

ALCOHOL WITHDRAWAL SYNDROME

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

Lisa W. Vercollone, MD, PharmD

Update in Hospital Medicine

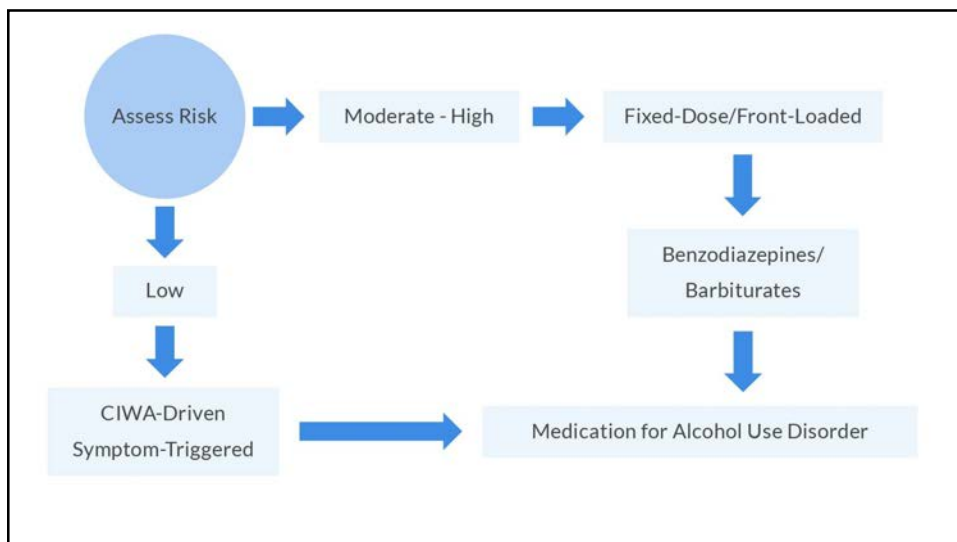
October 23, 2023

DISCLOSURES

None

OBJECTIVES

- Discuss the various approaches to managing alcohol withdrawal syndrome using benzodiazepines and phenobarbital.
- Highlight the unique pharmacokinetic and pharmacodynamic features of phenobarbital as they apply to the treatment of alcohol withdrawal.
- Analyze and apply a front-loaded phenobarbital monotherapy protocol.
- Review available medications for the treatment of alcohol use disorder.





The ASAM
CLINICAL PRACTICE GUIDELINE ON
**Alcohol
Withdrawal
Management**

CLINICAL PRACTICE GUIDELINE

The ASAM Clinical Practice Guideline on Alcohol
Withdrawal Management

Guideline Committee Members (alpha order):

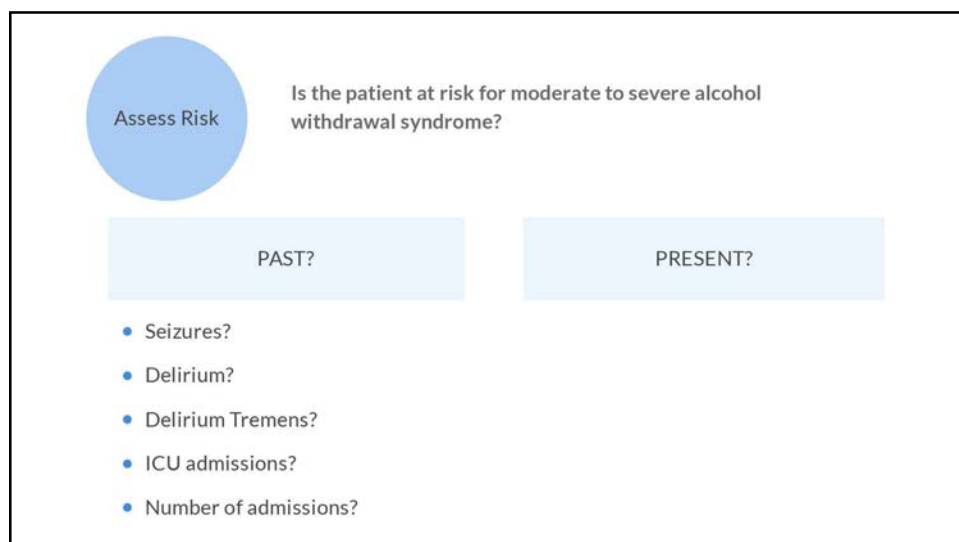
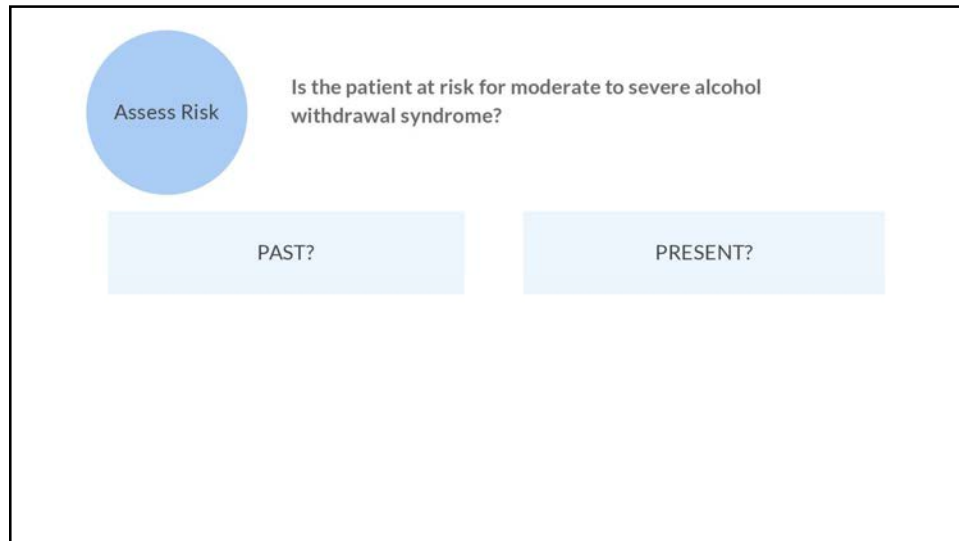
Anika Alvarez, MD, MS, DFASAM, FACP
Kurt Kleinich, MD, FASAM
Julie A. Kuo, DO, FASAM
George Kolodner, MD, DLFAPA, FASAM
Gerald E. Muri, MD, PhD
William F. Murphy, DO, MS, DFASAM
Carlos F. Tirado, MD, FASAM
Cory Waller, MD, MS, DFASAM, FACEP
Lewis S. Nelson, MD, FASAM, FACEP, FACMT (Chair)

