ALCOHOL WITHDRAWAL SYNDROME

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

Lisa W. Vercollone, MD, PharmD

Update in Hospital Medicine

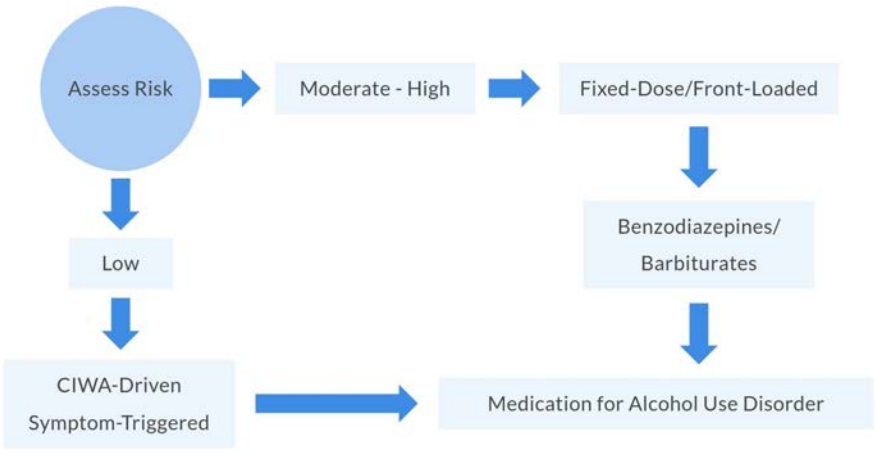
October 7, 2024

DISCLOSURES

None

OBJECTIVES

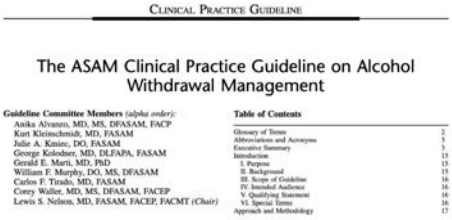
- Discuss the various approaches to managing alcohol withdrawal syndrome using benzodiazepines and phenobarbital.
- Highlight the unique pharmacokinetic and pharmacodynamic features of phenobarbital as they apply to the treatment of alcohol withdrawal.
- Analyze and apply a front-loaded phenobarbital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



AMERICAN SOCIETY OF ADDICTION MEDICINE

Guideline on Alcohol Withdrawal Management 2020

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 Alvanzo, MD, MS, DFASAM, FACP
Kurt Kleinschmidt, MD, FASAM
Jullie A. Kmiec, DO, FASAM
George Kolodner, MD, DLFAPA, FASAM
Gerald E. Marti, MD, PhD
William F. Murphy, DO, MS, DFASAM
Carlos F. Tirado, MD, FASAM
Corey Waller, MD, MS, DFASAM, FACEP
Lewis S. Nelson, MD, FASAM, FACEP, FACMT *(Chair)*

Table of Contents

Assess Risk

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

Assess Risk

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

PAST?

PRESENT?

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?

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?	PRESENT?
• Seizures?	• Vital signs?
• Delirium?	• Tremors?
• Delirium Tremens?	• Diaphoresis?
• ICU admissions?	• CIWA-Ar?
• Number of admissions?	• 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

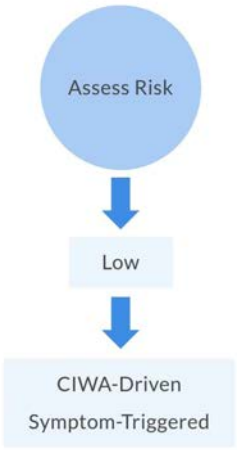
CIWA - Ar (Alcohol - revised)

TABLE 1. Alcohol Withdrawal Severity.

Severity Category	Associated CIWA-Ar Range*	Symptom Description
Mild	CIWA-Ar < 10	Mild or moderate anxiety, sweating and insomnia, but no tremor
Moderate	CIWA-Ar 10-18	Moderate anxiety, sweating, insomnia, and mild tremor
Severe	CIWA-Ar ≥19	Severe anxiety and moderate to severe tremor, but not confusion, hallucinations, or seizure
Complicated	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

*Throughout 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 Saitz, MD, MPH; Michael F. Mayo-Smith, MD, MPH; Mark S. Roberts, MD, MPP; 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; Ulrika 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

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 ← 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

CASE - KH

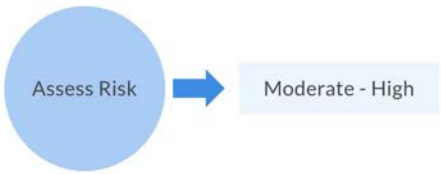
26W PMH AUD, GAD, PTSD and eating disorder admitted for alcohol withdrawal syndrome.

