**Phenobarbital-Facilitated Treatment of Alcohol Withdrawal**

1. **Rationale**
	1. Alcohol withdrawal syndrome is a medical condition characterized by an imbalance between inhibitory neurotransmitter GABA and excitatory neurotransmitter NMDA receptor stimulation to chronic alcohol intake.
	2. Benzodiazepines
		1. Considerable data exist on the effectiveness of benzodiazepines for the management of alcohol withdrawal syndrome.
		2. Benzodiazepines have demonstrated effectiveness both in improving discomfort associated with acute withdrawal and in decreasing risk of progression to seizures and delirium tremens
			1. No consensus regarding which benzodiazepine is best, how it should be administered or at what dosages
				1. IV regimens typically include those with rapid onset and longer durations of actions, such as diazepam and lorazepam, to utilize the self-tapering effect of the drug to its advantage
		3. However, some patients with severe alcohol use disorder may not respond adequately to benzodiazepines as gradual changes to the GABAa receptor subunit conformations occur with chronic heavy alcohol use and may result not only in tolerance to alcohol, but also in cross tolerance to benzodiazepines. Additionally, benzodiazepines may pose challenges in medically and surgically hospitalized patients by increasing risk for over-sedation, encephalopathy and agitation in an already compromised patient population. It may be challenging to identify these patients a priori, resulting in escalating doses of benzodiazepines, possible respiratory compromise, aspiration, delirium, and paradoxical disinhibition and agitation.
			1. Refractory alcohol withdrawal syndrome: defined as >10 mg lorazepam equivalents in 1 hour or >40 mg lorazepam equivalents in 4 hours
	3. Phenobarbital
		1. Alternative to benzodiazepines
			1. Benzodiazepines appear to function by increasing the frequency of the GABAa chloride channel opening, an action that requires presynaptic presence of GABA, barbiturates offer an alternate mechanism of action that involves both glutamate (decreased activity via AMPA and kainite receptor engagement) and GABA (increased duration of GABAa channel opening, unique binding site compared with alcohol and benzodiazepines). These differences are believed to result in a reduced incidence of cross-tolerance between phenobarbital and alcohol (patients can tolerate large doses of phenobarbital without significant respiratory depression).
		2. Advantages of phenobarbital vs benzodiazepines
			1. Longer half-life
				1. Long half-life helps to treat severe alcohol withdrawal syndrome, prevent delirium tremens and ease burden of administration, and allows for gradual transition off of therapy
			2. Tapering effect
				1. No need for additional outpatient prescriptions (more for ED use)
			3. Attractive mechanism of action

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|  | **Lorazepam** | **Diazepam** | **Phenobarbital** |
| Mechanism of Action | Enhancement of the inhibitory effect of GABAa on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (less excitable state) and stabilization. | Potentiates activity on GABAa receptors and inhibits the NMDA and AMPA receptors |
| Routes of Administration | PO, IV, IM, SL | IV, PO, IM, PR | PO, IV, IM |
| Onset | IV: 2-3 minPO: 15-30 min | IV: 1-2 minPO: 1-2 min | IV: 5 minPO: 60 min |
| Duration | IV: 6-8 hours | IV: 1-2 hours | IV: >6 hoursPO: 10-12 hours |
| Half-life | IV: 14 hoursPO: 12 hours | IV: 87 hoursPO: 100 hours | 53-118 hours (eliminates needs for tapering) |
| Metabolism | Hepatic (inactive) | Hepatic (active) | Hepatic |
| Excretion | Urine | Urine | Urine |
| Therapeutic Drug Monitoring | NA | NA | 10-40 mcg/mL (obtain level at least 4 hours after dose) |
| Adverse Effects | -drowsiness, sedation, paradoxical reactions-Apnea, respiratory depression | -drowsiness-Headache, ataxia-respiratory depression | -Ataxia, drowsiness-Hypotension, bradycardia (rapid administration >60 mg/min should be avoided)-Apnea, respiratory depression |
| Drug Interactions |  |  | Strong 3A4 Inducer |
| Equivalent Dose to 10g ETOH | 1 mg | 5 mg |  |

1. **Evidence**
	1. Phenobarbital for Emergency Room Alcohol Withdrawal Syndrome
		1. Nelson et al.
			1. Retrospective study performed during a benzodiazepine shortage. Three alcohol withdrawal protocols were compared: one using IV diazepam, one using both IV lorazepam and phenobarbital, and one only using IV phenobarbital
			2. Initially there were 299-500 patients in each group and 100 patients were selected at random from within each group. Fewer patients with severe withdrawal were in the diazepam group.
			3. Protocols

