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Comparison of Phenobarbital Monotherapy to a Benzodiazepine-based Regimen for Management of Alcohol Withdrawal Syndrome in Trauma Patients

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Abstract

BACKGROUND: Alcohol withdrawal syndrome (AWS) is associated with increased morbidity and mortality in the trauma population. Benzodiazepines (BZD) are standard of care for AWS; however, given the risk of delirium with BZDs and reports of BZD-refractory withdrawal, phenobarbital (PHB) has emerged as an alternative therapy for AWS. Safety and efficacy studies of PHB for AWS in trauma patients are lacking. Our aim is to compare a BZD versus PHB protocol in the management of AWS in trauma patients.

METHODS: We performed a retrospective cohort study at a level 1 trauma center of patients at risk for AWS managed with either a BZD or a low dose oral PHB regimen. Patients were excluded if they were taking benzodiazepines or barbiturates prior to admission, received propofol or dexmedetomidine prior to initiation of the study drug, presented with delirium tremens or seizures, or died or discharged within 24 hours of presentation. The primary outcome was complicated AWS (seizures or alcohol withdrawal delirium/delirium tremens). Secondary outcomes included uncomplicated AWS, therapy escalation, oversedation, delirium-, ICU-, and ventilator-free days, and length of stay (LOS).

RESULTS: 411 patients were identified; 118 received BZD, and 293 received PHB. The odds of developing complicated AWS with PHB versus BZD-based therapy were not statistically significant (OR 0.52; 95% CI, 0.21-1.39); however, patients receiving PHB were less likely to develop uncomplicated AWS (OR 0.08; 95% CI, 0.04-0.14) and less likely to require escalation

of therapy (OR 0.45; 95% CI, 0.24-0.84). The PHB group had a LOS 3.1 days shorter than the BZD group (p=0.002). There was no difference in ICU-, ventilator-, or delirium-free days.

CONCLUSIONS: A PHB-based protocol for the management of AWS is a safe and effective alternative to BZD-based regimens in trauma patients.

Level of evidence: Level IV, retrospective cohort

Keywords: alcohol withdrawal syndrome, delirium tremens, trauma, phenobarbital

Background

Alcohol use disorder (AUD) is a common and life-threatening condition affecting over 14.5 million people in the United States.[1] Alcohol withdrawal syndrome (AWS) occurs in individuals with AUD when alcohol intake suddenly ceases or decreases, thus causing a dysregulation of the γ-aminobutyric acid (GABA) and glutamate neurotransmitters.[2] Since their development in the 1970s, benzodiazepines (BZD) have been the standard of care for AWS with replicated efficacy in preventing alcohol withdrawal seizures and delirium tremens.[3-7] However, delirium and BZD-refractory AWS have been reported with BZDs, leading to the use of alternative agents.[8] Phenobarbital (PHB) has recently been explored as one alternative to BZDs for AWS. The linear kinetics, predictable serum levels, excellent bioavailability, and long half-life of PHB make for a desirable pharmacokinetic profile.[9] Additionally, multiple recent studies showcase the safety and efficacy of PHB as an alternative to BZDs.[10-15]

In December 2019, the trauma service at our level I trauma center transitioned from a symptom-triggered BZD-based protocol to a prophylactic scheduled, oral PHB monotherapy protocol for AWS.[13] Two studies have investigated PHB use in trauma patients, both analyze intravenous (IV) or intramuscular (IM) PHB loading doses followed by an oral taper.[14-15] Our protocol differed in that it uses an oral PHB taper without a loading dose with rescue IV doses for severe symptoms.

AWS is a common but life-threatening condition in trauma patients for which the ideal treatment remains unknown. The purpose of this study was to compare the efficacy and safety of a BZD-based regimen to an oral PHB monotherapy regimen for management of AWS in trauma

patients. We hypothesized that PHB has similar efficacy without additional significant safety concerns as compared to a symptom-triggered BZD-based protocol for AWS.

Methods

We conducted a single center pre- and post- retrospective cohort study at an American College of Surgeons-verified level 1 trauma center. All adult patients admitted from January 1, 2018, to July 31, 2021 were screened for inclusion. The PHB-based AWS management protocol was implemented on January 1, 2020; therefore, patients admitted prior to this date were included in the BZD group and patients admitted after this date were in the PHB group. The STROBE cohort checklist was used to ensure proper reporting of methods, results, and discussion (Supplemental Digital Content, SDC 1, http://links.lww.com/TA/D211)[16].

Inclusion and Exclusion Criteria

Patients admitted to the trauma service were included if they were ≥ 18 years of age with an order for a BZD-based therapy for management of AWS (BZD-group) or received at least 1 dose of PHB for AWS (PHB-group). Exclusion criteria were prescription for PHB, BZDs, or primidone prior to admission, intubated and receiving propofol or dexmedetomidine prior to initiation of BZD or PHB regimens, or discharged or died within 24 hours of presentation to the hospital. This study was approved by the institutional review board as an exempt study.

