

Introduction

Over 8 million people are affected by alcohol dependence and 50% will experience symptoms of withdrawal when alcohol is removed. 5% will present with severe alcohol withdrawal with symptoms including seizures and hallucination. DSM-5 defines alcohol withdrawal, but there is no consistent definition for severe alcohol withdrawal in the literature. Studies have used elevated CIWA-Ar Scores and/or symptoms refractory to high dose benzodiazepines¹⁻³

Benzodiazepines have been standard of care for decades, but phenobarbital has become popular treatment option due to its

- Mechanism of Action
- Pharmacokinetics
- Drug Shortages

Phenobarbital was added to Regions Hospital alcohol withdrawal order set 12/2017

- Dosing: 10 mg/kg (ideal body weight) IV loading dose
 - Followed by: 65 mg IV q6h prn
 - Option for scheduled taper
- Criteria for Phenobarbital Use
 - Initial Prediction Alcohol Withdrawal Severity Scale score of $\geq 4^{4-5}$
 - Initial CIWA-Ar Score > 15
 - Uncontrolled alcohol withdrawal with benzodiazepines
- Use with Caution: Patients that have received significant benzodiazepine dosing
- Intensive Care Unit (ICU) level of care monitoring for IV loading dose

Outcomes

Primary Outcome:

- To measure hospital length of stay in patients with severe alcohol withdrawal who received phenobarbital for alcohol withdrawal and patients with severe alcohol withdrawal received benzodiazepines alone

Secondary Outcomes:

- To measure percentage of patients requiring ICU admission and ICU length of stay, percentage of patients requiring mechanical ventilation and duration of mechanical ventilation, and adjunctive haloperidol and/or dexmedetomidine usage in each group

Methods

Observational cohort, retrospective chart review:

- 50 Patients presenting between 01/01/2018 to 12/31/2018
 - Received Phenobarbital for Alcohol Withdrawal
- 50 Patients presenting between 01/01/2014 to 12/31/2018
 - Did not receive phenobarbital
 - Matched 1:1 to phenobarbital group based on:
 - Age (within 5 years), Sex, and Highest Recorded CIWA-Ar Score (within 2)

Inclusion Criteria:

- Ages 18 – 80 years old
- Documented CIWA-Ar score > 15 with receipt of at least one dose of phenobarbital and/or lorazepam or diazepam for the treatment of alcohol withdrawal
- Diagnosis of alcohol withdrawal with an associated ICD-9 or ICD-10 code for alcohol use disorder

Exclusion Criteria:

- Patients diagnosed with cirrhosis or severe liver disease defined as Child-Pugh class C
- Recent traumatic brain injury within the last month
- Pregnancy
- Documented allergy to any barbiturate or benzodiazepine
- Patients receiving phenobarbital that are unable to be matched to a patient receiving benzodiazepine monotherapy

Results

Table 1. Patient Demographics

	Any Phenobarbital n = 46 median (IQR)	Phenobarbital monotherapy n = 4 median (IQR)	Benzodiazepines monotherapy n = 46 median (IQR)
Male: n (%)	37 (81)	2 (50)	37 (81)
Age, years	49.5 (41.25, 55.75)	54 (51.75, 55.5)	50 (38.25, 55.5)
Initial CIWA Score	16 (10, 22.75)	19.5 (14.5, 25.25)	17 (9.5, 24.5)
Highest Recorded CIWA Score:	25 (19, 29)	20 (16.5, 25.25)	23 (18, 27)
Duration of CIWA Assessments, days	3.5 (2.4, 4.7)	2.2 (1.8, 2.8)	3.7 (3.0, 5.8)
Number of Medication Administrations	11 (7, 22.25)	4 (2, 6)	20 (13, 31.75)

