MEMO

Yale NewHaven Health

To: **YNHHS Medical Staff**

From: **YNHHS ICU Committee**

Subject: **Phenobarbital for Alcohol Withdrawal Syndrome Dosing Guidelines**

Date: **April 16, 2020**

Situation: There is a need to provide guidance for the dosing of phenobarbital for the management of alcohol withdrawal syndrome (AWS).

Background: Due to the current surge in critically ill, intubated patients in the ICU, current supplies of sedatives, including benzodiazepines, are anticipated to be in critical short supply. Benzodiazepines are recommended for the treatment of AWS.[1] Evidence suggests that phenobarbital is a safe and effective alternative drug therapy.[2-6] Phenobarbital's longer half-life, lack of cross-tolerance, reliable pharmacokinetic profile, and affinity to both gamma-aminobutyric (GABA) and glutamate receptors make it an appropriate alternative agent to benzodiazepines for the treatment of AWS in patients with active alcohol use and at high risk for AWS (such as prior symptomatic withdrawal), and for the treatment of symptomatic AWS.[5]

Assessment: In the setting of benzodiazepines critical shortage, phenobarbital could be considered for the management of AWS. There is a need to provide guidance for the dosing of phenobarbital for management of AWS.

Recommendation: This phenobarbital dosing guideline provides guidance for the use of phenobarbital for the management of AWS and promote safe and appropriate use of phenobarbital in this setting.

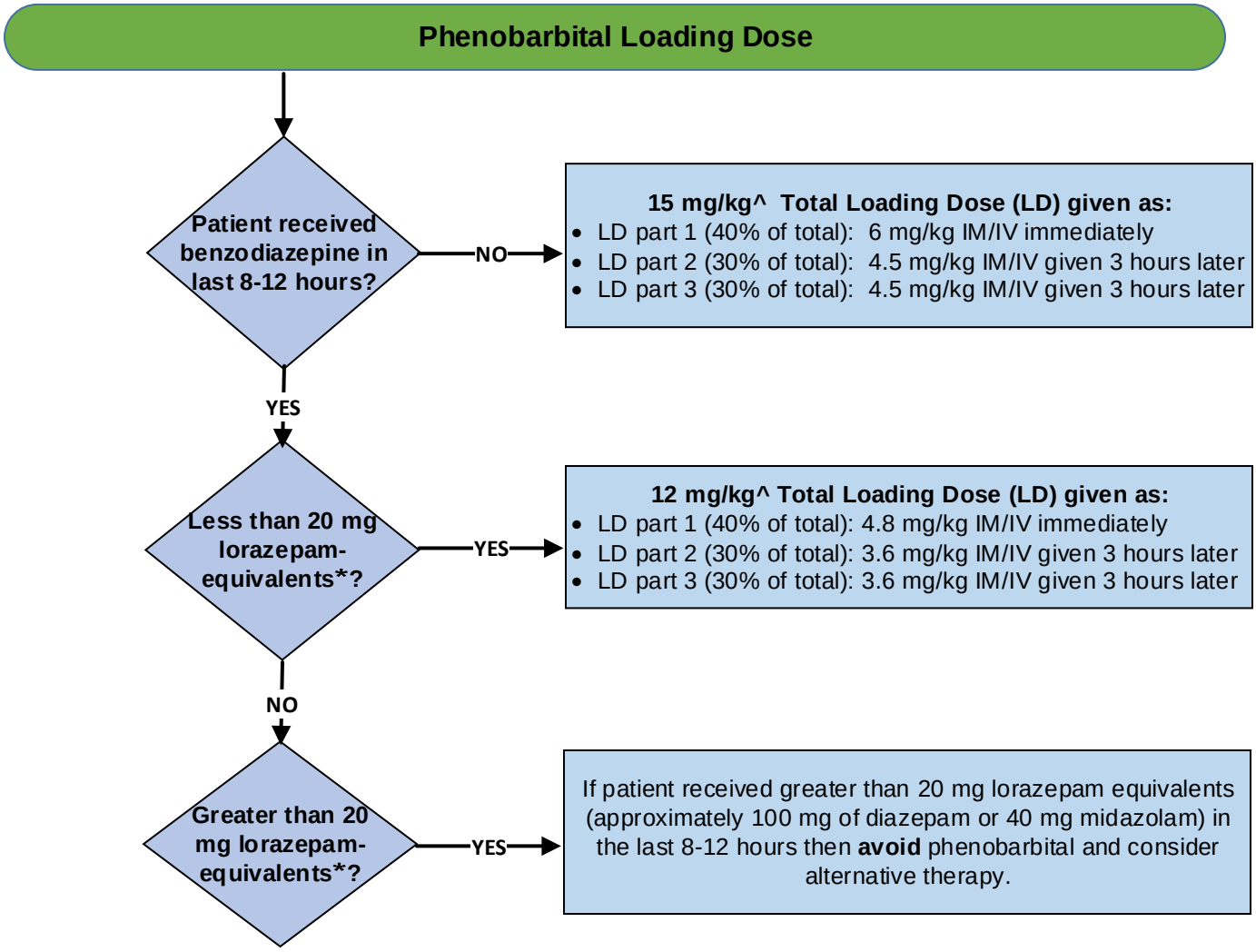
The guideline entails administering a phenobarbital loading dose (LD) followed by a maintenance phenobarbital taper in patients with AWS or at high risk for AWS.[5,7] LD should be initiated in intensive care unit, emergency department, or step-down unit, with continuation of the maintenance phenobarbital taper on general patient care units.