Alcohol Withdrawal Management Protocols

The BZD AWS protocol used prior to January 1, 2020 is shown in **Figure 1a**. The protocol was physician managed. Patients with AUD were started on diazepam as needed for

subjective signs and symptoms of alcohol withdrawal. Lorazepam was the preferred agent in patients 65 years and older or who had a history of liver disease. If alcohol withdrawal symptoms remained uncontrolled, the BZD was transitioned to a scheduled regimen with increases in dose and frequency of administration. The route of administration was changed to IV if acute symptom control was required. Adjunctive agents such as atypical antipsychotics and dexmedetomidine were initiated if the BZD failed to control symptoms.

The PHB AWS protocol is shown in **Figure 1b**. Patients with AUD were risk-stratified into low and high risk, based on their withdrawal history, and started on the appropriate prophylactic oral PHB regimen. If AUD was suspected but history was unable to be obtained, the choice of regimen was at the provider's discretion until an accurate history could be collected. Phenobarbital 65 mg IV every 1 hour as needed was available if breakthrough symptoms occurred despite the oral taper. The breakthrough doses were titrated to a goal RASS of 0 to -1.[11-12, 14-15] (Supplemental Figure 1, http://links.lww.com/TA/D212) For patients requiring multiple breakthrough doses of IV PHB, the scheduled PHB regimen could be escalated by increasing the dose or extending the taper. If the patient developed delirium tremens (DT), then patients were transitioned to the DT algorithm of the protocol (**Figure 1b**). The cumulative maximum PHB dose was 20 mg/kg ideal body weight (IBW). Concomitant use of BZDs was discouraged. Adjunctive agents such as atypical antipsychotics and dexmedetomidine were used for management of acute agitation if the breakthrough PHB doses were not effective.

Definitions

Complicated AWS was defined as development of alcohol withdrawal seizures or DT. Patients were classified as having DT if they had a positive (CAM-ICU assessment with alcohol withdrawal autonomic symptoms (i.e., SBP > 140 mmHg and HR > 100 bpm).[17] Patients were considered to have uncomplicated AWS if they did not develop complicated AWS but required an as needed dose of a BZD (BZD-group) or phenobarbital (PHB-group) for management of subjective withdrawal symptoms, required escalation of the initial regimen used for management of AWS, or documented signs and symptoms of alcohol withdrawal in the EMR (i.e., tremors, irritability, agitation, anxiety)[17]. Oversedation and undersedation were defined as a RASS of $\leq$ -2 and $\geq$ +2, respectively (Supplemental Figure 1, http://links.lww.com/TA/D212).

For the BZD-group, escalation of therapy was defined as transition from a symptom-triggered to a scheduled BZD regimen, increase in BZD dose or administration frequency, or change to IV route due to need for acute symptom management. For the PHB-group, patients were considered to have an escalation of therapy if the PHB taper was extended, PHB dose was increased, or if the regimen was changed to the IV route for acute symptom management. Oversedation was defined as a RASS of $\leq$ -2. Requirement of adjunctive medications included administration of antipsychotics, alpha$_2$-agonists, valproic acid, or phenobarbital (BZD-group only). Concomitant sedating medications were defined as administration of gabapentin, narcotics, trazodone, or mirtazapine.

Outcomes

The primary outcome was incidence of complicated AWS. Secondary outcomes included development of uncomplicated AWS, incidence of escalation of therapy, need for adjunctive medications, intubation due to somnolence after PHB or BZD administration, incidence of oversedation, delirium-free and coma-free days while alive at 14 days, ventilator-free days and ICU-free days at 28 days, total study drug administered (phenobarbital (mg/kg), lorazepam equivalents (mg), and hospital length of stay (LOS).

Analysis

Demographic data is reported using numbers and percentages for categorical variables and means with standard deviations for continuous variables. A chi-square test was used for nominal variables and a student's t-test was used from continuous variables. The primary and secondary outcomes were assessed by a univariate analysis followed by a multivariable linear regression adjusted for adjusted for Injury Severity Score (ISS), ethnicity, blunt injury, history of epilepsy, history of uncomplicated alcohol withdrawal, and history of alcohol withdrawal seizures. Data were obtained from the trauma registry and the electronic medical record (EMR). Analysis was performed with Stata 15 (College Station, TX).

Results

There were 411 patients included for analysis (Supplemental Figure 2, http://links.lww.com/TA/D213); 118 (28.7%) received BZD, and 293 (71.3%) received PHB (**Table 1**). Patients were mostly white, male, and 50 years old (mean). Patients receiving PHB were more likely to have Hispanic ethnicity (5.8% vs 2.5%, p = 0.03) and more severe injuries

(ISS 16.3 vs 7.8, p < 0.001). Patients in the BZD group were more likely to have history of epilepsy (4.2% vs 1.0%, p = 0.03), alcohol-related seizure (14.45 vs 4.8%, p = 0.001), and uncomplicated withdrawal (25.4% vs 12.0%, p = 0.001). The BZD group had higher initial RASS scores (0.93 vs. -0.12, p<0.001). There was no difference in percentage presenting with TBI, AIS head score, or mechanism of injury. There was also no difference in history of cirrhosis, uncomplicated alcohol withdrawal, or polysubstance abuse.

