Penn Medicine
Lancaster General Health

Phenobarbital Monotherapy for Severe Alcohol Withdrawal

Mitchell West, DO, MHA
Addiction Medicine

March 20, 2025

PSNA Educational Event

As an approved event, the following items need to be reviewed:

- There are no partial hours associated with this opportunity; you MUST attend the entire event in order to be awarded contact hours.
- There are no reported conflicts of interest with any of our speakers or with any of the planning committee members.
- This program is sponsored by Penn Medicine Lancaster General Health.
- In order to be awarded PSNA contact hours, you **MUST ALSO** complete the evaluation form.
- If you do not attend the entire course AND complete the evaluation, you will not be awarded the contact hours approved for this activity.
- A certificate will be awarded once an evaluation is submitted.

This activity has been awarded 1 contact hours. Penn Medicine Nursing is approved as a provider of nursing continuing professional development by Pennsylvania State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. Approval # 136-3-H-22.

Financial Disclosure

- The Planners, Nurse Planner, Content Experts, and Presenter attest that they have no financial relationship(s) to disclose with ineligible companies.

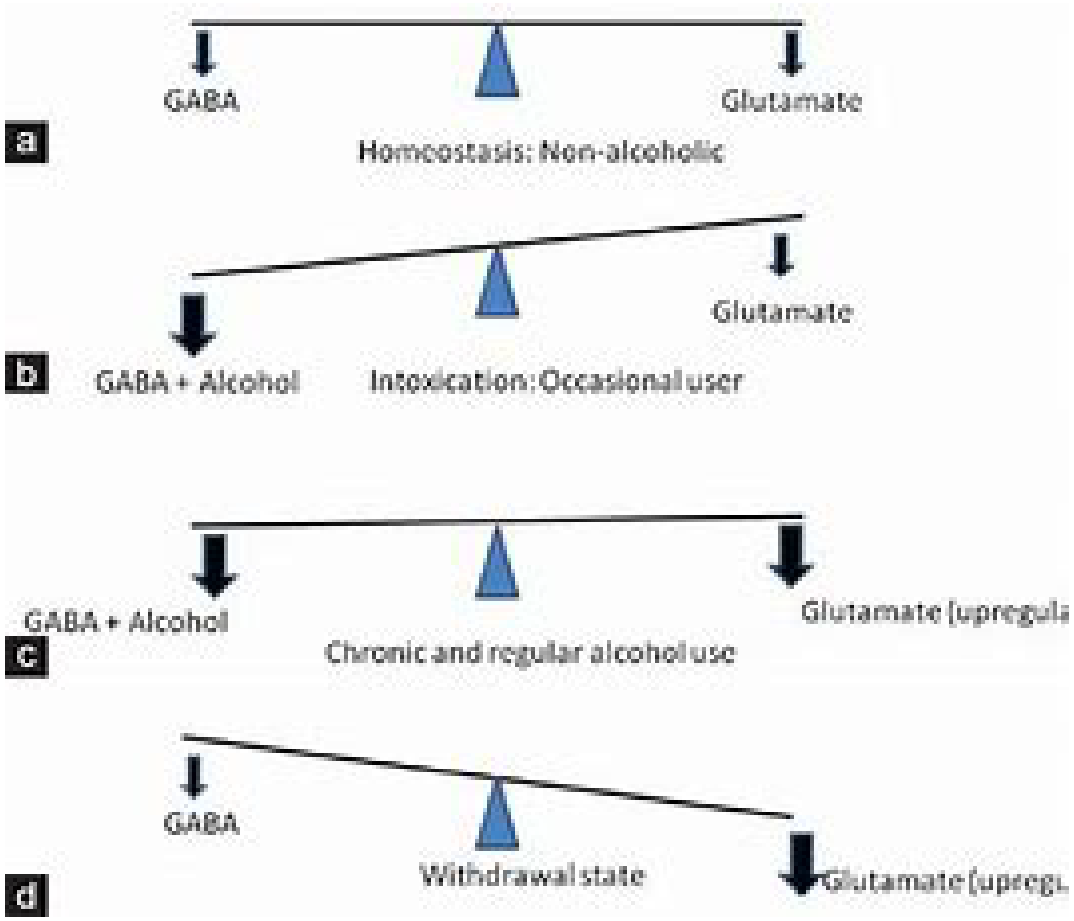
Learning Objectives

- Describe the roles of various receptors in alcohol withdrawal.
- Discuss the pharmacology of phenobarbital and its effectiveness for alcohol withdrawal.
- Apply phenobarbital loading and maintenance dosing in practice.