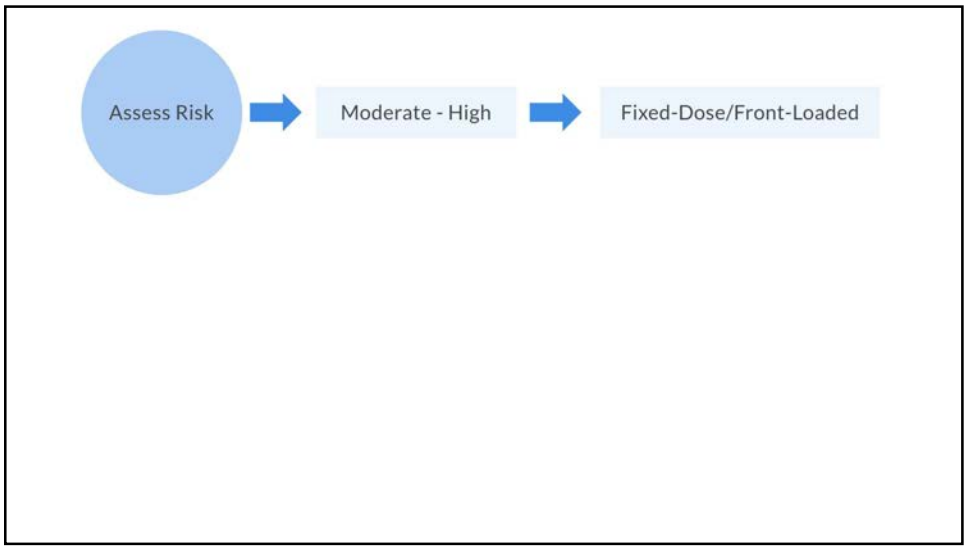
- **Subjective:**
  - Nausea. No vomiting. Anxiety. Headache.
- **Physical exam:**
  - HR 115, BP 132/88.
  - Anxious. Tremulous. Not diaphoretic.
  - No auditory or visual hallucinations.
- **CIWA:** 14
- **Labs:**
  - Blood alcohol level = 260 mcg/mL
  - Urine toxicology screen: negative
  - Na 133,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

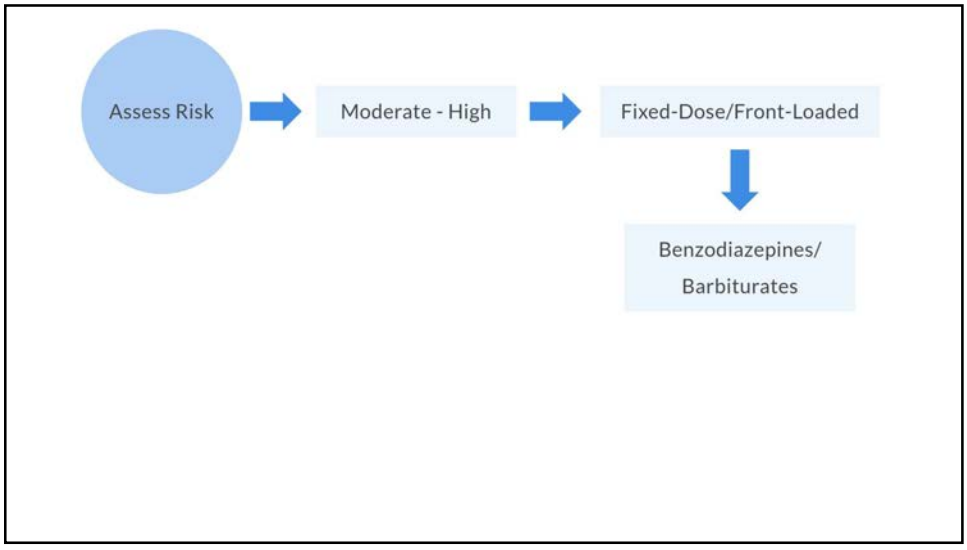
CASE - KH

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

Past	Present
• 25 admissions • No complications	• 17 drinks/day • CIWA 14 • BAL 260 • Tachycardiac • Tremulous




