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Research Article

# Phenobarbital versus Lorazepam for the Management of Alcohol Withdrawal Syndrome (AWS) in Hospitalized Patients- A Retrospective Cohort Study

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## Abstract

**Aim:** To compare efficacy of Phenobarbital (PB) and Benzodiazepines (BDZ) primary therapy for alcohol withdrawal syndrome (AWS) across the continuum of care from the emergency department, medical floor, and Intensive Care Unit (ICU). **Methods:** We conducted a retrospective cohort study on patients hospitalized for AWS from 2019 to 2022. Patients were categorized into those treated with lorazepam using the revised Clinical Institute Withdrawal Assessment of alcohol scale (CIWA-Ar) and those treated with PB based on the Richmond Agitation- Sedation scale (RASS). The primary outcome was the rate of ICU admission. Secondary outcomes included hospital and ICU lengths of stay (LOS), rates of Mechanical Ventilation (MV), use of adjunctive medications, and mortality. We also performed a cost analysis. **Results:** 300 patients met the inclusion criteria, of whom 152 received PB and 148 received lorazepam. As compared to lorazepam, PB therapy was associated with significantly lower rates of ICU admission (5.3% vs. 13.5%, p=0.014), MV (0.7% vs. 9.5%, p=0.0004), adjunctive use of dexmedetomidine (1.3% vs. 9.5%, p=0.0016), lower mean ICU (0.21 vs. 1.07 days, p=0.003) and hospital LOS (4.89 vs. 6.16 days, p=0.004), and lower total hospital cost of care ($12,617 vs. $16,137). **Conclusion:** Our study showed that, across the continuum of care from the ED to inpatient units, PB monotherapy for AWS resulted in a significant reduction in need for ICU admission, MV, use of adjunctive sedating agents, and both ICU and hospital LOS as compared to lorazepam. Prospective, randomized controlled studies that compare PB vs. BDZs for AWS are needed.

**Keywords:** Alcohol withdrawal syndrome; Phenobarbital; Lorazepam; Hospitalized patients; ICU admission; Dexmedetomidine; Cost analysis

## Introduction

Alcohol Use Disorder (AUD) kills over 3 million people each year globally and accounts for 6 percent of global deaths [1]. In the United States, AUD is the fifth leading risk factor for premature death and disability [2]. Alcohol Withdrawal Syndrome (AWS) manifests due to the abrupt reduction or discontinuation of long-standing alcohol use [3]. It is characterized by symptoms of autonomic hyperactivity that begin within 6 to 24 hours of abrupt cessation of alcohol use. Symptoms range in severity from mild to moderate, including irritability, tremors, fever, diaphoresis, hyperreflexia, hypertension, confusion, and agitation, to more severe life-threatening forms like seizures, hallucinations, delirium tremens, and coma [4]. These effects are mediated through ion channel adaptations and altered current flows (i.e., reduction of neuro-inhibitory gamma-aminobutyric acid (GABA) receptor sensitivity, enhanced sensitivity of neuroexcitatory glutamate receptors, and increased density of voltage-gated calcium channels [5]. Chronic alcohol overuse decreases GABA-mediated neuroinhibitory activity and increases glutamate-mediated neuroexcitatory activity. Patients may present to the hospital with clinical features of AWS or develop them after hospitalization for alternative medical conditions. In patients with AWS, 5% progress to alcohol withdrawal delirium or delirium tremens (DT), requiring ICU care [6]. Prompt recognition and timely management of AWS are essential to minimize patient morbidity and mortality.