Phenobarbital monotherapy is a front-line therapy for alcohol withdrawal.

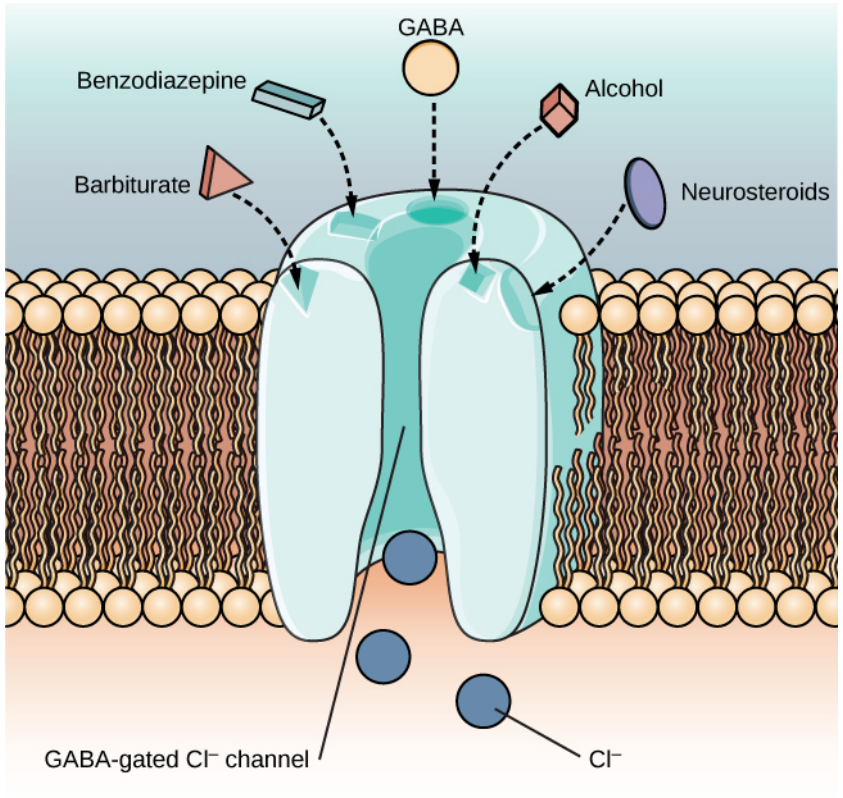
- Replacing benzodiazepines at many institutions because it provides faster and more definitive therapy for alcohol withdrawal, while avoiding extended ICU stays for repeated doses of benzodiazepines.
- Beneficial for the treatment of AWS, both in the emergency and inpatient settings and both as monotherapy or in conjunction with benzodiazepines.
- Safe for patients without severe hepatic impairment, has a better mechanism of action and longer half-life than benzodiazepines, and leads to less delirium and agitation.
- Effective for alcohol withdrawal at a dose of ~10-20 mg/kg.