Assess Risk
Moderate - High
Fixed-Dose/Front-Loaded


Assess Risk
Moderate - High
Fixed-Dose/Front-Loaded
Benzodiazepines/
Barbiturates

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

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

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

A: Symptom-triggered CIWA-driven benzodiazepines
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
D: Front-loaded phenobarbital

CASE - KH

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

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

~~A: Symptom-triggered CIWA-driven benzodiazepines~~
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
D: Front-loaded phenobarbital

CASE - KH

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

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

~~A: Symptom-triggered CIWA-driven benzodiazepines~~
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
D: Front-loaded phenobarbital

Shared Decision Making

CASE - KH

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

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

~~A: Symptom-triggered CIWA-driven benzodiazepines~~
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
D: Front-loaded phenobarbital

Shared Decision Making → Benzodiazepines

CASE - KH

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

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

~~A: Symptom-triggered CIWA-driven benzodiazepines~~
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
~~D: Front-loaded phenobarbital~~

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
chlordiazopoxide	5 - 30 hr	yes; 40 - 120 hr	1 - 4 hr	PO	hepatic CYP-mediated oxidation

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
chlordiazopoxide	5 - 30 hr	yes; 40 - 120 hr	1 - 4 hr	PO	hepatic CYP-mediated oxidation

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
chlordiazopoxide	5 - 30 hr	yes; 40 - 120 hr	1 - 4 hr	PO	hepatic CYP-mediated oxidation

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
chlordiazopoxide	5 - 30 hr	yes; 40 - 120 hr	1 - 4 hr	PO	hepatic CYP-mediated oxidation

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
chlordiazopoxide	5 - 30 hr	yes; 40 - 120 hr	1 - 4 hr	PO	hepatic CYP-mediated oxidation

SHORT-ACTING BENZODIAZEPINES

	half-life	active metabolites	time to peak conc (Cmax)	formulation	metabolism
lorazepam	10 - 20 hr	none	1 - 2 hr	PO/IV/IM/SL	conjugation
oxazepam	5 - 15 hr	none	1 - 4 hr	PO	conjugation

SHORT-ACTING BENZODIAZEPINES

	half-life	active metabolites	time to peak conc (Cmax)	formulation	metabolism
lorazepam	10 - 20 hr	none	1 - 2 hr	PO/IV/IM/SL	conjugation
oxazepam	5 - 15 hr	none	1 - 4 hr	PO	conjugation

SHORT-ACTING BENZODIAZEPINES

	half-life	active metabolites	time to peak conc (Cmax)	formulation	metabolism
lorazepam	10 - 20 hr	none	1 - 2 hr	PO/IV/IM/SL	conjugation
oxazepam	5 - 15 hr	none	1 - 4 hr	PO	conjugation

SHORT-ACTING BENZODIAZEPINES

	half-life	active metabolites	time to peak conc (Cmax)	formulation	metabolism
lorazepam	10 - 20 hr	none	1 - 2 hr	PO/IV/IM/SL	conjugation
oxazepam	5 - 15 hr	none	1 - 4 hr	PO	conjugation

SHORT-ACTING BENZODIAZEPINES

	half-life	active metabolites	time to peak conc (Cmax)	formulation	metabolism
lorazepam	10 - 20 hr	none	1 - 2 hr	PO/IV/IM/SL	conjugation
oxazepam	5 - 15 hr	none	1 - 4 hr	PO	conjugation

CASE - KH

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

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 $\geq$ 15
D: As soon as possible

CASE - KH

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

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 $\geq$ 15
D: As soon as possible

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, 2020.

CASE - KH

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

You decide to proceed with front-loaded benzodiazepines.

Why is diazepam the benzodiazepine of choice?

A: Long half-time
B: Fast time to peak concentration (Cmax)
C: Can be given PO, IM or IV
D: All of the above

CASE - KH

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

You decide to proceed with front-loaded benzodiazepines.

Why is diazepam the benzodiazepine of choice?

A: Long half-time
B: Fast time to peak concentration (Cmax)
C: Can be given PO, IM or IV
D: All of the above

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 (≥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.grepmed.com/images/9144/agitation-nursing-richmond-diagnosis-rass

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 (≥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.grepmed.com/images/9144/agitation-nursing-richmond-diagnosis-rass

CASE - ML

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

What is the preferred option to treat his alcohol withdrawal syndrome?

