

Critical Review Form

Meta-analysis

[Mo Y, Thomas MC, Karras GE Jr. Barbiturates for the treatment of alcohol withdrawal syndrome: A systematic review of clinical trials. J Crit Care. 2016 Apr;32:101-7.](#)

Objectives: “to assess the efficacy and safety of barbiturates with or without BZDs [benzodiazepines] versus BZDs for the treatment of AWS [alcohol withdrawal syndrome] in the acute setting. Additionally, the secondary objective was to evaluate the clinical utility and potential of PB [phenobarbital] in terms of preventing or reducing ICU admission as well as mechanical ventilation in patients developing acute AWS.” (p. 102)

Methods: This systematic review sought to include studies involving inpatients with AWS in which any barbiturates, given as single agents or with other agents, were compared to benzodiazepines, also given alone or in combination with other agents. Randomized controlled trials and observational studies with comparison groups were eligible for inclusion. A literature search using MEDLINE, EMBASE, and the Cochrane Library was conducted in July 2015, and a manual review of relevant citations was performed. The primary outcomes assessed were total cumulative doses of barbiturates and benzodiazepines, duration of delirium, number of seizure episodes, and respiratory or cardiovascular complications. Secondary outcomes were ICU and hospital length of stay.

Eight articles were found meeting inclusion criteria; of these, one was excluded due to small size and an unbalanced sample size between groups, leaving 7 articles in the final review. Three of these studies were randomized controlled trials, one was blinded without description of randomization, and three were retrospective cohort studies. The [Mixed Methods Appraisal Tool \(MMAT\)](#) was used to evaluate the methodological quality of the included studies.

Guide	Question	Comments
I	<i>Are the results valid?</i>	
1.	Did the review explicitly address a sensible question?	Yes. The authors sought to evaluate the safety and efficacy of barbiturates for the management of alcohol withdrawal syndrome. Given the reported drawbacks of exclusively using benzodiazepines for these patients (Pandharipande 2006 , Hack 2006) and the frequency of drug shortages affecting availability, evaluation of alternative treatments seems worthwhile.
2.	Was the search for relevant studies detailed and exhaustive?	No. The authors searched MEDLINE, EMBASE, and the Cochrane Library, but did not search CINAHL, relevant conference abstracts, or the gray literature , increasing the risk of publication bias . Additionally, clinicaltrials.gov

		was not searched for relevant unpublished or ongoing clinical trials.
3.	Were the primary studies of high methodological quality?	No. Three of the studies scored 50% on the MMAT while 4 scores 75%. This suggest moderate overall quality of evidence.
4.	Were the assessments of the included studies reproducible?	Yes. The authors used the Mixed Methods Appraisal Tool (MMAT) to evaluate the methodological quality of the included studies. This is an easy to use tool that has demonstrated high interrater reliability .
II.	<i>What are the results?</i>	
1.	What are the overall results of the study?	<p><u>Randomized controlled trials</u></p> <ul style="list-style-type: none"> • Rosenson et al: double-blind, randomized, placebo-controlled trial in the ED, single dose of phenobarbital vs. placebo. <ul style="list-style-type: none"> ○ Decreased ICU admission rate in phenobarbital group (difference 27%, 95% CI 14% to 41%) • Kaim et al: randomized, partially double-blind trial comparing pentobarbital, chlordiazepoxide, perphenazine, and paraldehyde. <ul style="list-style-type: none"> ○ No difference in alcohol withdrawal symptoms (based on subjective clinical assessment). • Hendey et al: double-blind, randomized trial of ED patients with alcohol withdrawal, treated with IV phenobarbital or IV lorazepam. <ul style="list-style-type: none"> ○ No difference in withdrawal symptom control, ED length of stay, hospital admission rate, or 48-hour follow-up CIWA score (though this was only performed in 40% of patients). <p><u>Prospective, ?randomized study</u></p> <ul style="list-style-type: none"> • Kramp et al: double-blind comparison of PO barbital vs. IV diazepam among patients with DTs presenting to a psychiatric hospital. <ul style="list-style-type: none"> ○ Among patients with grade 1 or 2 DTs, “severity and duration of the acute state” were similar for both groups, but barbital was superior to diazepam in patients with grade 3 DTs. This was based on a purely subjective outcome measure. <p><u>Retrospective studies</u></p> <ul style="list-style-type: none"> • Michaelson et al: retrospective study at two hospitals, one of which treated DTs with phenobarbital while the other treated with phenobarbital until 2001 when

		<p>it began giving diazepam.</p> <ul style="list-style-type: none"> ○ No difference was observed between phenobarbital and diazepam with regards to duration of DT, length of stay, or respiratory or cardiovascular complications. ● DUBY et al: a retrospective before and after study in which protocolized care involving escalating doses of benzodiazepines followed by escalating doses of phenobarbital was compared to non-protocolized care in ICU patients with alcohol withdrawal syndrome. <ul style="list-style-type: none"> ○ Protocolized care was associated with reduced ICU length of stay (5.2 vs. 9.6 days), need for mechanical ventilation (5% vs. 22%), ventilator days (1.31 vs. 5.6 days), benzodiazepine use, and need for continuous sedation. ○ Of note, phenobarbital was given to very few patients in both groups.
2.	How precise are the results?	See above. While quantitative results were reported for certain outcomes, they were not provided for most of the studies.
3.	Were the results similar from study to study?	No. There was a great deal of clinical and methodological heterogeneity between studies, precluding the pooling of results. The outcomes differed from study to study, making a direct comparison of the results impossible. Overall, the studies all seem to suggest that phenobarbital is at least safe and as effective as alternative treatments (primarily benzodiazepines) with some suggestion that it is more effective at reducing ICU admission rates and length of stay.
III.	<i>Will the results help me in caring for my patients?</i>	
1.	How can I best interpret the results to apply them to the care of my patients?	This limited data seems to suggest that barbiturates are safe and effective at managing alcohol withdrawal syndrome in multiple settings. They appear to be at least as effective as benzodiazepines, may reduce ICU admission when used in the emergency department, and may reduce ICU length of stay and need for mechanical ventilation.
2.	Were all patient important outcomes considered?	No. This systematic review was limited to outcomes reported in the studies, and did not report seizure frequency, changes in severity of withdrawal symptoms, overall need for hospital admission, or need for telemetry monitoring.
3.	Are the benefits worth the	Uncertain. While this meta-analysis does suggest that

	costs and potential risks?	phenobarbital is a safe and effective alternative to benzodiazepines in the management of alcohol withdrawal syndrome, these results are based on low to moderate quality evidence with a great deal of clinical and methodological heterogeneity. In addition, this evidence does not definitively prove that phenobarbital is superior.
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Limitations:

1. The authors did not search CINAHL, relevant conference abstracts, or the [gray literature](#), increasing the risk of [publication bias](#). Additionally, [clinicaltrials.gov](#) was not searched for relevant unpublished or ongoing clinical trials.
2. Studies from non-English language journals were excluded.
3. The quality of the included evidence was moderate at best, with MMAT ratings of 50% (n=3) and 75% (n=4).
4. There was a great deal of [clinical and methodological heterogeneity](#) between studies, including study location (ED vs. ICU vs. admitted patients) and clinical outcome. Results could hence not be pooled.
 - a. Three of the included studies used purely subjective outcome criteria.

Bottom Line:

This systematic review of the literature identified multiple articles that appear to demonstrate the safety and efficacy of barbiturates for the management of alcohol withdrawal syndrome in multiple settings, including the ED.