The cornerstone of AWS management is directed at counteracting the abnormal withdrawal pathophysiology with appropriate pharmacotherapy to prevent secondary complications. Timely and effective treatment can prevent the progression to severe AWS and the associated significant morbidity and mortality. The search for a safe and effective agent with fast onset action, easy titration, negligible abuse potential, wide therapeutic window, and minor liver metabolism has been a long-term goal to treat this disorder and has resulted in extensive research and developments in the past three decades. In the mid-20th century, many hospitals used intravenous ethanol to treat and prevent the progression of AWS. However, due to ethanol's variable and unpredictable pharmacokinetics coupled with its toxicity and narrow therapeutic index, there was a substantial need for a better treatment modality [7]. Advancements in molecular chemistry led to the discovery of benzodiazepine (BDZ) receptors on the GABAA channel complex in the 1970s [8]. BDZs allosterically bind to these receptor complexes, which leads to increased frequency of channel opening, and enhanced neuro-inhibitory GABAergic activity mitigating withdrawal signs and symptoms of AWS. Shortly after their introduction, BDZs, which were promoted heavily by the pharma industry, became the first line of treatment for AWS. Certain BDZs offer the advantages of various modes of delivery (intravenous, intramuscular, and oral) and, when needed, both rapid onset and longer duration of action [9]. BDZs, however, have a narrow therapeutic index and unpredictable pharmacokinetics and pharmacodynamics when used for AWS patients. Doses needed for control of agitation are often close to and overlap with doses resulting in central nervous system (CNS) and respiratory depression and pulmonary aspiration. In addition, serum concentrations of BDZs are not readily available and do not correlate with pharmacologic effects.

When used for AWS, BDZs are administered in one of three strategies: front-loading, fixed-dose or symptom-triggered. In most hospitals that can provide frequent monitoring of patients, symptom-triggered strategy has gained popularity [6]. The most common validated tool used to assess symptoms of AWS is 10-item Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) [10] (Table 1). Currently, BDZs remain the most widely used and preferred pharmacotherapy for AWS. Unfortunately, many patients with AWS are resistant to BDZ pharmacotherapy. Escalation of BDZ treatment can result in paradoxical agitation and enhanced delirium, yet such non-responders will have increased risks of respiratory depression and aspiration. Pharmacologically, BDZs do not function to suppress central glutamate upregulation that is present in those with AWS. Therefore, high doses of BDZs coupled with needed adjunctive pharmacologic therapy in BDZ-resistant AWS patients often leads to increased frequencies of ICU admissions, pulmonary aspiration, and mechanical ventilation, with a resultant long length of hospital stay [11]. Recognition of BDZ-resistant AWS patients led to a "BZ stewardship" movement seeking adjuncts to limit BDZ use. Adjunctive drugs have included baclofen, gabapentin, valproic acid, topiramate [12], and dexmedetomidine [13] but phenobarbital has demonstrated the most promising efficacy [14].

| Symptom | Scoring |
|---|---|
| Nausea/ vomiting | |
| No nausea and no vomiting | 0 |
| Mild nausea and no vomiting | +1 |
| (More severe symptoms) | +2 |
| (More severe symptoms) | +3 |
| Intermittent nausea with dry heaves | +4 |
| (More severe symptoms) | +5 |
| (More severe symptoms) | +6 |
| Constant nausea, frequent dry heaves and vomiting | +7 |
| Tremor- Arms extended and fingers spread apart | |
| No tremor | 0 |
| Not visible, but can be felt fingertip to fingertip | +1 |
| (More severe symptoms) | +2 |
| (More severe symptoms) | +3 |
| Moderate, with patient's arms extended | +4 |
| (More severe symptoms) | +5 |
| (More severe symptoms) | +6 |
| Severe, even with arms not extended | +7 |
| Paroxysmal sweats | |
| No sweat visible | 0 |
| Barely perceptible sweating, palms moist | +1 |
| (More severe symptoms) | +2 |
| (More severe symptoms) | +3 |
| Beads of sweat obvious on forehead | +4 |
| (More severe symptoms) | +5 |
| (More severe symptoms) | +6 |
| Drenching sweats | +7 |
| Anxiety | |
| No anxiety, at ease | 0 |
| Mildly anxious | +1 |
| (More severe symptoms) | +2 |
| (More severe symptoms) | +3 |
| Moderately anxious, or guarded, so anxiety is inferred | +4 |
| (More severe symptoms) | +5 |
| (More severe symptoms) | +6 |