Population: This phenobarbital dosing guideline is recommended for patients who are at risk for AWS to prevent worsening of symptoms or patients with active AWS. Patient must be in the **intensive care unit, emergency department, or step-down unit to initiate phenobarbital therapy.**

Inclusion Criteria	Exclusion Criteria
• Patient with active AWS. • Patient must be in the intensive care unit, emergency department, or step-down unit to initiate phenobarbital therapy.	• If patient received greater than 20 mg lorazepam equivalents (approximately 100 mg of diazepam or 40 mg midazolam) in the last 8-12 hours then **avoid** phenobarbital and consider alternative therapy. • Patients who have started on another phenobarbital regimen for treatment of alcohol withdrawal or for other indications.

YNHHS Phenobarbital for Alcohol Withdrawal Guideline

Due to the risk of additive side effects, concomitant benzodiazepines are NOT recommended for the management of AWS. Discontinue any standing and PRN benzodiazepine orders.



***20 mg lorazepam equivalent is about 100 mg of diazepam and 40 mg midazolam.**

^Other dosing and administration caveats:

- Dose based on **ideal body weight (IBW)** unless patient actual body weight is less than IBW then use actual body weight.
- IM route is preferred to minimize side effects (over-sedation and respiratory compromise), but can be given IV.
- If given IV and patient is still symptomatic after 30 minutes, give LD part 2 or part 3 after 30 minutes.
- If total LD (15 mg/kg) was not given and there are no side effects but patient is still experiencing AWS symptoms, consider administering remainder of LD so that total of 15 mg/kg is given. See Appendix.

Monitoring (Day 1):

- Vital signs (blood pressure, heart rate, and respiratory status) 15 minutes after dose administration then every 2 hours for 24 hours after dose administration.
- Hold therapy if blood pressure <90/50 mm Hg, heart rate <50 bpm, respiratory rate <10 bpm, or RASS score <-2.
- CIWA (non-critical care units) and MINDS (critical care) can be used to assess patient's withdrawal severity but not to determine dosing during the use of phenobarbital.
- Consider ordering serum phenobarbital level 5 hours after the LD as it might assist with further phenobarbital administration if patient experiences any phenobarbital-related adverse events. Serum concentrations greater than 30 mcg/ml have been associated with greater risk of adverse effects.

Symptoms Worsen After Loading Dose

The maximum peak effect of phenobarbital is at around 5 hours for IM (15 minutes for IV). If patient's AWS symptoms worsen based on CIWA (non-critical care units) and MINDS (critical care) assessment 5 hours post phenobarbital total LD administration (15 mg/kg), consider alcohol withdrawal symptoms management as listed below.

