Management of Alcohol Withdrawal Syndrome with a Focus on Phenobarbital

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NC DEPARTMENT OF HEALTH AND HUMAN SERVICES

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We have no relevant financial conflicts of interest to disclose

Objectives

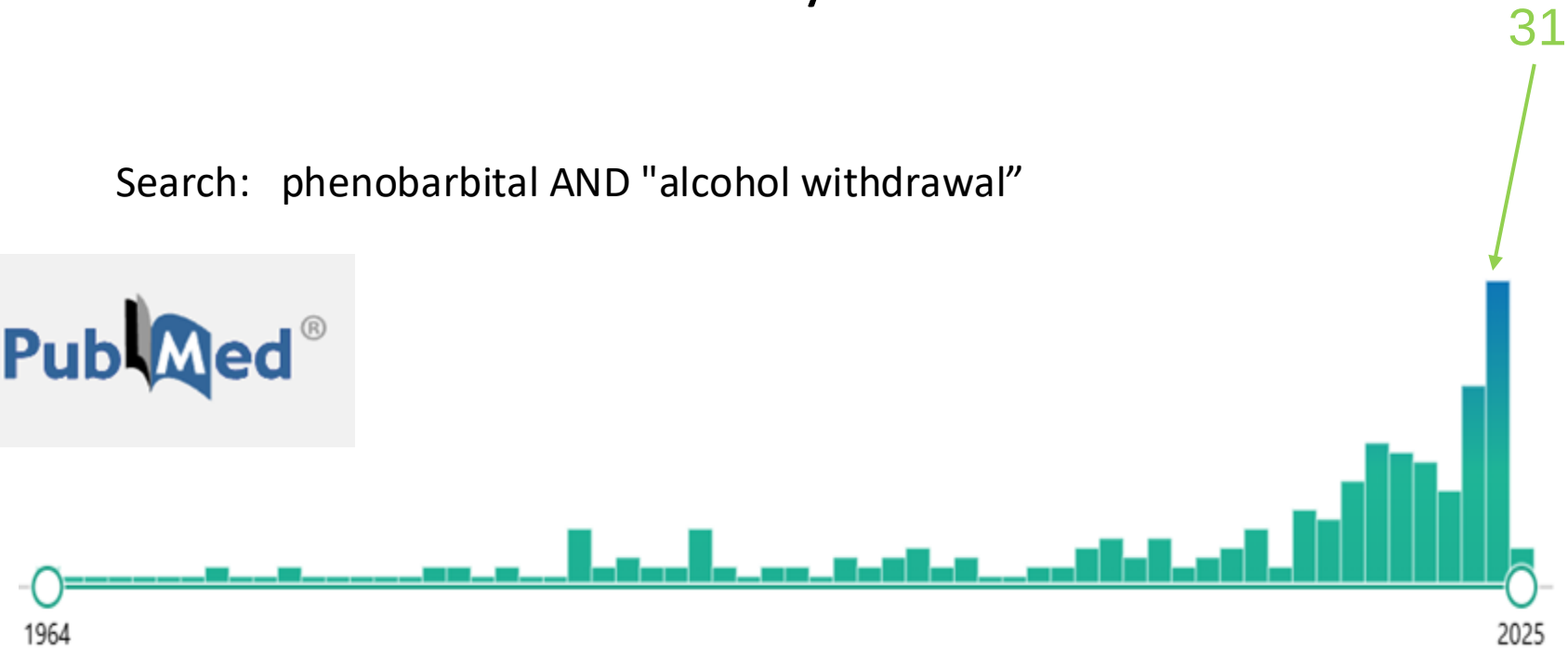
At the conclusion of this activity participants will be able to:

1. Discuss the recent literature supporting the use of phenobarbital in alcohol withdrawal syndrome

2. Identify advantages and disadvantages of using phenobarbital in scheduled protocols across different healthcare settings

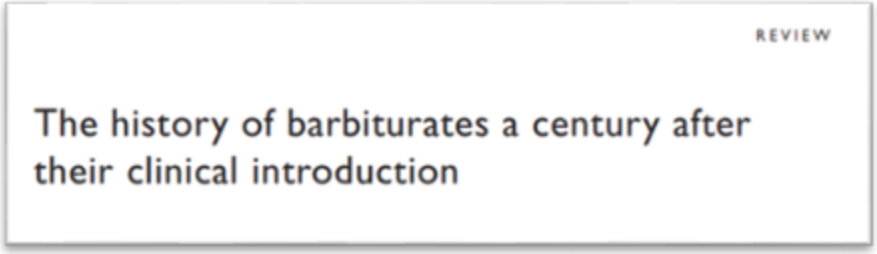
PHB for alcohol withdrawal syndrome

Search: phenobarbital AND "alcohol withdrawal”



PubMed query as of 2/3/2025*

History of phenobarbital



- Introduced in 1912 (Luminal) as a hypnotic, then for seizures
  - Dr. Alfred Hauptmann
- First medication to predictably and reliably treat AWS
- Used since the 1920s for AWS
- Widely used for many conditions in the 1930s-50s
- Main drawbacks were physical dependence and potential for overdose death
- Other barbiturates were associated with deaths in clinical studies

Lopez-Munoz et al. Neuropsychiatric Disease and Treatment. 2005
The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. American Society of Addiction Medicine. 2020.

