ALCOHOL WITHDRAWAL SYNDROME

CASE-BASED APPROACH TO THE INPATIENT MANAGEMENT OF ALCOHOL WITHDRAWAL SYNDROME

Lisa W. Vercollone, MD, PharmD

Updates in Hospital Medicine

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DISCLOSURES

None

OBJECTIVES

- Discuss the various approaches to managing alcohol withdrawal syndrome including symptom-triggered and fixed-dose regimens of both benzodiazepines and phenobarbital.
- Review DSM-5 diagnostic criteria for alcohol use disorder.
- Highlight phenobarbital mechanism of action and pharmacokinetics as they apply to the treatment of alcohol use disorder.
- Perform a brief literature review on a couple recent studies using phenobarbital for the treatment of alcohol withdrawal syndrome.
- Review available medications for the treatment of alcohol use disorder.

APPROACHES TO THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME

CIWA-driven symptom-triggered

Use in patients with low risk for alcohol withdrawal seizures or other complications

Fixed dose benzodiazepine

History of or active severe withdrawal

Fixed dose phenobarbital

History of or active severe withdrawal

Strong consideration if benzo non-responder

CASE - KH

26W alcoholic with PMH GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

STIGMATIZING LANGUAGE!

AVOID	PREFERRED
alcoholic	person with alcohol use disorder
alcoholism	alcohol use disorder

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

- 2 standard size (750 mL) bottles of wine and 4-7 tequila shots daily for 3 weeks
- First admission for management of alcohol withdrawal 8/2019. Last admission 3 weeks ago. 25 admissions in less than 2 years.
- Frequent blackouts and falls
- No history of DT, withdrawal seizure, ICU admission
- No other substances
- Takes naltrexone 50 mg po daily.

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Drinking 2 standard size (750 mL) bottles of wine and 4-7 tequila shots daily for 3 months.

https://pubs.niaaa.nih.gov/publications/Audit.pdf Assessed 6/23/2021.

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Drinking 2 standard size (750 mL) bottles of wine and 4-7 tequila shots daily for 3 months.

Calculate the number of drinks per day.

Wine: 1500 mL wine / 150 mL = 10 drinks
Tequila: 7 shots = 7 drinks

Total: 17 drinks per day or 119 drinks per week

EXCESSIVE DRINKING

What is excessive drinking?

- For women, 4 or more drinks during a single occasion.
- For men, 5 or more drinks during a single occasion.

What is heavy drinking?

- For women, 8 or more drinks per week.
- For men, 15 or more drinks per week.

https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm. Accessed 8/15/2021.

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Subjective:

- Nausea. No vomiting. Anxious. Headache.

Physical exam:

- HR 115, BP 132/88.
- Anxious. Tremulous. Not diaphoretic.
- No auditory or visual hallucinations.

Labs:

- Blood alcohol level = 260
- Urine toxicology screen: negative
- Na 133, K 4.0, ALT 54, AST 132, Tbili 0.4, albumin 4.5, plt 273

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

What is her CIWA score?

CIWA - AR

Clinical Institution Withdrawal Assessment - Alcohol Revised (CIWA - Ar)

Assign score of 0 - 7 based on severity:

- Nausea and vomiting
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Tactile disturbances
- Auditory hallucinations
- Visual hallucinations
- Headache
- Orientation (up to score of 4)

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CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Let's review the keys points:

1. Number of drinks per day: 17
2. Number of admissions for management of alcohol withdrawal syndrome (detox's): 25
3. History of withdrawal seizures, ICU admissions, or delirium tremens: 0
4. Active signs or symptoms of withdrawal: tachycardia, anxiety, tremors, CIWA 14
5. BAL on arrival: 260

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Which is the MOST appropriate treatment plan?

A: Symptom-triggered CIWA-driven protocol starting once no longer intoxicated
B: Symptom-triggered CIWA-driven protocol with first dose now for CIWA 14
C: Fixed-dose benzodiazepine protocol with lorazepam starting once no longer intoxicated
D: Fixed-dose benzodiazepine protocol with lorazepam starting now for CIWA 14

1994: SAITZ ET AL. INDIVIDUALIZED TREATMENT

Individualized treatment for alcohol withdrawal: a randomized double-blind controlled trial.