Table of Contents

| | |
|----------------------------|----|
| Glossary of Terms | 2 |
| Abbreviations and Acronyms | 3 |
| Executive Summary | 3 |
| Introduction | 13 |
| I. Purpose | 13 |
| II. Background | 15 |
| III. Scope of Guideline | 16 |
| IV. Intended Audience | 16 |
| V. Qualifying Statements | 16 |
| VI. Special Terms | 16 |
| Approach and Methodology | 17 |

Assess Risk

Is the patient at risk for moderate to severe alcohol
withdrawal syndrome?



KINDLING EFFECT

- Repeated alcohol withdrawal episodes will become progressively worse
 - Increased neuronal excitability and sensitivity
 - Exacerbated neurochemical imbalances
- Supports aggressive treatment of even mild withdrawal episodes
- May contribute to relapse risk and cognitive impairment

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

Assess Risk

Is the patient at risk for moderate to severe alcohol withdrawal syndrome?

PAST?

PRESENT?

- Seizures?
- Delirium?
- Delirium Tremens?
- ICU admissions?
- Number of admissions?

Assess Risk

Is the patient at risk for moderate to severe alcohol withdrawal syndrome?

PAST?

- Seizures?
- Delirium?
- Delirium Tremens?
- ICU admissions?
- Number of admissions?

PRESENT?

- Vital signs?
- Tremors?
- Diaphoresis?
- CIWA-Ar?
- RASS?

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT

CIWA - Ar (Alcohol - revised)

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)

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT

CIWA - Ar (Alcohol - revised)

TABLE 1. Alcohol Withdrawal Severity.

| Severity Category | Associated CIWA-Ar Range ^a | Symptom Description |
|--------------------|---------------------------------------|---|
| <i>Mild</i> | CIWA-Ar < 10 | Mild or moderate anxiety, sweating and insomnia, but no tremor |
| <i>Moderate</i> | CIWA-Ar 10-18 | Moderate anxiety, sweating, insomnia, and mild tremor |
| <i>Severe</i> | CIWA-Ar ≥ 19 | Severe anxiety and moderate to severe tremor, but not confusion, hallucinations, or seizure |
| <i>Complicated</i> | CIWA-Ar ≥ 19 | Seizure or signs and symptoms indicative of delirium – such as an inability to fully comprehend instructions, clouding of the sensorium or confusion – or new onset of hallucinations |

^aThroughout this document, we provide examples for withdrawal severity using the CIWA-Ar, although other scales can be used. Regardless of the instrument used, there is a wide variety in the literature and in practice as to which scores best delineate mild, moderate and severe withdrawal. Classification of withdrawal severity is ultimately up to the judgment of clinicians and the choice of reference range may be based on their particular patient population or capabilities.

ASAM CPG on Alcohol Withdrawal Management, 2019.





CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT

CIWA - Ar (Alcohol - revised)

August 17, 1994

Individualized Treatment for Alcohol Withdrawal A Randomized Double-blind Controlled Trial

Richard Saltz, MD, MPH; Michael F. Mayo-Smith, MD, MPH; Mark S. Roberts, MD, MPH; et al

> Author Affiliations

JAMA. 1994;272(7):519-523. doi:10.1001/jama.1994.03520070039035

- Patients admitted for the treatment of alcohol withdrawal at an inpatient detoxification unit at the VA
- Exclusion criteria: History of seizure; acute medical or psychiatric hospitalization

Original Investigation

May 27, 2002

Symptom-Triggered vs Fixed-Schedule Doses of Benzodiazepine for Alcohol Withdrawal A Randomized Treatment Trial

Jean-Bernard Daeppen, MD; Pascal Gache, MD; Ulika Landry, BA; et al

> Author Affiliations | Article Information

Arch Intern Med. 2002;162(10):1117-1121. doi:10.1001/archinte.162.10.1117

- Patients with alcohol dependence entering an alcohol treatment program
- Exclusion criteria: Abstinence less than 72 hr; major cognitive, psychiatric or medical comorbidity

CIWA-DRIVEN SYMPTOM-TRIGGERED PROTOCOL

CIWA - Ar (Alcohol - revised)

- Low risk for severe withdrawal
- Able to communicate
- Not delirious
- Diagnostic uncertainty

CIWA-DRIVEN SYMPTOM-TRIGGERED PROTOCOL

Brigham and Women's Hospital Standard CIWA Protocol

| CIWA 0 - 7 | CIWA 8-15 | CIWA > 15 |
|---|--|---------------------------|
| No medication indicated | lorazepam 2 mg IV/PO x 1 | lorazepam 4 mg IV/PO 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 - KH

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

- **Amount and duration:**
 - 2 standard size (750 mL) bottles of wine and 4-7 tequila shots daily for 3 weeks (17 drinks/day)
- **Last admission:**
 - 3 weeks ago
- **Total number of admissions:**
 - 25 admissions in 3 years
- **Withdrawal history:**
 - No history of DT, withdrawal seizure, or ICU admissions
- **Co-occurring substance use disorders:**
 - None

CASE - KH

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

- **Subjective:**
 - Nausea. No vomiting. Anxiety. Headache.
- **Physical exam:**
 - HR 115, BP 132/88.
 - Anxious. Tremulous. Not diaphoretic.
 - No auditory or visual hallucinations.
- **CIWA: 14**
- **Labs:**
 - Blood alcohol level = 260 mcg/mL
 - Urine toxicology screen: negative
 - Na 133, K 4.0, ALT 54, AST 132, Tbili 0.4, albumin 4.5, plt 273

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 - Nausea. No vomiting. Anxiety. Headache.
- Physical exam:
 - HR 115, BP 132/88.
 - Anxious. Tremulous. Not diaphoretic.
 - No auditory or visual hallucinations.
- CIWA: 14 ← moderate alcohol withdrawal
- Labs:
 - Blood alcohol level = 260 mcg/mL
 - Urine toxicology screen: negative
 - Na 133, K 4.0, ALT 54, AST 132, Tbili 0.4, albumin 4.5, plt 273

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Past

- 25 admissions
- No complications

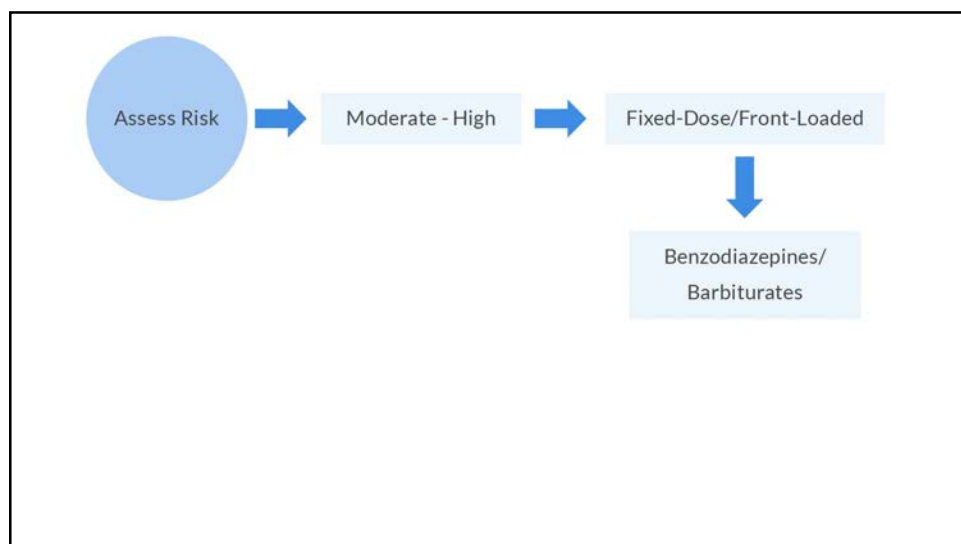
Present

- 17 drinks/day
- CIWA 14
- BAL 260
- Tachycardiac
- Tremulous

Assess Risk



Moderate - High



RISK OF MODERATE TO SEVERE WITHDRAWAL APPROACHES

Fixed-dose benzodiazepines

Moderate to high risk for severe withdrawal
Short-acting benzo with slow taper
Risk of over and under dosing