| | |
|---|---|
| Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions | +7 |
| Agitation | |
| Normal activity | 0 |
| Somewhat more activity than normal activity | +1 |
| (More severe symptoms) | +2 |
| (More severe symptoms) | +3 |
| Moderately fidgety and restless | +4 |
| (More severe symptoms) | +5 |
| (More severe symptoms) | +6 |
| Paces back and forth during most of the interview, or constantly thrashes about | +7 |
| Tactile disturbances | |
| None | 0 |
| Very mild itching, pin and needles, burning, or numbness | +1 |
| Mild itching, pin and needles, burning, or numbness | +2 |
| Moderate itching, pin and needles, burning, or numbness | +3 |
| Moderately severe hallucinations | +4 |
| Severe hallucinations | +5 |
| Extremely severe hallucinations | +6 |
| Continuous hallucinations | +7 |
| Auditory disturbances | |
| Not present | 0 |
| Very mild harshness or ability to frighten | +1 |
| Mild harshness or ability to frighten | +2 |
| Moderate harshness or ability to frighten | +3 |
| Moderately severe hallucinations | +4 |
| Severe hallucinations | +5 |
| Extremely severe hallucinations | +6 |
| Continuous hallucinations | +7 |
| Visual disturbances | |
| Not present | 0 |
| Very mild sensitivity | +1 |
| Mild sensitivity | +2 |
| Moderate sensitivity | +3 |
| Moderately severe hallucinations | +4 |
| Severe hallucinations | +5 |
| Extremely severe hallucinations | +6 |

| | |
|---|---|
| Continuous hallucinations | +7 |
| Headache/ fullness in head | |
| Not present | 0 |
| Very mild | +1 |
| Mild | +2 |
| Moderate | +3 |
| Moderately severe | +4 |
| Severe | +5 |
| Very severe | +6 |
| Extremely severe | +7 |
| Orientation/ clouding of sensorium | |
| Oriented, can do serial additions | 0 |
| Can't do serial additions or is uncertain about date | +1 |
| Disoriented for date by no more than 2 calendar days | +2 |
| Disoriented for date by more than 2 calendar days | +3 |
| Disoriented to place or person | +4 |
| **Score** | **Withdrawal level** |
| </= 8 | Absent or minimum withdrawal |
| 9-19 | Mild to moderate withdrawal |
| >/= 20 | Severe withdrawal |

**Table 1:** Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) [30].

Before BDZ became commercially available in the 1970s, PB, a barbiturate, was often used to treat AWS. Until recently, PB has principally been used for those with severe AWS as an adjunctive treatment to BDZ therapy. Compared to BDZs, PB binds on a different site of the same GABAA receptor complex and increases the duration of the chloride channel opening to enhance neuro-inhibition, similar to BDZs. PB increases chloride conductance to a greater degree than BDZs and, at high doses, may even open the GABAA channel in the absence of GABA. Unlike BDZs, PB suppresses the upregulated excitatory glutamatergic pathways in those with AWS. PB therapy targets the pathophysiology of AWS and is pharmacologically more attractive than BDZ therapy. In addition, PB can be given orally or parenterally with predictable pharmacokinetics and clinical effects. PB dosing results in predictable PB serum concentrations, which correlate with desired clinical effect. In addition, PB has a greater therapeutic index than BDZs, with the desired therapeutic levels or effects significantly lower than toxic ones. PB is not associated with respiratory depression when dosed appropriately for AWS [15].

When used for AWS, PB is often administered as a symptom-triggered strategy with Richmond Agitation-Sedation Scale (RASS) as a clinically validated assessment tool [16] (Table 2). Initial and subsequent dosing strategies can be oral or intravenous for BDZ treatment.

| Patient description | Definition | Scoring |
|---|---|---|
| Combative | Overtly combative, violent, immediate danger to staff | +4 |
| Very agitated | Pulls or removes tube(s) or catheter(s); aggressive | +3 |
| Agitated | Frequent non-purposeful movement, fights ventilator | +2 |
| Restless | Anxious but movements not aggressive vigorous | +1 |
| Alert and calm | | 0 |
| Drowsy | Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds) | -1 |
| Light sedation | Briefly awakens with eye contact to voice (<10 seconds) | -2 |
| Moderate sedation | Movement or eye opening to voice (but no eye contact) | -3 |
| Deep sedation | No response to voice, but movement or eye opening to physical stimulation | -4 |
| Unarousable sedation | No response to voice or physical stimulation | -5 |