Design	Randomized double-blind controlled trial at an inpatient detoxification unit in a VA medical center
Population	Patients admitted for the treatment of alcohol withdrawal who could give informed consent and had no history of seizures
Exclusion criteria	History of seizure; acute medical or psychiatric hospitalization
Goals/outcomes	Duration of medication treatment and total chlordiazepoxide administered
Interventions	Randomized to fixed regimen of chlordiazepoxide vs symptom-triggered regimen of chlordiazepoxide
Results/conclusions	Symptom-triggered decreases treatment duration and total dose of chlordiazepoxide needed. No differences in withdrawal severity.

2002: DAEPPEN ET AL: SYMPTOM-TRIGGERED VS FIXED

Symptom-triggered vs fixed schedule doses of benzodiazepine for alcohol withdrawal

Design	Prospective, randomized, double-blind controlled trial
Population	Patients with alcohol dependence entering an alcohol treatment program
Exclusion criteria	Abstinence less than 72 hr; major cognitive, psychiatric or medical comorbidity
Goals/outcomes	Total amount and duration of treatment with oxazepam, the incidence of complications, and the comfort level
Interventions	Randomized to 2 groups: symptom-triggered oxazepam vs scheduled oxazepam + prn
Results/Conclusions	Symptom-triggered treatment resulted in reduction in number of patients who received oxazepam and the mean dose and duration of oxazepam

SYMPTOM-TRIGGERED VS FIXED DOSE BENZODIAZEPINES

Outstanding concerns

- CIWA - Ar was designed and validated for clinical use in an inpatient setting but excluded active medical illness.
- Literature overall is not representative of the general medicine population.
- Inconsistencies due to the subjective nature of CIWA - Ar.
- Labor intensive for nursing staff.
- Hospitalized patients without alcohol use disorder may be placed on symptom-triggered protocol inappropriately.

J Gen Intern Med 2019 Jun;34(6):1018-1024.

2019: HOLLECK ET AL. SYMPTOM-TRIGGERED META-ANALYSIS

Symptom-triggered therapy for alcohol withdrawal syndrome: a systematic review and meta-analysis of RCT

Design	Systematic review of RCT of 6 studies involving 664 patients (included Saitz et al and Daeppen et al.)
Population	Low risk patients with alcohol withdrawal syndrome in specialized detoxification setting
Goals	Comparing symptom-triggered to fixed dose benzodiazepine therapy
Results/Conclusions	Moderate evidence suggests symptom-triggered therapy improved duration of therapy and total benzodiazepine dosage. Insufficient evidence to conclude major outcomes.

SYMPTOM-TRIGGERED VS FIXED DOSE BENZODIAZEPINES

Symptom-triggered

- Must be able to communicate and is not showing signs of delirium.
- No history of severe withdrawal

Fixed dose

- High blood alcohol level
- Already showing signs of severe withdrawal
- Preferred in patient with a history of severe withdrawal
  - Alcohol withdrawal-related seizures
  - ICU admission(s)
  - Delirium tremens

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Which is the MOST appropriate treatment plan?

A: Symptom-triggered CIWA-driven protocol starting once no longer intoxicated
B: Symptom-triggered CIWA-driven protocol with first dose now for CIWA 14
C: Fixed-dose benzodiazepine protocol with lorazepam starting once no longer intoxicated
D: Fixed-dose benzodiazepine protocol with lorazepam starting now for CIWA 14

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Which is the MOST appropriate treatment plan?

Correct answer(s):

D: Fixed-dose benzodiazepine protocol with lorazepam starting now for CIWA 14

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Why are these answers incorrect?

A: Symptom-triggered CIWA-driven protocol starting once no longer intoxicated
B: Symptom-triggered CIWA-driven protocol with first dose now for CIWA 14
C: Fixed-dose benzodiazepine protocol with lorazepam starting once no longer intoxicated

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Key points...

