

## Medical Management of Acute Alcohol Withdrawal in Hospitalized Patients at a Community Based Network of Hospitals: A Retrospective Cohort Study

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### Abstract

**Background:** In the United States over 500,000 episodes of alcohol withdrawal require pharmacological treatment each year [1]. The medications for withdrawal treatment in the U.S. are benzodiazepines and barbiturates. Studies suggest these treatments are equivocal, [2] however, studies comparing outcomes of the two medications have been limited.

**Objective:** The primary objective of this study is to compare alcohol withdrawal treatment with benzodiazepine and phenobarbital medication classes alone or in combination in hospitalized patients in a 8 hospital community-based healthcare system.

**Methods:** This is a retrospective review of 1,602 hospital encounters with a principal diagnosis of alcohol withdrawal from 01/01/2018 to 12/31/2019. Encounters were evaluated for type of pharmacologic treatment, 30-day readmission rate, ICU admission, and intubation rates.

**Results:** When comparing the treatment groups, patients in the phenobarbital treatment group compared to the benzodiazepine group had a statistically significant higher admission to ICU at 42% versus 28% respectively ( $p=0.0160$ ). Phenobarbital and benzodiazepines were not statistically significantly different in intubation rate ( $p=0.3690$ ) or 30-day readmission rate ( $p=0.8626$ ). Rates of 30-day readmission and intensive care (ICU) admission were statistically significant between the three pharmacologic treatment groups ( $p<0.001$ ) with the combination of phenobarbital and benzodiazepines demonstrating the highest rates of both.

**Conclusion:** In other similar studies [8-11], there are varied outcomes in relation to ICU admission, intubation and 30-day re-admission rates when comparing benzodiazepines and phenobarbital. This study further demonstrates variation in these outcomes. Due to these substantial differences in outcomes when comparing phenobarbital and benzodiazepines, higher level studies are needed to provide conclusive evidence that phenobarbital is equivocal or superior to use of benzodiazepines for the treatment of alcohol withdrawal.

**Keywords:** acute alcohol withdrawal; benzodiazepines; phenobarbital

## Background

It is estimated by the National Institute on Alcohol Abuse and Alcoholism, that there are approximately 15 million Americans with alcohol use disorder (AUD). The complications of AUD lead to significant resource utilization, morbidity, and mortality [1]. Between 2006 and 2010 the annual number of alcohol-associated deaths in the United States was approximately 88,000, or 9.8% of all US deaths [2]. In the United States over 500,000 episodes of alcohol withdrawal require pharmacological treatment each year, and between 2000 and 2015 the rate of hospitalizations complicated by alcohol use continued to increase from 90.45 to 156.98 per 10,000 population [1, 3]. In the same time period, the rates of alcohol related psychoses in patients hospitalized with alcohol withdrawal and alcohol treatment length of stay increased in the United States (26% to 51% of hospitalizations and 2.3 to 3.5 days respectively) [1]. Alcohol related illness was the 20th most expensive inpatient condition contributing to Medicaid expenditures in 2017 [4]. The two most-used medications for withdrawal treatment in the U.S. are benzodiazepines and Phenobarbital [5, 6].

Benzodiazepines are standard of care for treatment of alcohol withdrawal due to rapid onset, wide safety margin, anxiolytic properties, and anticonvulsant properties. Benzodiazepines increase the frequency of the GABA-A chloride channel opening, cellular hyperpolarization, and central nervous system depression by postsynaptic inhibition. Benzodiazepines can be used either per a fixed-dosage scheduled taper or a symptom-triggered taper. When a symptom-triggered taper is used, the Clinical Institute Withdrawal Assessment for Alcohol, CIWA or CIWA-Ar (revised version), is a 10-item scale frequently used in the assessment and management of alcohol withdrawal [3, 5, 6]. According to the most recent ASAM 2020 guideline, benzodiazepines are still considered first line therapy for patients at risk for acute moderate or severe alcohol withdrawal in the hospitalized setting [5].

Phenobarbital, a barbiturate, is an alternative therapeutic option for management of alcohol withdrawal syndrome. It works by potentiating activity on the GABA receptors as well as antagonistic activity on NMDA and AMPA receptors. The mechanism is different from benzodiazepines which only act on GABA receptors. Phenobarbital has a longer half-life of 80-120 hours compared to 14-20 of lorazepam which decreases administration burden and allows for gradual tapering of therapy [7, 8, 9].

