Critical Review Form
Therapy

PGY-2

Nelson AC, Kehoe J, Sankoff J, Mintzer D, Taub J, Kaucher KA. Benzodiazepines vs barbiturates for alcohol withdrawal: Analysis of 3 different treatment protocols. Am J Emerg Med. 2019 Apr;37(4):733-736.

Objectives: "to describe the effectiveness of three alcohol withdrawal protocols during three time periods utilizing benzodiazepines and barbiturates for the acute treatment of alcohol withdrawal in the emergency department." (p. 734)

Methods: This single-center, retrospective, observational study enrolled patients seen at Denver Health Medical Center in Denver, Colorado between April 1st, 2016 to January 31st, 2018. Patients aged 18 years or older receiving at least one dose of treatment for alcohol withdrawal according to a documented Severity of Ethanol Withdrawal Scale (SEWS) score were eligible for inclusion. Pts who were pregnant were excluded, as were those without a documented SEWS score, those who were incarcerated, and those who did not receive treatment as part of the institutional SEWS protocol.

Patients received one of three different treatment protocols based on the availability of IV benzodiazepines and barbiturates at the time of treatment. These three treatment protocols were: 1) IV diazepam alone (April 2016 to January 2017), 2) IV lorazepam and IV phenobarbital (June 2017 to July 2017), and 3) IV phenobarbital alone (December 2017 to January 2018).

The primary outcome was the rate of ICU admission from the ED. Secondary outcome measures were rate of mechanical ventilation, rate of hospitalization, hospital length of stay, ICU length of stay, total of dose of benzodiazepines, total dose of phenobarbital, and number of protocol violations.

During the lorazepam and phenobarbital period, 320 patients were enrolled; 299 patients were enrolled during the phenobarbital only period; "over 500 patients" were enrolled during the diazepam period. A convenience sample of 100 patients was enrolled from each of these groups and included in the final analysis.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. "Dependent on availability of IV benzodiazepines and barbiturates over the time period analyzed, 3 separate protocols were developed to account for product availability." (p. 734). It is possible, though less likely, that

		this method of group allocation could lead to selection bias. While a convenience sample of 100 patients in each group was included in the study analysis, the authors do not state how these convenience samples were obtained.
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	N/A. Patients were not randomized and allocation was based purely on the date the patient arrived in the ED.
3.	Were patients analyzed in the groups to which they were randomized?	N/A. Again, patients were allocated based on date of ED arrival. The authors do not mention any patients enrolled during one period who received treatment based on the protocol from a different period.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes. Patients were similar with respect to gender, age, and median initial SEWS score. More patients in the lorazepam + phenobarbital group (n = 19) and phenobarbital alone group (n = 16) had an initial severity of withdrawal rated as severe compared to the diazepam group (n = 8). Fewer patients in the phenobarbital alone group (63%) had a primary diagnosis of alcohol withdrawal syndrome compared to the other two group (83% in each).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes (in theory), as there was no blinding. However, it is unlikely that this would have led to any degree of performance bias on the part of the patients.
2.	Were clinicians aware of group allocation?	Yes. Again, no blinding was performed. While it is possible that this could lead to performance bias on the part of the clinicians, this was a retrospective study and clinicians caring for the patient would not have been aware of the study or outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. There is no mention of blinding of outcome assessors. However, the outcomes were fairly objective and it is unlikely that observer bias would have influenced the results.
4.	Was follow-up complete?	Yes. Outcome data was available for all patients in the final analysis.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• There was no significant difference in the primary outcome of ICU admission: 22% in the diazepam group vs. 23% in the lorazepam/phenobarbital group vs. 24% in the phenobarbital group (p = 0.99).

		• Overall admission rates were significantly higher in the phenobarbital group (54%) compared to the diazepam group (35%), with a smaller difference when compared to the lorazepam/phenobarbital group (47%); p = 0.024. • Rate of intubation and mean days on the ventilator were similar between groups. • Average ED length of stay was somewhat higher in the lorazepam/phenobarbital group (10.28 hours) compared to the diazepam group (8.13 hours), and the phenobarbital group (9.47 hours); p = 0.01. There was no difference in floor or ICU length of stay between the groups. • Total diazepam equivalents were, of course, highest in the diazepam group and lowest in the phenobarbital alone group. • There were significantly more protocol violations in the phenobarbital group vs. the lorazepam+phenobarbital group (58% vs. 22%).
2.	How precise was the estimate of the treatment effect?	Uncertain. The authors provide no confidence intervals.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Likely yes. This study was conducted in a large, urban ED in the US with a likely group of patients similar to those seen in our institution for alcohol withdrawal.
2.	Were all clinically important outcomes considered?	No. The authors did not look at the incidence of other adverse events such as hypoxia, seizure, need for physical restraint, but they did seem to look at the most clinically relevant outcomes.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. It would appear that when compared with use of an IV benzodiazepine alone, use of IV phenobarbital increases the need for hospital admission. It is likely that this difference is due to increased physician concern with the use of this agent, leading to over-admission for observation and monitoring rather than any clinical difference in the effect of phenobarbital on withdrawal symptoms and need for airway monitoring. Phenobarbital does appear to be as safe as benzodiazepines, though this study was limited by its methodology.

Limitations:

1. **The retrospective nature of this study places it at high risk of selection bias.**
2. **The authors perform their analysis with a "convenience sample" of 100 patients in each group, but they do not state how these convenience samples were obtained.**

3. **The authors do not provide measures of effect size and do not report 95% confidence intervals or other meaningful measures of precision for their results.**

4. **There were significantly more protocol violations in the phenobarbital group vs. the lorazepam+phenobarbital group, likely due to unfamiliarity with phenobarbital.**

5. **Given the nature of the intervention, it is quite possible that familiarity with IV phenobarbital rather than actual clinical effect led to some of the differences in outcomes.**

Bottom Line:

This retrospective, observational study comparing three protocols for the management of alcohol withdrawal syndrome found no difference in the primary outcome of ICU admission between protocols involving IV benzodiazepines alone, a combination of IV benzodiazepines with IV phenobarbital, and IV phenobarbital alone. The significantly higher admission rates with IV phenobarbital may be related to comfort-level of physicians with this medication. The study was rather limited by its retrospective nature and poor reporting on the part of the authors.