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| Mild SEWS 1-6 | Moderate SEWS 7-12 | Severe SEWS ≥13 |
| Lorazepam 2 mg IV or phenobarbital 65 mg IV | Phenobarbital 260 mg IV x1 followed by lorazepam 4 mg IV x1 or phenobarbital 130 mg IV | Initial SEWS: Phenobarbital 650 mg Not initial SEWS: phenobarbital 260 mg x3 followed by lorazepam 4 mg IV or phenobarbital 130 mg IV |

* + - 1. Results
				1. Protocol violations occurred in 58% of patients in the phenobarbital group (explaining use of benzo in these patients and low phenobarbital doses)

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| Outcome | Diazepam | Lorazepam+Pheno | Phenobarbital | P Value |
| ICU Admission | 8 (22) | 11 (23) | 13 (24) | 0.99 |
| Overall Admission | 35 | 47 | 54 | P=0.024 |
| Intubation | 1 | 3 | 3 | P=0.55 |
| Days Intubated | 2 | 1 | 2 | P=0.49 |
| Total Diazepam Equivalents, mg | 1543 | 97 | 29 | P=0.0001 |
| Total phenobarbital, mg | 0 | 257.4 | 454 | P=0.0001 |

* 1. Benzodiazepines with Concomitant Phenobarbital for Refractory Alcohol Withdrawal Syndrome
		1. Gold et al.
			1. Retrospective cohort study to determine whether a strategy of escalating doses of benzodiazepines in combination with phenobarbital would improve outcomes
			2. 95 patients admitted to the MICU for treatment of severe alcohol withdrawal. ICU admission criteria: 200 mg diazepam within 4 hours or >40 mg diazepam as a single dose. Pre- vs post guideline comparison
			3. Protocol
				1. Diazepam 10 mg IV, if significant agitation, escalating doses of diazepam (100-150 mg/dose). If agitation was controlled for 1 hour, continue diazepam at max dose. If significant agitation within 1 hour, use escalating doses of IV phenobarbital (65 mg, 130 mg, 260 mg ) with diazepam. If agitation controlled, continue diazepam, it significant agitation, consider propofol.
			4. Results
				1. Less mechanical ventilation with post-guideline (47.3 vs 21.9%, p=0.008)
		2. Duby et al.
			1. Single center pre-post study aiming to compare the outcomes of critically ill patients with AWS when treated with a protocolized approach vs non protocolized approach
			2. Protocol
				1. If RASS ≥1: determine effective dose: diazepam 10 mgx2 then 20 mgx2, then 30 mgx2, then 60 mgx2, then 80 mgx2, then 120 mg at 15 minute intervals🡪if RASS≥1, administer phenobarbital 60 mg, then 120 mg then 240 mg at 30 minute intervals
			3. Results

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| Outcome | Pre (N=60) | Post (N=75) | P Value |
| ICU LOS | 9.6 +/- 10.5 | 5.2 +/- 6.4 | 0.0004 |
| Time on vent, days | 5.6 +/- 13.9 | 1.31 +/0 | <0.0001 |
| Intubation due to AWS | 12 (22) | 18 (24) | <0.001 |

* 1. Phenobarbital Monotherapy for Alcohol Withdrawal Syndrome
		1. Tidwell et al.
			1. Retrospective cohort study comparing patients treated with CIWA-triggered benzodiazepines versus patients treated after implementation of a phenobarbital protocol. The phenobarbital protocol involved fixed doses of phenobarbital supplemented with small doses of PRN lorazepam if needed
			2. Phenobarbital protocol:

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| Risk Factor | Phenobarbital Dosage |
| Active DT | 260 mg IV x1 dose, 97.2 mg PO TID x6 doses, 64.8 mg PO TID x6 doses, 32.4 mg PO TID x6 doses |
| History of DT | 97.2 mg PO TID x6 doses, 64.8 mg PO TID x6 doses, 32.4 mg PO TID x6 doses |
| No history of DT | 64.8 mg PO TID x6 doses, 32.4 mg PO TID x6 doses |
| Plus lorazepam 1 mg IV q4h PRN agitation |