Effect of Alcohol on GABA and Glutamate Receptors



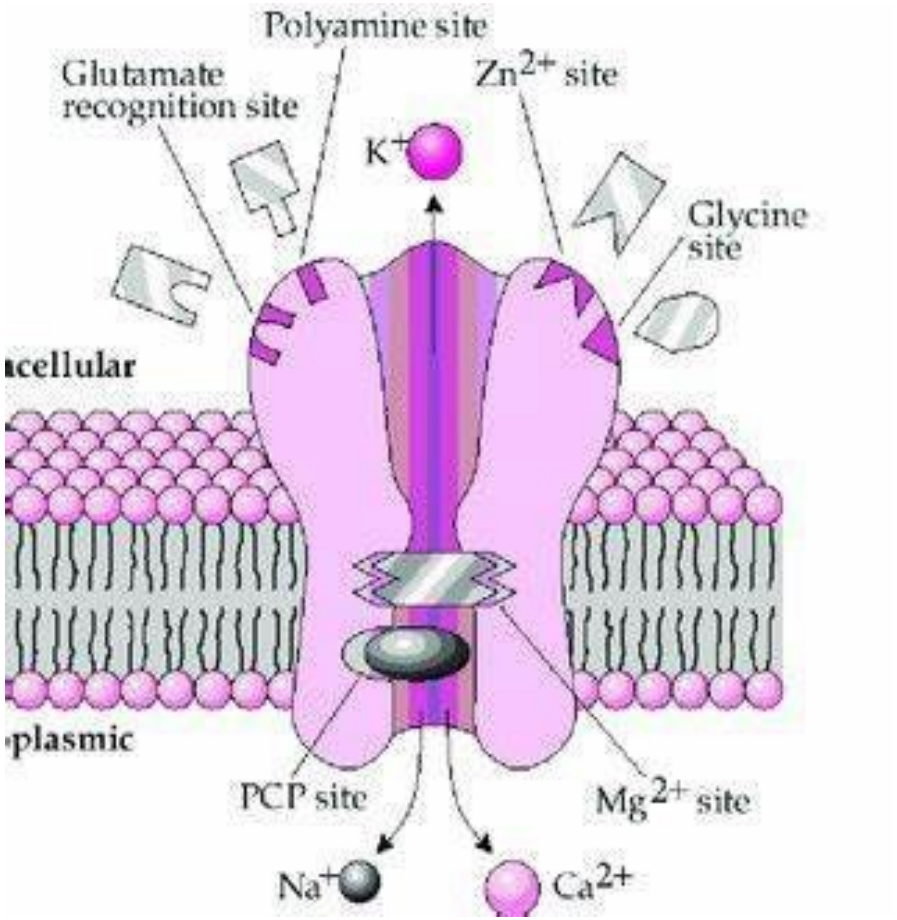
a. Normal homeostasis
b. Intoxication (Occ) Increased GABA activity due to ETOH
c. With chronic use, Glutamate receptors are up regulated
d. In withdrawal, GABA activity is reduced and up to maintain homeostasis regulated Glutamate activity is unopposed and results in increased CNS hyperactivity