There have been a limited number of studies comparing the use of benzodiazepines and phenobarbital as treatment for the symptoms of alcohol withdrawal. In 2017, Hammond and colleagues conducted a meta-analysis concluding that phenobarbital appears to be as effective as a monotherapy for mild-moderate alcohol withdrawal cases as other GABA agonists [9]. Specifically, there were similar rates of treatment failure, ICU admissions, length of stay. There was however a significant decrease in need for mechanical ventilation utilizing phenobarbital compared to benzodiazepines (21.9% vs 47.3% respectively) [9]. In 2013, Rosenson et al published data supporting phenobarbital use in the Emergency Department setting for the reduction of ICU admissions by 17%, however there was no difference between ICU length of stay or total hospital length of stay. There was no difference in incidence of adverse events such as intubation, seizure, mechanical restraints, or need for a bedside sitter [7]. Nisavic and colleagues compared the use of a fixed dose taper of benzodiazepines with a phenobarbital fixed taper and found no significant difference between hospital length of stay, ICU length of stay, over sedation, or seizures [10]. Nelson and colleagues compared three separate withdrawal protocols between diazepam alone, intravenous lorazepam as well as intravenous phenobarbital, and phenobarbital alone in a retrospective observational study. This study found that there was no difference between the rate of ICU admission from the Emergency department, rate of mechanical ventilation, and no difference between non-intensive care unit length of stay [11]. Most recently in 2021, Hawa and colleagues similarly compared benzodiazepines to phenobarbital in a 3-hospitalcommunity-based system. In this study, patients who received phenobarbital had a statistically significant reduced length of stay and lower rates of 30-day readmission. Additionally, there was a trend but not statistically significant for ICU transfer in the phenobarbital group compared to the benzodiazepine group (3.23% compared to 7.04%  $p=0.1114$ ) [8].

## Objective

The primary objective of this study is to compare alcohol withdrawal treatment with benzodiazepine and phenobarbital medication classes alone or in combination in hospitalized patients of a large community-based hospital network.

## Methods

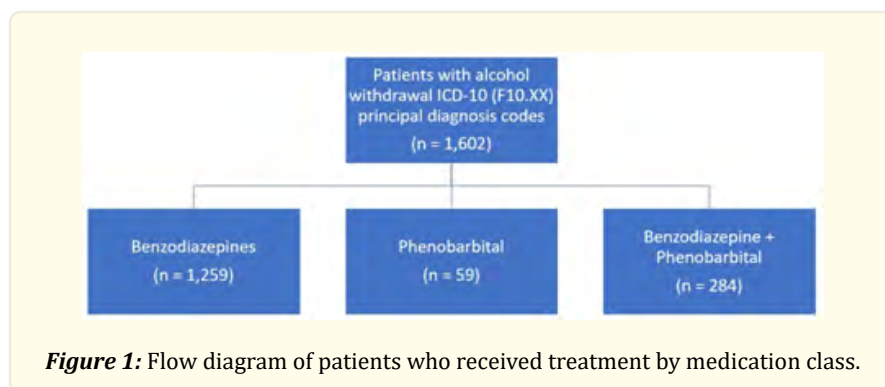
This retrospective study was conducted at Kettering Health; an eight-hospital health care system in Ohio. This study was approved by the Institutional Review Board as exempted review on October 9<sup>th</sup>, 2020 [1625194-1]. Adult patients with a principal ICD-10 diagnosis code of alcohol withdrawal (F10.xx) from January 1<sup>st</sup>, 2018 to December 31<sup>st</sup> 2019 were reviewed for study inclusion. Patients were included if they were 18 years or older and received at least one dose of either a benzodiazepine or phenobarbital. Patients were excluded if they were <18 years old, treated in the emergency department and subsequently discharged, and patients admitted for alcohol withdrawal, but not administered any doses of medication. The electronic medical record queried for data points and end points of interest. Data points collected included: 30-day hospital readmission, admission to the intensive care unit (ICU), and intubation with presumptive mechanical ventilation.

## Statistical analysis

Data was evaluated for assumptions (eg. normality, homogeneity of variances, etc.), checked for outliers, and assessed for systematic bias to ensure valid analysis. Significance was evaluated at  $\alpha < 0.05$ . Analyses was conducted using SAS® v9.4. Descriptive statistics were performed to describe and summarize the data. The corresponding mean, SD, frequency, and percent distribution was reported. Bivariate analysis was performed using independent sample t-test, chi-square test to determine association between study groups (benzodiazepine only, phenobarbital only, and both benzodiazepine and phenobarbital) and study outcomes.

## Results

A total of 1,602 hospital encounters with a principal diagnosis of alcohol withdrawal met inclusion criteria for study analysis during the study period January 1<sup>st</sup>, 2018 to December 31<sup>st</sup>, 2019. Of the 1,602 hospital encounters, 1,259 were treated with benzodiazepines alone, 59 were treated with phenobarbital alone, and 284 were treated with both phenobarbital and benzodiazepines. Figure 1.