* + - 1. Results

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| Outcome | CIWA-Ar (N=60) | Phenobarbital (N=60) | P Value |
| ICU stay  | 4.4 (3.9) | 2.4 (1.5) | <0.001 |
| Hospital stay | 6.9 (6.6) | 4.3 (3.4) | 0.004 |
| Total lorazepam equivalents, mg | 35.2 (48.5) | 11.3 (18) | <0.001 |
| Ventilator use, number of patients | 14 | 1\* | <0.001 |
| Dexmedetomidine use | 17 | 4 | 0.002 |
| \*Intubation procedure was performed prior to patient receiving any phenobarbital |

* + 1. Nisavic et al.
			1. Retrospective study comparing patients treated with a benzodiazepine protocol versus a phenobarbital monotherapy protocol at Massachusetts General Hospital between 2007-2011.
			2. Management strategy was chosen by treating clinicians with most being treated with a benzodiazepine strategy (419 vs 143). Patients treated with phenobarbital were considerably higher risk (higher rate of current seizure, prior seizure and delirium tremens)
			3. Phenobarbital protocol
				1. Initial loading dose of 6-15 mg/kg based on IBW in divided doses over several hours (40% loading dose given immediately, 30% of loading dose 3 hours after 1st admin, 30% of loading dose given 3 hours after 2nd IM admin and check serum phenobarb level 5 hours after 3rd IM administration)
				2. Subsequently patients received small maintenance doses for up to a week

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| Risk | Phenobarbital Dosage |
| Low risk AWD (not meeting criteria for high medium risk) | Use PRN benzodiazepines |
| Medium risk AWD (see below) | -Minimal or no risk of respiratory compromise: 10-12 mg/kg-+risk of sedation or respiratory compromise: 8-10 mg/kg-+severe risk of sedation of respiratory compromise: 6-8 mg/kg |
| High Risk AWD (see below) | -Minimal or no risk of respiratory compromise: 12-15 mg/kg-+risk of sedation or respiratory compromise: 8-10-12 mg/kg-+severe risk of sedation of respiratory compromise: 6-10 mg/kg |
| High Risk | A: prior history of alcohol withdrawal, including history of alcohol withdrawal seizures/DT and recent alcohol use (more than 2 weeks in duration) ORB: identification of early symptoms of alcohol withdrawal despite concurrent positive blood alcohol level |
| Medium Risk | Alcohol use disorder plus 2 or more of the following: 2 or more days since last drink, positive blood alcohol on admission, autonomic dysfunction with BAL >1000 mg/L, elevated MCV and/or AST:ALT ratio, prior history of significant alcohol use, age >35 years old, presence of burn related injuries or long bone fractures |
| Risk of sedation | Age >65yo, hepatic dysfunction, administration of opiates, acute head injury with need for frequent neurological exams, recent administration of benzodiazepines or other sedatives |
| Respiratory compromise | Need for oxygen supplementation, pneumonia, rib fractures, chest tubes, pulmonary contusions, C-collar/brace |

* + - 1. Results
				1. Phenobarbital patients were sicker yet their outcomes were equivalent to the benzodiazepine group

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| Outcome | Benzodiazepines (N=419) | Phenobarbital (N=143) | P Value |
| Seizures  | 4 (1) | 1(1) | NS |
| ICU Admissions | 48 (12) | 17 (12) | P=0.28 |
| Hospital LOS | 5.14 +/- 5.54 | 5.31 +/- 2.91 | P=0.73 |
| ICU LOS | 3.56 /- 3.19 | 3 +/- 2.91 | P=0.53 |
| Among patients initially treated with benzodiazepines, 16 were benzodiazepine refractory and required treatment with phenobarbital protocol and responded appropriately. |

* + 1. Waldee et al.
			1. Retrospective observational study describing use of phenobarbital monotherapy to prevent or treat alcohol withdrawal among 122 psychiatric inpatients
			2. 70% of patients had symptoms of alcohol withdrawal. History of alcoholism: average of 17 drinks/day and 25 years of drinking history.
			3. Patients were treated with oral +/- IM phenobarbital. Average cumulative dose was 421 mg+/-288 mg. Ten patients received additional treatments (including clonidine, diazepam, lorazepam).
			4. Results
				1. No patients required transfer out of the psychiatric unit
				2. 34/36 patients being treated prophylactically developed no symptoms of withdrawal
				3. Safety: no appreciable effect on respiratory rate

Why? These patients were prescreened before admission to the psych unit thereby eliminating any other medical or surgical issues. This likely means the 5-10% intubation rate in other studies are potentially due to other issues not necessarily the alcohol withdrawal