GABA Receptor

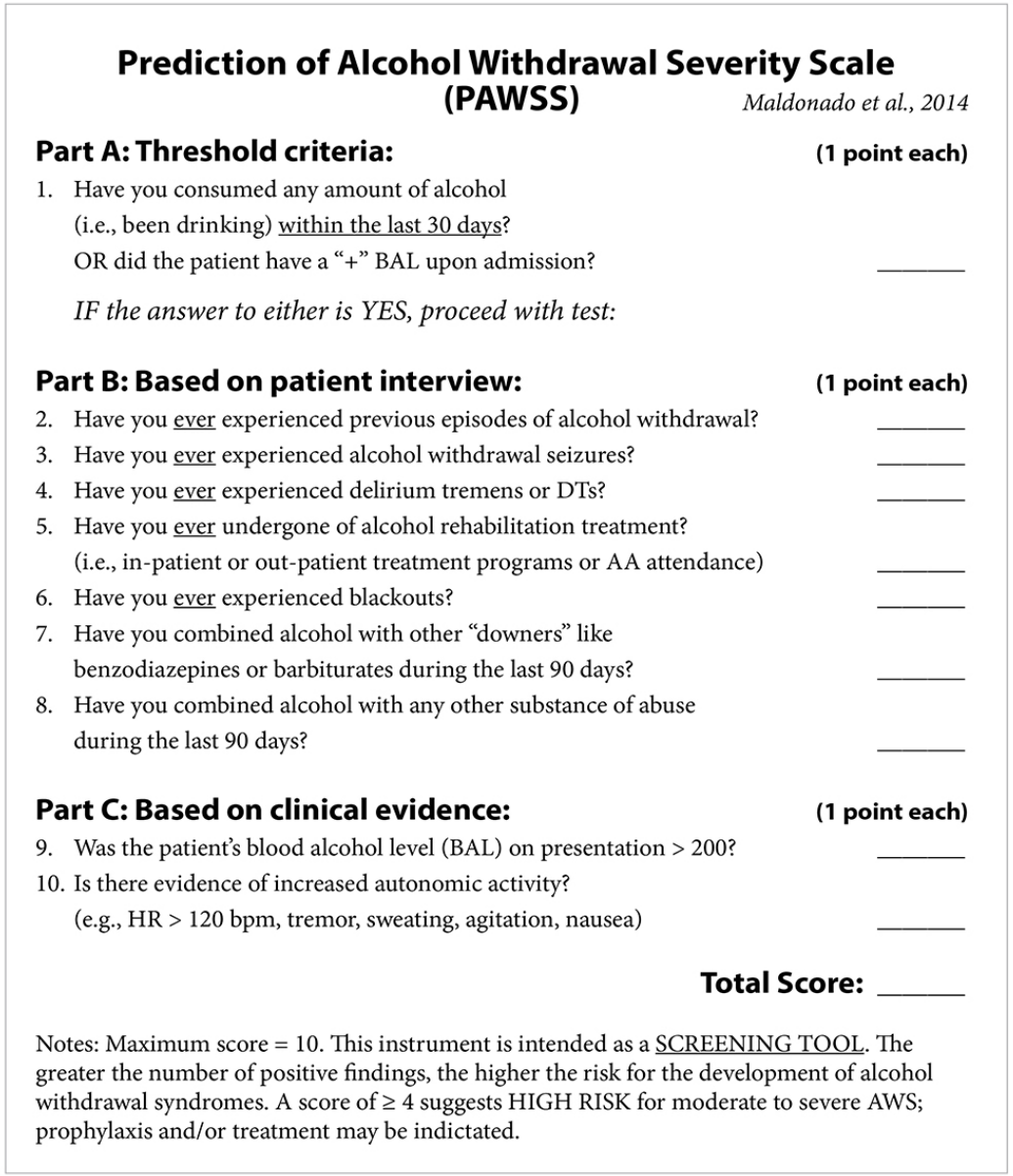


- GABA receptors are inhibitory and cause increase in intracellular Chloride
- Alcohol stimulates GABA
- BZD increase the frequency of chloride channel opening. Requires the presence of GABA to work. May account for BZD resistance
- Barbiturates increase the duration of chloride channel opening.
- BZD and phenobarbital work synergistically

Glutamate NMDA Receptors



- These are excitatory receptors that are responsible for the neuroexcitability seen in acute withdrawal
- **The N-methyl-D-aspartate receptor** (also known as the NMDA receptor or NMDAR), is a glutamate receptor and predominantly Ca ion channel found in neurons.
- Alcohol has an inhibitory effect on glutamate activity. Acute exposure to alcohol reduces glutamatergic activity while also stimulating GABAergic activity.



Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Maldonado et al., 2014

Part A: Threshold criteria: (1 point each)

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

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

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

2. Have you ever experienced previous episodes of alcohol withdrawal? _____
3. Have you ever experienced alcohol withdrawal seizures? _____
4. Have you ever experienced delirium tremens or DTs? _____
5. Have you ever undergone of alcohol rehabilitation treatment? (i.e., in-patient or out-patient treatment programs or AA attendance) _____
6. Have you ever experienced blackouts? _____
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 alcohol withdrawal syndromes. A score of ≥ 4 suggests HIGH RISK for moderate to severe AWS; prophylaxis and/or treatment may be indictated.

