**Critical Review Form**
**Therapy**

PGY-4

Tidwell WP, Thomas TL, Pouliot JD, Canonico AE, Webber AJ. Treatment of Alcohol Withdrawal Syndrome: Phenobarphital vs CIWA-Ar Protocol. Am J Crit Care. 2018 Nov;27(6):454-460.

**Objectives:** **To establish and study the efficacy of a "simple and practical phenobarbital protocol" (p. 455) for the management of alcohol withdrawal syndrome (AWS).**

**Methods:** **This retrospective cohort study was conducted in the medical ICU (MICU) of a private teaching hospital in Nashville, Tennessee from January 1, 2016 to June 30, 2017. Patients admitted and treated for the onset or prevention of AWS were eligible for inclusion. Prior to 2017, the standard of care for treating AWS involved a Patients Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)-based protocol that utilized benzodiazepines, but in 2017, a phenobarbital protocol was developed as an alternative course. Patients were excluded if they received CIWA-Ar-based treatment for more than 24 hours before starting the phenobarbital protocol, received no dose of either protocol, were pregnant, left against medical advice within 24 hours of presentation, died within 24 hours of presentation, or were receiving phenobarbital as an outpatient.**

**Cases were screened and sorted into one of two groups (CIWA-Ar based treatment group vs phenobarbital group) with the goal of having equal numbers in each group. Patients in the phenobarbital group received a tapered regimen of phenobarbital with an initial dose based on risk factors. Subsequent dosages and the duration of the taper were at the discretion of the treating physician. Patients in the CIWA-Ar group were treated according to a protocol based on serial CIWA-Ar scores. The primary outcome measure was ICU length of stay. Secondary outcomes included hospital LOS, need for mechanical ventilation, and use of adjunctive sedating agents.**

**Out of 147 patients screened for eligibility, 120 met inclusion criteria. Sixty patients were included in the CIWA-Ar group and 60 in the phenobarbital group. The mean age in each group was 52 and 45 years, and 72% and 73% were male.**

| Guide | | Comments |
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| **I.** | **Are the results valid?** | |
| **A.** | **Did experimental and control groups begin the study with a similar prognosis?** | |
| 1. | Were patients randomized? | No. In essence, this was a before and after study, with allocation to the CIWA-Ar vs phenobarbital group dependent on timing of MICU admission. This method of group allocation is at risk selection bias as well as the risk of other co-interventions being implemented during |

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| | | the study. |
| 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? | Likely yes. Patients were similar with respect to gender, race, comorbid conditions, history of previous withdrawal symptoms, abnormal liver enzymes, and presence of active alcohol withdrawal on admission. Patients in the CIWA-Ar group were older, but this is unlikely to be clinically significant. No measure of alcohol withdrawal severity was provided for the two groups and history of prior seizures or seizures during admission was not mentioned. |
| **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? | • Patients in the phenobarbital group had a significantly shorter mean ICU length of stay: 4.4 days vs. 2.4 days, difference -2.0 (95% CI -3.0 to -0.9).<br>• Patients in the phenobarbital group also had a significantly shorter hospital length of stay: 6.9 days vs. 4.3 days, difference -2.6 (95% CI -4.5 to 0.7).<br>• Patients in the phenobarbital group were far less likely to require mechanical ventilation than those in |

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| | | the CIWA-Ar group, with a relative risk of 0.07, 95% CI 0.01 to 0.53.<br>• Patients in the CIWA-Ar group received significantly more benzodiazepines: mean 35.2 vs. 11.3 lorazepam equivalents.<br><br>95% CIs calculated using: https://www.medcalc.org/calc/comparison_of_means.php |
| 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? | No. This study only enrolled patients already admitted the MICU, rather than patients seen in the ED. There was also very little racial diversity in this study (95% of patients in both groups were white) and there was a fairly low incidence of polysubstance abuse. |
| 2. | Were all clinically important outcomes considered? | Yes. Given that the study was conducted in an ICU (and hence need for ICU admission could not be studied as an outcome), the authors did consider most relevant outcomes. They did not assess mortality (which would be expected to be low) or seizure frequency. |
| 3. | Are the likely treatment benefits worth the potential harm and costs? | Yes. It would appear, based on these data, that use of phenobarbital in the treatment of alcohol withdrawal in patients admitted to the ICU results in faster discharge from the ICU, faster discharge home, and decreased need for mechanical ventilation, with no apparent significant adverse outcomes. |

## Limitations:

1. **This was a non-randomized, retrospective study (essentially a before and after study), and is hence subject to multiple sources of bias including a high likelihood of cointerventions and the risk of selection bias.**

2. **Lack of blinding in this study raises the possibility of performance bias. Specifically, unfamiliarity of clinicians with use of phenobarbital may have unintentionally affected patient care, resulting in an underestimation of the effect on ICU length of stay.**

3. **Only patients admitted to the ICU were included. This was likely a cohort of patients with more severe, possibly benzodiazepine-refractory, alcohol withdrawal, and likely does not represent the full spectrum of the disease seen in our emergency department (external validity).**

4. **Patients in this study were almost entirely white and had a very low incidence of polysubstance abuse, also limited the external validity of the results when compared to our patient population.**

5. **Retrospective studies such as this should provide detailed information on how the chart review conducted (Gilbert 1996 and Worster 2004), including who abstracted data and how this was done. The authors do not provide any of these details.**

6. **The primary outcome, length of stay, was reported as a mean rather than a median, which would have been more appropriate for such non-parametric data.**

7. **While a A *post hoc* power analysis was performed, such an analysis should be performed *a priori* and provides no meaningful information when done after the study has been completed.**

**Bottom Line:**

**This small, retrospective, before and after study found that use of a phenobarbital protocol for management of alcohol withdrawal syndrome in a medical ICU, when compared with a CIWA-Ar-based benzodiazepine protocol, resulted in a significant decrease in length of ICU stay (difference -2 days; 95% CI -3.0 to -0.9 days), shorter overall hospital length of stay, and decreased need for mechanical ventilation. Only ICU patients were enrolled in this study, and further research in our clinical setting to understand the effects of phenobarbital more accurately.**