Fall of phenobarbital

- Fell out of favor in the 1960s due to side effects and “narrow therapeutic window” as benzodiazepines rose to prominence
- 1962 drug-dependence committee set up by President Kennedy – “may be as many as 250,000 Americans addicted to barbiturates”

- “Acute poisoning by overdose of barbiturates”

- 1960 – clordiazepoxide (Librium)
- 1963 – diazepam (Valium)
  - FDA approval later expanded to include AWS

Lopez-Munoz et al. Neuropsychiatric Disease and Treatment. 2005
The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. American Society of Addiction Medicine, 2020.

Phenobarbital today

- FDA approved for: seizure disorders
- **The use of phenobarbital in alcohol withdrawal syndrome is considered “off-label” use**

Lewis et al. Phenobarbital. StatPearls. 2024.

What's wrong with benzos?

- Benzodiazepines are considered the standard of care for AWS
- Limitations:
  - Some patients do not respond to benzodiazepines - ?GABA downregulation
  - Benzodiazepine-related delirium and other adverse events
  - CIWA-based protocols are time-intensive, user-dependent, reactive rather than proactive
- Interest in alternatives to benzos including agents besides PHB
  - gabapentin
  - alpha 2 agonists (clonidine and dexmedetomidine)
  - valproic acid

Pharmacology of PHB

- Acts at GABA-A receptor subunit → elongates opening duration of chloride channels → CNS depression
- Absorption: occurs quickly after administration
  - Oral: 30 minutes -1hr
  - IV: 5 minutes
- Metabolism: mostly via acetylation in liver (hepatic microsomal enzyme system)
- Half life up to 5 days

Lewis et al. Phenobarbital. StatPearls. 2024.

Dosing strategies

- Load based strategies
  - Typical starting range 10 mg/kg IBW
  - Protocols vary widely from 5-15 mg/kg IBW
  - Route of loading dose varies: IM vs IV
    - “Load” maybe be given as a single dose or split into 2-3 separate doses
- Fixed dosing protocols
  - Example
    - 64.8 mg TID x 2 days
    - 32.4 mg TID x 2 days
    - 16.2 mg BID x 1 day
- Symptom-triggered protocols