1. Number of drinks per day: 17
2. Number of admissions for management of alcohol withdrawal syndrome (detox's): 25
3. History of withdrawal seizures, ICU admissions, or delirium tremens: 0
4. **Active signs or symptoms of withdrawal: CIWA 14**
5. **BAL on arrival: 260**

ACTIVELY WITHDRAWING WITH POSITIVE BLOOD ALCOHOL LEVEL!

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Proceed with fixed dose benzodiazepine with lorazepam.

Day 1:

- Lorazepam 2 mg with interval...
  - Every 1 hour if suspect severe alcohol withdrawal
  - Every 4 hours if prophylaxis in non-communicative patient
- Hold dose if...
  - patient exhibits NO signs of alcohol withdrawal (stable vital signs, no evidence of tremor or agitation)
  - evidence of benzodiazepine intoxication (sedation, nystagmus, ataxia, slurred speech, disinhibition, delirium)
- Continue x 24 hours
- Notify provider if no improvement after two consecutive doses or worsening of symptoms.

BWH Alcohol Withdrawal Guidelines. Accessed 6/18/2021.

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Receives lorazepam 12 mg in the first 24 hours (-- lorazepam 2 mg po q4h)

Day 2:

- She is looking better today. CIWA < 5.
- Initiate taper by 20-25% per day:
  - Day 2: Lorazepam 1.5 mg po q4h x 24 hrs
  - Day 3: Lorazepam 1 mg po q4h x 24 hrs
  - Day 4: Lorazepam 1 mg po q6h x 24 hrs
  - Stop on day 5

BWH Alcohol Withdrawal Guidelines. Accessed 6/18/2021.

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Discharge day:

- Off all benzodiazepines.
- Formulated a structured aftercare plan with the team of social workers.
- Patient is wanting to resume her home naltrexone 50 mg po qday
  - Expresses concern she doesn't always remember to take it.
  - Finds it helpful when she does take it.

MEDICATIONS FOR ALCOHOL USE DISORDER (MAUD)

Disulfiram - 1949

Naltrexone - 1994

Acamprosate - 2004

NALTREXONE

Reduces positive reinforcement

Mechanism	Mu-receptor antagonist. Blocks stimulation of dopamine reward system.
Metabolism	Hepatic
Half-life	4 hours
Adverse reactions	Nausea, vomiting, abdominal pain, headache, dizziness, hepatotoxicity
How supplied	PO and IM
Dosing	50 mg po daily or 380 mg IM once monthly

NALTREXONE

Clinical considerations

- Elevated LFTs: check LFTs prior to initiation and prescribe unless severe elevations in transaminases.
- GI upset: initiate with 25 mg po x 1 dose and monitor for symptoms (usually occurs within a few hours)
- Relapse: counsel patients to continue taking.
- Acute pain: unresponsive to opioids.
- IM formulation: Vivitrol
  - Poor adherence to PO naltrexone
  - Bypasses first pass metabolism
  - Once monthly dosing

CASE - KH

26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

Discharge day:

- Off all benzodiazepines.
- Formulated a structured aftercare plan with the team of social workers.
- Patient is wanting to resume her home naltrexone 50 mg po qday
  - Expresses concern she doesn't always remember to take it.
  - Finds it helpful when she does take it.

Arrange for outpatient appointment to receive Vivitrol injection next week.

Prescribe a bridge prescription for naltrexone 50 mg po daily to take until her appointment.

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

Bedside RN performs an abbreviated version of Audit - C questionnaire and pages you with concerns about the results.

AUDIT - C

Alcohol Use Disorders Identification Test-Concise (AUDIT-C)

- Brief alcohol screening instrument that reliably identifies persons who are hazardous drinkers or have active alcohol use disorders
- Modified version of the 10-item AUDIT developed by the WHO and published in 1998.

