Alcohol Withdrawal Management: Beyond Benzos

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Disclosure Information

- Presenter 1: Michael Weaver, MD, DFASAM
  - No Disclosures
- Presenter 2: Martha J Wunsch, MD, DFASAM
  - No Disclosures

Learning Objectives

- Identify different evidence-based pharmacologic options for treatment of withdrawal from alcohol and/or sedatives
- Recognize risks and benefits of pharmacologic options for sedative withdrawal treatment, including phenobarbital, gabapentin, and other medications
- Discuss treatment of complex sedative withdrawal syndromes in different settings

Alcohol Withdrawal: Basic Concepts

Alcohol withdrawal

- Widespread use of alcohol makes alcohol withdrawal syndrome the most common withdrawal syndrome
- 20% of patients with alcohol use disorder will develop severe alcohol withdrawal
- Withdrawal is worsened by concurrent medical and/or psychiatric illness

Significance of kindling

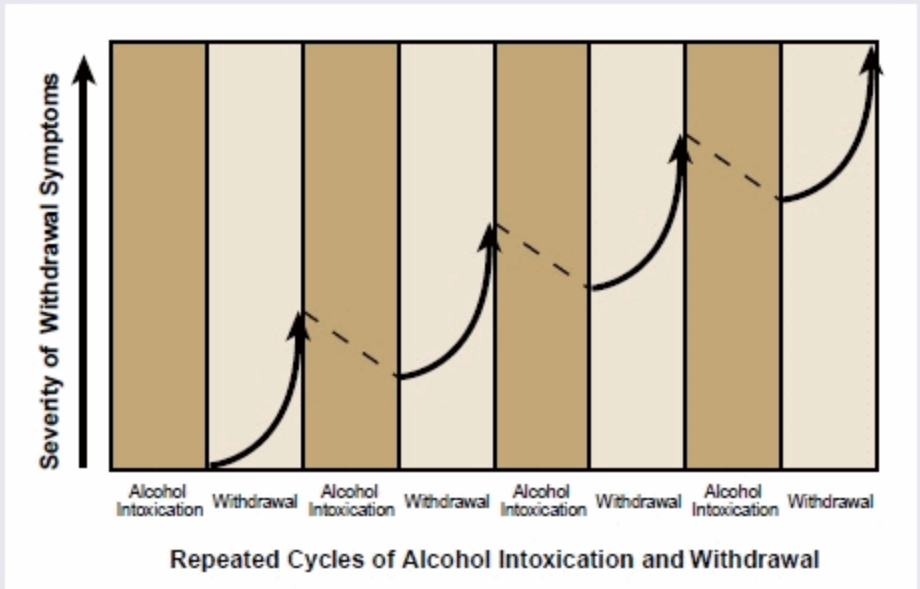


Figure 1 Graphic representation of the kindling concept during alcohol withdrawal. The term "kindling" refers to the phenomenon that people undergoing repeated cycles of intoxication followed by abstinence and withdrawal will experience increasingly severe withdrawal symptoms with each successive cycle.

- The more a patient has withdrawal, the more likely the patient will have withdrawal again

Becker HC. Kindling in alcohol withdrawal. Alcohol Health Res World 1998;22(1):25-33

Spectrum of alcohol withdrawal

Syndrome	Clinical Findings	Onset and Duration
Minor	Tremulousness, anxiety, headache, diaphoresis, palpitations, anorexia, GI upset, insomnia, normal MS	6-36 hours, symptoms may begin before BAL returns to 0
Seizure	Generalized, tonic-clonic, status epilepticus is rare	8-48 hours, peaks after 24 hours after last drink, MAY BE FIRST SYMPTOM OF WITHDRAWAL
Alcoholic Hallucinosis	Transient usually visual (may be auditory and tactile hallucinations) Normal VS and intact orientation	12-48 hours
Delirium Tremens	Disorientations, hallucinations, agitation, autonomic instability	48-96 hours