Simple…

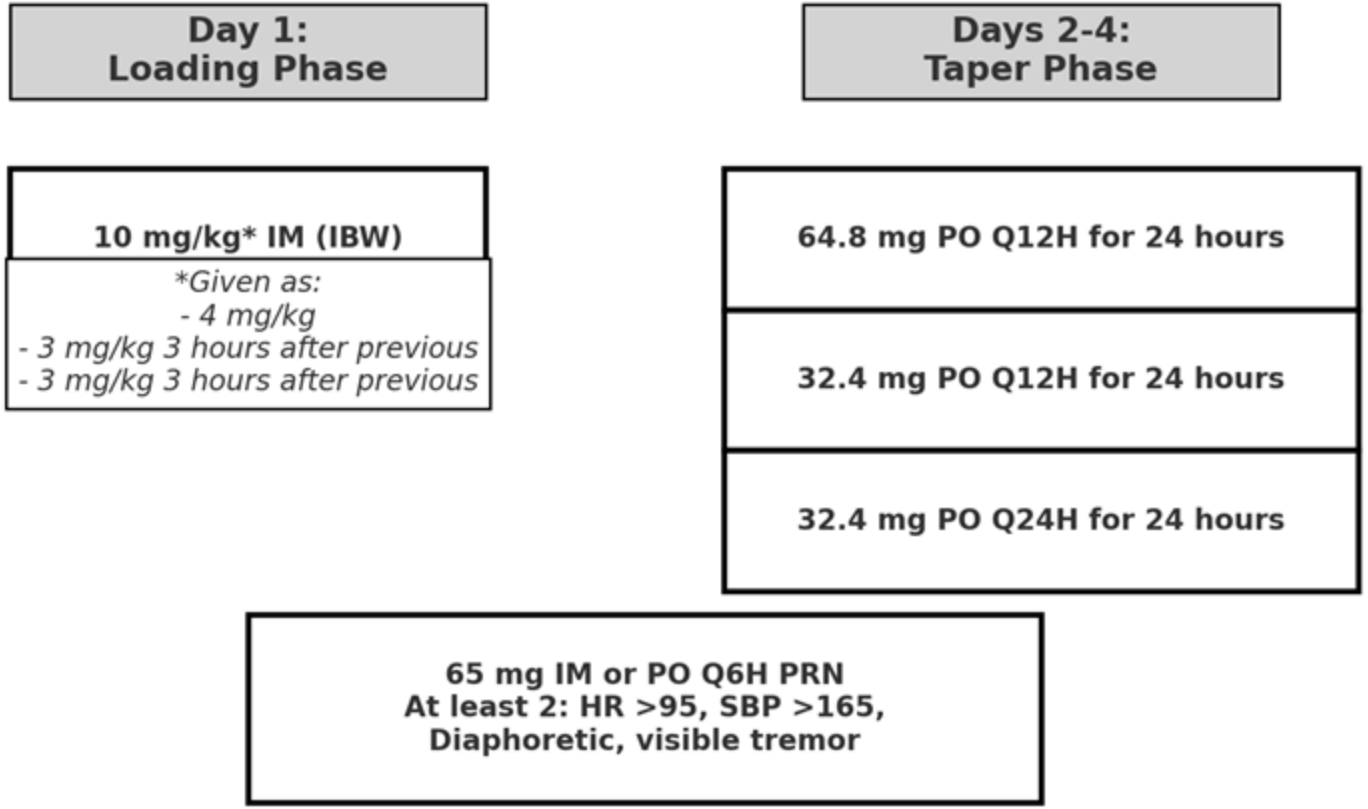


Figure recreated from: Kessel et al. Annals of Pharmacotherapy. 2024.

A lil' more complicated….

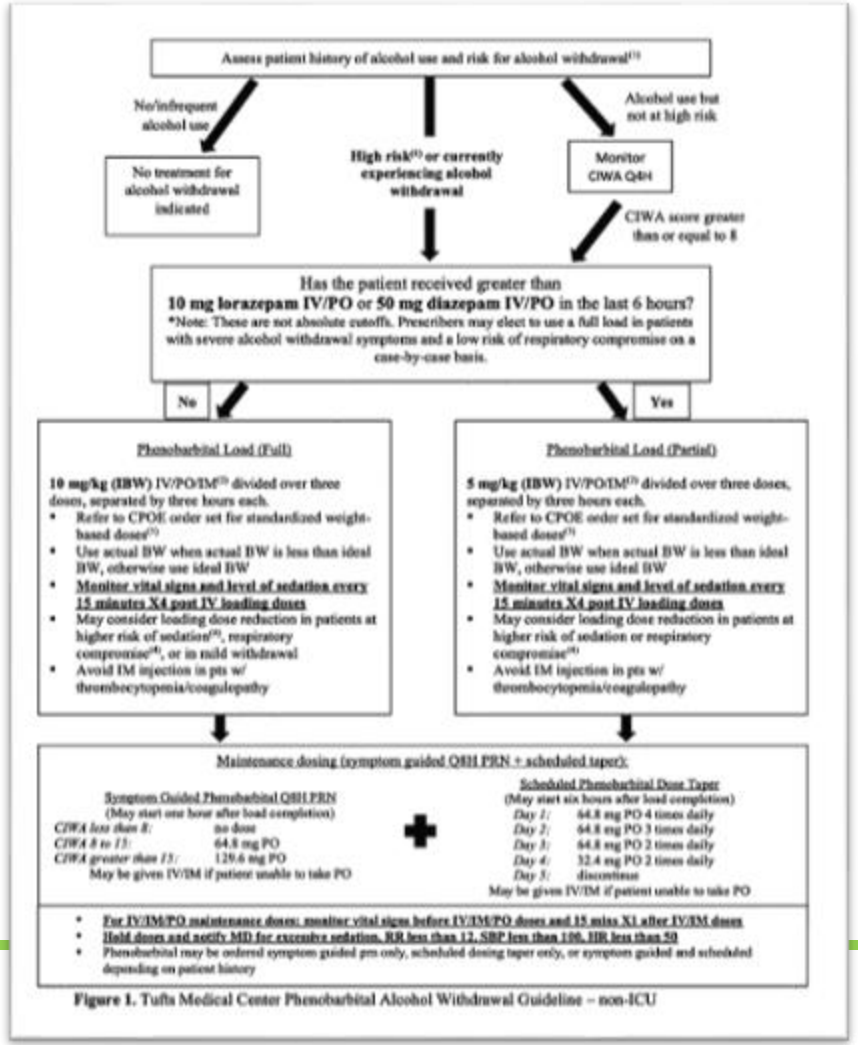


Figure 1. Tufts Medical Center Phenobarbital Alcohol Withdrawal Guideline – non-ICU

Tufts Medical Center, Non-ICU Phenobarbital Clinical Practice Guideline. 2020.