Questions	0	1	2	3	4
1) How often did you have a drink containing alcohol in the past year?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
2) How many drinks did you have on a typical drinking day in the past year?	0 to 2	3 or 4	5 or 6	7 to 9	10 or more
3) How often did you have 6 or more drinks on one occasion in the past year?	Never	Less than Monthly	Monthly	Weekly	Daily or almost daily

Total Score: _____ [ ] Positive [ ] Negative
Positive: Either a) Total score ≥4 (for men) or ≥3 (for women)

https://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm

https://cde.drugabuse.gov/instrument. Assessed 6/23/2021.; BWH Alcohol Withdrawal Guidelines. Accessed 3/4/2021

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

Bedside RN performs an abbreviated version of Audit - C questionnaire and pages you with concerns about the results.

- **Your patient scored a 7 on AUDIT-C: POSITIVE**

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

Bedside RN performs an abbreviated version of Audit - C questionnaire and pages you with concerns about the results.

- Patient is denying heavy alcohol use to you but admits to having a couple beers yesterday. Last drink 10 hours ago.
- CIWA score = 3 (mild tremor with outstretched arms and mild anxiety)
- No other medical records in your EMR

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

Bedside RN performs an abbreviated version of Audit - C questionnaire and pages you with concerns about the results.

- Add BAL to initial labs --> BAL 55 mg/dL (5 hours ago).

ALCOHOL METABOLISM

Zero order kinetics: constant amount of drug is eliminated per unit time

Blood alcohol levels fall at a rate of about 20 mg/dL/h

Toxicity states in non-tolerant individual:

- Low levels (10 to 50 mg/dL)—decreased anxiety, feelings of well-being, increased sociability
- Moderate levels (80 to 100 mg/dL)—impaired judgment and motor function
- Higher levels (150 to 200 mg/dL)—marked ataxia, reduced reaction time, blackout
- Anesthetic levels (300 to 400 mg/dL)—severe motor impairment, vomiting, loss of consciousness
- Lethal level (400 to 500 mg/dL and above)

ASAM Principles of Addiction Medicine, 6th edition. Chapter: The Pharmacology of Alcohol.

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

BAL 55 mg/dL: 5 hours ago. Last drink: 10 hrs ago.

- 5 hours x 20 mg/dL = 100 mg/dL
- 100 mg/dL + 55 mg/dL = 155 mg/dL at the time of last drink
- Higher levels (150 to 200 mg/dL)--marked ataxia, reduced reaction time, blackout
- 5 hours since BAL of 55 = current BAL < 10

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

What is your next step?

A: No changes to treatment plan
B: Place on CIWA and symptom-triggered regimen of lorazepam
C: Start fixed-dose benzodiazepine regimen with lorazepam
D: Give phenobarbital 8 mg/kg IV loading dose

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

What is your next step?

Correct answer(s):

B: Place on CIWA and start symptom-triggered regimen of lorazepam

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

Place on CIWA and start symptom-triggered regimen of lorazepam

CIWA 0 - 7	CIWA 8-15	CIWA > 15
No medication indicated	lorazepam 2 mg x 1	lorazepam 4 mg x 1
Continue CIWA q4h	Continue CIWA q4h	Call provider to reassess
Stop CIWA after 6 consecutive scores less than 8.	If no improvement in CIWA after 2 consecutive doses or if patient shows worsening of symptoms, contact provider to change regimen.	

CASE - AF

60M PMH HTN, HLD, and tobacco use disorder actively smoking 1 ppd (40+ pack year history) admitted for chest pain.

Place on CIWA and start symptom-triggered regimen of lorazepam

Don't forget to add...
- Thiamine 100mg PO daily
- Folic acid 1 mg PO daily
- Multivitamin 1 tablet PO daily

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

- Middle school math teacher
- Describes herself as a "social drinker" prior to COVID-19.
- Drinking increased over the past year when school went to all remote learning. Then further increased during summer months/school vacation.
- Admits to trying to cut back in preparation for the new school year starting next month.
- Never sought treatment for heavy alcohol use.