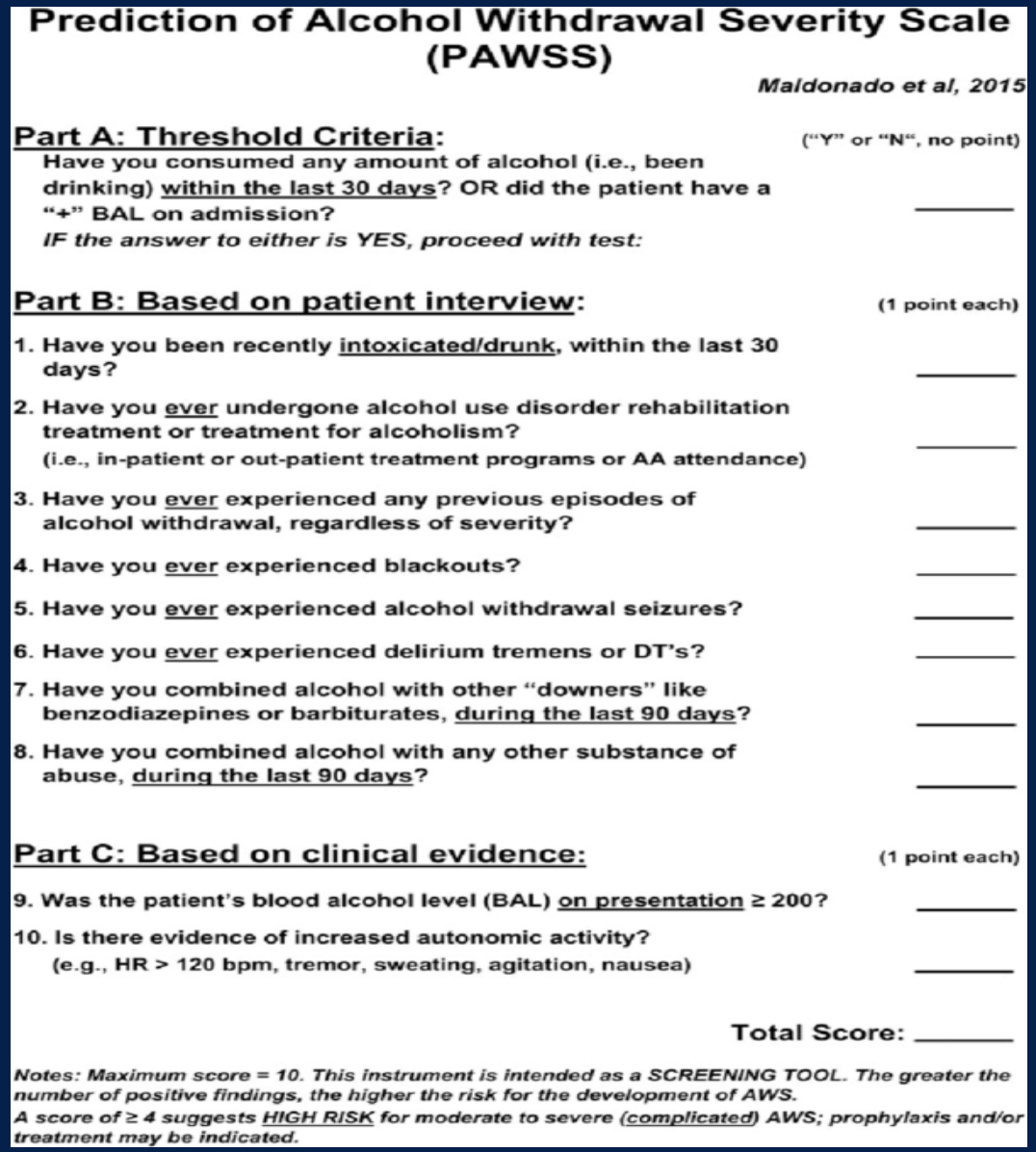
Predicting severity of alcohol withdrawal

Severity = Intensity of Treatment

- Little consensus about the best way to predict that a severe syndrome will develop
- Factors making prediction difficult
  - Number of days of drinking to create physical dependence has not been reliably determined
  - Patients do not accurately report time of last drink
  - Patients minimize past withdrawal
  - Unaware of past complications
- Helpful tips
  - Obtain information from collateral sources about drinking and past withdrawal
  - Measure blood alcohol concentration

Risk of more severe withdrawal

- Past history of
  - Delirium tremens
  - Seizures
- Objective signs
  - Sweating
  - Tremor
  - Pulse >100 bpm
- Comorbid medical disease, especially infection
- Positive blood alcohol concentration in the presence of signs of withdrawal
  - Unable to tolerate low BAL
- The more risk factors that are present, the more the risk for severe or complicated withdrawal is increased



Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Maldonado et al, 2015

Part A: Threshold Criteria: ("Y" or "N", no point)

Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 days? OR did the patient have a "+" BAL on admission? _____

IF the answer to either is YES, proceed with test:

Part B: Based on patient interview: (1 point each)

1. Have you been recently intoxicated/drunk, within the last 30 days? _____
2. Have you ever undergone alcohol use disorder rehabilitation treatment or treatment for alcoholism? (i.e., in-patient or out-patient treatment programs or AA attendance) _____
3. Have you ever experienced any previous episodes of alcohol withdrawal, regardless of severity? _____
4. Have you ever experienced blackouts? _____
5. Have you ever experienced alcohol withdrawal seizures? _____
6. Have you ever experienced delirium tremens or DT's? _____
7. Have you combined alcohol with other "downers" like benzodiazepines or barbiturates, during the last 90 days? _____
8. Have you combined alcohol with any other substance of abuse, during the last 90 days? _____

Part C: Based on clinical evidence: (1 point each)

9. Was the patient's blood alcohol level (BAL) on presentation ≥ 200? _____
10. Is there evidence of increased autonomic activity? (e.g., HR > 120 bpm, tremor, sweating, agitation, nausea) _____

Total Score: _____

Notes: Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of AWS.
A score of ≥ 4 suggests HIGH RISK for moderate to severe (complicated) AWS; prophylaxis and/or treatment may be indicated.

Maldonado JR et al. Alcohol Alcohol. 2015 Sep;50(5):509-18.

Risk Assessment Tool: PAWSS

- Prior alcohol withdrawal
- Numerous inpatient admissions for treatment of w/d
- Comorbid medical or surgical illness
  - Pneumonia, coronary artery disease, alcohol-related liver disease
  - Trauma, burn injury
- Older age (>65 years)
- Long duration of heavy and regular alcohol use
- Marked autonomic hyperactivity on presentation
- Physiological dependence on benzodiazepines or barbiturates

Assessment and Monitoring

Utilize multiple sources…..

- Clinical assessment: Ask the patient directly about alcohol and sedative-hypnotic use. If possible, obtain collateral information.
- Alcohol withdrawal severity scale - Clinical Institute Withdrawal Assessment –Alcohol Revised (CIWA-Ar)
- Laboratory workup (CBC, electrolytes, Mg,Ca,phosphate, LFTs, breathalyzer or BAL)
- Urine toxicology
  - Caveat: simple toxicology screens often miss clonazepam, lorazepam and alprazolam
  - Detection of clonazepam is 21% by immunoassay and 70% by LC-MS with cut-off at 200 ng/dl