**Table 2:** Richmond Agitation-Sedation Scale (RASS) [31].

Due to PB's gaining popularity as a potentially better first-line pharmacotherapy to treat AWS, several comparison studies with BDZ treatment have been published. Most studies, however, are limited in scope to the outpatient setting or isolated hospital areas [e.g., hospital floor, ICU, or ED only]. Therefore, this study was designed to compare PB and BDZ primary therapy for AWS across the continuum of care from the ED, medical floor, and ICU and to better characterize key metrics on efficacy and morbidity with these two AWS treatment strategies.

## Materials and Methods

### Study design and participants

We conducted a retrospective single-center cohort study of hospitalized patients between January 1, 2019 to December 31, 2022 at a 329-bed community teaching hospital in central Massachusetts. The study inclusion criteria included patients admitted to the medical floors with an admission diagnosis of alcohol withdrawal syndrome and age greater than18 years old. The exclusion criteria included patients: 1) who were currently pregnant or had a positive pregnancy test; 2) who left against medical advice within 24 hours of their presentation; 3) who were incarcerated; 4) transferred from or to another facility; 5) who received neither PB nor BDZ for the treatment of alcohol withdrawal; and 6) with a documented allergy to either BDZ or PB. The data was obtained by reviewing patients' medical records, including demographic information, past medical history, medications, labs, and course during hospitalization. The Institutional Review Board approved the study.

### Exposure and Outcomes

The patients were categorized into those who received PB or lorazepam based on physician preference and institutional protocol. The protocol involved the administration of lorazepam using the revised Clinical Institute Withdrawal Assessment of alcohol scale (CIWA-Ar) and phenobarbital based on the Richmond Agitation-Sedation scale (RASS). The details of the administration of lorazepam as per the modified CIWA-Ar protocol have been demonstrated in Table 3. There were instructions to notify the practitioner if patients scored '7' for any of the CIWA parameters or had a total CIWA score >40 if the patient required more sedation than suggested in the protocol and if the lorazepam dose exceeded 40 mg in 24 hours. CIWA-Ar scoring was discontinued if the patient scored 0 for four consecutive periods or eight consecutive hours. Patients in the PB group received a weight-based loading dose of PB at 10 mg/kg/dose IV in the emergency department, followed by a maintenance dose based on the RASS (Table 4). Per the protocol, a maximum cumulative dose of 20 mg/kg of PB could be safely administered on the medical floors within the first 24 hours.

| Condition | Dose/Route/Rate | Instruction |
|---|---|---|
| CIWA score 5-10 (slight symptoms) | 2 mg PO every 2 hours PRN | If able to take orally |
| CIWA score 11-15 (mild symptoms) | 4 mg PO every 2 hours PRN | If able to take orally |
| CIWA score 16-20 (moderate symptoms) | 6 mg PO every 2 hours PRN | If able to take orally |
| CIWA score >20 (severe symptoms) | N/A | Parenteral route preferred |
| *PRN- as needed; #NPO- nothing by mouth | | |

| Lorazepam tab | |
|---|---|
| PO Q2H PRN* | Per modified CIWA-Ar protocol |
| Lorazepam injection (for NPO# patients, if modified CIWA scores >20 ) | |
| IV/ IM Q2H PRN* | Per modified CIWA-Ar protocol |
| *PRN- as needed; #NPO- nothing by mouth | |

**Table 3:** Lorazepam protocol.

| Phenobarbital tab | |
|---|---|
| PO 97.2 mg Q1H PRN* mild agitation | RASS = +1 |
| PO 194.4 mg Q1H PRN* moderate agitation | RASS >= +2 |
| Phenobarbital injection (for NPO# patients) | |
| IV / IM 130 mg Q1H PRN* mild agitation | RASS = +1 |
| IV / IM 260 mg Q1H PRN* moderate agitation | RASS >= +2 |
| *PRN- as needed; #NPO- nothing by mouth | |

**Table 4:** Phenobarbital protocol.

Demographic data collected included age, sex, weight, height, Body Mass Index (BMI), and ethnicity. Clinical data collected included co-morbidities, medications received, need for ICU admission, need for invasive mechanical ventilation, and total length of hospital and ICU stay.