Drug interactions

- Potent CYP450 inducer
  - Concurrently administered drugs may be metabolized faster and excreted → treatment failure
- Potential substrates
  - Antiplatelets and Anticoagulants (warfarin, clopidogrel, apixaban)
  - Antiretrovirals
  - Anti-hypertensives (CCBs, ARBs, beta blockers)
  - Psychotropics (SSRIs, antipsychotics)
  - Methadone

Gilani B, Cassagnol M. Biochemistry, Cytochrome P450. StatPearls. 2023.

Special populations

- Hepatic Impairment
- Renal Impairment
  - 25-50% eliminated in urine
- Pregnancy: Category D
  - Crosses placenta, high concentrations in fetal brain, liver
  - Withdrawal syndromes
- Breastfeeding
  - Present in breast milk, can cause sedation in infant
- Elderly

Lewis et al. Phenobarbital. StatPearls. 2024.

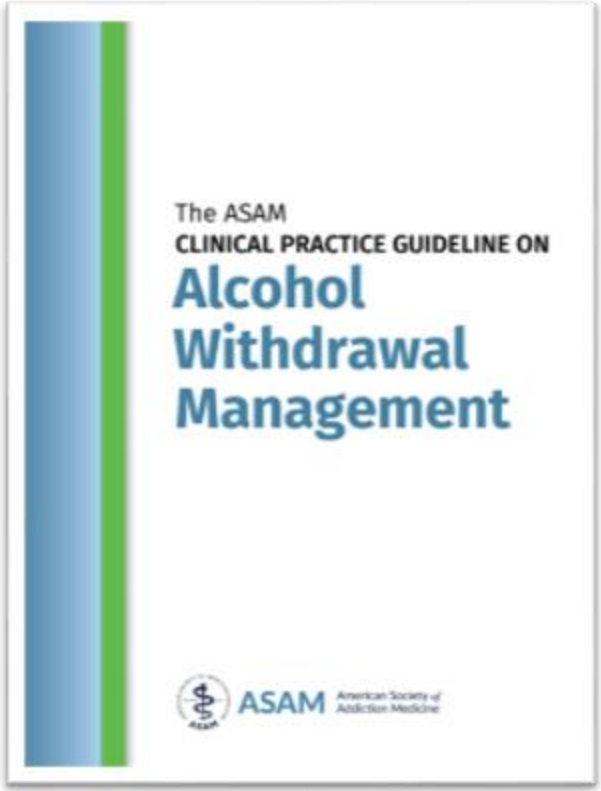
ASAM Clinical Practice Guideline

Literature review: up to **2017**

"Benzodiazepines are recommended as the primary medication to prevent the development of severe, complicated, or complications of withdrawal."

"Carbamazepine, gabapentin, or phenobarbital can be used for patients experiencing **mild or moderate** withdrawal who have a contraindication for benzodiazepine use."

"Phenobarbital is the preferred alternative for patients experiencing **severe** withdrawal. However, given its narrow therapeutic window, phenobarbital should only be used by clinicians experienced with its use."



The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. American Society of Addiction Medicine, 2020.

