Critical Review Form
Therapy

Rosenson J, Clements C, Simon B, Vieaux J, Graffman S, Vahidnia F, Cisse B, Lam J, Alter H. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. J Emerg Med. 2013 Mar;44(3):592-598.

Objectives: To test the hypothesis that "a single dose of intravenous (i.v.) phenobarbital combined with a standardized, symptom-guided lorazepam-based alcohol withdrawal protocol would result in a decreased intensive care unit (ICU) admission." (p. 593)

Methods: This prospective, randomized, double-blind, placebo-controlled study was conducted in the ED of the Alameda County Medical Center in Oakland, California from January 2009 to March 2010. Adult patients (aged 18 years or older) presenting to the ED with suspected acute alcohol withdrawal syndrome (AAWS) requiring placement on the institutional lorazepam-based alcohol withdrawal protocol for AAWS were eligible for enrollment if they were felt to require hospital admission. Exclusion criteria included pregnancy; allergy to phenobarbital, lorazepam, phenytoin, or carbamazepine; known severe hepatic impairment; inability to obtain IV access; or primary diagnosis other than alcohol withdrawal.

Patients were randomized to receive either a single dose of phenobarbital (10 mg/kg in 100 mL of normal saline) or 100 mL of normal saline (placebo). All study patients were treated according to the institutional lorazepam-based alcohol withdrawal protocol.

The primary outcome was the initial level of hospital admission from the ED, defined as ICU (nurse:patient ratio = 1:2), telemetry (nurse:patient ratio = 1:3), or floor (nurse:patient ratio = 1:4). Secondary outcomes were need for continuous lorazepam infusion, hospital length of stay, total amount of lorazepam used, and incidence of adverse events.

During the study period, 460 patients were seen in the ED for alcohol withdrawal; of these, 198 were enrolled, but only 102 met inclusion criteria and were hence included in the analysis (51 in the phenobarbital group, 51 in the placebo group). The median age in the two groups was 46 and 48 years, respectively, and 46% and 45% were male.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized, purportedly in a 1:1 fashion, to either an initial dose of phenobarbital (10 mg/kg) or saline. Randomization occurred using a random number-generator program (sequence generation).
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?	Likely yes. The authors specify that randomization occurred in the Pharmacy Department and presumably clinicians were not involved in the randomization process or the preparation of medications (phenobarbital vs. saline). It seems likely that subversion of the randomization process would not have been possible (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	Seemingly yes. The authors do not mention any crossover and it seems reasonable to conclude that an intention to treat analysis was performed. However, a large number of patients were enrolled and treated according to the study protocol, but later excluded either because their primary diagnosis was not AWS or because they were not admitted.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, initial alcohol withdrawal clinical assessment score, initial heart rate, presence of altered level of consciousness, presence of auditory or visual disturbances, and time to treatment. Patients in the placebo group had a somewhat higher incidence of sweats (63% vs. 49%) and anxiety (84% vs. 68%).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. While the authors do not specifically mention blinding of patients, they do note that, "All study investigators, enrolling providers, nursing staff, statisticians, and research assistants were blinded to group allocation for the duration of the study." (p. 593) Based on this information, it seems likely that patients were also not aware of group allocation.
2.	Were clinicians aware of group allocation?	No. As noted above, providers were blinded to group allocation. Phenobarbital and placebo boluses were

		provided, “as clear solutions in same-sized, identical-appearing covered plastic bags, prepared by the pharmacy and infused over 30 min.” (p. 593)
3.	Were outcome assessors aware of group allocation?	No. See above. Unblinding of group allocation did not occur until after completion of data analysis.
4.	Was follow-up complete?	Yes. It appears that follow-up data (which was limited to in-hospital outcomes) was available for all patients.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• Administration of a single dose of IV phenobarbital resulted in a significant reduction in ICU admission rates: absolute risk reduction (ARR) 17%, 95% CI 4% to 32%. o There was no statistically significant difference in rates of telemetry (ARR -6%, 95% CI -25% to 13%) or floor admission (ARR -12%, 95% CI -31% to 7%) and no difference in ICU of hospital length of stay. • There was no difference in maximum AWCA score between the groups (median score difference 2, 95% CI -0.2 to 3). • Phenobarbital resulted in a significant decrease in the need for a continuous lorazepam infusion (ARR 27%, 95% CI 14% to 41%) and a decrease in the total amount of lorazepam required. • There was no difference in adverse outcomes, need for intubation, seizure, need for mechanical restraints, or need for a bedside sitter.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Yes. This study was conducted at a large urban hospital in the US. It seems reasonable to assume that patients in the study would be similar to patients presenting to our ED with alcohol withdrawal syndrome. Perhaps the biggest difference is the use of a lorazepam-based alcohol withdrawal protocol utilized at the study center. We use no such protocol in our institution and management of alcohol withdrawal is likely to be highly variable. Use of phenobarbital at our institution, in the absence of such a protocol, may not have the same effect size as seen in the study.

2.	Were all clinically important outcomes considered?	Yes. The outcomes included level of care (ICU vs. telemetry vs. floor admission), total amount of benzodiazepine administered, length of stay, and relevant adverse outcomes including incidence of seizures. As the authors chose to only include patients who were felt to require admission to the hospital, they were not able to assess the impact of phenobarbital on rates of hospital discharge.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. This study suggests that among patients admitted to the hospital for alcohol withdrawal syndrome, use of phenobarbital in conjunction with benzodiazepines reduces ICU admission rates and benzodiazepine requirements with no increase in the incidence of adverse events. Phenobarbital is a relatively cheap medication and any cost difference would be more than offset by a reduction in ICU cost.

Limitations:

1. **No power analysis was conducted to ensure an adequate sample size to avoid a type II error.**

2. **More than half of randomized patients were not included in the analysis; this was mostly due to AWS not being a primary admission diagnosis, as well as lack of admission. These exclusions following randomization do not follow a true intention to treat analysis. An additional 48 eligible patients, admitted to the hospital with a primary diagnosis of AWS, were not enrolled.**

3. **This study was conducted in a single center using an institutional alcohol withdrawal protocol; these results will need to be validated in additional centers where such protocols may be different or may not exist at all (external validity).**

4. **The authors mention using an Alcohol Withdrawal Clinical Assessment (AWCA) score, but provide no information on this score nor references to supports its validity and reproducibility.**

Bottom Line:

This small, single-center, randomized controlled trial found that use of a single bolus of IV phenobarbital among patients admitted to the hospital with a primary diagnosis of alcohol withdrawal syndrome resulted in a decrease in the need for ICU admission (ARR 17%, 95% CI 4% to 32%). There was no observed effect on hospital of ICU length of stay or any adverse events. This single center study will need to be validated in additional centers whose alcohol withdrawal protocols may be different or nonexistent.