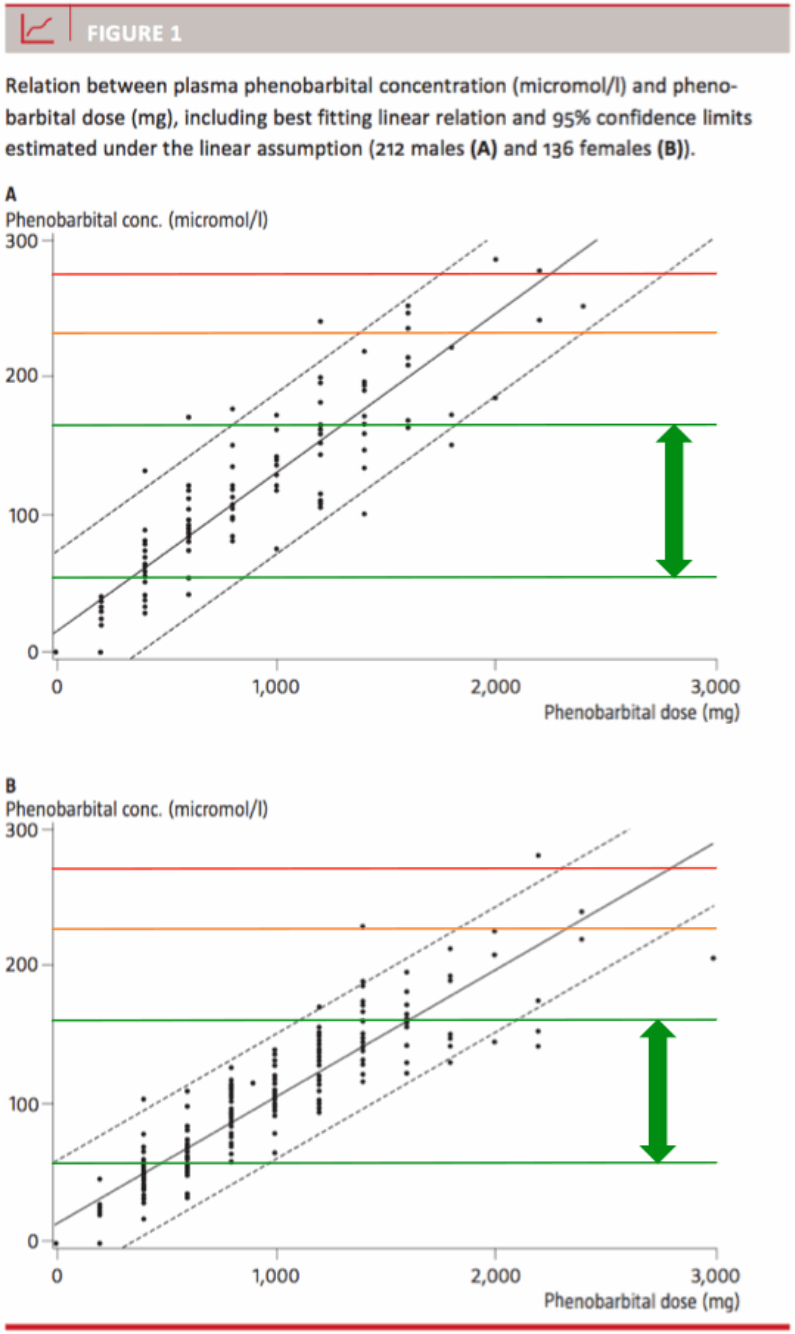
FIGURE 2. Prediction of Alcohol Withdrawal Severity Scale developed by Maldonado and colleagues.[36]

Advantages of Phenobarbital over BZD

- Phenobarbital is more powerful than benzodiazepines
- Predictable pharmacokinetics. Phenobarbital has a linear dose/level relationship. BZD have various metabolism and active metabolites.
- Predictable pharmacodynamics. Some patients with AWS respond to small doses of BZD and others require very high doses and some are refractory.
- Wide therapeutic index. Pt's can receive 10-25 mg/kg to get to a level of 10-40 ug/ml but toxic levels require doses > 40 mg /kg
- Less delirium and paradoxical reactions.
- Phenobarbital’s efficacy may be limited by suboptimal dosing

Phenobarbital Dosing

- Phenobarbital is front loaded in severe AWS, not uptitrated like BZD
- Dosing is based on ideal body weight
- The phenobarbital level is a linear function of the amount of phenobarbital administered
- A 10 mg / kg loading dose will result in a drug level of appx 15/ug/ml. This dose is far from a "toxic dose"
- Phenobarbital has a long half life and auto tapers
- Phenobarbital has direct effect on GABA receptors and it inhibits glutamate receptors



15ug/ml

- The drug level is a linear function of the amount administered'
- Red line is level associated with stupor / coma
- Yellow line – mild toxicity, ataxia and nystagmus
- Green lines are therapeutic levels for epilepsy
- 1000 mg of phenobarbital would achieve desirable levels in most patients.