Patients in the BZD group received a median cumulative dose of 1.95 mg lorazepam equivalents. In the PHB group, patients received a mean cumulative dose of 5.9 mg/kg IBW. In the PHB group, 67 (22.9%) patients received at least one dose of a BZD medication (median lorazepam equivalents 0.44mg).

Primary and secondary outcomes are shown in **Table 2**. There was no difference between the BZD- and PHB-group for the primary outcome of incidence of complicated AWS (7.6% v. 5.5%, p=0.41). After controlling for potential confounders, there was no difference in the incidence of complicated AWS (OR 0.52, 95% CI 0.21 - 1.39. Logistic and linear regression results are shown in **Table 3** and **Table 4**.

Patients in the PHB group had less uncomplicated AWS (10.2% vs 62.7%, p < 0.001) and required fewer regimen escalations (14.0% vs 23.7%, p = 0.017). After adjusting for confounders with logistic regression, patients in the PHB group were less likely to develop uncomplicated AWS (OR 0.08, 95% CI 0.04 - 0.14) or require an escalation of regimen (OR 0.45, 95% CI 0.24 - 0.84). There was no difference between need for intubation due to medication overdosing, time

at RASS goal, or oversedation/undersedation. Mortality did not differ between the two groups. Patients in the PHB group had an adjusted hospital LOS 3.12 days shorter than the BZD group (p = 0.002).

Discussion

In this retrospective cohort study comparing an oral PHB regimen to a BZD-based regimen for AWS in trauma patents, we found no difference in incidence of complicated AWS or medication-related ADEs, suggesting PHB is as efficacious and safe as BZD for management of AWS. Patients in the PHB group also experienced significantly less rates of uncomplicated AWS, need for regimen escalation, and hospital LOS, revealing the PHB protocol successfully prevented AWS while also being an easier regimen to implement given the need for less adjustments after PHB was initiated. Our study is the largest one to date analyzing PHB for AWS management in the trauma population and the only one describing the use of a primarily oral PHB regimen in this patient population.

Our results corroborate those of other PHB studies, further validating PHB as a safe and effective alternative to BZDs. Nisavic et. al., completed a retrospective cohort study comparing a parenteral PHB loading dose plus taper protocol to a scheduled BZD regimen for AWS management in a general medicine population, finding no difference in incidence of complicated AWS.[11] The same protocols were compared in a surgical-trauma population, which demonstrated a lower rate of severe and uncomplicated AWS and need for adjunctive neuroleptic agents in the PHB group.[15] In a case series assessing a similar parenteral PHB load and taper protocol for AWS management in 31 trauma patients, no patients developed complicated AWS; however,

29% of patients required administration of a non-BZD rescue therapy after initiation of PHB.[14] In a retrospective study comparing an oral PHB regimen, similar to the one in our study, and a CIWA protocol in a MICU setting, the patients in the PHB group had a shorter ICU and hospital length of stay and less need for adjunctive medications.[13] However, 18% of patients in the PHB cohort required rescue doses of lorazepam.

While we also found a lower rate of uncomplicated withdrawal and shorter hospital LOS in our study, patients in the PHB group received more adjunctive medications. The contrasting study results are most likely explained by the difference in PHB regimens used. The previous studies conducted in the trauma population used a parenteral PHB loading dose ranging from 6-15 mg/kg followed by a week-long taper.[11,14-15] Our protocol was an oral based regimen without a loading dose. A parenteral loading dose rapidly achieves a higher serum level, which could explain why no difference in severe AWS and a higher requirement of adjunct medications in the PHB cohort was seen in our study.[18] While Tidwell et. al., also used an oral PHB regimen without a loading dose, their PHB protocol consisted of a six-day taper versus our three-day taper.[13] The additional days receiving the higher PHB doses may have provided better control of AWS symptoms, leading to less adjunctive medication use. Another major difference was the BZD regimens used: our protocol primarily used an as needed diazepam regimen while the other studies used a lorazepam-based regimen.[11,13, 15] Diazepam's longer half-life may have led to better control of the patient's AWS symptoms in our study, and thus, a lower rate of complicated AWS in the BZD group. Lastly, our definition for adjunctive medication use was broader than the one used in the previously described studies. Other studies defined adjunctive medication use

as neuroleptic medications given for management of AWS symptoms. Due to the retrospective design of our study, it was not possible to determine the indication for the adjunctive medication.

A major concern with PHB is its safety profile, specifically respiratory depression leading to intubation. However, multiple studies have consistently demonstrated safe use of PHB even with large loading doses.[10-15] Oks et al., performed a retrospective observational investigation of safety of PHB for AWS.[12] They reported a 20% incidence of intubation; however, PHB did not appear to be the proximate cause of respiratory failure in any of those patients despite patients receiving an average of 25 mg/kg (total body weight) of PHB. Tidwell et. al., showed a significant decrease in ventilator use in the PHB cohort.[13] In the study by Nejad et. al., fewer patients in the PHB group experienced adverse drug events such as somnolence and no difference was observed in the number of patients requiring transfer to an ICU for AWS.[15] Our study further supports the safety of PHB as we found no difference in need for intubation secondary to PHB or need for ICU transfer due to AWS; however, more patients in the PHB group experienced oversedation during their admission (35% vs. 25%, p=0.065). This result is surprising given the significantly smaller cumulative PHB dose used in our study (median cumulative dose of PHB was 270 mg) compared to studies with higher total dosing (mean cumulative dose of PHB administered was 854.7 mg) and no reports of oversedation.[15] In our study, the ISS was significantly higher in the PHB group; therefore, the patient's underlying injuries could have contributed to the difference in oversedation observed between the two cohorts. Additionally, the higher use of sedating adjunctive medications in the PHB group in our study may have played a role in the larger oversedation rates.

