a CYP3A4 inducer – check in with your friendly neighborhood pharmacist regarding dose adjustments
  - Diagnostic uncertainty as to whether the patient actually has alcohol withdrawal – phenobarbital has a half-life elimination of ~ 79 hours!
  - Concomitant administration of opioids or other sedating medications
  - Patients who previously received large amounts of benzodiazepines

Phenobarbital Dosing, Monitoring & Safety

- **Loading dose:** 10mg/kg of ideal body weight. For a 65kg person, this dose would be 650mg once!
  - This corresponds to a serum drug level of approximately 15 ug/mL, whereas mild toxicity begins at around 50 ug/mL
  - Threshold for toxicity is **lower** if benzodiazepines are on board
- Subsequent PRN dosing regimens:
  - 130mg Q 15-30 minutes PRN until resolution of symptoms
- Serum phenobarbital levels & cumulative dose:
  - optimal serum phenobarbital levels for alcohol withdrawal are somewhat unclear still. Therapeutic serum levels for seizure treatment are 15-40 ug/mL
  - The optimal **cumulative** dose of phenobarbital is also unclear – some have proposed 20 mg/kg as the maximum

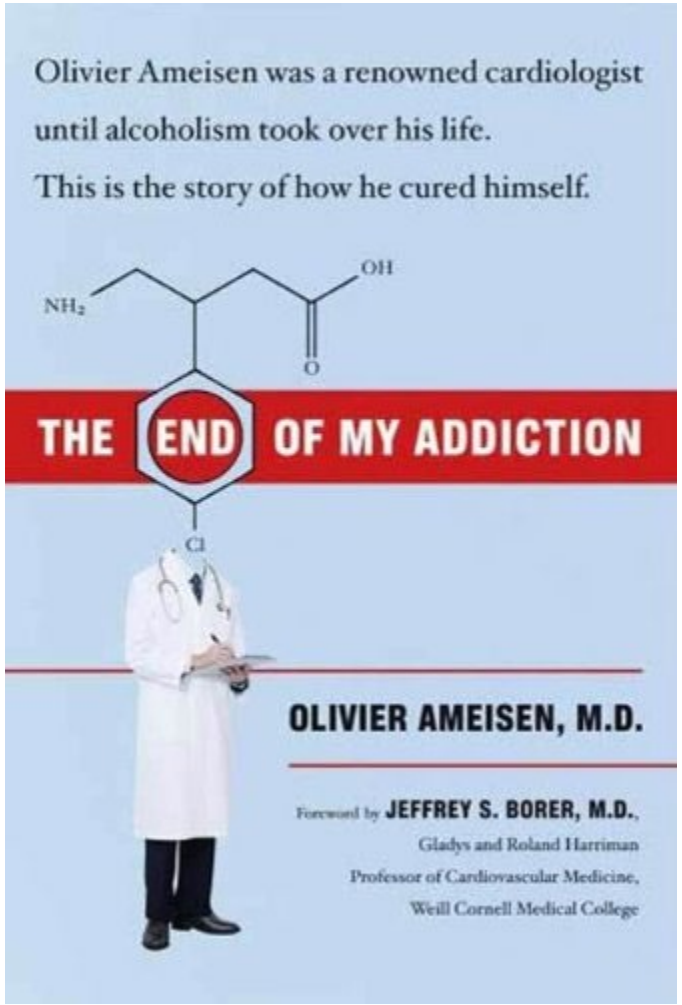
Benzodiazepines

- **Short-acting**
  - Best for older patients, patients with severe liver disease
- **Long-acting**
  - Consider chlordiazepoxide (Librium) in younger, healthier patients due to auto-taper effect, less reinforcing pharmacodynamics
- **Monitoring parameters:**
  - Number of hours since the patient's last drink
  - Total benzodiazepine dose required in 24 hours
  - Over-sedation/respiratory depression

Contraindications	Caution
Hypersensitivity to Benzodiazepines	COPD, sleep apnea, myasthenia gravis
Angle-closure glaucoma	Co-administration with any opioid or other medication that causes respiratory suppression

What about baclofen?

- Not recommended by ASAM Practice Guideline
- Cochrane review 2019: insufficient and low quality evidence to recommend one way or another
- In the absence of evidence strongly supporting using it, why not choose an evidence-based alternative?
- There is a small cohort of strong supporters of using baclofen



Supportive Measures

- Electrolytes
  - Monitor K, Mg, Phos
  - Some patients with severe alcohol use disorder may have refeeding syndrome
- Thiamine
  - IV or IM 200mg daily for 3-5 days for prevention of Wernicke's encephalopathy
- Glucose
- Again, consider addition of carbamazepine

After the acute withdrawal period

- Discontinue symptom-triggered scoring once the patients is 96 hours from last drink or sooner if symptoms are absent
- Discuss planning for sobriety after hospital discharge (ideally some of this takes place on admission as well)
- Discuss medications, social support, common triggers for return to drinking
- Provide anticipatory guidance: patients may experience withdrawal symptoms such as tremulousness or difficulty sleeping for several months – gabapentin can help with some of these symptoms
- The most common symptom that triggers return to drinking is difficulty sleeping, consider addressing insomnia treatment prior to discharge

Naltrexone (Revia, Vivitrol)

- Mu-opioid receptor antagonist
- **NNT to prevent return to any drinking = 20; NNT to prevent return to heavy drinking = 12**
- Avoid in patients with decompensated cirrhosis or on chronic opioid therapy; need at least 7 days off opioids before the first dose
- Will need monitoring for hepatotoxicity after 2 weeks of therapy
- Common side effects: headache, nausea, anhedonia
- Dosing:
  - PO: 50-150mg daily, start with 50mg
  - IM: 380mg Q28 days – wait to see if PO is tolerated first

Acamprosate (Camperal)

- GABA agonist/glutamate antagonist – reduces alcohol cravings and associated with better abstinence compared to naltrexone
- **NNT to prevent return to any drinking = 12; NNT for any reduction in risk of drinking = 9**
- Contraindicated in patients with CrCl < 30, adjust dosing if CrCl is 30-50
- Good option for patients whose liver disease precludes Naltrexone
- Dosing: 330mg TID to start, then 666mg TID
- Common side effects: diarrhea, rarely suicidal ideation

Disulfuram (Antabuse)

- Best for highly motivated patients with significant social support, patients who have someone to monitor medication adherence (adolescents and incarcerated patients) and **without** a condition that would be exacerbated by a disulfuram reaction
- No effect on alcohol cravings
- Aldehyde dehydrogenase inhibitor
- Dosing: 250-500mg daily for 1-2 weeks, then 250mg daily

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WHO Fact Sheet

CDC Fact Sheet

Montana DPHHS Fact Sheet Alcohol Use In Montana

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