RASS

Richmond Agitation Sedation Scale (RASS)

Score	State		
+ 4	Combative		
+ 3	Very agitated		
+ 2	Agitated		
+ 1	Restless		
0	Alert and calm		
-1	Drowsy	eye contact > 10 sec	Verbal Stimulus
-2	Light sedation	eye contact < 10 sec	
-3	Moderate sedation	no eye contact	
-4	Deep sedation	physical stimulation	Physical Stimulus
-5	Unarousable	no response even with physical	

Ely EW, et al. *JAMA*. 2003;289(22):2983-2991.
Sessler CN, et al. *Am J Respir Crit Care Med*. 2002;166(10):1338-1344.

CIWA

Clinical Institute Withdrawal Assessment for Alcohol – revised (CIWA-Ar) scale

Clinical Institute Withdrawal Assessment for Alcohol revised	
Symptoms	**Range of scores**
Nausea or vomiting	0 (no nausea, no vomiting) –7 (constant nausea and/or vomiting)
Tremor	0 (no tremor) – 7 (severe tremors, even with arms not extended)
Paroxysmal sweats	0 (no sweat visible) – 7 (drenching sweats)
Anxiety	0 (no anxiety, at ease) – 7 (acute panic states)
Agitation	0 (normal activity) – 7 (constantly trashes about)
Tactile disturbances	0 (none) – 7 (continuous hallucinations)
Auditory disturbances	0 (not present) – 7 (continuous hallucinations)
Visual disturbances	0 (not present) – 7 (continuous hallucinations)
Headache	0 (not present) – 7 (extremely severe)
Orientation/clouding of sensorium	0 (orientated, can do serial additions) – 4 (Disorientated for place and/or person)

Minds Score

- **Mild withdrawal (score <15)**: Check MINDS every 2 hours and adjust phenobarbital dosing accordingly.
- **Moderate withdrawal (score 15-19)**: Check MINDS every hour and adjust phenobarbital dosing accordingly.
- **Severe withdrawal (score >19)**: Check MINDS every 20 minutes and administer higher doses of phenobarbital as needed.

The MINDS protocol is particularly useful in ICU settings because it relies on objective criteria rather than patient self-reporting.

Phenobarbital Levels

- Prediction of Phenobarbital Level from cumulative Dose

- Phenobarbital Level in ug/ml = 1.5 (Dose in mg/kg

- 15ug/ml = 1.5 (10 mg/kg)

When to check phenobarbital level

- Phenobarbital levels usually aren't necessary unless:
- If you lost track of how much phenobarbital the patient received
- If the plasma level is >30 and the patient is still agitated evaluate for other causes of agitation
- The ideal level for DT's isn't known but for epilepsy it's 15-40 and toxicity is rare with levels
- < 60.
- For most patients, a level of 15 ug/ml is not excessively sedating

Table 3
Outcomes and clinical characteristics

Outcome or clinical characteristic	CIWA-Ar arm (n = 60)	Phenobarbital arm (n = 60)	*P*
ICU stay (midnights), mean (SD)	4.4 (3.9)	2.4 (1.5)	<.001
Hospital stay (midnights), mean (SD)	6.9 (6.6)	4.3 (3.4)	.004
Total lorazepam equivalents, mean (SD), mg	35.2 (48.5)	11.3 (18)	<.001
Ventilator use, No. of patients	14	1	<.001
Dexmedetomidine use, No. of patients	17	4	.002
Olanzapine use, No. of patients	7	5	.54
Haloperidol use, No. of patients	10	4	.08
Quetiapine use, No. of patients	5	2	.24

