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Phenobarbital and/or benzodiazepines for recurrent alcohol withdrawal: A self-controlled, retrospective cohort study

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ABSTRACT

Background: While there is ample data supporting the use of barbiturates and benzodiazepines (BZDs) for the treatment of alcohol withdrawal, there is a paucity of information on treating recurrent withdrawal among high healthcare utilizing patients. The purpose of this study was to assess the efficacy and safety of phenobarbital (PB), with or without adjuvant BZDs, for treatment of acute alcohol withdrawal in the emergency department (ED) in patients with high rates of recurrent withdrawal.

Methods: This non-matched, self-controlled, retrospective cohort study evaluated patients seen in the ED of an urban trauma center and safety-net teaching hospital between July 1st, 2018, and July 31st, 2019. Patients treated for alcohol withdrawal were included if they had at least one visit where they received intravenous PB with or without BZDs, then during a separate encounter received BZD only. Each encounter was then assigned to a treatment group based on administration of PB only, BZD only, or the combination of PB and BZD. The primary outcomes were admission to hospital or discharge and return to the ED for any reason within 48 h of disposition.

Results: A total of 137 unique patients were included, with 642 encounters composed of 245 PB only, 293 BZD only, and 104 combination visitations. No significant difference was found between the PB, BZD, or combination treatment groups for rates of admission (36.7%, 38.9%, and 46.1% respectively) or for return within 48 h (17.1%, 15.0%, and 13.5%). There was a significantly longer ED length of stay for the combination group (8.6 h) compared to either the PB or BZD only groups (6.4 and 7.0 h, respectively, $p < 0.05$) but not between the monotherapy groups. There were significantly higher rates of ICU admission and hypotension when PB and BZDs were used together (8.6% and 15.4%) versus either agent alone (PB 2.9% and 5.7%, BZD 3.8% and 4.5%, $p < 0.05$).

Conclusion: Among patients with multiple visits presenting with alcohol withdrawal, treatment with PB, BZDs, or both did not result in significantly different rates of admission or readmission within 48 h. Receiving a combination of PB and BZDs was associated with significantly longer ED length of stay, more ICU care, and increased incidence of hypotension as compared to either PB or a BZD alone.

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1. Introduction

Emergency department (ED) visits related to alcohol are a common and increasing occurrence. ED visits in the United States related to alcohol consumption increased more than 60% from 2006 to 2014 [1]. This increase is related to both acute and chronic complications of alcohol consumption, including withdrawal. Pharmacological treatment of alcohol withdrawal syndrome (AWS) has traditionally relied on benzodiazepines (BZDs), specifically lorazepam and diazepam. However, increasingly literature has supported use of phenobarbital (PB) either as an adjunct or primary agent for AWS [2-8]. In one ED trial, a single dose of PB in addition to symptom driven lorazepam was shown to reduce intensive care unit (ICU) admission rates and less overall BZD doses [3]. As monotherapy, symptom-triggered PB was shown to be equivalent to symptom-triggered lorazepam followed by an outpatient BZD taper for reducing withdrawal symptoms during the ED visit and for 48 h after discharge [4]. Other trials have demonstrated benefit with phenobarbital in inpatient and critical care settings but there is continued debate about its role for AWS in the ED. [5-6,8–11].

Diazepam and PB have long half-lives (20–50 h and 53–140 h) that exceed the duration of ED visits posing the potential for adverse events once patients leave the ED. [12] Studies have shown that up to 44% of AWS patients have return visits for withdrawal, but to-date no study has looked at the optimal treatment for the acute management of patients with high-recidivism [11–13]. The purpose of this study was to assess the efficacy and safety of PB, with or without adjuvant BZDs, for treatment of acute alcohol withdrawal in the ED caring for a large

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urban patient population with high rates of recurrent ED visits for withdrawal.