The primary outcome included the rate of admission to the ICU. Secondary outcomes included total ICU and hospital LOS measured in days, invasive mechanical ventilation rate, use of adjunctive medications, and mortality. Adjunctive pharmacotherapies included medications used in addition to phenobarbital or benzodiazepine for the management of alcohol withdrawal symptoms and included quetiapine, olanzapine, haloperidol, and dexmedetomidine. In addition, mean doses of PB and lorazepam received in oral and IV formulations were calculated, and the costs were computed per hospital-approved pricing.

### Statistical Analyses

Data was entered in the excel spreadsheet and was analyzed using SPSS (Statistical Package for Social Sciences) version 20. Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency, and proportions for qualitative variables. Chi-square was applied to test the statistical association between qualitative variables. Unpaired t-test and Mann Whitney U test were applied respectively to test the mean difference of quantitative variables following normal and non-normal distribution. The level of significance was set at 5%.

## Results

A total of 318 patients were screened, and 300 met the inclusion criteria. Of the 300 patients, 152 received PB as an actual weight-based loading dose in the emergency department, followed by dosing per RASS protocol on the medical floors, and 148 received lorazepam as per CIWA-Ar protocol. The mean patient age was 56 and 51 years in the PB and lorazepam groups, respectively (p=0.001). Demographic data, including sex, weight, height, Body Mass Index (BMI), and ethnicity, had similar distribution between both groups (Table 5).

| Patient Characteristic | Phenobarbital group (N=152) N (%) | Lorazepam group (N=148) N (%) | P value |
|---|---|---|---|
| Mean age — years | 50.6 | 55.6 | 0.001 |
| **Sex —no. (%)** | | | |
| Male | 123 (80.9) | 116 (78.4) | 0.584 |
| Female | 29 (19.1) | 32 (21.6) | 0.584 |
| Caucasian | 123 (80.9) | 120 (81.1) | 0.384 |
| Hispanics | 11 (7.2) | 3 (2) | 0.384 |
| African American | 6 (3.9) | 10 (6.8) | 0.384 |
| Asian | 2 (1.3) | 4 (2.7) | 0.384 |
| Others | 10 (6.6) | 11 (7.4) | 0.384 |
| **Primary Outcomes** | | | |
| ICU admissions — no. (%) | 8 (5.3) | 20 (13.5) | 0.014 |
| **Secondary Outcomes:** | | | |
| Mechanical ventilation — no. (%) | 1 (0.7) | 14 (9.5) | 0.0004 |
| Death — no. (%) | 1 (0.7) | 5 (3.4) | 0.117 |
| **Adjunctive medications used** | | | 0.585 |
| Dexmedetomidine — no. (%) | 2 (1.3) | 14 (9.5) | 0.0016 |
| Quetiapine | 4 (3.2) | 12 (8.1) | 0.199 |
| Olanzapine | 13 (8.5) | 22 (14.9) | 0.199 |
| Haloperidol | 8 (5.3) | 15 (10.1) | 0.199 |
| Mean length of hospital stay (days) | 4.89 | 6.16 | 0.004 |
| Mean length of ICU stay (days) | 0.21 | 1.07 | 0.003 |
| Mean cost per unit- oral PB or oral lorazepam ($) | 5.42 | 6 | NA |
| Mean cost per unit- IV PB or oral lorazepam ($) | 426 | 12.4 | NA |
| Mean cost of hospital stay ($) | 12,617 | 16,137 | NA |
| Mean cost of ICU stay ($) | 1400 | 7134 | NA |
| NA: Not Available | | | |