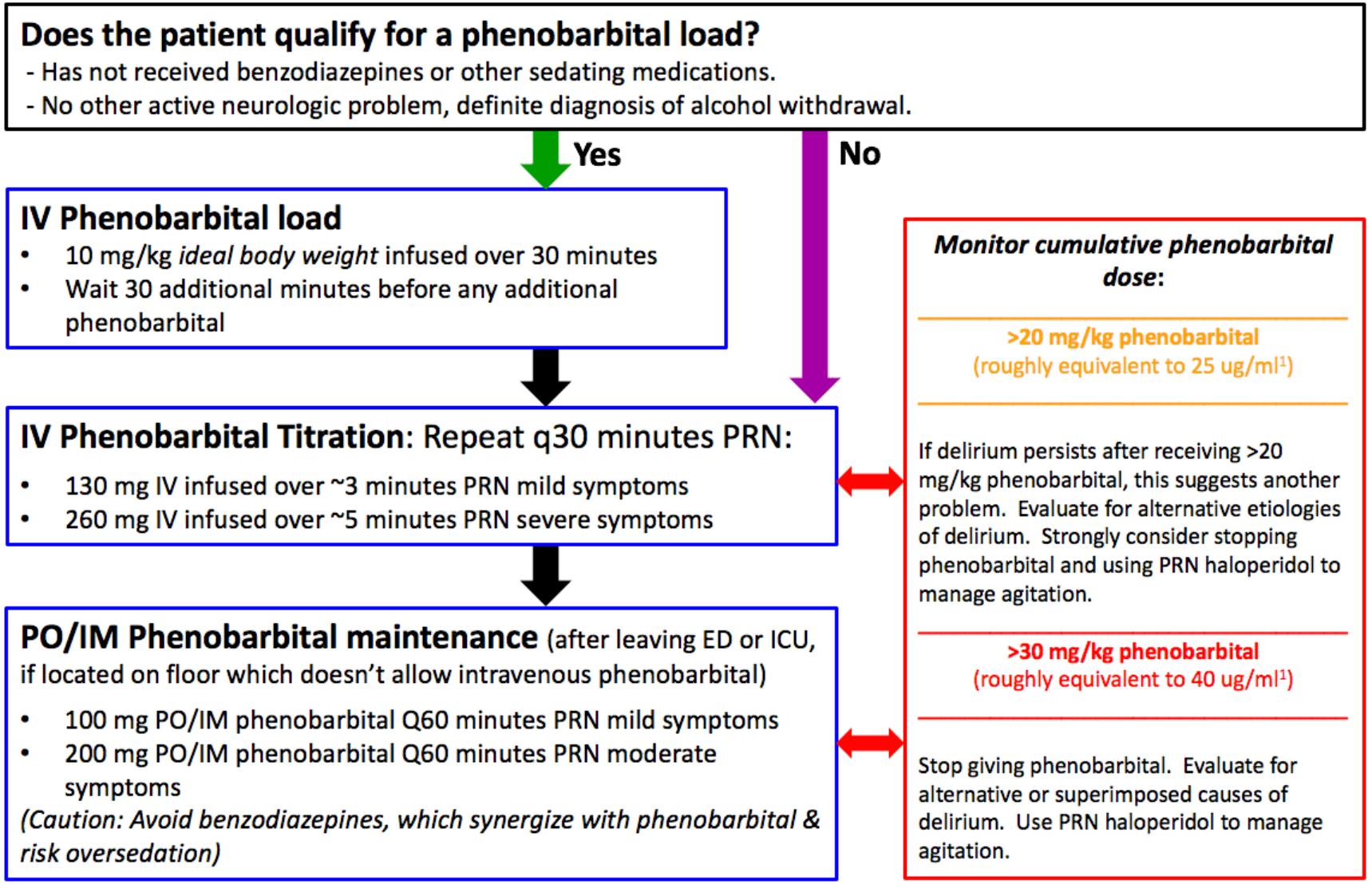
Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; ICU, intensive care unit.

interpretation of phenobarbital levels

	Conventional Units (ug/ml)	SI units (uM/L)
Therapeutic Range, Epilepsy	15-40 ug/mL	64-172 uM/L
Mild signs of toxicity usually noted (e.g. ataxia, nystagmus)	>50 ug/mL	>215 uM/L
Severe toxicity can occur (e.g. stupor/coma)	>65 ug/mL	>280 uM/L
Therapeutic range, Monotherapy for EtOH withdrawal	~10-40 ug/mL (??)	~43-172 uM/L (??)