As previously mentioned, the PHB protocol used in our study is unique as it is an oral based regimen without a loading dose. This PHB protocol created by our trauma service was chosen for multiple reasons with the main goals being prevention of AWS regardless of severity, increase in protocol ease of use, and cost-effectiveness. First, the kindling hypothesis suggests that withdrawal severity increases with each subsequent withdrawal episode; therefore, a prophylactic PHB regimen rather than symptom-triggered was selected to prevent both uncomplicated and complicated AWS.[19] Second, the protocol's prophylactic standardized dosing and use of RASS for assessing AWS symptoms and oversedation allowed for easy protocol initiation without need for dosing calculations and surveillance of the patient's withdrawal course without necessitating additional monitoring and documentation outside of what is already required for all trauma patients. We chose not to use CIWA as it has not been validated in trauma patients, and underlying injuries could falsely elevate CIWA scores, causing unnecessary PHB or BZD administrations. In addition, obtaining a CIWA score requires patients to communicate, which could be difficult for patients with certain injuries (e.g., traumatic brain injury or significant facial fractures).[20-23] Use of other severity symptom scores that overcome these limitations such as the Minnesota Detoxification Scale would have required significant personnel training and creation of documentation tools in the EMR, limiting a timely implementation of the new protocol. As for dosing, given our team's minimal use of PHB prior to protocol initiation, PHB's long half-life, and concern for PHB-induced respiratory depression with higher doses, we chose a more conservative regimen. We also did not use a loading dose, allowing providers to adjust and/or discontinue PHB if the patient became over-sedated or new collateral information was obtained regarding the patient's alcohol abuse and withdrawal history after PHB was started. Lastly, due to the significant cost difference between PHB formulations, we utilized an oral

based regimen. Based on average wholesale price (AWP), the cost of a loading dose for a 70 kg patient ranges from $215 - $663 when using a loading dose of 6-15 mg/kg. The oral regimen ranges from $2-10 based on which risk algorithm is used. The AWPs for PHB formulations are listed in Supplemental Table 1, http://links.lww.com/TA/D214.[24]

Our study has several limitations that should be considered. This was a retrospective study of a protocol change at a single institution; therefore, the results may be limited at other institutions due to patient demographics and other factors. Due to the retrospective design, determination of the primary and some secondary outcomes relied on accurate documentation in the EMR. We accounted for this by having an objective definition of uncomplicated and complicated AWS that would be consistently and accurately documented. Additionally, given that our service did not use a severity symptom scale such as CIWA or RASS in the BZD group, administration of as needed BZD was based on the provider's subjective assessment of the patient's withdrawal symptoms, potentially leading to inappropriate BZD administrations and falsely elevating the incidence of uncomplicated AWS. Another limitation is that the two protocols differed both in type of drug and protocol trigger, limiting the identification of the specific component of the protocol transition that had the greatest impact. In addition, given that the BZD protocol was symptom-triggered and the definition for uncomplicated AWS included administration of a BZD, this outcome is biased in favor of the PHB protocol as it is a prophylactic regimen; however, prevention of AWS regardless of severity was a primary goal when developing the PHB protocol. Therefore, it was imperative to assess the PHB protocol's ability to successfully prevent uncomplicated AWS.

Despite these limitations, we found that the prophylactic oral PHB protocol successfully prevented uncomplicated AWS and was as effective as our prior BZD protocol in preventing complicated AWS without causing more respiratory depression or need for ICU transfer. This adds to the existing literature supporting the efficacy and safety of PHB as an alternative to BZD for AWS management. Prospective, randomized controlled studies in these patient populations are needed to validate the current findings in the literature. In addition, studies comparing different PHB protocols are required to determine which type of PHB protocol (prophylactic vs. symptom triggered), route of PHB delivery, and safety and symptom severity score with PHB use are superior for management of AWS.