A: CIWA-driven symptom-triggered benzodiazepines
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
D: Front-loaded phenobarbital

CASE - ML

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

What is the preferred option to treat his alcohol withdrawal syndrome?

~~A: CIWA-driven symptom-triggered benzodiazepines~~
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
D: Front-loaded phenobarbital

CASE - ML

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

What is the preferred option to treat his alcohol withdrawal syndrome?

~~A: CIWA-driven symptom-triggered benzodiazepines~~
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
D: Front-loaded phenobarbital

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

CASE - ML

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

What is the preferred option to treat his alcohol withdrawal syndrome?

~~A: CIWA-driven symptom-triggered benzodiazepines~~
B: Fixed-dose benzodiazepines
C: Front-loaded benzodiazepines
D: Front-loaded phenobarbital

EHR, 2009: "required intubation and dexmedetomidate despite escalating doses of diazepam" → Benzodiazepine non-responder?

CASE - ML

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

What is the preferred option to treat his alcohol withdrawal syndrome?

~~A: CIWA-driven symptom-triggered benzodiazepines~~
~~B: Fixed-dose benzodiazepines~~
~~C: Front-loaded benzodiazepines~~
D: Front-loaded phenobarbital

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

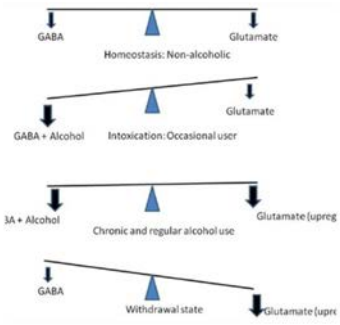


Image: https://medicinespecifics.com/alcohol-withdrawal-gaba-mechanism/. Accessed 5/24/2020

- 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 PHARMACOKINETICS AND PHARMACODYNAMICS

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

Mechanism of action

GABA CHLORIDE CHANNEL	GLUTAMATE RECEPTOR
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	**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
- **Fast peak effect (Cmax)**
  IV/IM: < 30 min
- **Long half-life**
  Approx 80 hours
- **Long elimination**
  > 2 weeks
- **Wide therapeutic index! (not narrow)**
  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

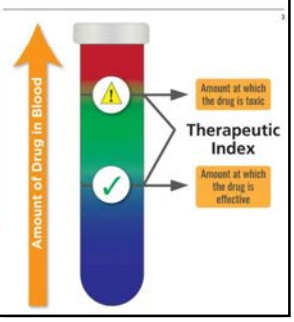
THERAPEUTIC INDEX

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

CASE - ML

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

What is the preferred option to treat his alcohol withdrawal syndrome?

~~A: CIWA-driven symptom-triggered benzodiazepines~~
~~B: Fixed-dose benzodiazepines~~
~~C: Front-loaded benzodiazepines~~
D: Front-loaded phenobarbital

CASE - ML

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

How should phenobarbital be dosed?

PHENOBARBITAL FOR ALCOHOL WITHDRAWAL PROTOCOL

Brigham and Women's Hospital and Massachusetts General Hospital

Psychosomatics
Volume 60, 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. [a,c], Shamim H. Nejad M.D. [d], Benjamin M. Isenberg B.A. [b], Ednan Khalid Bajwa M.D. [e], Paul Currier M.D. [e], Paul M. Wallace B.A. [f], George Velmahos M.D. [g], Timothy Wilens M.D. [b,c]

- 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

Shamim Nejad M.D. [a], Mladen Nisavic M.D. [b,c], Andreas Larentzakis M.D. [d], Suzan Diikink M.D. [e], Yuchiao Chang Ph.D. [f], Alexander R. Levine Pharm.D. [g], Marc de Moya M.D. [h], George Velmahos M.D. [f]

- 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

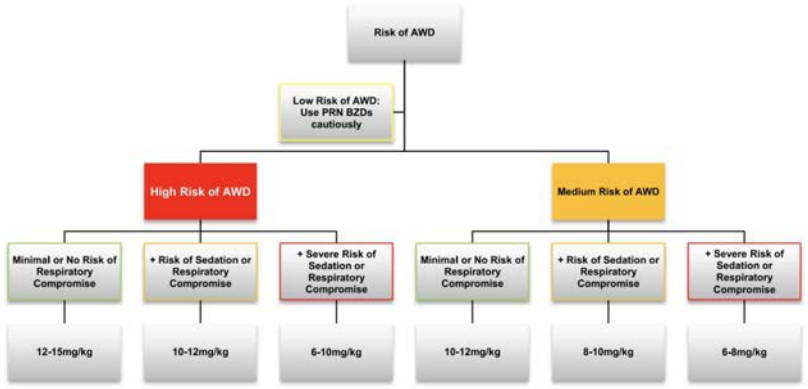
- High vs. medium

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.

