Intravenous Phenobarbital Guideline for Alcohol Withdrawal Syndrome in the TBICU/SICU

Background

Alcohol withdrawal syndrome (AWS) is a condition frequently seen in the ED that can lead to dangerous outcomes if left untreated, including seizures, hallucinations, delirium tremens, prolonged ICU stay, and death. Chronic alcohol consumption leads to inhibitory GABAA receptor downregulation and excitatory N-methyl-D-aspartate (NMDA) receptor upregulation. Patients with prolonged alcohol consumption and histories of complicated AWS (seizures, hallucinations, etc.) may be refractory to benzodiazepine (BZD) therapy, requiring large amounts of BZD. The Prediction of Alcohol Withdrawal Severity Scale (PAWSS) is highly sensitive and specific for predicting complicated alcohol withdrawal in admitted medicine patients.[1] PHB, a GABAA channel agonist, acts at a different site than BZD and alcohol to treat AWS. The long half-life of PHB allows for a single administered IV dose and has a sustained effect on AWS, including decreased ICU admissions and total BZD use, potentially faster time to hospital discharge, and a potential reduction in mechanical ventilation.[2-5]

I. Inclusion Criteria for IV Phenobarbital Protocol

- Adult AWS patients with predicted complicated AWS (PAWSS ≥ 4) or reported complicated history of AWS (seizures, hallucinations, delirium tremens, prior intubation/ICU admission related to their AWS)
- Adult AWS patients currently experiencing withdrawal symptoms
- Patients physically located in ICU bed at time of administration
- Approval by a Trauma/Critical Care physician

**Patients with uncontrolled withdrawal despite 4 mg of lorazepam equivalent BZD should be screened for inclusion*

Exclusion Criteria	Contraindications
• Age < 18 years old • Agitation due to reasons other than AWS, such as psychiatric disorders or other substances of abuse • Pregnant • Hypotensive (MAP < 65 mmHg) • Transaminase(s) > 10 times upper limit of normal (lab values not required for administration of PHB) • ED waiting room or any location without cardiac and respiratory monitoring at bedside	• Hypersensitivity to PHB/barbiturates • Dyspnea or airway obstruction • Porphyria
Relative Exclusion Criteria	
• Received > 4 mg of lorazepam equivalent BZD in ≤ 2 hours (reference appendix B for equivalent doses)	

A. Phenobarbital IV Dosing

- If utilized as monotherapy: PHB 5 – 10 mg/kg IVPB of **ideal body weight (IBW),** rounded to nearest 130 mg
    - If actual body weight < IBW, **utilize actual body weight**
- If ≤ 4 mg of lorazepam equivalent administered ≤ 2 hours prior*:

    - PHB 260 mg slow IV push x one dose
    - If no reduction in symptoms, may administer additional 130 mg IV every 15 – 30 minutes
        - Maximum cumulative dose of 10 – 15 mg/kg of **IBW**
        - If actual body weight < IBW, utilize **actual body weight**
        - If patient is still experiencing withdrawal symptoms after completing dose/load of PHB (5-10 mg/kg IVPB as monotherapy or 10-15 mg/kg IBW cumulatively), move to standard CIWA benzodiazepine protocol (see below)
- If > 4 mg of lorazepam equivalent BZD administered ≤ 2 hours prior*:
    - Relative exclusion of PHB, caution if utilized
    - Consider institutional CIWA-AR as an alternative

** Doses of benzodiazepines with prolonged half-lives (i.e., clonazepam, clorazepate, diazepam, etc.) could have prolonged effects, even if administered more than 2 hours prior*

B. Administration

- Bolus doses of 5 – 10 mg/kg should be administered and diluted in 100 mL of sodium chloride
    - Administer **no faster than 60 mg/min**
- Doses of 260 mg and 130 mg doses can be administered as slow IV push or diluted in 100 mL of sodium chloride
    - Administer **no faster than 60 mg/min**

C. Monitoring and Safety

- Monitor for **a minimum of 2 hours after PHB administration**
    - Blood pressure should be assessed every 15 – 30 minutes
    - Continuous pulse oximetry and waveform capnography should be monitored
- Document CIWA-AR prior to administration and **2 hours after initiation of PHB therapy**
- If hypotension occurs (MAP < 65 mmHg or systolic blood pressure < 90 mmHg):
    - Administer appropriate crystalloid fluid bolus
    - If unresponsive to fluid bolus, initiate vasopressor therapy
- If respiratory depression occurs (breaths per minute < 8:
    - Initiate supplemental oxygen
    - Secure airway if needed