2. Methods

2.1. Study design and setting

This was a non-matched, self-controlled, retrospective cohort study using a three-armed analysis comparing intravenous phenobarbital, intravenous benzodiazepines, or the combination for the treatment of acute alcohol withdrawal in patients with repeat visits presenting to the ED of an urban level 1 trauma center and safety-net teaching hospital. A self-controlled model was used to reduce the effects of individual variability on pharmacokinetics, pharmacodynamics, and the presentation of alcohol withdrawal while comparing the different treatment strategies. Data was collected from the electronic health record (Siemens INVISION, Malvern, PA) and automated dispensing cabinet information (Omnicell, Mountain View, CA) for patients seen between July 1st, 2018 through July 31st, 2019. The data was de-identified to be compliant with the Health Insurance Portability and Accountability Act for statistical analysis.

2.2. Inclusion and exclusion criteria

Patients had to be 18 years of age or older, be treated for alcohol withdrawal in the ED, have received intravenous (IV) PB with or without IV BZDs during one encounter, then during a separate encounter within the study period, receive IV BZDs without PB. Patients were excluded if the studied drugs were administered for indications other than the treatment of alcohol withdrawal, or they did not receive any of the studied drugs prior to the final disposition. Each unique patient must have had at least 1 encounter allocated to either of the PB-containing groups and at least 1 encounter in the BZD only group. For the BZD containing groups, oral agents were included in dosing calculations if at least one dose of BZD was given IV.

2.3. Interventions

The symptom-triggered dosing strategies recommended by the institution for the use of each agent were as follows: IV PB 130 mg to 260 mg every 30 min, lorazepam 2 mg every 30–60 min, and diazepam every 15–30 min with escalating doses of 10, 20, 20, 40, 40, and 80 mg. The decision to use any agent, or in combination, was at the treating physician's preference and all dosing strategies used, recommended or not, were included in the analysis. Benzodiazepine equivalents were defined as 2 mg lorazepam, 10 mg diazepam, 5 mg midazolam, and 25 mg chlordiazepoxide irrespective of route. Outpatient BZD tapers following the ED visit were not recommended but patients were included if utilized. Summation of doses given include only those from the time of first medication administration to final disposition. Medications given after final disposition were not included as they did not contribute to the primary outcome of admission or discharge.

2.4. Outcomes

Primary outcomes were admission or discharge from the ED determined at the time of final disposition recorded by the treating physician and readmission defined as return to the ED for any reason within 48-h after the time of final disposition. Secondary outcomes included level of care on admission, the ED length of stay (LOS), and specific adverse events including bradypnea (respiratory rates (RR) of <10 breaths per minute), need for mechanical ventilation, hypotension (mean atrial pressure < 65 or SBP <90 or DBP <60 mmHg), or seizure. Additional data collected included number of doses and cumulative weight-based dosing of drug, first and highest Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) score, as well as patient demographics and clinical characteristics.

2.5. Statistical analysis

Analysis was performed using STATA (College Station, TX) using ANOVA for continuous variables, Pearson Chi2 for categorical data, and logistic regression. For all analyses, encounters were used to represent the cases in the population (n).

2.6. Data sharing statement

The information used in this study was obtained from Zuckerberg San Francisco General Hospital medical records and is not publicly available.

3. Results

The inclusion criteria were applied to the collected data set which identified 150 unique patients as having 669 separate ED encounters. Of these, 27 encounters were excluded which resulted in 13 patients being fully removed from the study. A total of 137 patients with 642 encounters composed of 245 PB only, 293 BZD only, and 104 combination visits were analyzed. Fig. 1 outlines this process. As this was self-controlled study, characteristics of the PB only, BZD only, and combination treatment groups were well balanced including mean age (49.3 vs. 48.2 vs. 48.8 years); proportion of men (85.7% vs. 88.4% vs. 91.3%); weight (79.0 vs. 78.6 vs. 81.3 kg); serum creatinine (0.75 vs. 0.75 vs. 0.70 mg/dL); history of any seizure (49.0% vs. 53.6% vs. 57.7%); or presentation with seizure (8.6% vs. 14.1% vs. 10.6%.) All factors were not found to have statistically significant differences ($p > 0.05$). Demographic and clinical characteristics are summarized in Table 1 and medication usage and monitoring is found in Table 2.