Front-loaded benzodiazepines

High risk of severe withdrawal
Rapid achievement of therapeutic levels

Front-loaded phenobarbital

High risk for severe withdrawal
Very rapid achievement of therapeutic levels
Strong consideration if benzo non- or poor responder

CASE - KH

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What is the preferred option for treating her alcohol withdrawal syndrome?

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Shared Decision Making

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Shared Decision Making



Benzodiazepines

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Shared Decision Making



Benzodiazepines

FIXED-DOSE BENZODIAZEPINES

Brigham and Women's Hospital Fixed-Dose Protocol

Day 1

- Lorazepam 2 mg IV/PO every 4 hours
- Hold dose if patient exhibits NO signs of alcohol withdrawal or evidence of benzodiazepine intoxication
- Continue x 24 hours
- Notify provider if no improvement after two consecutive doses or worsening of symptoms.

Days 2-5

- Calculate cumulative dose from day 1
- Initiate taper by 20-25% per day

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

FRONT-LOADED BENZODIAZEPINES

Main principles:

- Achieve therapeutic serum concentrations rapidly
- Use a benzodiazepine with a fast peak onset to prevent dose-stacking
- Taper occurs via metabolism

Symptom-triggered front-load dosing

- Option 1: Diazepam 20 mg PO/IV every hour while CIWA-Ar > 10
- Option 2: Diazepam 20 mg PO/IV every hour for 1-2 hours or until patient is sedated (RASS < 0)

Fixed-dose

- Option 3: Diazepam 20 mg PO/IV every 2 hours x 3 doses

LONG-ACTING BENZODIAZEPINES

| | half-life | active metabolites | time to peak conc (Cmax) | formulation | metabolism |
|------------------|------------|--------------------|--------------------------------|-------------|--------------------------------|
| diazepam | 20 - 80 hr | yes; 40 - 120 hr | 5-15 min (IV) to 0.5-1 hr (PO) | PO/IV/IM/PR | hepatic CYP-mediated oxidation |
| chlordiazepoxide | 5 - 30 hr | yes; 40 - 120 hr | 1 - 4 hr | PO | hepatic CYP-mediated oxidation |

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| oxazepam | 5 - 15 hr | none | 1 - 4 hr | PO | conjugation |

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You decide to proceed with front-loaded benzodiazepines.

When is the preferred time to start front-loaded benzodiazepines?

- A: 6 hours after the last reported drink
- B: Once BAL is less than 100
- C: Once CIWA ≥ 15
- D: As soon as possible

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TIMING OF INITIATION OF TREATMENT

It is not necessary to wait for a certain...

- Amount of time since last drink
- Blood alcohol level threshold
- CIWA-Ar score threshold to be met

Preventative pharmacotherapy - indicated if at risk for severe or complicated withdrawal

ASAM CPG on Alcohol Withdrawal Management, 2019.

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CASE - ML

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

- **Amount and duration:**
 - Six 25 oz cans of beer + 1 pint vodka daily (35 drinks/day) x 2 years
- **Last admission:**
 - 6 years ago
- **Total number of admissions:**
 - 5 admissions in his lifetime
- **Withdrawal history:**
 - Seizures, delirium tremens, ICU admissions with intubation
- **Co-occurring substance use disorders:**
 - None

CASE - ML

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

- Subjective:
 - Nausea, shakes, headache, severe anxiety
- Physical exam:
 - HR 102, BP 173/111
 - Restless, agitated, tremulous, diaphoretic, no visual hallucinations
- RASS: 2
- Labs:
 - Blood alcohol level = 120 mcg/mL

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 mvmt, fights ventilator |
| 1 | Restless | Anxious but movements not aggressive or vigorous |
| 0 | | Alert and calm |
| -1 | Drowsy | Sustained awakening to voice (≥ 10 sec) |
| -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.grepremed.com/images/9144/agitation-nursing-richmond-diagnosis-rass>

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EHR, 2009: "required intubation and dexmedetomidine despite escalating doses of diazepam"

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Benzodiazepine non-responder?