Generally treat in inpatient setting

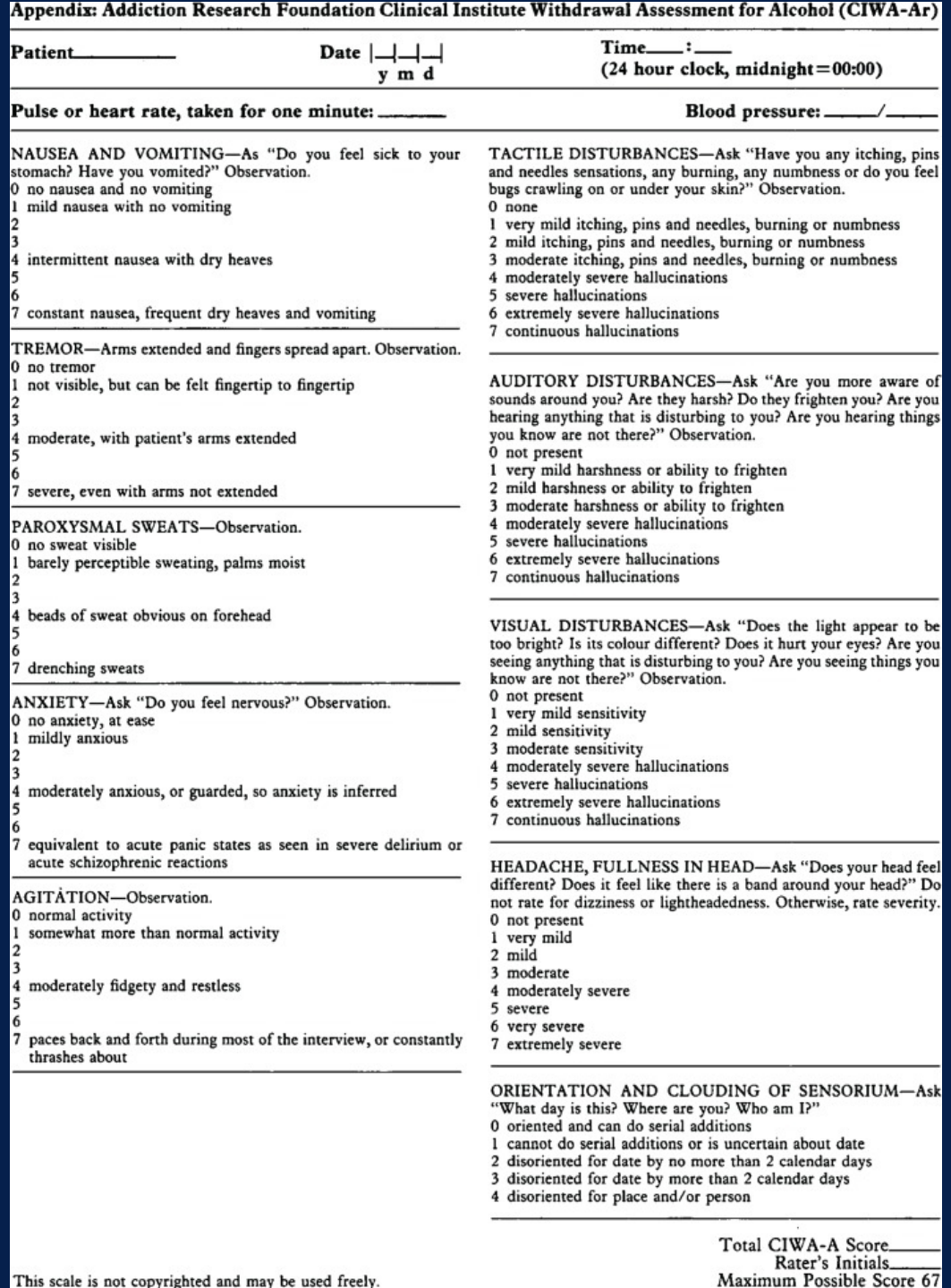
- Hospital ward or facility with medical management
- Alcohol withdrawal is a life-threatening condition
- Remove from drinking environment
- Comorbidity
  - Medical
  - Psychiatric

Laboratory abnormalities

- Serum chloride <96 mmol/l
  - Main ‘inhibiting’ ion in CNS
  - Indicator of hyperexcitability
- Lower platelet count
- Lower hemoglobin (anemia)
- Higher alanine aminotransferase (ALT)

Monitoring

- Optimal monitoring frequency is a balance between clinical need and feasibility
- Reassess every 1-4 hours for 24 hours, as clinically indicated
- Once stabilized (CIWA-Ar <10 for 24 hours), monitoring can be extended to every 4-8 hours as clinically indicated



Appendix: Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

Patient_____ **Date** |_|_|_| y m d **Time**__:__ (24 hour clock, midnight=00:00)

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

NAUSEA AND VOMITING—As "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 mildly 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 or numbness
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 colour 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 not 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 and/or person

Total CIWA-A Score_____
Rater's Initials_____
Maximum Possible Score 67

This scale is not copyrighted and may be used freely.

Pitfalls of the CIWA-Ar

- Only 3/10 observable traits (tremor, sweats, agitation)
- Language and cultural barriers may be present
- Medical and mental status can alter responses

Knight E, Lappalainen L. *Can Fam Physician* 2017;63(9):691-695.

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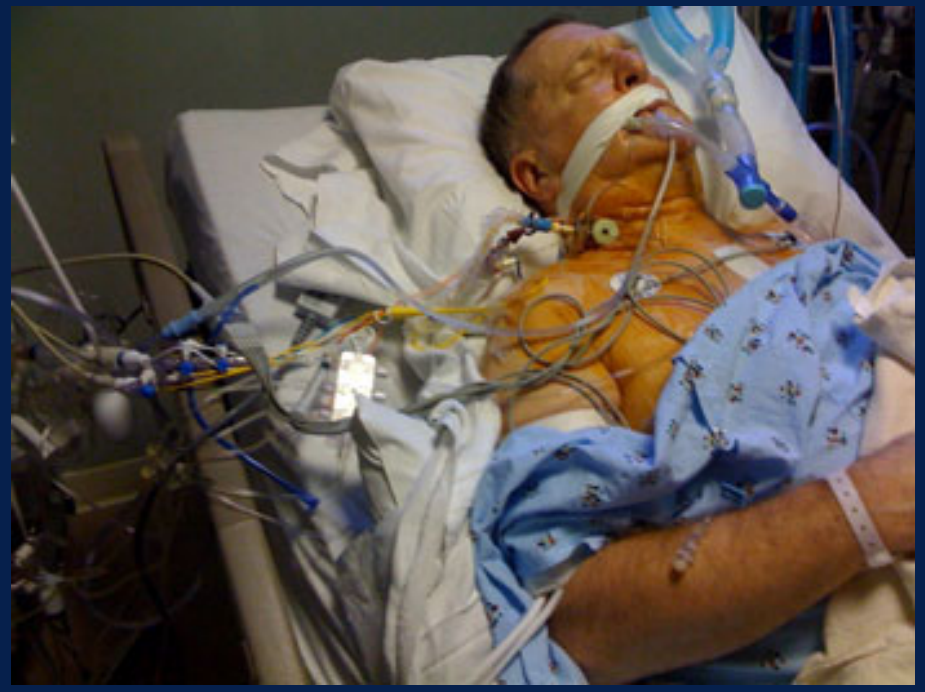
An Alternative: Objective Alcohol Withdrawal Scale (OWS)