In each treatment group, the mean of the first and highest CIWA-Ar scores did not differ significantly. For use of PB in the monotherapy and combination group the total number of doses given and the cumulative doses did not differ, even when normalized to weight-based dosing. For the groups given BZDs, significantly more administrations (2.6 vs. 1.6, $p < 0.05$), total cumulative doses (5.3 vs. 3.3 mg, $p < 0.05$), and average weight-based doses (0.04 vs. 0.07 mg/kg, $p < 0.05$) were used in the monotherapy group compared with the combination group.

The primary outcomes of admission to the hospital and return to the ED for any reason within 48 h of discharge did not differ significantly between treatment groups. The reasons for returning to the ED were mostly recurrent intoxication or withdrawal. Patients who were admitted and required lower levels of care (medical, surgical, etc.) also did not differ significantly between groups. However, patients requiring ICU level care were significant higher in the combination group (8.6%) compared to PB or BZD alone (2.9% and 3.8%, $p < 0.05$). There was a significantly longer ED LOS for the combination group (8.6 h) as compared to either the PB or BZD only groups (6.4 and 7.0 h, respectively, $p < 0.05$) but not between the monotherapy groups themselves.

Adverse events involving respiratory depression were minimal with 1 event in both monotherapy groups and 2 in the combination group which did not reach significance. Across all visitations, only 3 patients received endotracheal intubation while in the ED, all of which were in the BZD only group. Of those, only 1 was due to the severity of withdrawal. Hypotension was found to be significantly more common in the combination group over either monotherapy group (15.4% vs. 5.7% vs. 4.5%, $p < 0.05$). No patients had an episode of seizure while in the ED. These results are summarized in Table 3.

4. Discussion

In this non-matched, self-controlled, retrospective analysis of patients frequently seen in the ED for alcohol withdrawal, the use of PB,