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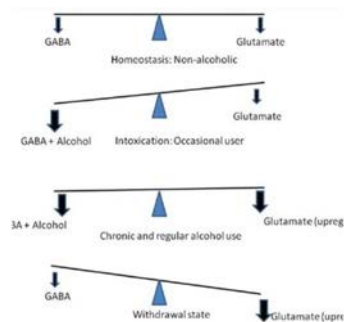


Benzodiazepine non-responder?

WHEN TO CONSIDER PHENOBARBITAL

- History of complicated withdrawal (delirium tremens, seizures, ICU admission)
- At risk for severe or complicated alcohol withdrawal
- Actively withdrawing despite high blood alcohol level
- Current severe alcohol withdrawal syndrome
- Delirium or encephalopathy
- Benzodiazepine non-response or benzodiazepine resistance

ALCOHOL WITHDRAWAL SYNDROME



- 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

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

PHENOBARBITAL PHARMACOKINETICS AND PHARMACODYNAMICS

What the body does to the drug and what the drug does to the body

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 AND PHARMACODYNAMICS

What the body does to the drug and what the drug does to the body



Fast onset of action

IV/IM: < 15 min; PO: 60 min



Wide therapeutic index! (not narrow)

15 - 40 mcg/mL

Toxic > 65 mcg/mL



Fast peak effect (C_{max})

IV/IM: < 30 min



Predictable

In the absence of benzodiazepines



Long half-life

Approx 80 hours



Metabolized CYP450

3A4 and 2E1



Long elimination

> 2 weeks



Weight-based front loading dosing

Ideal body weight

THERAPEUTIC INDEX

Phenobarbital serum concentrations:

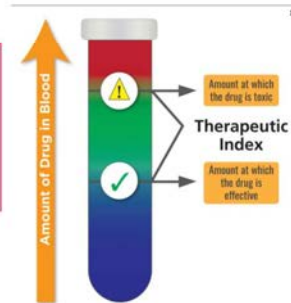
- Therapeutic range, epilepsy: 15 - 40 mcg/mL
- Mild signs of toxicity: > 50 mcg/mL
- Severe toxicity: > 65 mcg/mL
- Therapeutic range, monotherapy for AWS = 10 - 40 mcg/mL

Phenobarbital 10 mg/kg alone CANNOT cause a toxic phenobarbital level

- Phenobarbital level (mcg/mL) = 1.5 x the dose (mg/kg)
- ex. 10 mg/kg dose = 15 mcg/mL
- 10 mg/kg phenobarbital alone CANNOT cause a toxic phenobarbital level

<https://emcrit.org/ibcc/etoh/>. Accessed 9.2.22

<https://clinicalinfo.hiv.gov/en/glossary/therapeutic-index-ti>. Accessed 9.12.22



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How should phenobarbital be dosed?

PHENOBARBITAL FOR ALCOHOL WITHDRAWAL PROTOCOL

Brigham and Women's Hospital and Massachusetts General Hospital



Psychosomatics
Volume 50, Issue 5, September–October 2019, Pages 458–467



Original Research Article

Use of Phenobarbital in Alcohol Withdrawal Management – A Retrospective Comparison Study of Phenobarbital and Benzodiazepines for Acute Alcohol Withdrawal Management in General Medical Patients

Mladen Nisavic M.D.,^{1,2,*} J. W. Shermim H. Nisavic M.D.,³ Benjamin M. Iuenberg B.A.,⁴ Ednan Khalid Buzen M.D.,⁵ Paul Currier M.D.,⁶ Paul M. Wallace B.A.,⁷ George Velimshos M.D.,⁸ Timothy Wilens M.D.,^{3,4}

- Phenobarbital is an effective and well tolerated alternative to BZD
- Overall rates of sedation appeared comparable
- LOS was not increased with phenobarbital.



Psychosomatics
Volume 61, Issue 4, July–August 2020, Pages 327–335



Original Research Article

Phenobarbital for Acute Alcohol Withdrawal Management in Surgical Trauma Patients—A Retrospective Comparison Study

Shermim Nisavic M.D.,¹ Mladen Nisavic M.D.,^{2,3,*} J. W. Shermim H. Nisavic M.D.,⁴ Andreas Larentzakis M.D.,⁵ Susan Dikink M.D.,⁶ Yuchiao Chang Ph.D.,⁷ Alexander B. Levine Pharm.D.,⁸ Marc de Mayo M.D.,⁹ George Velimshos M.D.,¹

- Phenobarbital found to have superior outcomes to BZD
- Decreased AWD and uncomplicated AWS
- Phenobarbital may be safer and potentially more effective