II. For Symptomatic or High-Risk Patients (PAWSS ≥4) NOT meeting Inclusion Criteria for IV Phenobarbital:

A. **If mechanically ventilated,** utilize Fixed dose Librium taper (1 week), or Lorazepam taper (if Librium contraindicated)
B. **If non-mechanically ventilated**, utilize symptom-triggered CIWA-AR

III. For Patients at LOW Risk (PAWSS <4) of Alcohol Withdrawal:

A. **If mechanically ventilated,** utilize Fixed dose Librium taper (1 week**)** or Lorazepam taper (if Librium contraindicated)
B. **If non-mechanically ventilated**, utilize symptom-triggered CIWA-AR

FIXED-DOSE TAPER

1. Treat with Chlordiazepoxide (Librium) according to dosing below (available as PO only)

- Longer acting than lorazepam
- Smoother taper
- Contraindicated in older adults (age >80), moderate to severe liver dysfunction or if unable to take PO

2. Lorazepam (available as IV/IM/PO) **ONLY if chlordiazepoxide is contraindicated:**

- Oral administration of lorazepam is preferred over parenteral routes of administration. However, IV administration should be considered for patients not tolerating oral administration
- Lorazepam can be administered IM if IV access is not available.
- Monitor for signs of propylene glycol toxicity (i.e. anion gap metabolic acidosis, osmolar gap) with administration of lorazepam continuous infusion

CHLORDIAZEPOXIDE	LORAZEPAM
25-50mg Q 6 HOURS FOR 48 HOURS	2 mg Q 12 HOURS FOR 72 HOURS
25-50mg Q 8 HOURS FOR 48 HOURS	1 mg Q 12 HOURS FOR 48 HOURS
25-50mg Q12 HOURS FOR 48 HOURS	1 mg Q 24 HOURS FOR 48 HOURS
25-50mg Q 24 HOURS FOR 24 HOURS	

- **For patients who will be discharged prior to completing their taper**
  - Lorazepam or chlordiazepoxide taper may be continued for patients being discharged to rehab facility, LTACH, SNF
  - Lorazepam or chlordiazepoxide taper should be discontinued for patients being discharged to shelter, home, or other non-medical facilty

SYMPTOM TRIGGERED MANAGEMENT (CIWA)

1. Inclusion Criteria
   - Patient should be in Intensive or Intermediate Care Units
   - This protocol is only indicated in **NON-mechanically ventilated** patients
2. Exclusion Criteria
   - Seizure on this admission from alcohol withdrawal

- Cannot/unable to answer questions
- Actively experiencing Delirium-Tremens (DTs)
- No history of recent alcohol intake in the last 7 days

3. Pharmacy: Inform physician that all pre-existing orders for benzodiazepines will be discontinued.
4. Dosing: Symptom-Triggered Dosing (PO or IV - IM if no IV access)
    - Assessment frequency can be decreased after 24 hours if, on 3 consecutive assessments, CIWA < 9
    - If after 72 hours CIWA remains < 9 and no symptoms of withdrawal then CIWA can be discontinued
    - In patients for whom control cannot be achieved with oral medications or who are unable to tolerate oral medications, IV midazolam is an available alternative
        i. Midazolam will be dosed *every 2 hrs as needed based on CIWA-AR scoring as below*
        ii. **Patients should be monitored closely after administration of all IV midazolam doses.**
        iii. All patients receiving IV midazolam for CIWA should have continuous monitoring with **telemetry and pulse oximetry**
        iv. If a patient's withdrawal symptoms are not well-controlled with dosing as above, can consider additional 1mg IV midazolam every 30 minutes PRN until CIWA score </= 8 if there is no evidence of sedation, respiratory depression, or hypotension

Withdrawal Score	Lorazepam Dose	Midazolam Dose (IV)	Reassessment Time
0-8	None	None	2 hours
9-13	1 mg	1 mg	1 hour
14-18	2 mg	2 mg	1 hour
19-23	3 mg	3 mg	1 hour
24 or more	4 mg	4 mg	30 min for up to 2 hours

- Lorazepam drip can be ordered for up to 8mg per hour for four hours if:
    i. If patient required for doses of lorazepam every thirty minutes for a total of 32 mg over two hours and CIWA score is still greater than 18
    ii. MD is at bedside and documents the need for lorazepam drip
    iii. Patient is in ICU status or is in the ED under monitoring status
    iv. Patient must be mechanically ventilated to initiate lorazepam drip