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| Time obtained | Mean change in RR | Mean change in SBP | Mean change in DBP | Mean change in HR |
| After first dose-baseline | -0.23 (-0.66 to 0.20), p=0.29 | -2.71 (-6.34 to 0.93), p=0.14 | -1.68 (-3.85 to 0.49), p=0.13 | -3.41 (-5.89 to -0.92), p=0.008 |
| Last measured-baseline | -0.22 (-0.69 to 0.24), p=0.35 | -9.76 (-14.08 to -5.44), p<0.001 | -6.64 (-9.16 to -4.12), p<0.001 | -8.03 (-10.93 to -5.13), p<0.001 |

* 1. Usage at BJH

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| Phenobarbital Select Patient Characteristics January 1, 2019-April 11, 2020 |
| Number of Phenobarbital Administrations at BJH | 1,841 |
| Number of Phenobarbital Administrations in 4400ICU | 109 |
| Number of Patients with Phenobarbital Administrations in 4400ICU | 20 |
| Phenobarbital Administrations in 4400ICU (N=109) |
| Age, years | 52 (40-63) |
| Gender, male | 19 (90) |
| Actual body weight, kg | 84 (68-90) |
| Ideal body weight, kg | 71 (66-80) |
| Dose, mg | 77 (30-130) |
| Dose, mg/kg actual body weight | 2 (1-2) |
| Dose, mg/kg, ideal body weight | 2 (1-2) |
| Dose10 mg/kg (612)26013097.264.832.4Other | 1332114160 |
| RouteOralIV | 45 (41)64 (59) |
| FrequencyOnceDailyBIDTIDAdditional PRN orders | 44 (40)3 (3)4 (4)58 (53)3 |
| Indication for PhenobarbitalAlcohol WithdrawalSeizuresSedation | 16 (80)2 (10)2 (10) |
| Concomitant benzodiazepine use, yes | 15 (75) |
| Intubated prior to phenobarbital, yes | 11 (55) |
| Hospital LOS, days | 27.5 (6.9-22.9) |
| ICU LOS, days\* | 9.2 (3.5-11.8) |
| All data presented as n(%) or median (IQR), as appropriate\*If >1 ICU admission: Only included ICU stay when phenobarbital was administered |