PHENOBARBITAL FOR ALCOHOL WITHDRAWAL PROTOCOL

Brigham and Women's Hospital and Massachusetts General Hospital

Step 1: Determine risk of severe or complicated withdrawal syndrome

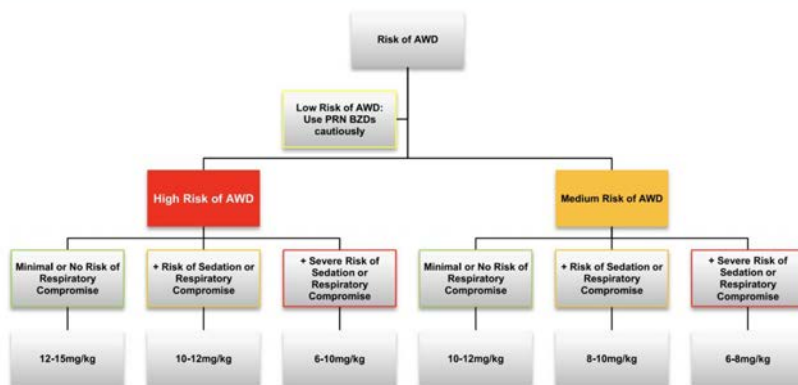
- High vs. medium

Step 2: Determine risk of complications

- Sedation
 - > 65 yo, hepatic dysfunction, narcotics, head injury, recent sedatives
- Respiratory compromise
 - pneumonia, rib fractures, chest tube, contusion, C-collar/brace

PHENOBARBITAL FOR ALCOHOL WITHDRAWAL PROTOCOL

Brigham and Women's Hospital and Massachusetts General Hospital



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

CASE - ML

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

How should phenobarbital be dosed?

High risk for severe withdrawal. Low risk for complications.

Phenobarbital 12 mg/kg based on ideal body weight of 74 kg.

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- Option 1: IV
 - phenobarbital 888 mg IV x 1 dose infused over 30 minutes
- Option 2: IM
 - phenobarbital 296 mg IM q 3 hours x 3 doses (total 888 mg)

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2 hours later completion of IV infusion: RASS +1

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Rescue dosing:

- Phenobarbital 65 - 130 mg IV/IM/PO q 1 hour as needed to reach goal
- Keep track of the cumulative dose
 - Soft stop: 20 mg/kg
 - Hard stop: 30 mg/kg

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Post-load taper is no longer advised.

RECENT LITERATURE

Journal of Medical Toxicology (2022) 18:198–204
<https://doi.org/10.1007/s13181-022-00900-6>

ORIGINAL ARTICLE

Front-Loaded Versus Low-Intermittent Phenobarbital Dosing for Benzodiazepine-Resistant Severe Alcohol Withdrawal Syndrome

Poorvi Shah¹ | Kati L. Stegner-Smith^{1,2} | Mohamad Rachid³ | Tabassum Hanif² | Kenneth W. Dodd^{1,4,5,6}

Received: 3 December 2021 / Revised: 4 May 2022 / Accepted: 10 May 2022 / Published online: 6 June 2022
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Received: 30 October 2022 | Revised: 26 April 2023 | Accepted: 26 April 2023
DOI: 10.1002/jmt.12347

ORIGINAL ARTICLE

Phenobarbital versus benzodiazepines in alcohol withdrawal syndrome

Deanna Malone¹ | Blair N. Costin^{1,2} | Dawn MacElroy¹ | Masha Al-Hegelan^{1,2} | Julie Thompson³ | Yurily Bronshteyn^{2,4}

- compared low-intermittent dosing vs. front-loaded phenobarbital in severe alcohol withdrawal

- front-loaded: less mechanical ventilation and less continuous sedation needed

- compared front-loaded phenobarbital vs. traditional benzodiazepine protocol

- phenobarbital: less respiratory complications; RASS more frequent at goal; significantly shorter ICU and hospital LOS

RECENT LITERATURE



The American Journal of Emergency Medicine

Volume 54, April 2022, Pages 263–266



Phenobarbital and/or benzodiazepines for recurrent alcohol withdrawal: A self-controlled, retrospective cohort study

Alex Steidle PharmD, BCPS, APH^{a,b}, ES - Curtis Geier PharmD, BCCKCP^a

Open Access Original Article

DOI: 10.7755/AJEM.13262

Phenobarbital Versus Lorazepam for Management of Alcohol Withdrawal Syndrome: A Retrospective Cohort Study

Fadi Hama¹, Lindsey Gilbert¹, Benjamin Gilbert¹, Vanessa Harwood¹, Aya Hama², Alaaeldin Al-Billal³, Mark Weiser⁴, Jeremy Albright¹, Caleb Schickel¹, Olu Al-Sosa¹

¹ Internal Medicine, St. Joseph Mercy Ann Arbor Hospital, Ann Arbor, USA; ² Internal Medicine/Palliative Care, St. Joseph Mercy Ann Arbor Hospital, Ann Arbor, USA; ³ Internal Medicine, St. Joseph Mercy Livingston Hospital, Howell, USA; ⁴ Pharmacy, St. Joseph Mercy Ann Arbor Hospital, Ann Arbor, USA; ⁵ Internal Medicine/Pediatrics, Baylor College of Medicine, Houston, USA; ⁶ Internal Medicine/Addiction Medicine, St. Joseph Mercy Ann Arbor Hospital, Ann Arbor, USA; ⁷ Statistics, St. Joseph Mercy Ann Arbor Hospital, Ann Arbor, USA