**Table 5:** Baseline characteristics of patients and outcomes between Phenobarbital and Lorazepam groups.

There was a statistically significant difference in the primary outcome between the groups, with the admission rate to the ICU 5.3% in the PB group versus 13.5% in the lorazepam group (p=0.014). There were also significantly lower rates of intubation (0.7% versus 9.5%, p=0.0004) and requirement of adjunctive dexmedetomidine (1.3% versus 9.5%, p=0.0016) in those treated with PB as compared to lorazepam. In addition, PB-treated patients had a decreased frequency of use of adjunctive sedating medications such as quetiapine, olanzapine, and haloperidol for AWS during their hospital stay [16.4% versus 22.3% (p=0.199), respectively. Although not statistically significant, PB-treated patients had a lower mortality rate (0.7% versus 3.4%, p=0.117). The mean LOS in the ICU (0.21 versus 1.07 days, p=0.003) and hospital (4.89 versus 6.16 days, p=0.004) was significantly lower in PB-treated patients.

In order to perform a cost analysis for both treatment groups, mean doses of PB- loading and maintenance dose combined and the mean dose of lorazepam received in both oral and IV formulations were calculated. Costs were computed for the same as per hospital-approved pricing. The mean oral PB dose was 460 mg, which cost $5.45 compared to the mean oral lorazepam dose of 12 mg at the cost of $6. The mean IV PB dose was 744 mg, which cost $426 in comparison to the mean IV lorazepam dose of 9 mg at the cost of $12.40. We also computed the mean hospital stay cost in both treatment groups, given that the average hospital cost in the US is $2,607 per day [17]. The total cost of stay based on the mean length of hospital stay calculation for PB and lorazepam groups were $12,617 and $16,137, respectively.

## Discussion

Most American adults consume alcohol at least once in their lifetime. Among them, 6.7% develop AUD, which accounts for over 140,000 deaths annually [1]. The repercussions of widespread and long-term alcohol abuse and resultant dependency include its devastating withdrawal effects upon abstinence. Therefore, withdrawal management strategies, including the most effective pharmacotherapies, are central to mitigating withdrawal-associated morbidity and mortality.

Although retrospective and non-controlled, this is the first study to demonstrate significant differences in the efficacy of PB versus lorazepam in the management of AWS for hospitalized patients across the continuum of care from ED arrival to hospital discharge. This study was conducted to better elucidate the best of current pharmacologic options for treating AWS. In our retrospective cohort, we studied the characteristics of patients treated with two different treatment modalities, PB versus lorazepam. We observed a relatively balanced distribution of patients in both protocols, indicating a sense of equipoise regarding the decision of the initial drug of choice. The decision possibly stemmed from consideration of both PB and lorazepam being equally effective with standard written protocols in place. The patients included in this study had similar baseline characteristics and similar incidences of comorbid conditions. We observed a significant increase in ICU admission and intubation rates in the lorazepam group, suggesting that the BDZ class of agents should not be the preferred pharmacologic option to treat AWS, as suggested by some authorities [18]. In our study, patients treated with lorazepam for AWS required treatment with adjunctive sedating agents more frequently to control AWS agitation and had significantly longer ICU and hospital LOS. In addition, we noted a concerning trend towards increased mortality in those treated with lorazepam compared to those treated with PB monotherapy for AWS. As we accounted for the safety and efficacy profile of both these medications, we also looked into the total cost incurred in administering these medications during hospitalization. While the parenteral cost of IV PB is more than that for lorazepam, the overall mean hospitalization cost in the PB-treated patients is lower due to lower LOS in the ICU and hospital.

The FDA has approved PB for use in the management of generalized tonic-clonic, status epilepticus, and partial seizures [19]. PB use for the treatment of AWS is an off-label indication. An extensive review of the published literature shows that phenobarbital is non-inferior to BDZ therapy for treating AWS. Some more recent studies further suggest that PB is slightly superior in specific metrics for treating AWS compared to BDZs [20-22]. Both PB and BDZs can be dosed orally or parenterally with rapid distribution to tissues and have long durations of action [beneficial auto-tapering effect] that make these classes of agents attractive for the management of withdrawal. PB, however, has several critical pharmacokinetic and pharmacodynamic advantages over BDZ treatment. First, PB dosing achieves reliably predictable serum concentrations that correlate closely with clinical effects. Second, PB has a wider therapeutic index with clinical effects often achieved well below doses that cause CNS and respiratory depression. Third, unlike BDZ, PB counteracts the CNS glutamate upregulation that occurs in those with AWS and does not result in paradoxical, increased agitation and delirium seen in certain patients treated with BDZ. Finally, compared to BDZ, PB facilitates greater neuro-inhibition via the GABAergic system. Factors that may limit PB use in hospitalized settings include its contraindications in those patients who are pregnant and have porphyria or hepatic or renal failure-associated encephalopathy. Caution and dose adjustments may also be necessary for those taking certain medications that interact with barbiturates (e.g., oral anticoagulants) [22,23].