PHB for alcohol withdrawal syndrome

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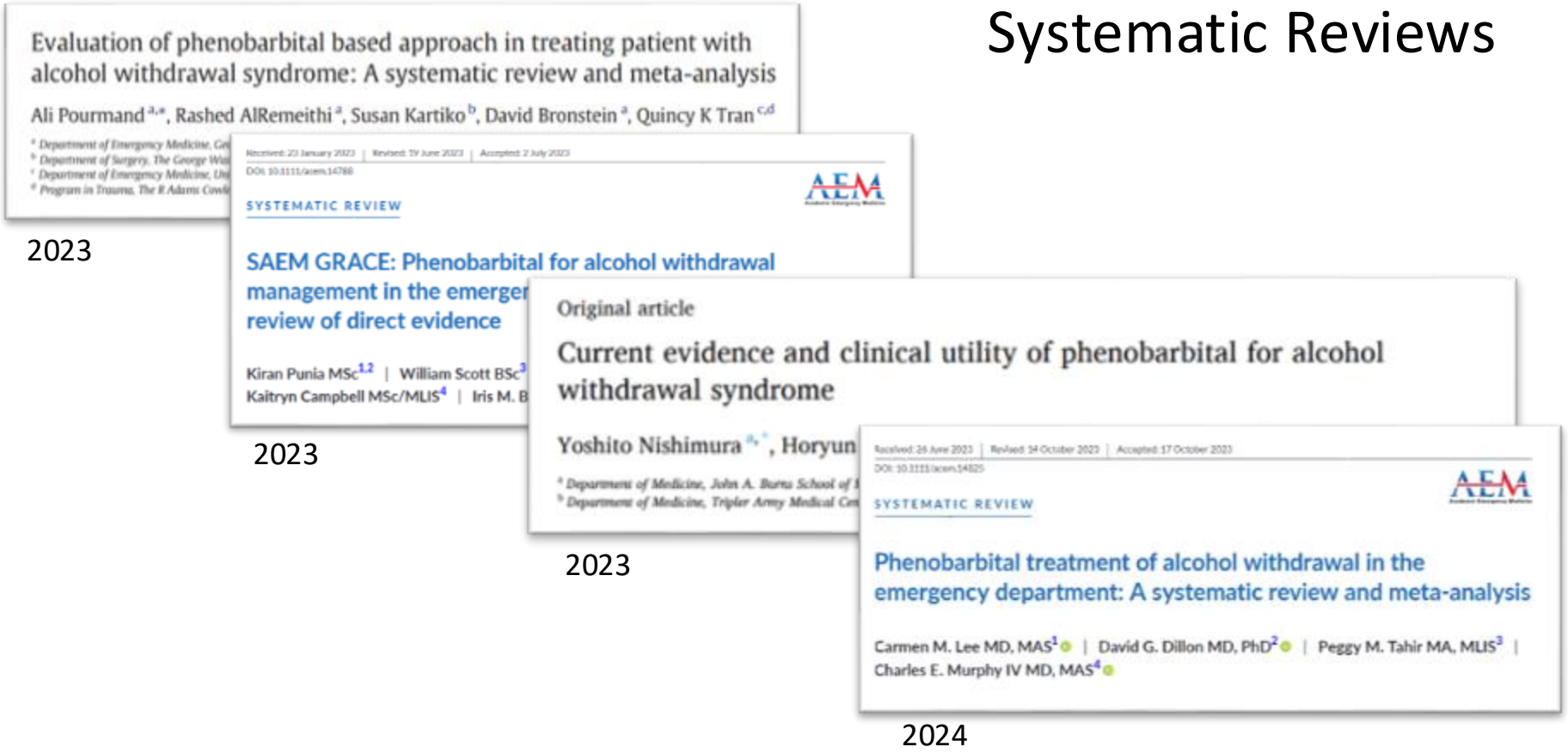
Systematic Reviews



Punia et al., Academic Emergency Medicine, 2023
Pourmand et al., The American Journal of Emergency Medicine, 2023

Nishimura et al., European Journal of Internal Medicine, 2023
Lee et al., Academic Emergency Medicine, 2024

Heterogeneity of the literature

Treatment setting
- ED
- Inpatient hospital floor
- ICU
- Withdrawal management facility / psychiatric unit

PHB monotherapy vs Benzos + PHB

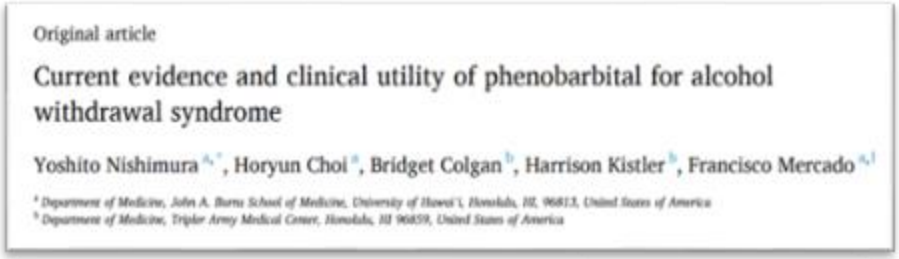
PHB protocol:
- Loading dose vs no loading dose
- Symptom triggered vs scheduled
- Cumulative dosing

Outcome measures
- ED to hospital admission rate
- ICU LOS
- Floor LOS
- Delirium, seizure, DTs
- Adverse events

Patient Selection
- Most severe AWS
- Benzo-non-responders
- Mild/mod/severe AWS

Setting: 9 ED, 11 ICU or general hospital floor

Dosing: very heterogeneous across studies,
some used PHB monotherapy, some PHB +benzos


Original article

Current evidence and clinical utility of phenobarbital for alcohol withdrawal syndrome

Yoshito Nishimura [a,*], Horyun Choi [a], Bridget Colgan [b], Harrison Kistler [b], Francisco Mercado [a,1]

[a] Department of Medicine, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI, 96813, United States of America
[b] Department of Medicine, Tripler Army Medical Center, Honolulu, HI 96859, United States of America

N= 20 studies
N = >1000 participants that received PHB monotherapy

Findings: considerable heterogeneity in terms of comparative group settings, PHB dosage, combined use of BZD, and outcomes
"PB monotherapy without BZD seems to have a better safety profile with fewer adverse events compared to combination therapy or BZD monotherapy"

Conclusions: *"While considerable heterogeneity exists among studies available, PB as monotherapy without BZD may be a safe and effective alternative in AWS treatment. Future prospective studies or trials should focus on the standardization of PB dosing and outcomes."*