Supplemental Digital Content:

SDC 1: STROBE cohort checklist for this study

SDC 2: Supplemental Figure 1

SDC 3: Supplemental Figure 2

SDC 4: Supplemental Table 1

References:

1. SAMHSA, Center for Behavioral Health Statistics and Quality. 2019 National Survey on Drug Use and Health. Table 5.4A – Alcohol Use Disorder in Past Year among Persons Aged 12 or Older, by Age Group and Demographic Characteristics: Numbers in Thousands, 2018 and 2019.
2. Attilia F, Perciballi R, Rotondo C, Capriglione I, Iannuzzi S, Attilia ML, et al. Alcohol withdrawal syndrome: diagnostic and therapeutic methods. *Riv Psichiatr*. 2018;53(3):118-122.
3. Kaim SC, Klett CJ, Rothfeld B. Treatment of the acute alcohol withdrawal state: a comparison of four drugs. *Am J Psychiatry*. 1969;125(12):1640-6.
4. Saitz R, O'Malley SS. Pharmacotherapies for alcohol abuse: withdrawal and treatment. *Med Clin North Am*. 1997;81(4):881-907.
5. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. *CMAJ*. 1999;160(5):649-55.
6. Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev*. 2010;(3):CD005063.
7. Kattimani S, Bharadwaj B. Clinical management of alcohol withdrawal: A systematic review. *Ind Psychiatry J*. 2013;22(2):100-108.
8. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21-6.

9. Tangmose K, Nielsen MK, Allerup P, Ulrichsen J. Linear correlation between phenobarbital dose and concentration in alcohol withdrawal patients. *Dan Med Bull*. 2010;57(8):A4141.
10. Rosenson J, Clements C, Simon B, Vieaux J, Graffman S, Vahidnia F, et al. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. *J Emerg Med*. 2013;44(3):592-598.
11. Nisavic M, Nejad SH, Isenberg BM, Bajwa EK, Currier P, Wallace PM, et al. Use of phenobarbital in alcohol withdrawal management - a retrospective comparison study of phenobarbital and benzodiazepines for acute alcohol withdrawal management in general medical patients. *Psychosomatics*. 2019;60(5):458-467.
12. Oks M, Cleven KL, Healy L, Wei M, Narasimhan M, Mayo PH, et al. The safety and utility of phenobarbital use for the treatment of severe alcohol withdrawal syndrome in the medical intensive care unit. *J Intensive Care Med*. 2020;35(9):844-850.
13. Tidwell, WP, Thomas RL, Pouliot JD, Canonico AE, Webber AJ. Treatment of Alcohol Withdrawal Syndrome: Phenobarbital Vs CIWA-Ar Protocol. *Am J Crit Care*. 2018;27(6): 454–60.
14. Ammar MA, Ammar AA, Rosen J, Kassab HS, Becher RD. Phenobarbital monotherapy for the management of alcohol withdrawal syndrome in surgical-trauma patients. *Ann Pharmacother*. 2021;55(3):294-302.
15. Nejad S, Nisavic M, Larentzakis A, Dijkink S, Chang Y, Levine AR, et al. Phenobarbital for acute alcohol withdrawal management in surgical trauma patients—a retrospective comparison study. *Psychosomatics*. 2020;61(4):327-335.

16. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies.
17. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed., American Psychiatric Association, 2013. DSM-V.
18. Ives TJ, Mooney AJ 3rd, Gwyther RE. Pharmacokinetic dosing of phenobarbital in the treatment of alcohol withdrawal syndrome. *South Med J.* 1991;84(1):18-21.
19. Maldonado JR, Sher Y, Ashouri JF, Hills-Evans K, Swendsen H, Lolak S, et al. The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol.* 2014;48(4):375-90.
20. Hecksel KA, Bostwick JM, Jaeger TM, Cha SS. Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. *Mayo Clin Proc*. 2008;83(3):274-9.
21. Higgins J, Bugajski AA, Church D, Oyler D, Parli S, Halcomb P, et al. A psychometric analysis of CIWA-Ar in acutely ill and injured hospitalized patients. *J Trauma Nurs*. 2019 Jan/Feb;26(1):41-49.
22. Carter W, Truong P, Sima AP, Hupe J, Newman J, Ebadi A. Impact of traumatic brain injury on Clinical Institute Withdrawal Assessment use in trauma patients: a descriptive study. *PMR*. 2021;13(2):159-165.
23. Steel TL, Giovanni SP, Katsandres SC, Cohen SM, Stephenson KB, Murray B, et al. Should the CIWA-Ar be the standard monitoring strategy for alcohol withdrawal syndrome in the intensive care unit? *Addict Sci Clin Pract*. 2021;24;16(1):21.

24. Phenobarbital: Drug Information. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. (Accessed on June 12, 2023.)

Figure Legends

Figure 1. A. Benzodiazepine Protocol. **B:** Phenobarbital Protocol. *****History of heavy alcohol use (≥8 drinks/wk for women or ≥15 drinks/wk for men) **OR** alcohol abuse with active signs/symptoms of withdrawal (not meeting high risk criteria); **History of alcohol withdrawal seizures **OR** history of DT