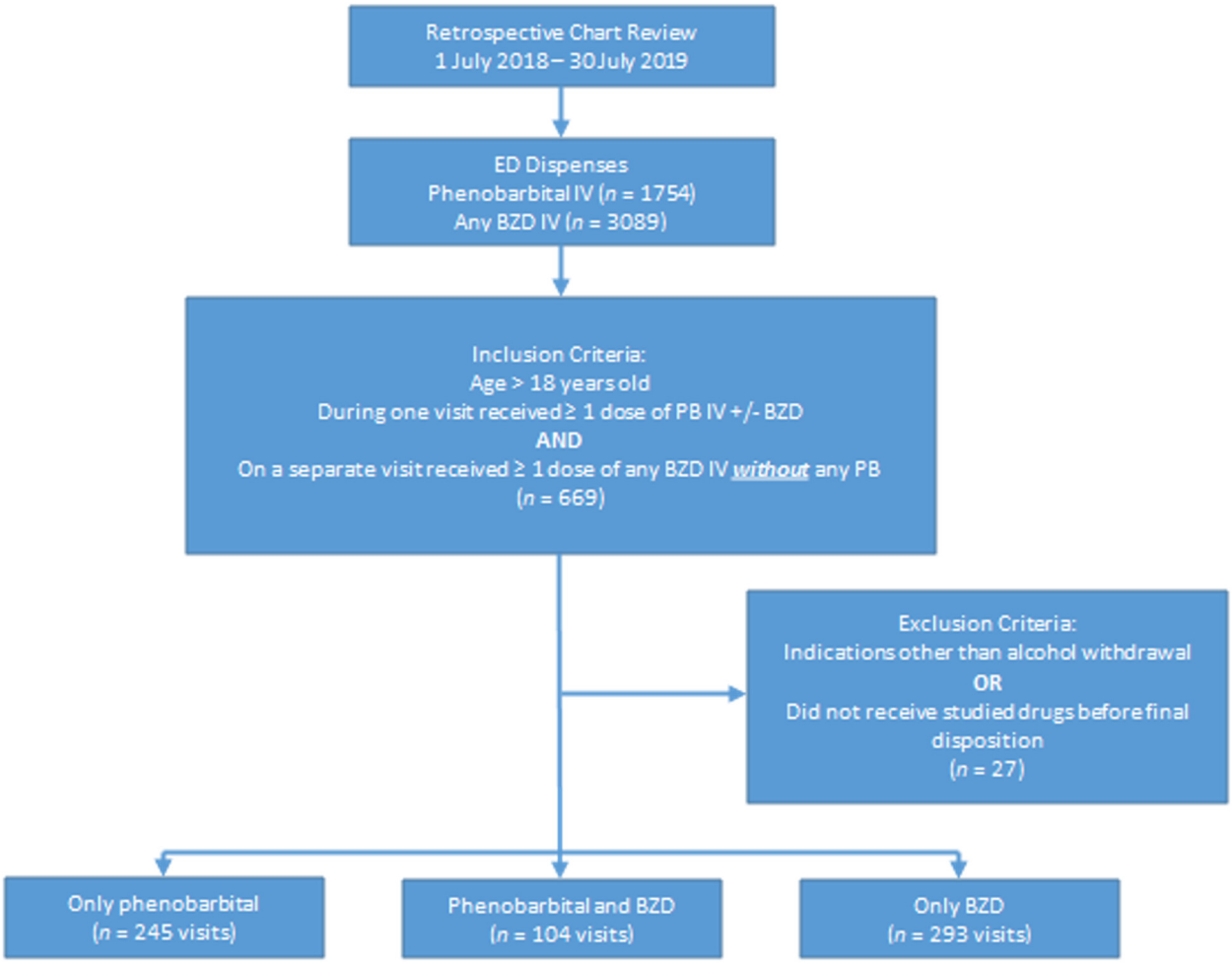

Fig. 1. Study flow diagram.

BZD, or the combination of both did not significantly affect rates of admission to the hospital or return to the ED within 48 h. However, secondary outcomes showed the combination of PB and BZD to be associated with increased ED LOS, higher rates of ICU care, and more episodes of hypotension.

It is unclear if the outcomes seen in the combination group were due to the severity of the patient presentation requiring more intensive management or by the synergistic nature of the medications. In the combination group, a typical timeline of events would be that one agent was used first, usually PB, for a given number of doses before changing to the other agent. This change may be due to perceived treatment failure by the treating physician as evidenced by the similar amount of drug used between the PB only and combination groups. Yet this is challenged by CIWA-Ar scoring, where both the first and

Table 1
Demographic and clinical characteristics

Characteristic	Phenobarbital ($n = 245$)	Phenobarbital & Benzodiazepine ($n = 104$)	Benzodiazepine ($n = 293$)	*P*
Unique patients[a]	120	62	137	
Age, mean ± S.D., yr	49.3 ± 10.7	48.8 ± 10.2	48.2 ± 10.8	*NS*
Sex, no. (%)				
Male	210 (85.7)	95 (91.3)	259 (88.4)	*NS*
Female	35 (14.3)	9 (8.7)	34 (11.6)	*NS*
Weight, mean ± S.D., kg	79.0 ± 16.0	81.3 ± 16.0	78.6 ± 14.6	*NS*
Height, mean ± S.D., cm	174 ± 9.7	175 ± 8.8	175 ± 9.8	*NS*
Creatinine concentration, mean ± S.D., mg/dL	0.75 ± 0.39	0.70 ± 0.33	0.75 ± 0.39	*NS*
Seizure history[b]	120 (49.0)	60 (57.7)	156 (53.6)	*NS*
Presented with seizure[c]	21 (8.6)	11 (10.6)	41 (14.1)	*NS*

[a] Each patient may have more than one encounter in a treat treatment group.
[b] Determined as having a documented seizure history in any encounter.
[c] Witnessed or unwitnessed seizure prior to or upon arrival to ED before administration of any study drug.