The objective alcohol withdrawal scale is applied as follows:

- Score 1 point for each of the following factors
  - ❑ Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥90 mmHg
  - ❑ Heart rate ≥90 beats/min
  - ❑ Tremor
  - ❑ Diaphoresis
  - ❑ Agitation
- If total ≥ 2 give 1 mg oral lorazepam (or 10 mg of diazepam)
- If total ≥ 3 give 2 mg oral lorazepam (or 20 mg of diazepam)
- Reassess every hour until score is <2 for 3 consecutive measures, then reassess every 6 hours for 24 hours, then every 24 hours for 72 hours, then discontinue

Knight E, Lappalainen L. *Can Fam Physician*. 2017;63(9):691-695

When do I consult the ICU?



- Hypotension
- Rapid fluctuation in vital signs
- Requiring large doses of cross-dependent medication
- Severe altered mental status
  - May not be able to protect airway

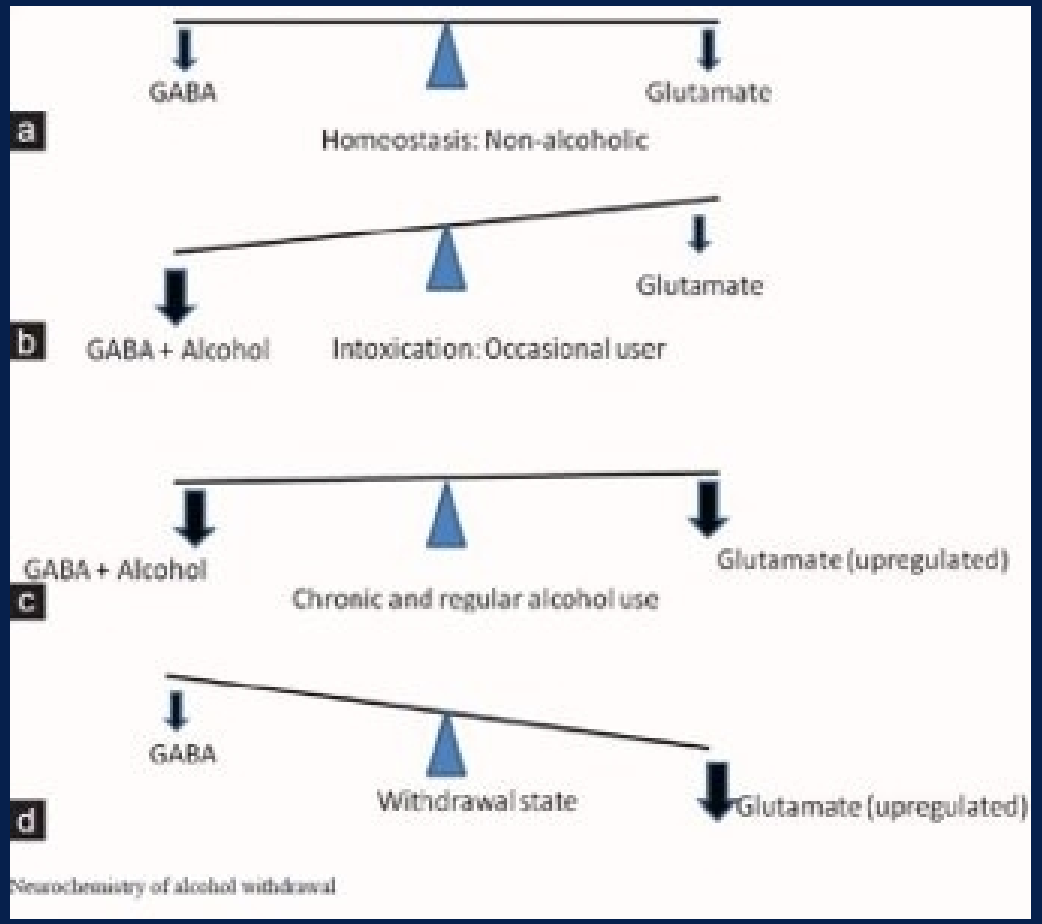
Treatment

Basic Principles

- Ask and examine the patient, use collaterals, assess regularly (CIWA-Ar or OWS)
- Order urine toxicology, interpret cautiously
- Treat early and aggressively with adequate doses of long-acting cross tolerant medications
  - INDIVIDUALIZE for elderly, liver disease, other substances
- Benzodiazepines are the cornerstone of treatment and reflect EBM for moderate-to-severe withdrawal.
- History of delirium tremens, seizures, multiple withdrawals/kindling=***HIGH RISK for complicated withdrawal***

Medications Used For AWS Monotherapy

- Targets the GABA and/or glutamate system
- Benzodiazepines
- Phenobarbital
- GABA sensitive anticonvulsants



Principles: Inpatient treatment of Severe Withdrawal

- All sedative hypnotics, benzodiazepines, barbiturates, Z-drugs, and alcohol exhibit cross-tolerance
- TREAT EARLY with ADEQUATE DOSES
  - It is important to medicate rapidly and in doses sufficient to suppress withdrawal symptoms
- Load with long-acting cross-tolerant medication (diazepam, phenobarbital) while giving shorter acting medications to “capture withdrawal”
- Advanced withdrawal is most safely managed in the intensive care environment

Determining the choice of BZD

	Diazepam (Valium)	Chlordiazepoxide (Librium)	Lorazepam (Ativan)	Oxazepam (Serax)