**Available Literature Supporting Phenobarbital for Alcohol Withdrawal Syndrome**

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| Author | Type of Study | N, Population, Study Groups | Dosing Regimen | Other Outcomes |
| Kaim 1972 | Prospective, randomized, partial double blind | N=188Male patients with DTLibrium N=46, Perphenazine N=46, PHB N=41, Paraldehyde N=55 |  | -1 death and 3 convulsions-No difference in duration or severity of DTs |
| Kramp 1978 | Randomized, double blind | N=91Hospitalized pts with impending DTsDiazepam (n=44) vs PHB (N=47) | Diazepam IM (Day 1 200 mg, Day 2 120 mg, Day 3 80 mg)PHB PO (Day 1 5g, Day 2 3g, Day 3 2g) | -No intubations/respiratory depression in either group-0 deaths, 2 seizures-PHN superior to diazepam for severe withdrawal/DT |
| Young 1987 | Prospective, uncontrolled | N=62ED patients with mild to moderate AWSPHB only | PHB IV 260 mg x1 then 130 mg q30 min until sedation or side effect | -No intubation/respiratory depression-92% discharged from ED-N=1 hypotension, N=2 lethargy, N=1 ataxia |
| Yeh 1992 |  | DSMIII criteria for substance abuse or dependence and history of AWS seizures |  | Oxazepam is short acting and therefore may confer poorer seizure prevention |
| Ives 1991 |  | Patients at risk of AWS |  | No outcomes or adverse events reported |
| Wiehl 1994 |  | Patients at risk of AWS |  | No outcomes or adverse events reported |
| Rosenthal 1998 | Prospective, randomized | N=42Inpatient detox unit patients with mild to moderate AWSPHB vs VPA+PHB | PHB PO (Day 1 60 mg q6h, Day 2 60 mg q8h, Day 3 60 mg q12h, Day 4 30 mg daily)VPA+PHB 60 mg PRN symptoms | -Respiratory outcomes not reported-Both regimens were effective in reducing AWS symptoms |
| Gold 2007 | Retrospective, cohort | N=95ICU patients with severe AWSDiazepam+PHBPreguideline (N=54) vs DIA+PHB post guidelines (N=41)-ICU admission if diazepam 200 mg within 4 hours or >40 mg diazepam as single dose | Escalating doses of PHB IV (65, 130, 260 mg) with physician determined diazepam PO/IV dosing to a max of 150 mg, if didn’t respond to 3 doses PHB, consider propofol | -Preguideline intubation rate 47%-Postguideline intubation rate 22%-ICU LOS correlated to amount of bzd received-ICU LOS and nosocomial complications occurred at the same rate in both groups |
| Lutzen 2008 | Retrospective | Inpatients admitted with pre DT/DT |  | -No respiratory depression in preDT group-9/73 cases of respiratory depression in patients with DTs |
| Michaelsen 2010 | Retrospective, cohort | N=194Inpatient psychiatric unit patients with mild to moderate AWSPHB (N=106) vs diazepam (N=88) | PHB PO/IV 100-200 q15 minDiazepam/Librium IV/PO 10-20 mg q15 min | -Intubation rate not statistically different (10% PHB group, 4% bzd group)-No difference in hospital LOS or ICU admission |
| Hendey 2011 | Prospective, randomized, double blind | N=44ED patients with AWSPHB N=25 vs Lorazepam N=19 | Lorazepam IV 2 mg at MD discretionPHB IV 260 mg IV x1, 130 mg at MD discretion | -Intubation rates not reported-No difference between ED LOS, baseline CIWA scores or 48-hour follow up between study groups |
| Rosenson 2013 | Prospective, randomized, double blind, placebo controlled | N=102ED patients with severe AWSPHB + lorazepam (N=52) vs lorazepam + saline (N=52) | PHB IV 10 mg/kg +/- lorazepam PO/IV per standard CIWA protocolNS +/- lorazepam PO/IV per standard CIWA protocol | -Intubation rate 2% for both groups-Fewer ICU admissions (9% vs 25%) in those who received PHB+lorazepam vs lorazepam alone-No difference in adverse events (seizures, ICU/hospital LOS, enhanced supervision) between groups |
| Duby 2014 | Retrospective, cohort | N=135ICU patients with severe AWSPHB+diazepam preguideline (N=65) vs PHB+diazepam postguideline (N=70) | Escalating doses of PHB (60 mg, 120 mg, 240 mg; route not indicated) after maximum 120 mg IV diazepam | -Intubation rates preguideline 22%, postguideline 5%-Postguideline study group with decreased ICU LOS, decreased sedation time and decreased vent days |
| Gashlin 2015 | Retrospective, cohort | N=28Non-ICU hospitalized patients with AWSDiazepam/lorazepam (N=21) vs PHB+BZD (N=7) | Escalating doses of PHB IV (65 mg, 130 mg, 260 mg, route not reported)20 mg diazepam (or lorazepam equivalent) until control of AWS | -Intubation rates not statistically significant (PHB+BZD=14%, BZD alone=5%)-Less BZD used in PHB+BZD group |
| Oks 2018 | Retrospective, observational study | N=87ICU patients with AWSPHB monotherapy  | PHB 130 mg IV q15 min until RASS 0 to -1 | -Intubation rate 17% (no pt intubated due to PHB alone)-Results indicate that PHB is safe to use |
| Tidwell 2018 | Retrospective cohort study | N=120ICU patients with AWSPHB N=60 vs CIWA-Ar N=60 | Starting PHB dose dependent on risk factors (active DT, history of DT or no history of DT) vs CIWA lorazepam | -Intubation rate N=14 in CIWA vs N=1 in PHB, p<0.001-ICU LOS 4.4 CIWA vs 2.4 days PHB, P<0.001, along with hospital LOS-Less dexmedetomidine use as well |
| Nisavic 2019 | Retrospective chart review | N=526Pts receiving pharmacologic treatment for AWSPHB N=143 vs BZD N=419 | Starting PHB dose dependent on risk factorsLoading doses were administered IM in3 doses q3h followed by a PO taper for <7 days and taper was achieved by decreasing dose by 50% q48h with discontinuation by day7 | -Intubation not reported-No difference in efficacy |
| Waldee 2019 | Retrospective pre- and post intervention observational study | N=122Patients admitted to a psychiatric ward for prevention or treatment of alcohol withdrawal receiving phenobarbital | Patients could’ve received PO+/- IM phenobarbMean cumulative dose 421 mg+/- 288 mg | -Primary outcome: respiratory rate (also BP and HR): baseline RR was 18.75 bpm and mean change was -0.22 bpm (p=0.35) |

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Appendix 1: Cookeville Regional Medical Center Adult Phenobarbital Treatment Pathway for Severe Alcohol Withdrawal Syndrome

Appendix 2: Salina Regional Health Center Protocol for Phenobarbital-Facilitated Treatment of Alcohol Withdrawal