Another observation from our study was the simpler, easier, and more effective utilization of RASS as a symptom screening tool for initial and repeated PB dosing compared to CIWA-Ar for BDZ dosing. CIWA-Ar is based on subjective parameters that

involve patient communication and is challenging for accurate scoring when used in patients with altered mental status [24]. It is also labor intensive, requiring 10-15 minutes to complete, with several studies demonstrating the difficulty associated with serial assessments [25,26]. On the other hand, RASS is a simpler tool aiding the nurses with an effortless and quick way to assess sedation similar to other sedation assessment tools (e.g., Riker Sedation-Agitation Scale, Ramsey) [27].

Prior studies have primarily compared BDZs and PB in ED and ICU patients in isolation. One meta-analysis that compared PB with lorazepam for treatment of AWS in an ICU setting showed a reduction in the length of hospital stay by 2.6 days in favor of PB. Still, the study was limited due to the lack of uniformity or a standardized phenobarbital dosing regimen across different studies [28]. Another study that compared PB with BDZs for AWS in an ICU setting demonstrated a decreased duration of AWS and ICU LOS without differences in hospital LOS or adverse events [29]. One well-designed, randomized, double-blind, placebo-controlled study of AWS in an ED demonstrated that a single dose of 10 mg/kg IV PB resulted in a decreased rate of ICU admission when combined with a standardized lorazepam-based AWS protocol [21]. One review article showed safety in using phenobarbital as a single agent for AWS, but data was mainly limited to use in the Emergency Department (ED) and ICU [30]. We designed this study to assess and compare the clinical profile and prognostic outcomes associated with lorazepam and phenobarbital use across the continuum of care from the ED to hospital discharge. Our primary outcome, the rate of ICU admission between treatment groups, was significantly lower in patients treated with PB monotherapy. We also demonstrated a decreased rate of mechanical ventilation in those treated with PB. This finding has been previously demonstrated in another study of PB-treated patients for AWS in an ICU setting [20]. Compared to PB, BDZs have a narrower therapeutic index, with patients often demonstrating marked variability in therapeutic and toxic effects after dosing. Literature and knowledge of PB pharmacology suggest a lower rate of CNS and respiratory depression associated with PB use in patients with AWS [21,22] (Figure 1).

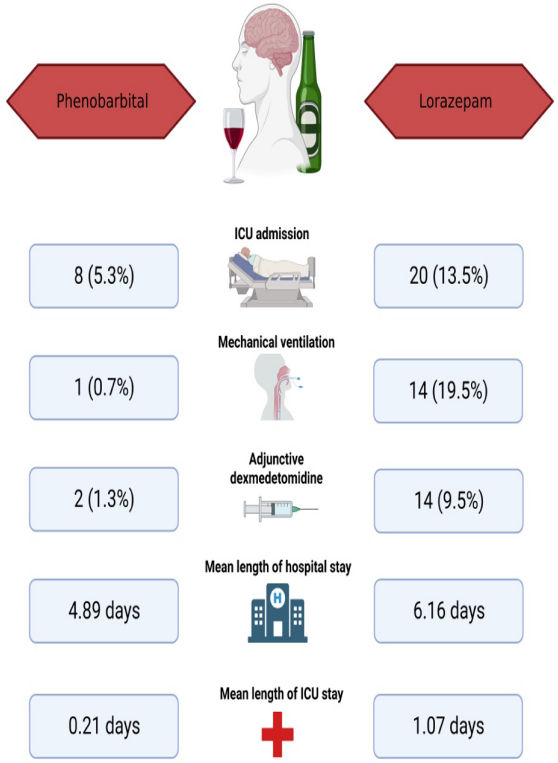


**Figure 1:** Outcomes for primary treatment of alcohol withdrawal syndrome with phenobarbital versus lorazepam in hospitalized patients [32].