**Figure 1:** Flow diagram of patients who received treatment by medication class.

When comparing the treatment groups across all the hospitals, patients in the phenobarbital treatment group compared to the benzodiazepine group had a statistically significant higher admission to ICU at 42% versus 28% respectively ( $p=0.0160$ ). Phenobarbital and benzodiazepines were not statistically significantly different in intubation rate ( $p= 0.3690$ ) or 30-day readmission rate ( $p= 0.8626$ ). Table 1

After determination of a cohort of patients who were treated with both benzodiazepines and phenobarbital, the outcomes were also evaluated by comparing the three groups. Rates of 30-day readmission and intensive care (ICU) admission were statistically significant between the three pharmacologic treatment groups ( $p < 0.001$ ). Specifically, the highest likelihood for 30-day readmission phenobarbital plus benzodiazepine treatment group at 22.89% compared to 11.86% and 12.63% for the phenobarbital group and the benzodiazepine group, respectively. Additionally, admission to ICU was the significant in comparing the three groups, and again with

the group receiving both phenobarbital and benzodiazepines with the highest rate at 57.04% compared to 42.37% and 27.88% for phenobarbital and benzodiazepines, respectively. Rates of intubation was not statistically significant in comparing the three groups (0.5653). Table 1.

Primary Outcome Comparison Between Two Treatment Groups				
Categorical Outcomes, n (%)	Benzodiazepines (n = 1,259)	Phenobarbital (n = 59)		P Value
30-day Readmission	159 (12.63%)	7 (11.86%)		0.8626
ICU Admission	351 (27.88%)	25 (42.37%)		0.0160
Mechanical Ventilation	17 (1.35%)	0 (0.00%)		0.3690
Primary Outcome Comparison Among Three Treatment Groups				
	Benzodiazepines (n=1,259)	Phenobarbital (n = 59)	Benzodiazepine + Phenobarbital (n = 284)	P Value
30-Day Readmission	159 (12.63%)	7 (11.86%)	65 (22.89%)	<0.0001
ICU Admission	351 (27.88%)	25 (42.37%)	162 (57.04%)	<0.0001
Mechanical Ventilation	17 (1.35%)	0 (0.00%)	5 (1.76%)	0.5653

**Table 1:** Primary Outcomes.

## Discussion

This retrospective cohort study evaluates the outcomes of ICU admission, intubation rate, and 30-day readmission for patients admitted for a principal diagnosis of Alcohol Related Disorders (F10.xx) between January 1<sup>st</sup>, 2018 to December 31<sup>st</sup> 2019. All patients were admitted to our community healthcare system of 8 hospitals which utilizes similar treatment protocols and processes. Our study demonstrates outcome differences based on medication utilized for acute alcohol withdrawal.

In other similar studies [8-11], there are varied outcomes in relation to ICU admission, intubation and 30-day readmission rates when comparing benzodiazepines and phenobarbital. This study further demonstrates variation in these outcomes. This study demonstrated statistically significant higher ICU admission for phenobarbital compared to benzodiazepines. This is directly different from the studies reported above by Hawa, Nisavic, and Nelson [8, 10, 11]. Furthermore, in contrast to the Hawa et al study specifically, this study did not demonstrate a significant difference in 30-day readmission rate when comparing phenobarbital to benzodiazepines where that study found an improvement in 30 day readmission rates for patients treated with phenobarbital. Similar to the Nelson study [11] however, this study also did not demonstrate differences in intubation rate or 30-day readmission when comparing benzodiazepines to phenobarbital.

## Limitations

Because this was a retrospective cohort study and the current ASAM (American Society of Addiction Medicine) national guidelines recommend use of benzodiazepines as first line, it was expected that there would be a substantial difference in number of encounters in each medication cohort. This has potential to disrupt the statistical power from the data set.

For this study, we did not look at standardization of treatment regime in each group, but simply by medication class. It is a reasonable assumption that most ordering provider utilized dosing within each medication class in the safe prescribing range for acute alcohol withdrawal due to processes in each hospital that are standard in the network. Furthermore, it is reasonable to assume that most providers utilized the protocols available for regimes for each medication class.

There is a potential selection bias with a trend toward phenobarbital with benzodiazepines in patients with more severe alcohol withdrawal risk based on history previous complicated withdrawal, multiple readmissions over a brief period, higher CIWA scores on admit that may favor phenobarbital initiation with benzodiazepines. This is an area of opportunity for evaluation in the future, but with our current electronic medical record data available, it was not possible for consideration with this study.

## Conclusion

This study further complicates the existing data for the outcomes related to use of benzodiazepines and phenobarbital in the treatment of acute alcohol withdrawal in the hospital-based setting. Due to these substantial differences in outcomes when comparing phenobarbital and benzodiazepines, higher level studies are needed to provide conclusive evidence that phenobarbital is equivocal or superior to use of benzodiazepines for the treatment of alcohol withdrawal. Additionally, specific patient-based factors which guide utilization of each medication type and outcomes from medication type would be beneficial in future studies.

## Funding Support

None.

## Conflicts of Interest

None.

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