Psychosomatics 2016:57:341–347

Review Article

The Role of Barbiturates for Alcohol Withdrawal Syndrome

Katherine Martin, M.D., Andrew Katz, M.A.

Background: *Benzodiazepine-resistant cases of alcohol withdrawal syndrome are common, and therefore alternate treatments are needed.* **Objective:** *Our aim was to conduct a systematic review of published reports on the use of barbiturates for alcohol withdrawal syndrome.* **Methods:** *We performed a systematic literature search of PUBMED for relevant citations that described the use of barbiturates either alone or in conjunction with other pharmacological agents to treat alcohol withdrawal syndrome.* **Results:** *A total of 15 citations were identified; 2 citations looked at barbiturates alone; 1 found barbiturates effective in an emergency department setting at treating seizures and preventing return visits. A second showed that barbiturates caused a relatively low rate of respiratory depression. Further, 5 citations compared barbiturates with benzodiazepines; 1 suggested that they were better at treating severe withdrawal, and another showed they were more effective at preventing seizures; 4 citations found they were as effective as benzodiazepines, but 1 found a higher rate of respiratory depression. Also, 3 citations compared a combination of barbiturates and benzodiazepines to benzodiazepines alone; 1 showed decreased ventilation, another showed fewer intensive care unit admissions, and a third showed better symptom control; 3 citations described detailed reports of barbiturate protocols. Lastly, 2 citations compared barbiturates with other agents and found them equivalent.* **Conclusion:** *Barbiturates provide effective treatment for alcohol withdrawal syndrome. In particular, they show promise for use in the emergency department and for severe withdrawal in the intensive care unit. Respiratory depression does not appear to be exceedingly common. Additional studies are needed to clarify the role of barbiturates in alcohol withdrawal syndrome.*

(Psychosomatics 2016; 57:341–347)

Key words: alcohol withdrawal, barbiturate, phenobarbital, delirium tremens, benzodiazepine-resistant.

BACKGROUND

Alcohol withdrawal syndrome (AWS) is a common reason patients are admitted to a general hospital and a frequent reason for psychiatric consultation. This diagnosis accounts for approximately 8% of all general admissions[1] and 21% of medical intensive care unit (ICU) admissions.[2] At present, symptom-triggered benzodiazepine treatment remains the most widely used strategy for treatment of alcohol withdrawal. However, benzodiazepine-resistant cases of AWS occur, and alternate strategies are needed.[3]

Barbiturates are one such alternate agent to treat AWS. Their mechanism of action is slightly different from benzodiazepines; benzodiazepines increase the

Received January 18, 2016; revised February 23, 2016; accepted February 24, 2016. From Assistant Clinical Professor of Psychiatry, University of South Florida College of Medicine, Tampa FL (KM); Department of Psychiatry, Lehigh Valley Health Network, Allentown, PA (KM); Department of Education, Lehigh Valley Health Network, Allentown, PA (AK). Send correspondence and reprint requests to Katherine Martin, M.D., Department of Psychiatry, Lehigh Valley Health Network, 1251 S Cedarcrest Blvd, Suite 202a, Allentown, PA 18103; e-mail: katherine_b.martin@lvhn.org

frequency of chloride channel opening caused by GABA-A receptor activation (requiring the presence of presynaptic GABA), whereas phenobarbital enhances GABA-A chloride currents by increasing the duration of chloride channel opening.[4]

Barbiturates offer several desirable characteristics. With an adequate loading schedule, therapeutic concentrations can be achieved quickly. Furthermore, phenobarbital, the most commonly studied barbiturate, is long acting, comes in multiple formulations (IV, IM, and PO), and is relatively inexpensive. Potential negative characteristics include the risk of respiratory depression as well as the induction of hepatic enzymes and the possibility for drug-drug interactions.[5]

Despite their use in AWS in Scandinavia for over 100 years,[6] there are relatively few studies looking at their effectiveness in AWS or comparing them with benzodiazepines for the treatment of AWS. We sought to review the literature to better characterize situations in which barbiturates might be useful for the treatment of AWS.

METHODS

We performed a PUBMED search of the literature using the terms "alcohol withdrawal" and "barbiturates," "phenobarbital," or "barbital." We identified 93 citations using these search terms. We supplemented the online searches with manual reviews of article reference lists as well as a review of neurology textbooks before 1980 when barbiturates were in more common use.[7,8] Both authors screened and selected relevant studies for inclusion. We found 15 citations that met criteria for inclusion. Given the small number of studies identified, we included a review of all studies found, regardless of type, that looked at barbiturates for the treatment of AWS, whether alone or in comparison to another pharmacological agent.

RESULTS

We identified 15 relevant articles related to barbiturates and alcohol withdrawal, which are listed in chronological order in the Table. There was 1 case study, 3 protocols, 3 retrospective chart reviews, 1 retrospective cohort study, 1 uncontrolled study, 1 controlled study, and 5 randomized controlled studies. The results are summarized below.

USE OF BARBITURATES ALONE FOR AWS

A total of 2 studies examined the use of barbiturates alone for AWS. An uncontrolled study by Young et al. analyzed 62 patients for alcohol withdrawal in an emergency department (ED) setting. They received 260 mg of phenobarbital IV followed by 130 mg every 30 minutes to the goal of light sedation. None of the 38 patients with withdrawal-related seizures had another seizure after phenobarbital therapy. Further, 92% of patients were discharged from the ED within 4 hours, and none returned to the ED after 1 week. A limitation to this study is that patients may have gone to an outside ED.[9]

Lutzen et al. conducted a retrospective chart review of inpatients in AWS treated with phenobarbital to assess for respiratory depression. There were no cases of respiratory depression in the pre-delirium tremens group, but there were 9 cases among 73 patients in the delirium tremens group. The authors concluded that the frequency of phenobarbital-induced respiratory depression was low, but that an ICU level of care should be available if necessary.[10]

COMPARISON OF BARBITURATES TO BENZODIAZEPINES FOR AWS

Several studies have compared barbiturates with benzodiazepines for AWS. Kaim et al. conducted a randomized, partially double-blind trial to evaluate the effectiveness of sodium pentobarbital ($n = 46$), chlordiazepoxide ($n = 46$), perphenazine ($n = 46$), and paraldehyde ($n = 55$) for the treatment of delirium tremens. Patients in the first 3 groups received IM injections followed by oral capsules, and the last group were given a liquid formulation. There were no differences in the duration or severity of AWS symptoms. However, a limitation of the study was that the researchers used subjective patient evaluations to measure outcomes.[11]

Kramp et al. compared barbital ($n = 47$) with diazepam ($n = 44$) in patients with varying degrees of alcohol withdrawal. The findings suggested a nonsignificant superior efficacy of diazepam for mild-to-moderate withdrawal. However, barbital was superior to diazepam for serious withdrawal. This study was