Nishimura et al., European Journal of Internal Medicine, 2023

Design: retrospective cohort

Participants: Severe AWS.
PHB group at baseline had more history of seizures/DTs

Interventions:
Fixed-dose PHB monotherapy (N=126)
vs benzodiazepines (N=98)


Research Report

Phenobarbital Versus Benzodiazepines for the Treatment of Severe Alcohol Withdrawal

Sage

Katherine M. Kessel, PharmD[1], Logan M. Olson, PharmD, BCCCP[1], Derek A. Kruse, MD[1], Elizabeth R. Lyden, MS[1], Kelsey E. Whiston, PharmD, BCCCP[1], Mindy M. Blodgett, APRN[1], and Alena A. Balasanova, MD[1]

Dosing: median PHB - 978.8mg, median benzo LME - 36.7mg

Outcomes: Length of stay, ICU LOS, incidence of adjunctive meds, incidence/duration of mechanical ventilation

Results:
- PHB had shorter LOS, less dexmedetomidine, less antipsychotic, less new mechanical ventilation
- Less mechanical ventilation in patients receiving phenobarbital is…

"consistent with previous studies, which have demonstrated either a decrease or no difference in mechanical ventilation among patients treated with phenobarbital compared to benzodiazepines."

Kessel et al. Annals of Pharmacotherapy. 2024.

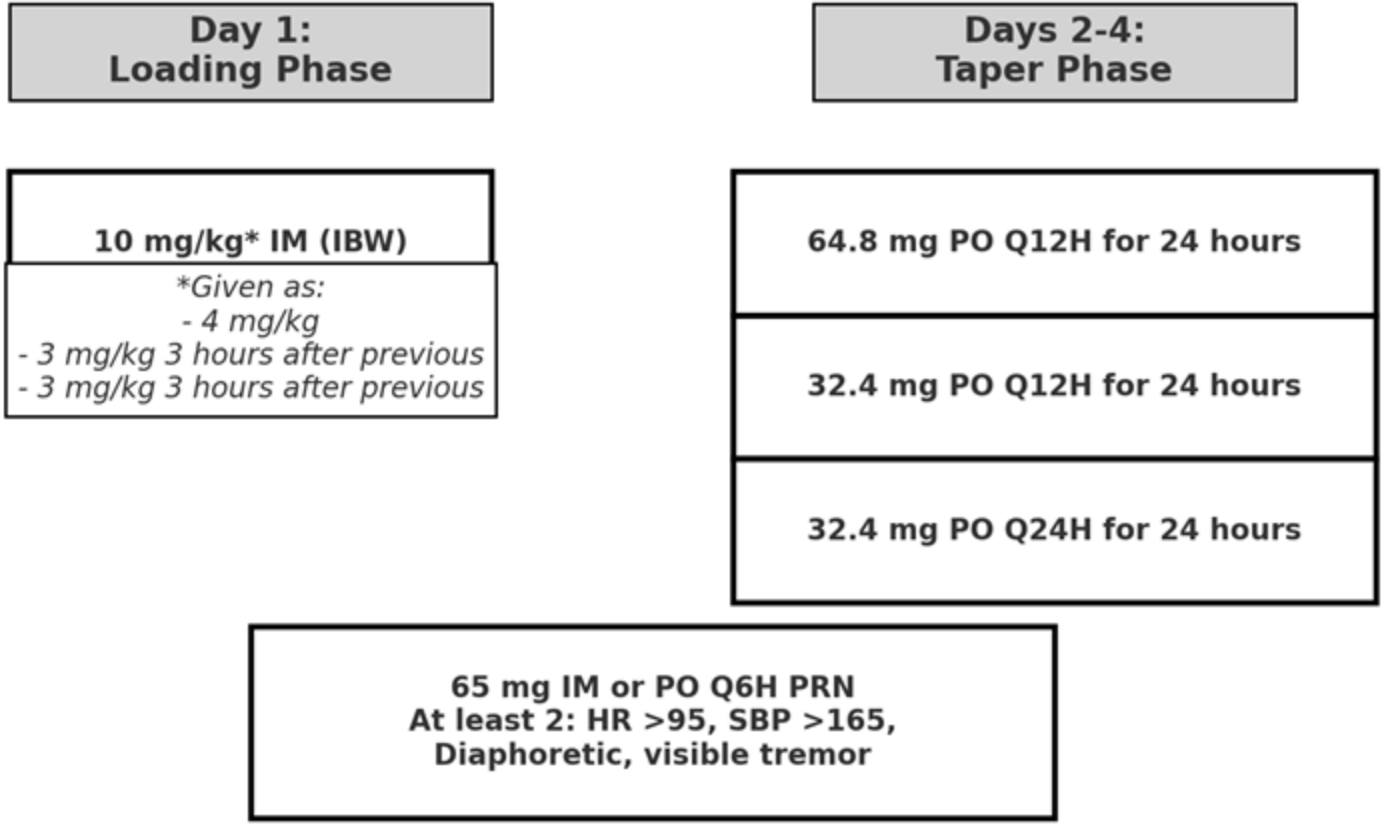


Figure recreated from: Kessel et al. Annals of Pharmacotherapy. 2024.