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

- Initially she is unable to quantify the amount of alcohol she drinks daily.
  - How often do you go to the liquor store (or order alcohol delivered to the house)? every 2 days
  - What do you buy when you go? 1 handle of whiskey (1.75 L)

Number of drinks/day = (1.75 L x 1000 mL = 1750 mL/ 2 days = 875 mL daily/45 mL per drink) = 19 drinks

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

Does he have an alcohol use disorder?

Refer to Diagnostic and Statistical Manual of Mental Disorders (DSM–5).

DSM-5 CRITERIA

In the past year, have you:

SEVERITY

Mild: 2 - 3 symptoms
Moderate: 4 - 5 symptoms
Severe: ≥ 6 symptoms

Our patient:

8 symptoms = Severe

1. Had times when you ended up drinking more, or longer, than you intended?
2. More than once wanted to cut down or stop drinking, or tried to, but couldn't?
3. Spent a lot of time drinking? Or being sick or getting over other aftereffects?
4. Wanted a drink so badly you couldn't think of anything else?

"This is new to DSM–5"

5. Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
6. Continued to drink even though it was causing trouble with your family or friends?
7. Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
8. More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
9. Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
10. Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
11. Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?

NIAAA: Alcohol Use Disorder: A Comparison Between DSM–IV and DSM–5. www.niaaa.nih.gov. Accessed June 2021.

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

Does he have an alcohol use disorder?

Refer to Diagnostic and Statistical Manual of Mental Disorders (DSM–5).

Diagnosis: severe alcohol use disorder.

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

Subjective:
- Nausea and mild headache.

Physical exam:
- HR 95, BP 126/76. CIWA 8.
- Slight tremor and mild diaphoresis.
- No auditory or visual hallucinations.

Labs:
- Blood alcohol level = 350
- Urine toxicology screen: negative
- Na 136, K 2.8, ALT 110, AST 305, Tbili 1, albumin 3.9, plt 140

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

Let's review the key points:

1. Number of drinks per day: 19
2. Number of admissions for management of alcohol withdrawal syndrome: 0
3. History of withdrawal seizures, ICU admissions, or delirium tremens: 0
4. Active signs or symptoms of withdrawal: CIWA 8
5. BAL of arrival: 350

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

What is the next best step:

A: Start symptom-triggered CIWA protocol since this is her first admission for management of alcohol use disorder
B: Place on fixed-dose benzodiazepine regimen starting now
C: Place on fixed-dose benzodiazepine regimen once her blood alcohol level returns to zero
D: Place on fixed-dose phenobarbital regimen starting now
E: Place on fixed-dose phenobarbital regimen once her blood alcohol level returns to zero

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

What is the next best step:

Correct answer(s):

B: Place on fixed-dose benzodiazepine regimen starting now
D: Place on fixed-dose phenobarbital regimen starting now

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

Why are these incorrect?

A: Start symptom-triggered CIWA protocol since this is her first admission for management of alcohol use disorder
C: Place on fixed-dose benzodiazepine regimen once her blood alcohol level returns to zero
E: Place on fixed-dose phenobarbital regimen once her blood alcohol level returns to zero

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

What is the next best step:

Correct answer(s):

B: Place on fixed-dose benzodiazepine regimen starting now
D: Place on fixed-dose phenobarbital regimen starting now

Before we make a decision, let's discuss the use of phenobarbital in alcohol withdrawal syndrome...

WHEN TO CONSIDER PHENOBARBITAL

- History of:
  - Delirium tremens
  - Alcohol withdrawal seizures
  - Benzodiazepine non-response or benzodiazepine resistance
  - Previous ICU admission for alcohol detox
- Showing current symptoms of delirium/encephalopathy
- With active DT's or severe withdrawal symptoms not responding to benzodiazepines
- At risk for paradoxical disinhibition with benzodiazepines:
  - Acute and chronic TBI
  - Neurodegenerative disorders
  - History of alcohol related black-outs and/or assaultive behavior