Figure 1a

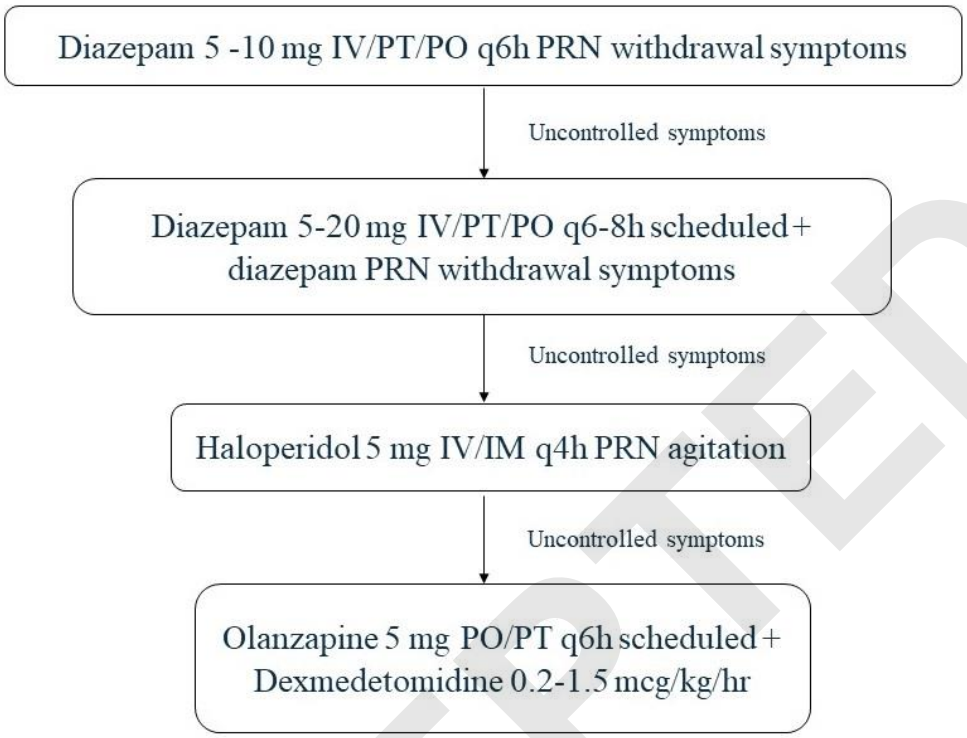


Figure 1b

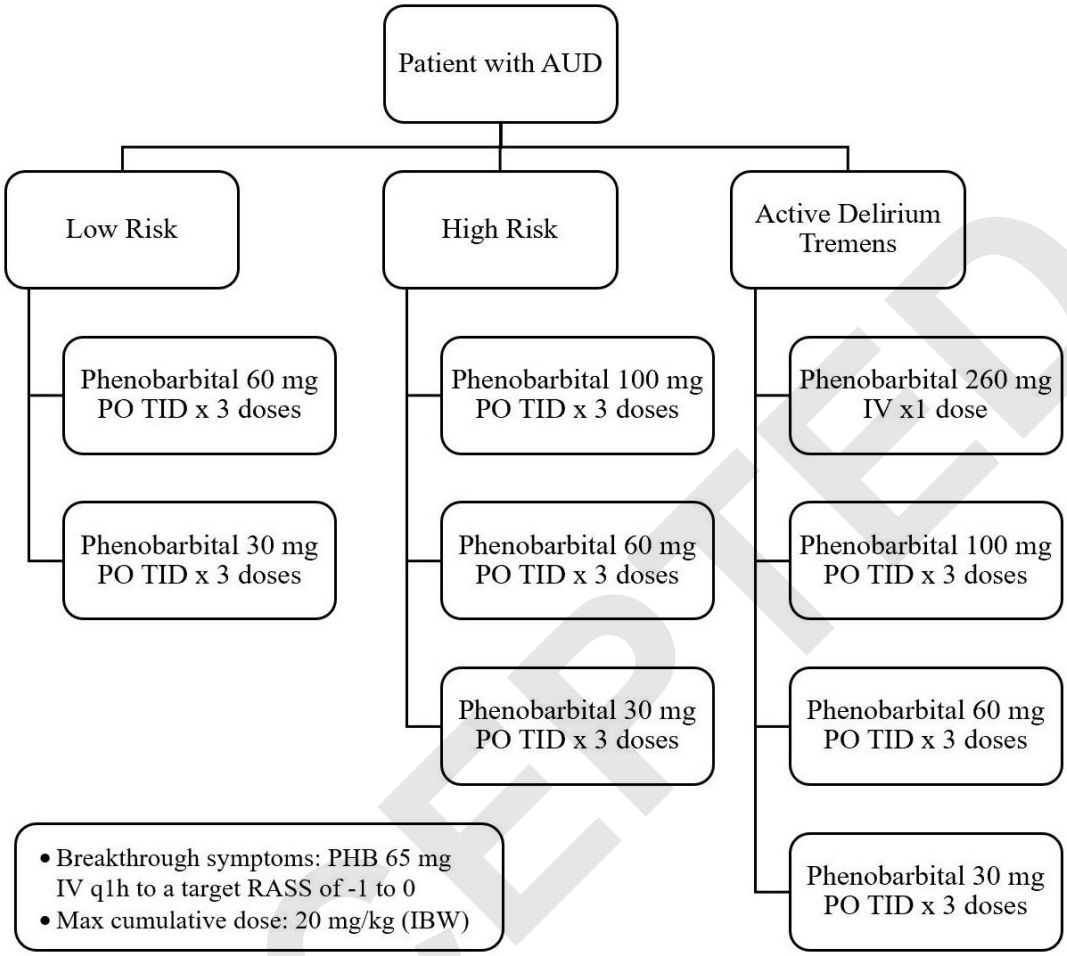


Table 1: Demographics

	BZD (n=118)	PHB (n=293)	p-value
Age	51.3 ± 14.3	49.3 ± 15.6	0.2
Sex (male)	105 (89.0%)	266 (90.8%)	0.58
Race • White • Black • Asian/Indian • Other • Unknown	 97 (82.2% 14 (11.9%) 1 (0.9%) 3 (2.5%) 3 (2.5%)	 232 (79.2%) 48 (16.4%) 1 (0.3%) 11 (3.8%) 1 (0.3%)	0.18
Ethnicity • Not Hispanic • Hispanic • Other	 113 (95.8%) 3 (2.5%) 2 (1.7%)	 276 (94.2%) 17 (5.8%) 0	0.033
IBW	68.2 ± 22/4	67.2 ± 8.5	0.65
Blunt	112 (94.9%)	262 (70.1%)	0.078
TBI	35 (29.2%)	85 (29.0%)	0.9
ISS	7.8 ± 8.4	16.3 ± 8.4	<0.001
AIS Head, mean	1.3 ± 1.6	1.3 ± 1.5	0.92
Initial GCS, mean	14.4 ± 1.5	14.3 ± 1.6	0.61
Initial RASS, mean	0.93 ± 0.3	-0.12 ± 1	<0.001
History of cirrhosis	4 (3.4%)	8 (2.7%)	0.72
History of epilepsy	5 (4.2%)	3 (1.0%)	0.033
History of alcohol-related seizure	17 (14.4%)	14 (4.8%)	0.001
History of Uncomplicated withdrawal	30 (25.4%)	35 (12.0%)	0.001
History of DT	4 (3.4%)	11 (3.8%)	0.86
History of polysubstance abuse	56 (47.5%)	114 (38.9%)	0.11
Median lorazepam equivalents received	1.95 mg	0.44 mg ± 1.1	
PHB equivalents received (mg/kg IBW)	14.05 mg	5.9 ± 4.6	

All values are reported as number (percentage) or mean ± standard deviation.

Abbreviations: BZD: benzodiazepine; PHB: phenobarbital; IBW: ideal body weight; TBI: traumatic brain injury; ISS (index severity score; AIS: abbreviated injury score; GCS: Glasgow Coma Score; RASS: Richmond Agitation & Sedation Scale; DT: delirium tremens.

Table 2: Primary and secondary outcomes

	BZD (n=118)	PHB (n=293)	p-value
Primary Outcomes			