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.

- 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)

CASE - ML

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

2 hours later completion of IV infusion: RASS +1

CASE - ML

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

2 hours later completion of IV infusion: RASS +1

Rescue dosing:

- Phenobarbital 2 mg/kg 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

CASE - ML

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

2 hours later completion of IV infusion: RASS +1

Rescue dosing:

- Phenobarbital 2 mg/kg 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

Post-load taper is no longer advised.

RECENT LITERATURE

Journal of Medical Toxicology (2022) 18:198–204
https://doi.org/10.1007/s13181-022-00900-8

ORIGINAL ARTICLE

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

Poorvi Shah[1] · Kati L. Stegner-Smith[1,2] · Mohamad Rachid[3] · Tabassum Hanif[3] · Kenneth W. Dodd[3,4,5,6]

Received: 3 December 2021 / Revised: 5 May 2022 / Accepted: 10 May 2022 / Published online: 6 June 2022
© American College of Medical Toxicology 2022

- compared low-intermittent dosing vs. front-loaded phenobarbital in severe alcohol withdrawal
- front-loaded: less mechanical ventilation and less continuous sedation needed

Received: 30 October 2022 | Revised: 26 April 2023 | Accepted: 26 April 2023
DOI: 10.1002/epc2.12347

ORIGINAL ARTICLE

WILEY

Phenobarbital versus benzodiazepines in alcohol withdrawal syndrome

Deanna Malone[1] | Blair N. Costin[1,2] | Dawn MacElroy[1] | Mashael Al-Hegelan[1,2] | Julie Thompson[3] | Yuriy Bronshteyn[2,4]

- 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 Stoidle PharmD, BCPS, APh [a, b], [a], Curtis Geier PharmD, BCCCP [a]

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

Open Access Original Article

DOI: 10.7759/cureus.13282

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

Fadi Hawa [1], Linsey Gilbert [2], Benjamin Gilbert [3], Vanessa Hereford [3], Aya Hawa [4], Alsadiq Al Hillan [5], Mark Weiner [6], Jeremy Albright [7], Caleb Scheidel [1], Ola Al-Sous [1]

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/Hepatology, 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 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 accp

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

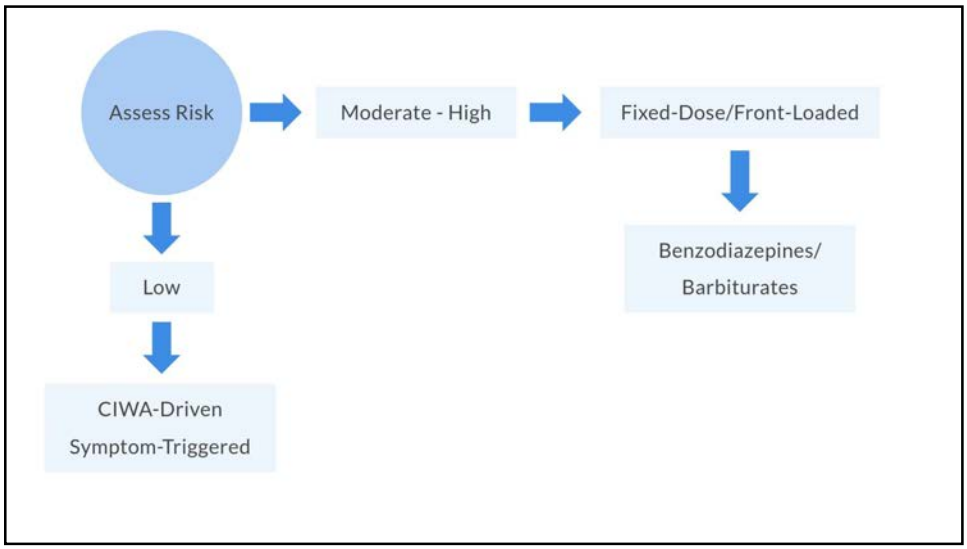
- Alcohol withdrawal seizures: 24-48 hours
- Delirium tremens: 48-90 hrs
- Consider increasing dose of benzodiazepine, switching to IV or switching to phenobarbital
- Consider adding antipsychotic (risperidone, quetapine, haloperidol)
- Goal RASS -1