RASS Score	Lorazepam Infusion Instructions	Assessment
>+2	Bolus 6 mg and initiate drip at 6 mg/h Bolus 4 mg for each RASS +4 Increase drip by 2mg/h if RASS >+3 after 2 hours	Q15 min until RASS Score 0-2
0-2	Continue at current rate (do not increase unless RASS >+2	Reassess q1h
<0	Decrease drip by 2mg/hr q2 hours as long as RASS <0; when drip weaned off, start (or resume) fixed dose taper	Reassess q2h

5. **Adverse effects of benzodiazepines** include but are not limited to: Respiratory Depression, Sedation (may lead to airway compromise), and Hypotension
6. Exercise extreme caution in patients with comorbid conditions and at risk for adverse events, including: age >65, risk for hypercapnia, OSA, OHS, COPD, neuromuscular diseases, renal dysfunction
7. Hold benzodiazepines and contact physician for:
    - BP < 110 mm Hg (Systolic)
    - RR < 10 breaths per minute
    - SpO2< 93
    - Patient unresponsive (RASS -4 to -5)
8. Contact physician if:
    - HR>110 per minute or SBP >160 mm Hg or DBP of > 100 mg Hg after 10 minutes of administering lorazepam
9. Vitamins/Mineral Supplementation
    - Thiamine 200mg IV once, then 200mg PO/IV daily x 3 days
        i. Consider higher doses (200 – 400mg every 8 hours x 2-3 days) if suspicion of Wernicke's is high (cognitive changes, paralysis of eye muscles, ataxia)
    - Folic Acid 1 mg PO or IV if no oral access daily for three days
    - Multivitamin 1 tab PO daily for three days
10. Additional PRN Medications to Consider
    - For control of persistent signs of adrenergic hyperactivity such as tachycardia and hypertension
        i. Metoprolol 5mg IV Q 6 hours PRN for SBP>160 or DBP > 100 mm Hg (hold for SBP <100 mm Hg, HR < 60 bpm)
        ii. Clonidine 0.1 mg PO Q 8 hours PRN SBP > 160 or DBP >100 mm Hg (hold for SBP <100 mm Hg, HR < 60 bpm)
    - Adjunctive therapy (in addition to benzodiazepines) to improve control of agitation
        i. Haloperidol 2.5 – 5mg IM every 4 – 6 hours scheduled or PRN
            1. Need ECG and recent electrolytes prior to administering
        ii. Phenobarbital 130mg IV q8h prn agitation (see above)
        iii. Monitor for signs of respiratory depression (RR < 10 breaths/min) and over-sedation (unresponsive)

- For adjunctive management of severe alcohol withdrawal (not to be used as monotherapy and/or in conjunction with clonidine). May consider for patients requiring lorazepam continuous infusion of >10mg/hr to control signs of adrenergic hyperactivity or prevent mechanical ventilation
  i. Dexmedetomidine - initiated at 0.2mcg/kg/hr and titrated to maintain RASS of 0 to -1 (unless otherwise ordered by provider). Titration range 0.2 – 1.5 mcg/kg/hour
     1. Hold for bradycardia (HR < 50 beats/min) and hypotension (BP < 90/60 mm Hg)
     2. Discontinue all existing orders for clonidine while utilizing dexmedetomidine

Appendix A. Prediction of Alcohol Withdrawal Severity Score (PAWSS)

Part A: Threshold Criterion	**"Y" or "N", no point**
Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 days? OR did the patient have a "+" BAL on admission? *IF the answer to either is YES, proceed with test:*	
Part B: Patient Interview	**1 point each**
1. Have you been recently intoxicated/drunk within the last 30 days?	
2. Have you ever undergone alcohol use disorder rehabilitation treatment or treatment for alcoholism? (i.e., in-patient or out-patient treatment programs or AA attendance)	
3. Have you ever experienced any previous episodes of alcohol withdrawal, regardless of severity?	
4. Have you ever experienced blackouts?	
5. Have you ever experienced alcohol withdrawal seizures?	
6. Have you ever experienced delirium tremens or DT's?	
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: 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, 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 AWS.
A score of ≥ 4 suggests HIGH RISK for moderate to severe (complicated) AWS; prophylaxis and/or treatment may be indicated.