Table 2
Medication and monitoring details

Detail	Phenobarbital ($n = 245$)	Phenobarbital & Benzodiazepine ($n = 104$)	Benzodiazepine ($n = 293$)	*p*
CIWA-Ar Score, mean ± S.D.				
First score	12.9 ± 6.6	13.6 ± 6.7	13.0 ± 6.6	*NS*
Highest score	13.9 ± 6.6	14.9 ± 7.5	13.7 ± 7.0	*NS*
Total dose, mean ± S.D., mg				
Phenobarbital	424 ± 234	405 ± 233	–	*NS*
Benzodiazepine	–	3.3 ± 4.2	5.3 ± 3.8	<0.05
Total dose, mean ± S.D., mg/kg				
Phenobarbital	5.5 ± 3.2	5.3 ± 3.3	–	*NS*
Benzodiazepine	–	0.04 ± 0.04	0.07 ± 0.05	<0.05
Number of doses, mean ± S.D., no.				
Phenobarbital	2.3 ± 1.4	2.3 ± 1.4	–	*NS*
Benzodiazepine	–	1.6 ± 1.1	2.6 ± 1.4	<0.05

Table 3
Outcome data

Outcome	Phenobarbital ($n = 245$)	Phenobarbital & Benzodiazepine ($n = 104$)	Benzodiazepine ($n = 293$)	p
Inpatient admission	90 (36.7)	48 (46.1)	114 (38.9)	*NS*
Return ≤48-h	45 (17.1)	14 (13.5)	44 (15.0)	*NS*
ED LOS, min	383 ± 8.8	514 ± 10	419 ± 9.0	<0.05
Disposition				
Medical / Surgical	82 (34)	39 (38)	103 (35)	*NS*
ICU	7 (2.9)	9 (8.6)	11 (3.8)	<0.05
Bradypnea[a]	1 (0.4)	2 (1.9)	1 (0.3)	*NS*
Hypotension[b]	14 (5.7)	16 (15.4)	13 (4.5)	<0.05

[a] Respiratory rate < 10 breaths per min.
[b] Mean atrial pressure < 65 mmHg or SBP <90 / DBP <60 mmHg.

highest recorded value did not differ significantly between any groups indicating similar severity of withdrawal. Of note, all patients included in this study had additional encounters for alcohol withdrawal that did not meet the inclusion criteria, often receiving only oral agents for management. Of the patients admitted to the ICU, 3 were intubated, all within the BZD only group, with one having facial trauma, one for agitation, and one for airway protection due to severe withdrawal symptoms.

The synergistic effects of combining barbiturates and benzodiazepines cannot be discounted for the potential to cause adverse events [14–16]. In this study, hypotension occurred more often in the combination group and while bradypnea was uncommon and did not reach statistical significance, there was a trend toward more events. Other studies did not see these complications [17]. Without a protocolized approach to combining the agents, the decision on which drug to use, at what dose, and when becomes complex [15,16,18]. This may help explain the significantly longer ED LOS seen in the combination group.

There may be some practical advantages to using PB over BZDs in the ED [19]. The pharmacokinetics of PB are such that control of withdrawal symptoms may be sustained longer compared with BZDs potentially eliminating the need for outpatient taper regimens [13,14,16,19]. This may translate to reduced use of hospital resources and fewer prescriptions for controlled substances written after discharge.

This study had some limitations due to the single-center, retrospective design. The most important was that treating physicians had the flexibility to use any agent for the treatment of alcohol withdrawal, and while there were institutional recommendations for the use of PB and BZDs, there was variability in practice. This study attempted to account for confounders by using self-controlled model, however, there will always be variation in the degree of intoxication, the severity of withdrawal, and timing of withdrawal symptoms by the individual. Future studies addressing dosing strategies for phenobarbital use in a high recidivism population, such as loading doses versus titrated dosing, may be beneficial.

5. Conclusion

Among patients with multiple visits presenting with alcohol withdrawal, treatment with phenobarbital, benzodiazepines, or both did not result in significantly different rates of admission or readmission within 48 h. Receiving a combination of phenobarbital and benzodiazepines was associated with significantly longer emergency department length of stay, more ICU admissions, and increased incidence of hypotension as compared to either phenobarbital or a benzodiazepine alone.

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Authors and contributions

AS and CG conceived and designed the study. CG supervised the conduct of the data collection. AS collected and managed the data. CG analyzed the data. AS drafted the manuscript and takes responsibility for the paper as a whole.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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