- compared BZD+phenobarbital vs. BZD alone vs. phenobarbital alone
- combination therapy: longer ED LOS, more ICU care, increase incidence of hypotension

- compared phenobarbital monotherapy vs. lorazepam monotherapy for alcohol withdrawal on the general medicine floor
- phenobarbital: statistically significant shorter hospital LOS

RESISTANT ALCOHOL WITHDRAWAL

- Phenobarbital
- Benzodiazepine adjuncts
 - phenobarbital
 - ICU not required
 - dexmedetomidine
 - activation of central pre- and postsynaptic α_2 -receptors in the locus coeruleus
 - reduced agitation
 - decreased benzodiazepine requirement = reduced prolonged delirium
 - bradycardia
 - propofol
 - GABA_A agonism + NMDA blockade
 - respiratory depression -> mechanical ventilation

RESISTANT ALCOHOL WITHDRAWAL

PHARMACOTHERAPY



Review of Therapeutics

Propofol for Treatment of Refractory Alcohol Withdrawal Syndrome: A Review of the Literature

Amy L. Brotherton, Eric P. Hamilton, H. Grace Kloss, Drayton A. Hammond

First published: 19 February 2016 | <https://doi.org/10.1002/phar.1726> | Citations: 30

- compared propofol with dexmedetomidine as adjuncts in AWS
- similar benzodiazepine- and haloperidol-sparing effects.

ALCOHOL WITHDRAWAL OR NON-ALCOHOL-RELATED DELIRIUM (NARD)?

Less than 72 hours

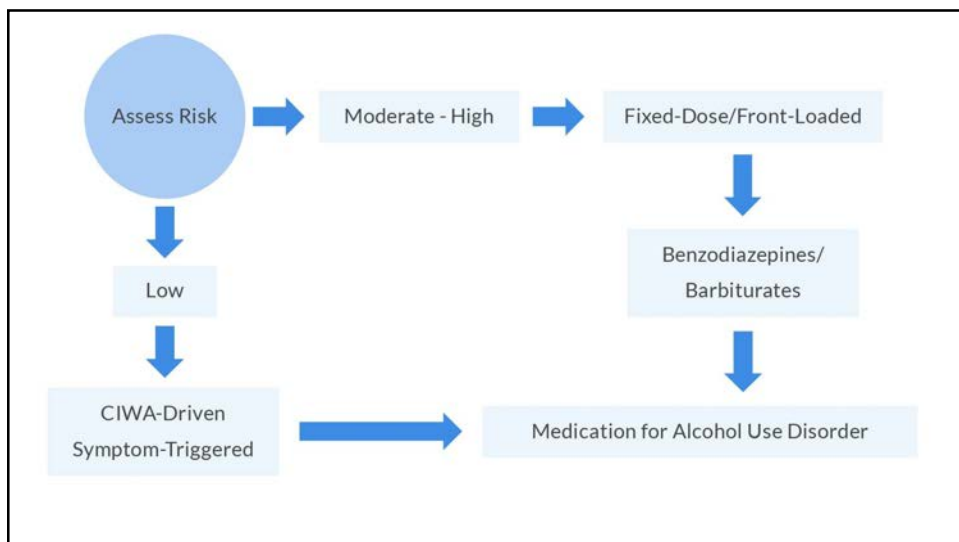
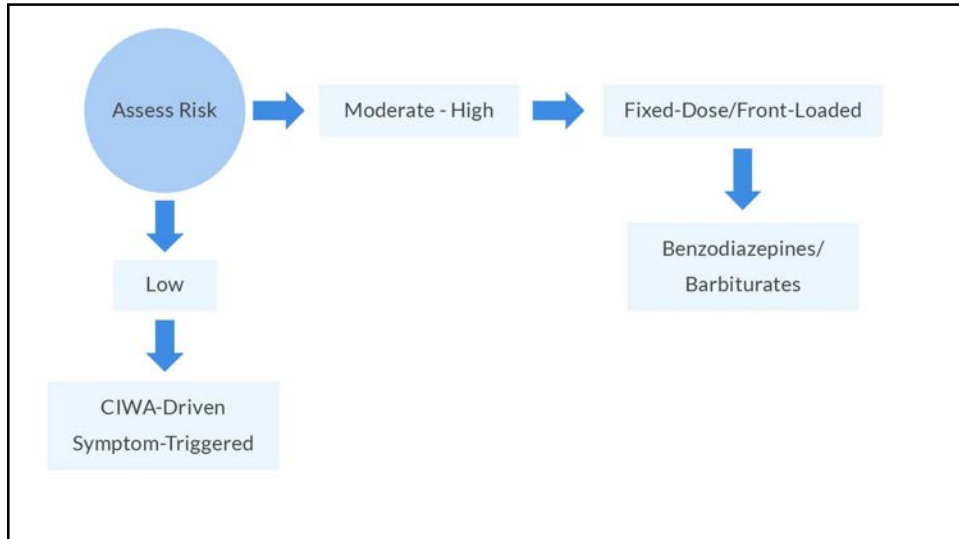
- Alcohol withdrawal seizures: 24-48 hours
- Delirium tremens: 48-90 hrs
- Consider increasing dose of benzodiazepine, switching to IV or switching to phenobarbital
- Consider adding antipsychotic (risperidone, quetiapine, haloperidol)
- Goal RASS -1