ALCOHOL WITHDRAWAL SYNDROME

Image: https://medicinespecifics.com/alcohol-withdrawal-gaba-mechanism/ Accessed 5/24/2020

- Down-regulation of inhibitory GABA receptors
- Up-regulation of excitatory NMDA/AMPA/kainate-subtype glutamate receptors
- Dysregulation of the inhibitory and excitatory neurotransmitter systems
- Super excitation of glutamate receptors = alcohol withdrawal syndrome

PHENOBARBITAL MECHANISM OF ACTION

GABA CHLORIDE CHANNEL

Benzodiazepines
- increase frequency of channel opening
- requires the presence of GABA

Barbiturates
- increased duration of channel opening
- does NOT require the presence of GABA
- no cross-tolerance

GLUTAMATE RECEPTOR

Benzodiazepines
- NO effect

Barbiturates
- inhibits glutamate receptors
- NMDA, AMPA, and kainate

PHENOBARBITAL PHARMACOKINETICS

Fast onset of action
IV/IM: < 30 min; PO: 60 min

Fast peak effect
IV/IM: < 30 min

Long half-life
Approx 80 hours

Long elimination
> 2 weeks

Wide therapeutic index
15 - 40 mcg/mL
Toxic > 65 mcg/mL

Predictable
in the absence of benzodiazepines

Metabolized CYP450
3A4 and 2E1

Weight-based front loading dosing
ideal body weight

2019: NISAVIC M ET AL. PHENOBARBITAL MONOTHERAPY

Nisavic et al. Psychosomatics. 2019; 60: 458 - 467.

Design	Retrospective chart review of patients admitted to a general hospital
Population	Patients who received pharmacological treatment for AUD and AWS
Goals/outcomes	Development of AWS-related complications (seizures, alcoholic hallucinosis, and alcohol withdrawal delirium), LOS, ICU admissions/LOS, ADR, AMA discharges
Interventions	Comparing patients treated with benzodiazepines (pre-intervention) vs patients treated after implementation of a phenobarbital-monotherapy protocol
Results/Conclusions	1) Phenobarbital is an effective and well tolerated alternative to BZD for treatment of AWS. 2) Overall rates of sedation appeared comparable. 3) LOS was not increased with phenobarbital.

2020: NEJAD, ET AL. PHENOBARBITAL VS FIXED-DOSE BZD

Nejad et al. Psychosomatics. 2020; 61: 327-335

Design	Retrospective chart review of patients admitted to a general hospital
Population	Patients presenting with acute surgical trauma and received pharmacological management for AWS
Goals/outcomes	Development of AWS: uncomplicated/minor and complicated (AWD, alcohol withdrawal seizures, alcoholic hallucinosis), hospital LOS, mortality, ADR
Interventions	Fixed-dose benzodiazepine protocol pathway vs phenobarbital protocol
Results/Conclusions	1) Phenobarbital in this setting found to have superior outcomes to BZD: decreased AWD and uncomplicated AWS. 2) Phenobarbital may be safer and potentially more effective

RISK OF ALCOHOL WITHDRAWAL

HIGH RISK

Past delirium tremens +/- past seizures and at least one of the following:
- Alcohol use > 2 weeks
- Active withdrawal symptoms
- + BAL, elevated MCV, elevated AST:ALT ratio

MEDIUM RISK

Active alcohol dependence plus two of the following:
- 2 or more days since last drink
- Elevated BAL
- Autonomic dysfunction with BAL > 100
- Elevated MCV and/or AST:ALT ratio
- Heavier and longer drinking history
- Age ≥ 35 years
- Burn related injuries
- Falls, particularly with long bone fractures

RISK OF COMPLICATIONS

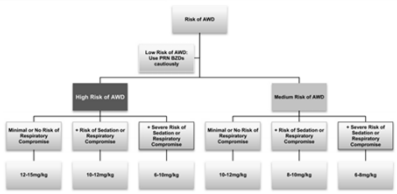
SEDATION

- Age greater than 65
- Hepatic dysfunction
- Narcotics
- Head injury (requiring neuro checks)
- Recent administration of benzodiazepines
- Current administration of sedatives

RESPIRATORY COMPROMISE

- Pneumonia
- Rib fractures
- Chest tubes
- Pulmonary contusion(s)
- C-collar/brace

PHENOBARBITAL PROTOCOL



Reiland et al. Psychosomatics. 2020;61. 327-339.