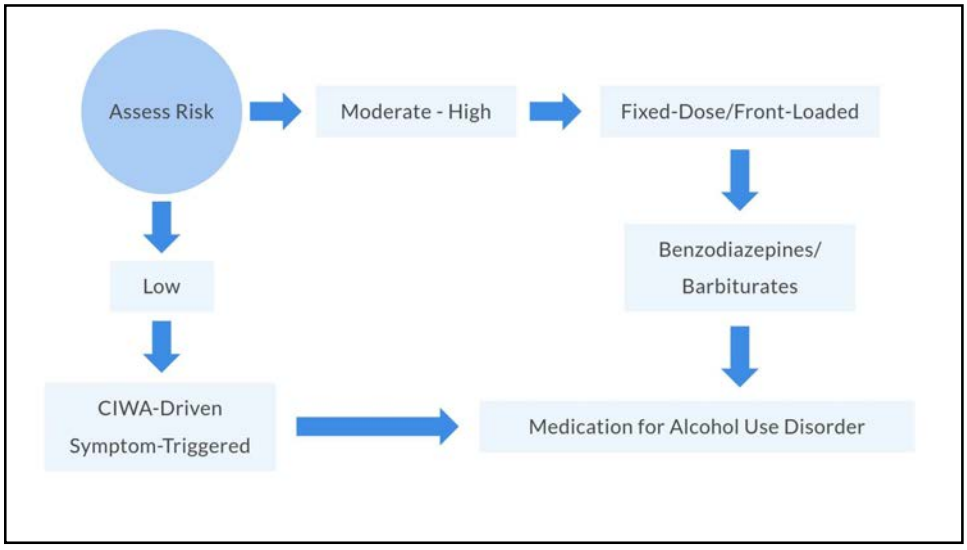
Greater than 72 hours

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

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

ASAM CPG on Alcohol Withdrawal Management, 2019.


Assess Risk
Moderate - High
Fixed-Dose/Front-Loaded
Benzodiazepines/
Barbiturates
Low
CIWA-Driven
Symptom-Triggered


Assess Risk
Moderate - High
Fixed-Dose/Front-Loaded
Benzodiazepines/
Barbiturates
Low
CIWA-Driven
Symptom-Triggered
Medication for Alcohol Use Disorder

MEDICATIONS FOR ALCOHOL USE DISORDER (MAUD)

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

MEDICATIONS FOR ALCOHOL USE DISORDER (MAUD)

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

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

PCSS 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)

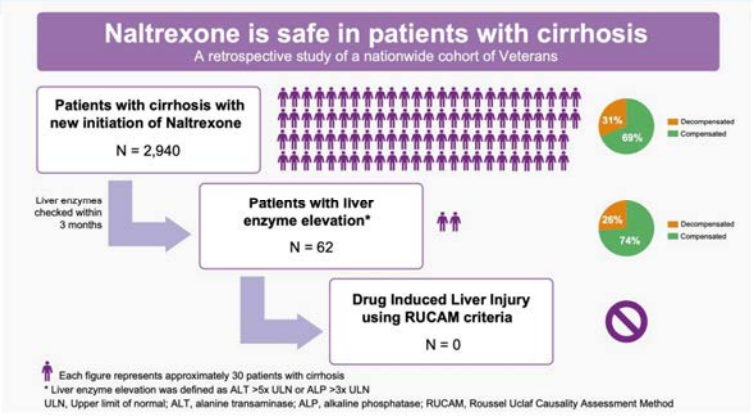
Edited by: 1st Adam Bisaga, MD (October 14, 2014;) 2nd Adam Bisaga, MD, (June 26, 2018)

Reviewed and Re-released: May 2022

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

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

NALTREXONE AND ALCOHOL-RELATED LIVER DISEASE



Thompson R, Taddei T, Kaplan D, Rabiee A. Safety of naltrexone in patients with cirrhosis. *JHEP Rep*. 2024;6(7):101095. Published 2024 Apr 10. doi:10.1016/j.jhepr.2024.101095

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 Jahn, MD; Timo Tarnaske; 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 effacious than placebo
- Rate of relapse in combined group was not statistically better than naltrexone alone

Original Contribution FREE

May 3, 2006

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?