Case 1

35-year-old gentleman presents for medically managed withdrawal management.

History of hypertension, complicated alcohol withdrawal, including withdrawal seizures and previous ICU stay at outside institution.

Recent pattern of use: 12-15 8% ABV 12 oz beers daily.

BAL on admission 0.35. AST mildly elevated, not >5x uln. Tbili and platelets normal.

CIWA 12. Vitally stable. He is 6’5”.

Case 1

1. Is the patient at a high enough risk for alcohol withdrawal that he warrants medically managed withdrawal management?
2. What is the appropriate level of care for him to undergo withdrawal management?
3. What are considerations in a load vs fixed dosing strategy for this patient?
4. Any reason to avoid phenobarbital?

Case 2

40 year old woman presents with a laceration to her hand requiring stitches but probably not surgery. BAL 0.3 on admission late Saturday evening. ED spoke with the hand surgeon on call who is planning to evaluate her first thing Sunday morning.

Recent pattern of drinking: 2 bottles of wine daily. No prior attempts at withdrawal management.

Vitally stable.

Case 2

1. Is the patient at a high enough risk for alcohol withdrawal that she warrants medically managed withdrawal management?
2. What is the appropriate level of care for her to undergo withdrawal management?
3. What are considerations in a load vs fixed dosing strategy for this patient?
4. Any reason to avoid phenobarbital?

Case 3

45 year old gentleman presents for medically managed withdrawal management.

Current pattern of use: 8-10 5% ABV beers daily. No prior attempts at withdrawal management.

BAL 0.05; CIWA 8 at intake. Vitally stable. Tolerating food and drink with mild nausea.

Case 3

1. Is the patient at a high enough risk for alcohol withdrawal that he warrants medically managed withdrawal management?
2. What is the appropriate level of care for him to undergo withdrawal management?
3. What are considerations in a load vs fixed dosing strategy for this patient?
4. Any reason to avoid phenobarbital?

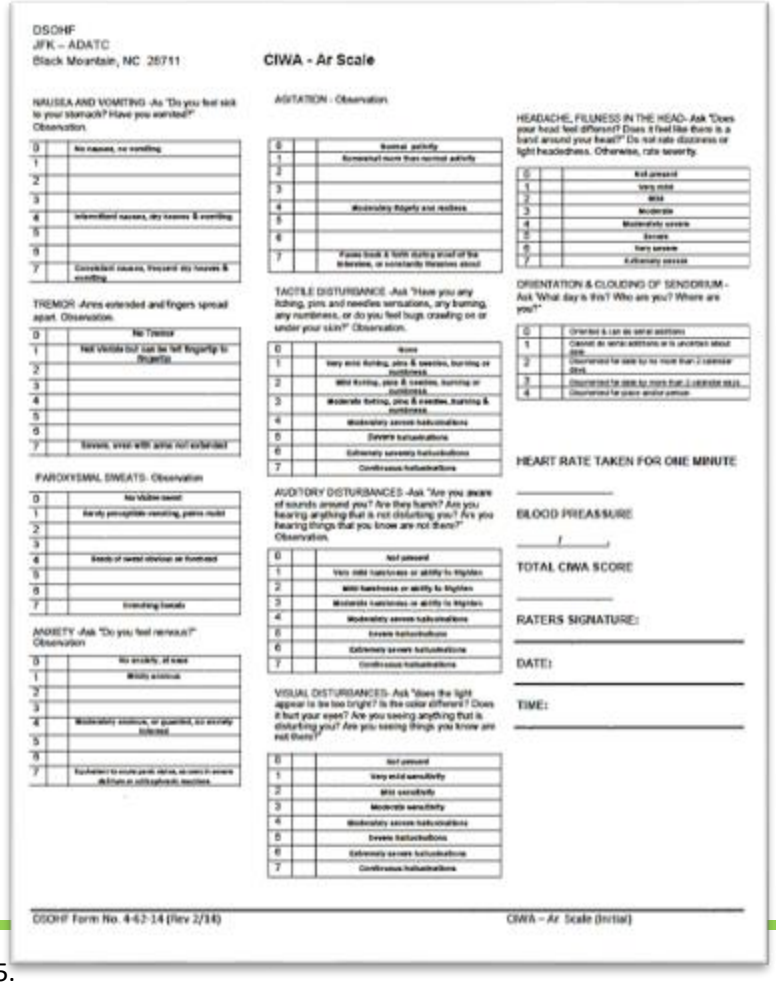
FAQs

- Can I safely administer a loading dose of phenobarbital in the presence of an elevated BAL?
- I am concerned my patient may leave the hospital against medical advice/prematurely. Should I be less inclined to use phenobarbital? Or should I be more inclined to use phenobarbital?
- What cut-offs should I use for liver disease when considering the use of phenobarbital?