Dose Equivalent	5 mg	25 mg	1 mg	15 mg
Onset of action	Rapid	Intermediate	Intermediate	Slow
Half-life	Long	Long	Short	Short
Active Metabolites	Yes	Yes	No	No
Hepatic Metabolism	Yes	Yes	No	No
Routes of Administration	PO, IV	PO	PO, SL, IV, IM	PO

- **Dose equivalents to 30 mg of Phenobarbital and 0.5 mg of Alprazolam**

Case 1

- 46 y/o woman has been drinking 4-5 glasses of wine **daily** for the past 6 months
- She is prescribed **alprazolam (Xanax) 1 mg 3 times daily** for Generalized Anxiety Disorder by her Primary Care Physician
- She is arrested for driving on a suspended license and incarcerated over the weekend
- After her second day of incarceration, she develops a **tremor** in both hands, is diaphoretic, anxious, and keeps swatting at flies that no one else can see

Case 1: Question

Which of the following medications is most appropriate to administer to this patient now?

A. Alprazolam

B. Phenobarbital

C. Risperidone

D. Thiamine

Case 1: Answer

Answer:

B. Phenobarbital

It is cross-tolerant with alcohol, long-acting, and not being used by the patient.

Patient using alprazolam with tolerance and amount of BZD needed is unknown.

Phenobarbital should be used by clinicians experienced with its use in settings that offer close monitoring.

Phenobarbital

Acts on GABA and glutamate signaling, while BZDs only augment GABA

PHB is appropriate for:

- Prophylaxis
- Severe or complicated AWS
- When BZD abuse is identified

Especially if:

- BZDs contraindicated
- Patient not responding to BZDs
- Clinicians have training and experience using it for AWS
- Patients are being observed

Because:

- No evidence of better efficacy than BZDs
- More side effects than BZDs
- Relatively narrow therapeutic window and long half-life (up to 7 days) make PHB difficult to dose accurately without training
- Is the next best alternative to BZDs for severe and complicated AWS

Example of Phenobarbital dosing using Risk Stratification

- Daily evaluation is required to determine dose decreases
- Low Risk: <4 risk points

Initial dose: Phenobarbital 30 mg po q 6 hours (= lorazepam 2 mg) until withdrawal “captured”