Management of alcohol withdrawal symptoms while on phenobarbital:

A. If **continuous sedation** is indicated or **RASS ≥2** after receiving entire total LD:

- Consider dexmedetomidine if clinically appropriate
- Due to the risk of additive side effects, avoid propofol or continuous benzodiazepine infusion for sedation

B. Emergent Symptoms:

- **Agitation/anxiety;** consider non-benzodiazepine alternatives:
  - Quetiapine 12.5-25 mg PO every 6-12 hours as needed for agitation or anxiety
  - Haloperidol 2.5 - 5 mg IV every 6 hours as needed for agitation or anxiety
  - Trazodone 12.5-25 mg PO every 12 hours as needed for agitation or anxiety
- **Tachycardia:** Consider beta-blockers as clinically appropriate
- **Hypertension:** Consider clonidine as clinically appropriate

Taper/Maintenance Dosing (Day 2 – 5)*

Day 2 and 3	Phenobarbital 64.8 mg IM/IV/PO every 12 hours for four doses
Day 4 and 5	Phenobarbital 32.4 mg IM/IV/PO every 12 hours for four doses

* The phenobarbital maintenance taper regimen should be started approximately 8 hours after the LD is completed (after completion of third dose of the LD).

For IV/IM administration, round up to the nearest administrable dose based on vial size, for example 32.4 mg round up to 39 mg.

Monitoring (Day 2 – 5):

- Monitor vital signs (blood pressure, heart rate, and respiratory status) every 4 hours while receiving phenobarbital maintenance taper regimen. Hold therapy if blood pressure <90/50 mm Hg, heart rate <50 bpm, respiratory rate <10 bpm, or RASS score less than -2.
- CIWA (non-critical care units) and MINDS (critical care) can be used to assess patient's withdrawal severity but not to determine dosing during use of phenobarbital.
- Maintenance regimen should not be delayed in the event that phenobarbital serum level has not resulted.

Discontinuation of therapy and discharge:

- Given phenobarbital's long half-life, discontinuation of phenobarbital taper earlier in the hospital course can occur in patients no longer experiencing withdrawal symptoms.
- A full 5-day admission to complete the detox is not always necessary.
- Patients should **not be continued** on phenobarbital upon discharge from the hospital, including those patients who leave against medical advice (AMA).
- If patient leaves AMA, patient should be warned of a greater potential for intoxication due to higher sensitivity to alcohol after phenobarbital therapy.

Appendix:

- Phenobarbital LD can be given intramuscularly (IM) or intravenously (IV). Administration of LD via the IM route is encouraged to decrease the risk of adverse events (over-sedation and respiratory compromise). IM administration can be given in deltoid or gluteus muscles. Give LD IV if platelet <50,000 per microliter, INR >2 or if patient is therapeutically anticoagulated.
- In patients who tolerate phenobarbital LD without adverse events and did not receive the maximum LD of 15 mg/kg but are experiencing symptoms of AWS 3 hours after total LD administration, consider administering LD4 for a total of 15 mg/kg, as noted in the algorithm.

  For example; three hours after the 3rd and final loading dose, a 70 kg IBW patient begins to experience symptoms of AWS. They had received the 12 mg/kg total LD. Therefore, consider administering a one-time dose (LD4) of 3 mg/kg IV/IM (70 kg x 3 mg/kg = 210 mg IV/IM).
- Drug interactions: Phenobarbital is metabolized hepatically via cytochrome P450. Contact pharmacy for relevance of any cytochrome P450 drug-drug interactions. Avoid administering phenobarbital with clozapine, dronedarone, itraconazole, nifedipine, nimodipine, ranolazine, rivaroxaban, and voriconazole.

References:

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2. Rosenthal RN, Perkel C, Singh P, Anand O, Miner CR. A pilot open randomized trial of valproate and phenobarbital in the treatment of acute alcohol withdrawal. *Am J Addict* 1998;7:189-97.
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