Hospital Length of Stay

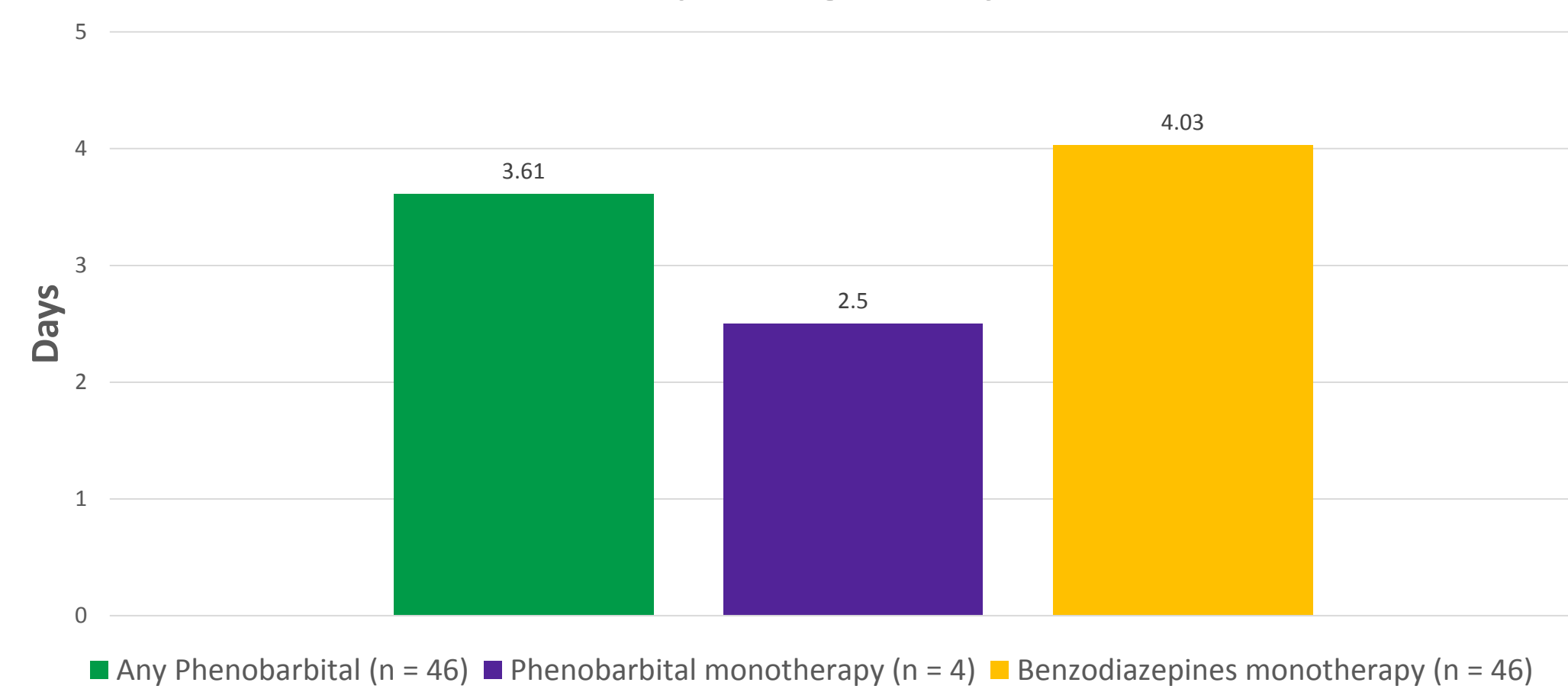
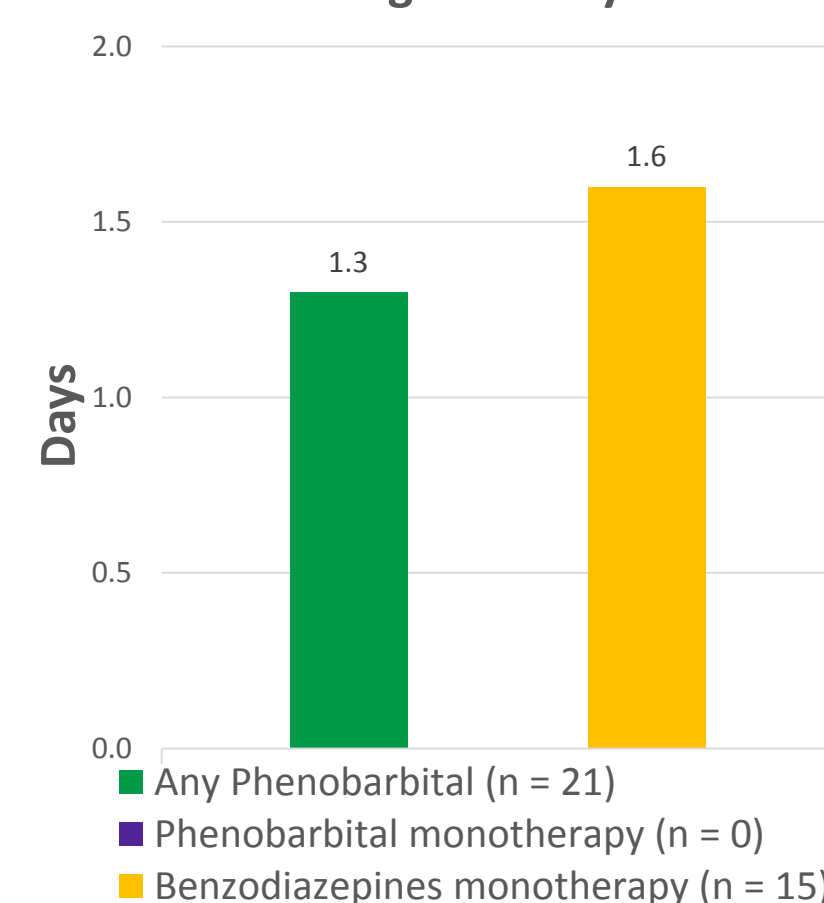