Limitations of symptom-triggered approaches

CIWA-Ar…

- Requires clinician training for reliable administration
- Takes significant time to administer and score
- Requires patients to be able to accurately self-report symptoms
- Is **not** reliable in presence of confounding medical conditions
- Is **not** reliable for patients who cannot reliably communicate accurate responses



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CIWA - Ar Scale

NAUSEA AND VOMITING -As "Do you feel sick to your stomach? Have you vomited?" Observation.

0		No nausea, no vomiting
1		
2		
3		
4		Intermittent nausea, dry heaves & vomiting
5		
6		
7		Constant nausea, frequent dry heaves & 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		
5		
6		
7		Severe, even with arms not extended

PAROXYSMAL SWEATS- Observation

0		No visible sweat
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 inferred
5		
6		
7		Equivalent to acute panic states as seen in severe delirium or 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 & forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCE -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 & needles, burning or numbness
2		Mild itching, pins & needles, burning or numbness
3		Moderate itching, pins & needles, burning & numbness
4		Moderately severe hallucinations
5		Severe hallucinations
6		Extremely severely hallucinations
7		Continuous hallucinations

AUDITORY DISTURBANCES -Ask "Are you aware of sounds around you? Are they harsh? Are you hearing anything that is not disturbing you? Are you hearing things that 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 the color different? Does it hurt your eyes? Are you seeing anything that is disturbing you? Are you seeing things you know are not there?"

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 THE HEAD- Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate dizziness or light headedness. 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 & CLOUDING OF SENSORIUM - Ask "What day is this? Who are you? Where are you?"

0		Oriented & 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

HEART RATE TAKEN FOR ONE MINUTE

_____

BLOOD PREASSURE

_____/_____

TOTAL CIWA SCORE

_____

RATERS SIGNATURE:

_____

DATE:

_____

TIME:

_____

DSOHF Form No. 4-62-14 (Rev 2/14) CIWA – Ar Scale (Initial)

Kast et al. Management of alcohol withdrawal syndromes in general hospital settings BMJ. 2025.
Sullivan et al. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). Br J Addict. 1989.

Limitations of symptom-triggered approaches (cont.)

Weaver et al, 2006:

- Compared symptom triggered and fixed schedule protocols and found higher rates of protocol errors in the symptom triggered group (odds ratio 2.6, 17.6% v 7.6% error rate, P=0.04)

Chen et al, 2018:

- Of 1102 CIWA-Ar encounters, only 50% of patients were appropriate for its use
- CIWA-Ar was adequately followed by nurses in 10% of cases

Symptom triggered approaches require education, training, and monitoring of competency of staff who implement the protocol

Kast et al. Management of alcohol withdrawal syndromes in general hospital settings BMJ. 2025.
Weaver et al. Alcohol withdrawal pharmacotherapy for inpatients with medical comorbidity. J Addict Dis. 2006.
Chen et al. Clinical institute withdrawal assessment (CIWA) protocol: Misunderstandings, misuse, and misadventures. Am J Respir Crit Care Med. 2018.

Changes in nursing workforce

2018 → 2022 saw a >400% increase in percentage of nursing workforce on travel contracts…

>5% of all nurses were on travel contracts in 2022

5% of the nursing workforce (approximately 195,000 RNs) left the nursing workforce due to the pandemic

If labor force patterns remain the same as today, the demand for RNs in 2036 will exceed supply by 9%, resulting in a shortage of 337,970 full-time equivalent (FTE) RNs

National Sample Survey of Registered Nurses (NSSRN). 2022-2023.

Future directions/questions/cautions

What we need:

Prospective RCT(s) of… 1) fixed-dose PHB vs 2) fixed-dose benzos vs
3) symptom-triggered PHB vs 4) symptom-triggered benzos

Controversial questions:

- What is the evidentiary requirement to supplant a treatment as the standard of care?
- Who funds research for a 113 year old drug (PHB) vs a 60+ year old drug (e.g. lorazepam or diazepam) in 2025?
- Polysubstance use is the rule not the exception – in what percentage of cases is CIWA-Ar valid in 2025?
- If the nursing crisis persists, is CIWA-Ar as viable a tool as it was in the 1980s and 1990s?
- If parenteral benzodiazepine shortages persist, should PHB be first-line?
    - Should PHB be first-line regardless?
- Is a PHB load in the ED an alternative to an admission for withdrawal management?

Thank you