Incidence of complicated alcohol withdrawal • Alcohol withdrawal seizure • Delirium tremens	9 (7.6%) 0 9 (7.6%)	16 (5.5%) 0 16 (5.5%)	0.41 0.41
Secondary Outcomes			
Mortality	1 (0.9%)	2 (0.7%)	0.86
Length Of Stay, days	7.6 ± 8.4	8.2 ± 9	0.46
Uncomplicated alcohol withdrawal	74 (62.7%)	30 (10.2%)	<0.001
Incidence of Regimen Escalation	28 (24%)	41 (14%)	0.017
Intubated Due to PHB		1 (0.3%)	
Intubated Due to BZD	0		
ICU Transfer due to withdrawal	3 (2.5%)	4 (1.4%)	0.4
Incidence of oversedation	30 (25.4%)	102 (34.8%)	0.065
Incidence of undersedation	31 (26.3%)	88 (30.0%)	0.45
Percentage Time at Goal RASS	97% ± 8%	96% ± 9%	0.51
Delirium-Free	13.5 ± 1.4	13.3 ± 2.1	0.19
ICU-Free Days	27.3 ± 2.8	26.9 ± 3.8	0.02
Ventilator-Free Days	27.7 ± 2.6	27.6 ± 2.6	0.13
Required Restraints	17 (14.4%)	51 (17.4%)	0.46
Required Adjunct Medication	71 (60.2%)	214 (73%)	0.01

All values are reported as number (percentage) or mean ± standard deviation.

Abbreviations: BZD: benzodiazepine; PHB: phenobarbital; RASS: Richmond Agitation & Sedation Scale.

Table 3: Logistic Regression – odds ratio for phenobarbital use (benzodiazepine used as reference); adjusted for ISS, ethnicity, blunt injury, history of epilepsy, history of uncomplicated alcohol withdrawal, and history of alcohol withdrawal seizures

	OR	95 % CI	p-value
Uncomplicated Withdrawal	0.08	0.04 - 0.14	<0.001
Complicated Withdrawal	0.52	0.21 - 1.39	0.20
Required Regimen Escalation	0.45	0.24 - 0.84	0.012

Table 4: Linear Regression for phenobarbital use (benzodiazepine used as reference); adjusted for ISS, ethnicity, blunt injury, history of epilepsy, history of uncomplicated alcohol withdrawal, and history of alcohol withdrawal seizures