After 24 hours of stability, decrease dose by eliminating one dose/day

PHB 30 mg po q 8 hours x 24 hours/ 3 doses

PHB 30 mg po q 12 hours x 24 hours/2 doses

PHB 30 mg po q d and then discontinue/ 1 dose

- Moderate Risk: 5-7 risk points

Initial dose: Phenobarbital 60-90 mg po q 6 hours (=lorazepam 4-6mg) until withdrawal “captured”

After 24 hours of stability, decrease dose by eliminating one dose/day

PB 60-90 mg po q 8 hours x 24 hours

PB 60-90 mg po q 12 hours x 24 hours

PB 60-90 mg po q d and then discontinue

Phenobarbital Dosing

- High Risk: >8 high risk or CIWA-Ar score >15

  If patient has had severe withdrawal in past &/or last drink was > 24-48h

  Consider an initial bolus of PHhanobarbital 120-240 mg IV or PO

  Obtain VS and CIWA-Ar q 4hrs or more frequently, reassess after 8 hrs of treatment

  Patients who are in this category usually need Phenobarbital 400 mg in the first 24 hours

Initial dose: Phenobarbital 90 mg po q 6 hours (=lorazepam 6mg) until withdrawal is “captured”

After 24 hours of stability, decrease dose by eliminating one dose/day

Phenobarbital 90 mg po q 8 hours x 24 hours

Phenobarbital 90 mg po q 12 hours x 24 hours

Phenobarbital 90 mg po q d and then discontinue

Medical Literature: Non-BZD, Non-Phenobarbital Options

Anticonvulsants: Carbamazepine and Gabapentin

Appropriate for:

- Mild or moderate AWS
- Outpatient treatment
- *Adjunct to benzodiazepine therapy*
  - *Ensure that an adequate dose of BZD has been administered*

Especially if:

- BZDs contraindicated
- Plan to use Gabapentin for ongoing Alcohol Use Disorder (AUD) treatment

Because:

- Sufficient evidence of efficacy and safety for mild to moderate AWS
- Compared to BZDs and Phenobarbital
  - Better safety profile
  - Less sedating
  - Lower risk of drug-drug interaction
- Evaluations of efficacy for patients requiring hospitalization is lacking

A Rapid Systematic Review (34 RCTs): The Effectiveness of Non-Benzodiazepine, Non-Barbiturate Medications for Alcohol Withdrawal Syndrome

- Risk of bias (RoB) assessment, qualitative synthesis of evidence, Grading of Recommendations Assessment, Development, and Evaluation (GRADEd)
- Gabapentin (n = 6), carbamazepine (n = 5), baclofen (n = 5), valproate (n = 3), clonidine/lofexidine (n = 3) and acamprosate (n = 2) all with >1 trial.
- Evidence of decreasing AWS vs standard benzodiazepine treatments
  - Gabapentin: 'moderate'
  - Carbamazepine, baclofen and valproate: 'low'
  - Acamprosate and clonidine/lofexidine 'very low'
  - Reported adverse events between these alternative medications and benzodiazepines or placebo were generally unremarkable.

Ghosh A et al, Alcohol Alcohol. 2021 Aug 30;56(5):513-534.

Alpha-2-adrenergic agonists and Beta-adrenergic antagonists

A2AAs and Beta-Blockers are appropriate for:

- Only as an adjunct to BZDs

A2AAs

- Autonomic hyperactivity and anxiety

Beta-Blockers

- Persistent hypertension or tachycardia

Because:

- They reduce the signs of sympathetic activation
- They do not treat the underlying syndrome
- They may mask signs of worsening syndrome

Dexmedetomidine and Propofol

Appropriate for:

- As an adjunct to BZDs
- For patients with AWS or Resistant Alcohol Withdrawal (RAW) being treated in the ICU and who already require intubation

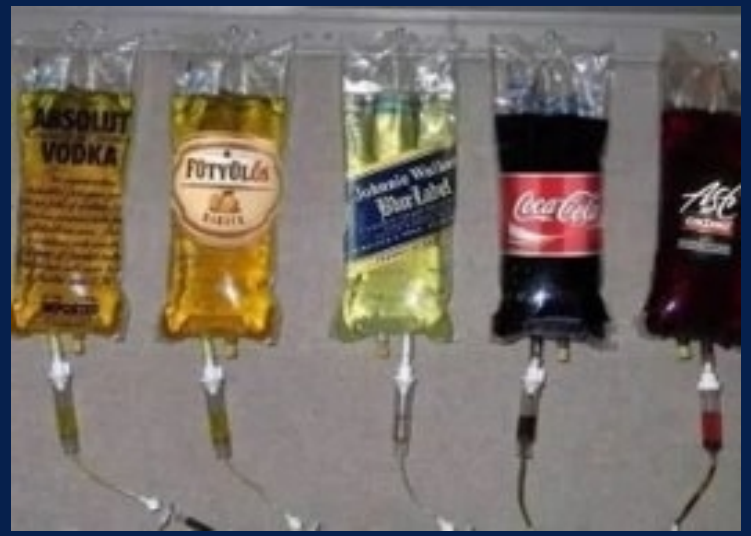
Because:

- They can reduce the agitation and delirium associated with AWS and RAW through sedation
- They do not treat the underlying syndrome

Do Not Use

To prevent or treat AWS:

- Alcohol
- Baclofen
- Magnesium (to treat AWS)



Because:

- Administration of oral or intravenous alcohol has no proven efficacy and known toxicity
- There's not enough evidence yet for baclofen
- There is evidence magnesium is not effective at treating AWS signs and symptoms

Case 2

- 34-year-old trans female (natal male) admitted to ED after partner noticed her “acting oddly—like she was very intoxicated…”
  - Altered consciousness→ Respiratory arrest → ICU
  - Intubated before permission obtained to speak with person at bedside.
- Labs:
  - UDAP + m-amphetamine, blood alcohol concentration= 0. Otherwise, unremarkable
- Day 2 Extubation attempted…
  - Autonomic instability, Irritable. Diagnosis: Stimulant toxicity
- DAY 4 Extubation successful, on room air.
  - Agitation persisted and increased.
  - And Dexmedetomidine initiated

Case 2

- Day 10 Addiction Medicine Consulted
  - Attempts to decrease dexmedetomidine unsuccessful
  - Patient is still severely agitated although autonomically stable (BP, HR)
- No further history available
  - Family estranged from patient and states “he’s a prostitute…”
  - No consent to speak with current supportive (sexual) partner present at bedside
  - Located person with consent; he has not seen patient in “years”
- Day 11: Patient HIV positive
  - Partner informed of result, asks to speak with addiction medicine team to provide more information.
  - Patient has been using GHB because alcohol makes her flush
  - Patient using every 20-30 minutes the day of admission
- Mental status never improved. Patient with comfort measures and dies at Day 45 of hospitalization.

Gamma-hydroxybutyrate (GHB) "Liquid Ecstasy"

- CNS Depressant
- Precursors
  - gamma-butyrolactone (GBL)
  - 1,4-butanediol (1,4-BD)
- High affinity for GHB-receptors, pre- and post-synaptic neurons
  - Overdose: Partial $GABA_b$ receptor agonist, metabolized to GABA
- Pharmacokinetics
  - Rapidly absorbed by the oral route
  - Peak blood concentrations within 1 hour
  - Metabolized in the liver
  - 20 to 60-minute half-life
  - Eliminated within 4–8 hours

McDonough M et al, Drug Alcohol Depend. 2004;75(1):3-9; Schep LJ et al, Clinical Toxicology, 2012;50(6):458-470

GHB

- Management of poisoning. Supportive care w respiratory and cardiovascular support.
- Withdrawal syndrome (chronic use): Persist for days in severe cases, cases of death.
  - Case Review: Severe withdrawal in 55% of cases with chronic use.
  - Auditory and visual hallucinations, tremors, tachycardia, hypertension, sweating, anxiety, agitation, paranoia, insomnia, disorientation, confusion, and aggression/combativeness.
  - Treatment
    - Benzodiazepine
    - Phenobarbital, baclofen, or propofol as second-line management options

Summary

- Monitor closely for severe alcohol withdrawal syndrome
  - Utilize clinical assessment scale, lab values
- Treat early and aggressively with adequate doses of long-acting cross tolerant medications
- Phenobarbital is an appropriate alternative to benzodiazepines
- Anticonvulsants (gabapentin or carbamazepine) are appropriate for mild or moderate withdrawal
- Alph-2-adrenergic agonists or beta-blockers are only used as adjuncts with cross-tolerant medications (BZD or phenobarbital)

Summary

- Dexmedetomidine and propofol are useful as adjuncts to cross-tolerant medications for patients in the ICU setting with severe alcohol withdrawal syndrome
- Not enough evidence available to recommend baclofen for treatment of AWS
- Gamma-hydroxybutyrate can cause a sedative withdrawal syndrome that is severe
  - Treat like severe AWS

References

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Questions?

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