Greater than 72 hours

- Consider benzodiazepine-induced delirium
- Reduce dose of benzodiazepine and add antipsychotic (risperidone, quetiapine, haloperidol)
- Look for other causes, i.e. NARD

Wartenberg A. Management of Alcohol Intoxication and Withdrawal. In: Ries RK, Fiellin DA, Miller SC, Saltz R, eds. The ASAM Principles of Addiction Medicine. 5th ed., Lippincott Williams & Wilkins; 2014 :635-651.

ASAM CPG on Alcohol Withdrawal Management, 2019.



MEDICATIONS FOR ALCOHOL USE DISORDER (MAUD)

All patients treated for alcohol withdrawal should be considered for MAUD.

MEDICATIONS FOR ALCOHOL USE DISORDER (MAUD)

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Disulfiram

Alcohol-sensitizing - Aversion Therapy

- MOA: Irreversible inhibition of aldehyde dehydrogenase --> build up of acetaldehyde
- Dosing: 250 - 500 mg po daily
- Induces severe GI distress in combination with ethanol
- Helps to contract with significant other/sober support to ensure adherence

Naltrexone

Reduces positive reinforcement

- MOA: Mu-receptor antagonist. Blocks stimulation of dopamine reward system
- Dosing: 50 mg po daily vs. 380 mg IM once-monthly
- Presence of physiologic opioid dependence --> severe precipitated opioid withdrawal
- Liver dysfunction (next slide)

Acamprosate

Reduces negative reinforcement

- MOA: GABA receptor agonist and NMDA receptor modulator
- Dosing: 666 mg po TID --> adherence is a major concern
- Metabolism: Does not undergo metabolism.
- Renally excreted. Avoid if GFR < 30 ml/min.

NALTREXONE AND LIVER FUNCTION TESTS



Providers
Clinical Support
System

PCSS Guidance

Topic: Monitoring of Liver Function Tests in Patients Receiving Naltrexone or Extended-Release Naltrexone

Original Author: Sandra A. Springer, M.D. (September 1, 2014; 1st revision October 14, 2014; 2nd revision October 9, 2017)

Edited by: 1st Adam Bisaga, MD (October 14, 2014); 2nd Adam Bisaga, MD, (June 26, 2018)

Reviewed and Re-released: May 2022

Level of evidence: High - prospective observational and randomized placebo-controlled trials.

- baseline LFTs prior to initiation are not necessary
- no empiric evidence to support frequency of monitoring hepatic enzymes

MAUD COMPARISON

Original Article

January 2003

Comparing and Combining Naltrexone and Acamprosate in Relapse Prevention of Alcoholism

A Double-blind, Placebo-Controlled Study

Falk Kiefer, MD, Holger John, MD, Timo Tanskanen, et al.

> Author Affiliations | Article Information

Arch Gen Psychiatry. 2003;60(1):92-99. doi:10.1001/archpsyc.60.1.92

- Acamprosate vs naltrexone vs acamprosate + naltrexone
- All significantly more efficacious than placebo
- Rate of relapse in combined group was not statistically better than naltrexone alone

Original Contribution

May 3, 2006

FREE

Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence

The COMBINE Study: A Randomized Controlled Trial

Raymond F. Anton, MD, Stephanie S. O'Malley, PhD, Domenic A. Ciraulo, MD, et al.

> Author Affiliations | Article Information

JAMA. 2006;295(17):2003-2017. doi:10.1001/jama.295.17.2003

- Naltrexone, acamprosate, and combination of naltrexone and acamprosate combined with medical management +/- cognitive behavioral intervention (CBI)
- No advantage of acamprosate over placebo either alone or when added to naltrexone

SUMMARY

- Symptom-triggered CIWA-driven approaches are not for everyone.
- Fixed or front-loaded benzodiazepine or phenobarbital regimens for patients with history of complicated withdrawal and/or at risk for 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.

Questions?