	B-coefficient	Std Error	p-value
Percent time at goal RASS	0.02	0.01	0.83
Hospital LOS	-3.12	0.98	0.002
ICU-free days	0.02	0.40	0.96
Ventilator-free days	-0.04	0.28	0.88
Required Restraints	-0.04	0.05	0.38
Delirium-free and coma-free days	0.07	0.24	0.77

Abbreviations: RASS: Richmond Agitation & Sedation Scale; LOS: length of stay.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	2-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 3
		(b) Give reasons for non-participation at each stage	Figure 3
		(c) Consider use of a flow diagram	Figure 3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	5

		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title

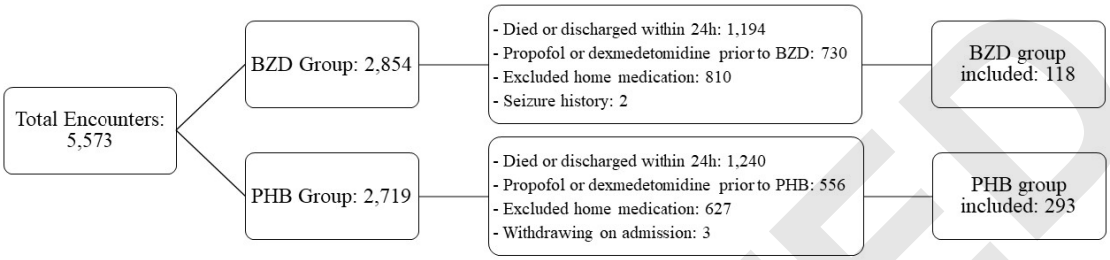
*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Supplemental Figure 1: Richmond Agitation & Sedation Scale

Richmond Agitation & Sedation Scale		
Score	**Description**	
+4	**Combative**	Violent, immediate danger to staff
+3	**Very agitated**	Pulls or removes tubes, aggressive
+2	**Agitated**	Frequent, non-purposeful movement, fights ventilator
+1	**Restless**	Anxious, apprehensive but movements not aggressive or vigorous
0	**Alert and calm**	
-1	**Drowsy**	Not fully alert, but has sustained awakening to voice (eye opening and contact ≥10 seconds)
-2	**Light sedation**	Briefly awakens to voice (eye opening and contact <10 seconds)
-3	**Moderate sedation**	Movement or eye-opening to voice (no eye contact)
-4	**Deep sedation**	No response to voice, but movement or eye opening to physical stimulation
-5	**Unarousable**	No response to voice or physical stimulation

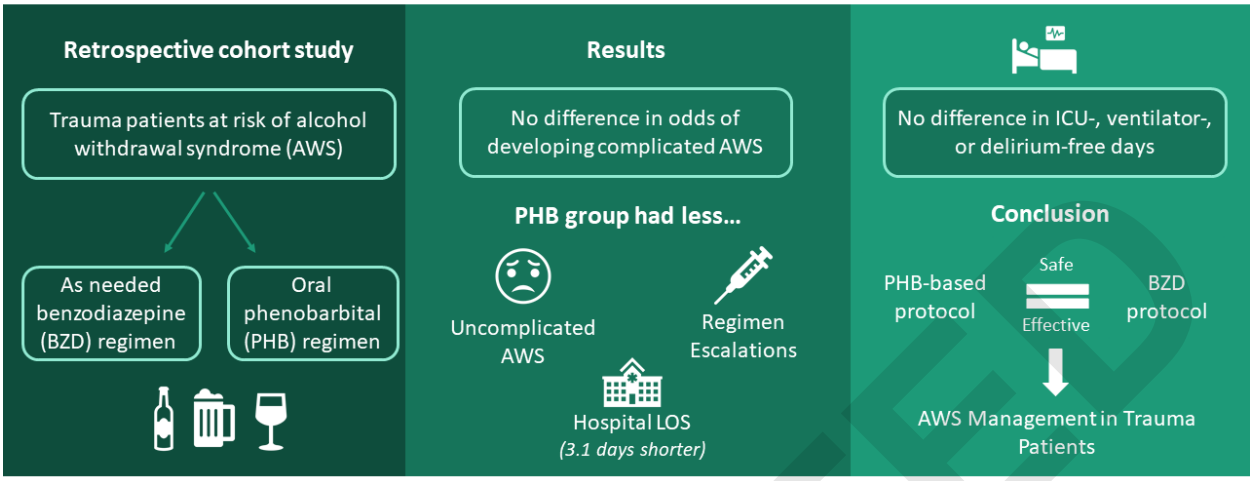
Supplemental Figure 2: Inclusion and Exclusion Flow Diagram



Supplemental Table 1: Average wholesale price for phenobarbital tablets and solution for injection

30 mg tablet (per each)	$0.11 - $0.42
60 mg tablet (per each)	$0.53
100 mg tablet (per each)	$0.74
65 mg/mL injection (per mL)	$25.00 - $31.62
130 mg/mL injection (per mL)	$66.00 - $82.08

Comparison of Phenobarbital Monotherapy to a Benzodiazepine-based Regimen for Management of Alcohol Withdrawal Syndrome in Trauma Patients



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