PHENOBARBITAL DOSING

Loading dose

- 6 - 15 mg/kg based on ideal body weight
- Given as one continuous infusion over 30 minutes or
- Fractionated into 3 doses given IV/IM every 3 hours

Taper

- Candidates:
  - history of severe withdrawal
  - continuing to show signs and symptoms of active withdrawal following the loading dose
- Begin on day 2 and continue for 4 days
  - 64.8 mg po twice daily x 2 days, then 32.4 mg po twice daily x 2 days

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

You decide to start fixed-dose phenobarbital.

- Risk of alcohol withdrawal: HIGH
- Risk of sedation: LOW
- Risk of respiratory compromise: LOW

Start phenobarbital 12 mg/kg loading dose

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

Phenobarbital 12 mg/kg loading dose. Ideal body weight = 65 kg.

Day 1:

- Total loading dose = 780 mg
- Give in 3 divided doses = 260 mg IM every 3 hours x 3 doses

What is your goal?

RICHMOND AGITATION SEDATION SCALE

Goal of RASS 0 to -1

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 movmt, 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

Image: https://www.greenmed.com/images/9144/agitation-nursing-richmond-diagnosis-rass

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

She completed her loading dose of 780 mg 2 hours ago.

- On reassessment, RASS 0.
- Order phenobarbital 64.8 mg po twice daily to start tomorrow.

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

She continues to do well on day 3 and you anticipate discharge tomorrow.

- She is interested in starting medication for alcohol use disorder.
- Her liver enzymes are improving but remain moderately elevated.

What are her options?

MEDICATIONS FOR ALCOHOL USE DISORDER (MAUD)

Disulfiram - 1949

Naltrexone - 1994

Acamprosate - 2004

DISULFIRAM

Alcohol-sensitizing - Aversion Therapy

Mechanism	Irreversible inhibition of aldehyde dehydrogenase --> build up of acetaldehyde
Metabolism	Hepatic and renal elimination
Half-life	12 hours (effects last much longer due to permanent enzyme inhibition)
Adverse reactions	Drowsiness, lethargy, hepatotoxicity, psychosis, seizures, peripheral neuropathy, optic neuritis
How supplied	PO
Dosing	250 - 500 mg po daily

DISULFIRAM

Clinical considerations

- Safety concerns: contraindicated in patients with significant coronary artery disease or heart failure, liver disease/varices, and pregnancy
- Disulfiram-ethanol reaction lasts up to 14 days
- Counsel patients to avoid all alcohol-containing products
- Helps to contract with significant other/sober support to ensure adherence

ACAMPROSATE

Reduces negative reinforcement

Mechanism	GABA receptor agonist and NMDA receptor modulator
Metabolism	Does not undergo metabolism. Renally excreted.
Half-life	32 hours
Adverse reactions	Diarrhea, insomnia
How supplied	PO
Dosing	666 mg po tid

ACAMPROSATE

Clinical considerations

- Cumbersome dosing: 2 large tablets three times daily -> adherence is a major concern
- Dose adjust if CrCl less than 30
- No drug interactions

CASE - AG

35W no significant PMH brought in by husband after he witnessed her have a seizure after attempting to cut back her alcohol intake.

She continues to do well on day 3 and you anticipate discharge tomorrow.

- She prefers to try acamprosate for now. Outpatient RX provided.
- Expresses concern about compliance "I know myself"

Plan for close follow-up with her primary care physician

Once liver function tests normalize, patient plans to pursue transition to naltrexone.

CASE - ML

51M PMH severe alcohol use disorder, hypertension, and anxiety admitted for alcohol withdrawal syndrome.