Figure 1. Primary Outcome: Hospital Length of Stay

ICU Length of Stay



Mechanical Ventilation Duration

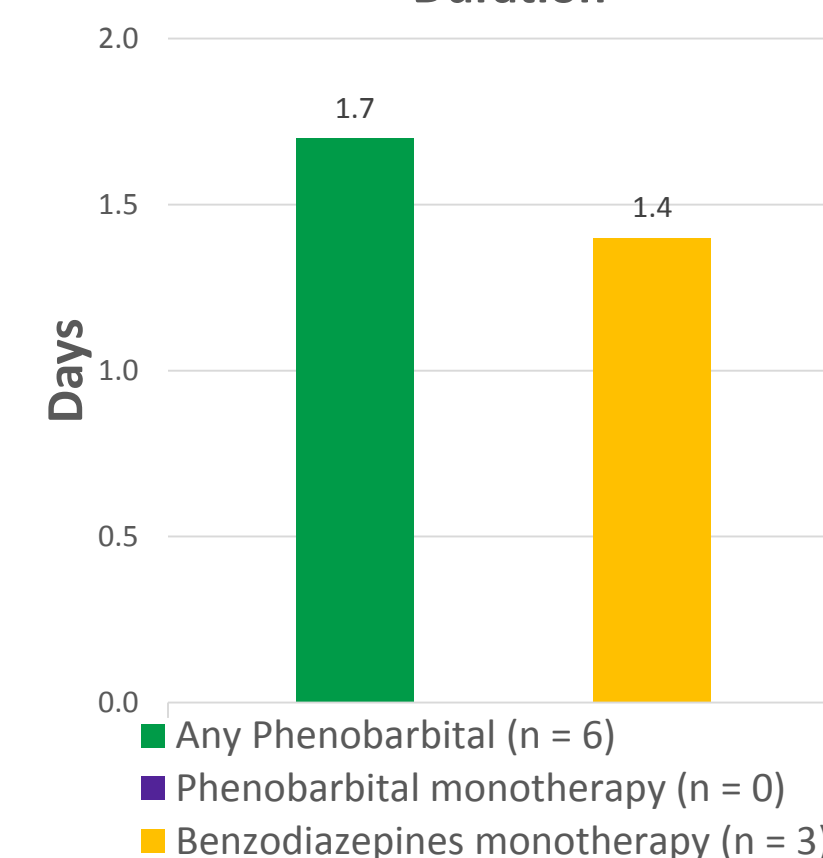


Figure 2. Secondary Outcomes: ICU Length of Stay & Mechanical Ventilation Duration

Table 2. Adjunctive Therapies

	Any Phenobarbital n (%)	Phenobarbital Monotherapy n (%)	Benzodiazepine Monotherapy n (%)
ICU Admission: n (%)	21 (45.7)	0 (0)	16 (34.7)
Mechanical Ventilation	6 (13)	0 (0)	3 (6.5)
Haloperidol	13 (28.3)	0 (0)	9 (19.6)
Dexmedetomidine	12 (26)	0 (0)	4 (8.7)
Any Adjunctive Med	17 (37)	0 (0)	11 (23.8)

Results Continued

Table 3. Phenobarbital Adjunctive Therapies

	Mechanical Ventilation n (%)	Haloperidol n (%)	Dexmedetomidine n (%)
Before Phenobarbital Administration	4 (66%)	4 (31%)	6 (50%)
After Phenobarbital Administration	2 (33%)	9 (69%)	6 (50%)

Conclusions

Phenobarbital administration during severe alcohol withdrawal may be associated with shorter duration of stay

- Less medication administrations, shorter ICU length of stay, longer duration of mechanical ventilation, more adjunctive medications

Strengths:

- Similar patient populations

Limitations:

- Only 4 (8%) of patients in the phenobarbital group received monotherapy
- Did not account for other benzodiazepines or antipsychotics
- Confusion among providers regarding level of care required for phenobarbital administration
- Unable to match 50 patients

Next Steps

- Education of providers
- Optimizing protocol
- Cost analysis
- Identifying optimal patient population

References

1. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Results from 2013 national survey on drug use and health: summary of national findings.
2. Schmidt, K. J., Doshi, M. R., Holzhausen, J. M., Natavio, A., Cadiz, M., & Winegardner, J. E. (2016). Treatment of severe alcohol withdrawal. *Annals of Pharmacotherapy*, 50(5), 389-401.
3. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub
4. Maldonado, J. R., Sher, Y., Ashouri, J. F., Hills-Evans, K., Swendsen, H., Lolak, S., & Miller, A. C. (2014). 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*, 48(4), 375-390.
5. Maldonado, J. R., Sher, Y., Das, S., Hills-Evans, K., Frenklach, A., Lolak, S., ... & Neri, E. (2015). Prospective validation study of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) in medically ill inpatients: a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol and alcoholism*, 50(5), 509-518.

Acknowledgements

- Pamala A. Pawloski, PharmD, BCOP, FCCP;
- Guidance and support for project creation
- Hollie Lawrence, PharmD, BCCCP
- Guidance and clinical advisor

Contact Information

Eric.J.Berg@healthpartners.com