Risk Stratification

- **Low Risk for *complicated* AWS:** PAWSS Score <4 (and clinical judgement)
  → **follow symptom triggered treatment**
- **Moderate-High Risk for *complicated* AWS:** PAWSS Score ≥ 4, history of complicated AWS and/or currently experiencing withdrawal symptoms
  → **follow IV Phenobarbital protocol**

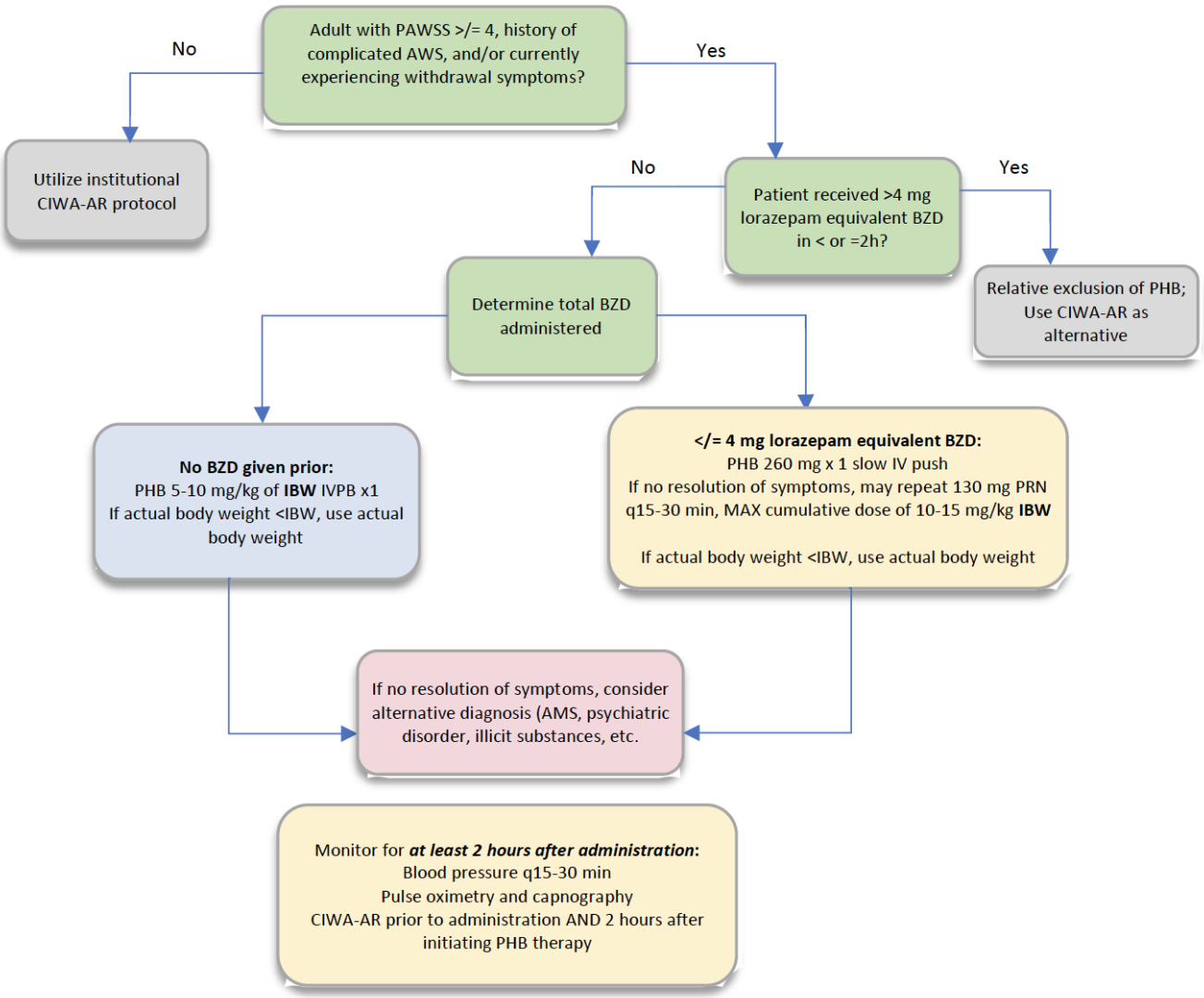
Complicated = Moderate or severe symptoms or having moderate severe alcohol withdrawal symptoms as indicated by a CIWA-AR score ≥ 15, including presence of symptoms severe enough for primary team to administer barbiturate or benzodiazepine agents

Appendix B. Benzodiazepine Conversions

Benzodiazepine	Equivalent dose (mg)	Routes of Administration
Alprazolam (Xanax®)	0.5	PO
Chlordiazepoxide (Librium®)	10	PO
Clobazam (Onfi®)	N/A	PO
Clonazepam (Klonopin®)	0.25	PO
Diazepam (Valium®)	5	PO, IM, IV, IN, PR
Lorazepam (Ativan®)	1	PO, IM, IV
Midazolam (Versed®)	2	IM, IV, IN
Temazepam (Restoril®)	30	PO

- Some references utilize 1mg lorazepam equivalent to 25mg of Chlordiazepoxide

Appendix C. IV Phenobarbital for Alcohol Withdrawal Algorithm



References

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