- Six 25 oz cans of beer + 1 pint vodka daily x 3 months (35 drinks/day)
- History of withdrawal related seizures, blackouts, delirium tremens and ICU admissions.
- Cannot recall last time he was abstinent

CASE - ML

51M PMH severe alcohol use disorder, hypertension, and anxiety admitted for alcohol withdrawal syndrome.

- Six 25 oz cans of beer + 1 pint vodka daily x 3 months (35 drinks/day)
- History of withdrawal related seizures, blackouts, delirium tremens and ICU admissions.
- Cannot recall last time he was abstinent

Hospital course:

- While in the ED, he received phenobarbital at 10 mg/kg IV loading dose = 800 mg.
- 3 hours later, he arrives on the floor...

CASE - ML

51M PMH severe alcohol use disorder, hypertension, and anxiety admitted for alcohol withdrawal syndrome. Loaded with phenobarbital 10 mg/kg load = 800 mg.

- He is feeling a little better but still complains of nausea, headache, anxiety.
- Exam: HR 102, BP 173/111, RR 18, O2 99% RA. Restless, anxious, tremulous, diaphoretic, no visual hallucinations
- RASS 2

CASE - ML

51M PMH severe alcohol use disorder, hypertension, and anxiety admitted for alcohol withdrawal syndrome. Loaded with phenobarbital 10 mg/kg load.

Alcohol withdrawal remains uncontrolled.

What do you do next?

A: Give phenobarbital 130 mg IM x 1 dose and reassess in one hour
B: Start symptom-triggered CIWA protocol with lorazepam
C: Start phenobarbital PO taper tomorrow morning
D: Give an additional phenobarbital 10 mg/kg loading dose

CASE - ML

51M PMH severe alcohol use disorder, hypertension, and anxiety admitted for alcohol withdrawal syndrome. Loaded with phenobarbital 10 mg/kg load.

Alcohol withdrawal remains uncontrolled.

Correct answer(s):

A: Give phenobarbital 130 mg IM x 1 dose and reassess in one hour

PHENOBARBITAL DOSING

Uncontrolled alcohol withdrawal syndrome after receiving loading dose:

- Give phenobarbital 65 mg - 130 mg IV/IM/PO every 1 hour as needed to achieve RASS goal of 0 to -1
- Remember to utilize adjunctive symptomatic management

WHY ARE THESE LESS PREFERRED OPTIONS?

B: Start symptom-triggered CIWA protocol with lorazepam

- Phenobarbital pharmacokinetics
- Avoid benzodiazepines after loading dose

C: Start phenobarbital PO taper tomorrow morning

- Uncontrolled alcohol withdrawal
- Peak effect of phenobarbital less than 30 min

D: Give an additional phenobarbital 10 mg/kg loading dose

- Adjust using additional as needed doses of phenobarbital

CASE - ML

51M PMH severe alcohol use disorder, hypertension, and anxiety admitted for alcohol withdrawal syndrome. Loaded with phenobarbital 10 mg/kg load.

- Pt receives phenobarbital 130 mg IM x 1
- You reassess in one hour: RASS 2
  - Repeat phenobarbital 130 mg IM x 1
- You reassess in 3 hours: RASS 1
  - Repeat phenobarbital 130 mg IM x 1
- **You reassess in 2 hours: RASS -1 --> You have reached your goal!**

Total dose = 800 mg IV + 130 mg IM + 130 mg IM + 130 mg IM = 1190 mg --> 14.9 mg/kg

SUMMARY

- Symptom-triggered CIWA-driven approaches definitely have their place in inpatient care but are not for everyone.
- Consider fixed-dose benzodiazepine or phenobarbital regimens for patients with history of complicated withdrawal and/or at risk of moderate to severe alcohol withdrawal.
- If choosing a phenobarbital loading dose approach, be sure to evaluate the patient post-treatment to confirm RASS goal has been met.
- There are three medications FDA-approved for treatment of alcohol use disorder. It is important to offer MAUD to all patients identified as having an alcohol use disorder.