This table is only intended to provide a rough concept of phenobarbital levels. The optimal phenobarbital levels in treatment of alcohol withdrawal remains unclear. Ultimately, doses need to be titrated based on clinical response. For example, patients with alcohol withdrawal will often have an excellent clinical response at phenobarbital levels which are below the traditional therapeutic range for epilepsy.

EtOH withdrawal tx: Continue until patient awake & calm



(1) For use in epilepsy, the therapeutic range of phenobarbital levels is 15-40 ug/ml, mild toxicity may occur >50 ug/ml, and severe toxicity (stupor/coma) may occur >65 ug/ml. The ideal therapeutic target of phenobarbital for alcohol withdrawal remains unclear. Maintaining the level <40 ug/ml should establish a margin of safety and fall within current practice standards regarding the use of phenobarbital. Note, however, that in patients who have received significant doses of benzodiazepines, synergistic toxicity due to the interaction of benzodiazepine and phenobarbital can occur at "therapeutic" phenobarbital concentrations.

Hepatic encephalopathy vs. alcohol withdrawal

	Alcohol withdrawal	Hepatic encephalopathy
Pathophysiology includes…	- *Neuroexcitation* due to inadequate stimulation of GABA receptors	- Excessive activity of inhibitory GABA receptors by various toxins
Typical clinical presentation to ICU	- Agitated delirium - Seizure(s)	- Hypoactive delirium - Somnolence, coma
Epidemiology	- Occurring within days of EtOH cessation - History of prior episodes of withdrawal upon cessation of alcohol.	- Often patients too sick to drink significant EtOH, may have stopped drinking in remote past (obtain a good history!) - History of prior episodes of hepatic encephalopathy
Physical examination	- Generalized ongoing tremor - Sympathetic activation (e.g. hypertension, tachycardia) - Visual hallucinations	- Asterixis ("flapping tremor")
Response to low-dose benzodiazepine	- May have minimal effect (patients generally relatively *resistant* to benzodiazepines).	- May cause somnolence.

The Internet Book of Critical Care, by @PulmCrit

References

Farkas J. Pulm-Crit – Evidence Update: Phenobarbital in Alcohol Withdrawal. July 15, 2019

Hayner CE, Wuestefeld NL. Phenobarbital treatment in a patient with resistant alcohol withdrawal syndrome. Pharmacotherapy 2009 Jul;29(7):875-8.

Schmidt KJ, Doshi MR, Holzhausen JM, Natavio A, Cadiz M, Winegardner JE. Treatment of Severe Alcohol Withdrawal. Ann Pharmacotherapy. 2016 May;50(5):389-401. Epub 2016 Feb 9.

Umar Z, Haseeb Ul Rasool M, et al. Phenobarbital and alcohol withdrawal syndrome: A Systematic Review and meta-analysis. Cereus 15(1): e33695

Ives TJ, Mooney AJ, Gwyther. Pharmacokinetic dosing of phenobarbital in the treatment of alcohol withdrawal syndrome Southern Med J, 84(1):18-21 Jan 1991

Ibarra F. Single dose phenobarbital in addition to symptom-triggered lorazepam in alcohol withdrawal. Am J Emerg Med. 2020;38(2):178-81.

MLADEN, Nejad, Isenberg. Use of phenobarbital in Alcohol Withdrawal Management- A retrospective Comparison Study of Phenobarbital and Benzodiazepines for Acute Alcohol Withdrawal Management in General Medical Patients. 2019 Sep-Oct;60 (5)458-467

Tidwell WP, Treatment of Alcohol withdrawal Syndrome: Phenobarbital vs CIWA-AR Protocol. American Journal of Critical Care. 2018; 27: 454-460

Ebling-Konig NE. Load and Go: Assessing Safety Outcomes of Patients Discharged From the ED After Receiving Phenobarbital for Alcohol Withdrawal. JACEP Open. Vol 5, Issue 3, June 2024

Questions?