Compared to lorazepam-treated patients, decreased hospital and ICU LOS for PB-treated patients is largely explained by its efficacy at doses that do not cause CNS and respiratory depression and the reduced need for adjunctive sedating agents that prolong patients' sedation and reduced delirium that invariably increases the LOS. In addition, PB has an added benefit of a prolonged elimination half-life allowing for auto-taper clinical effects. However, this is not uniquely different from certain BDZs (e.g., diazepam and chlordiazepoxide) with similar pharmacokinetics utilized to treat AWS [31,32].

Cost comparisons between PB versus BDZ treatment protocols are essential. Consideration must be given to both the cost of the pharmacotherapy chosen and the hospitalization cost with each strategy. Tidwell et al. demonstrated a substantially increased cost associated with PB therapy for AWS, principally associated with the cost of IV PB. Oral dosing of BDZs and PB are comparable, but the use of IV PB is currently more expensive than IV BDZ. However, when considering the cost savings of decreased ICU admission rates and ICU and hospital LOS, PB monotherapy costs less than BDZ treatment. In our study, we computed the mean cost of hospitalization associated with the two treatment groups. We noted that the costs of PB-treated patients were slightly lower than those treated with lorazepam ($12,617 vs. $16,137), supporting the overall cost-effectiveness of PB therapy.

## Limitations

The most significant limitations of our study are its retrospective, non-controlled design and small sample size. In addition, our study was limited to one hospital and may not be generalizable to other hospitals or healthcare centers with a differing patient population. The choice of PB versus lorazepam for treatment was entirely based on physician preference, with no defined guidelines. There was no comparison of the treatment groups' average RASS and CIWA-Ar scores. There was a lack of data regarding the indication for intubation in the patients. We could not determine if the patients were intubated for airway protection or had respiratory failure. We did not study delirium, hallucinations, or seizure rates in both treatment groups. We did not calculate the rate of readmission in either group.

## Conclusion

Our study strongly suggests that PB monotherapy is preferable to treatment with lorazepam for AWS. Across the continuum of care from the emergency department to inpatient units, we have shown that PB monotherapy for AWS results in a significant reduction in the need for ICU admission, mechanical ventilation, use of adjunctive sedating agents, and reduction in both ICU and hospital lengths of stay as compared to lorazepam. In addition, PB monotherapy demonstrated a trend toward reducing mortality and economic utility with our cost analysis. Our study was not designed primarily to look at PB monotherapy-associated cost reductions. However, a decreased need for ICU admission and shorter length of stay suggests that significant cost savings are achievable with PB while considerably decreasing morbidity and mortality from AWS. Due to the global magnitude of AUD and its associated healthcare ramifications, further research is needed. Prospective, randomized studies that compare PB with commonly used BDZs (e.g., diazepam, lorazepam) are needed to further our understanding and optimize patient management for AWS.

## Author Contributions

JS and MG conceived the idea for the study. SP and HSG designed and undertook the literature review. SP, HSG, SAK and GS collected data. SP and HSG analyzed and interpreted the data. MG performed the statistical analysis. SP formulated the figures and tables. SP, HSG and SAK wrote the first draft of the manuscript. MG, JS, MB, SAK, GS and SVG revised the subsequent drafts of the manuscript. All authors reviewed and agreed on the final draft of the manuscript.

## Conflict of Interest Statement

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

## Ethical Considerations

Institutional review board statement: The study was reviewed and approved by Saint Vincent- MetroWest Medical Center Institutional Review Board [(Approval No. 2020-020)].

## Informed Consent Statement

The informed consent requirement was waived by Saint Vincent- MetroWest Medical Center Institutional Review Board [(Approval No. 2020-020)].

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