

Benzodiazepines in Alcohol Withdrawal Syndrome: Preventing “Kindling”
Author: William Fox, MD // Editor: Larissa Velez, MD (Program Director, EM / Toxicology,
UTSW / Parkland)

One of the major pillars of treatment for delirium tremens/alcohol withdrawal syndromes is the use of benzodiazepines to sedate the patient. Benzodiazepines are also used at the onset of withdrawal symptoms to ultimately prevent the development of severe withdrawal. **The prevention of withdrawal symptoms in the short-term also can improve future episodes, in what is called the “kindling hypothesis”.** The article I chose describes this hypothesis, how it relates to worsening DT/AWS, and how benzodiazepine use can modulate its’ activity and reduce the incidence of future seizure events by preventing the current event.

The authors start by describing the basic concept of electrical kindling, which is based on the observation that **repeated, subconvulsive electrical stimuli, when applied to an organism’s central nervous system, will result in gradually increasing EEG responses, eventually resulting in full convulsions.** The withdrawal of alcohol in a dependent person results in a hyperactive state due to the increase in **NMDA-modulated stimulant activity and a decrease in GABA-modulated inhibitory activity.** The authors note that this increased neurological stimuli is similar to the electrical stimuli, and a number of studies have shown **worsening withdrawal symptoms with successive alcohol dependence-withdrawal events.** This effect is called “kindling”, and is caused by long term changes in the NMDA and GABA receptor units. The lead author was previously involved in a study that used rats to show the effectiveness of Phenobarbital in reducing the severity of seizure activity in alcohol withdrawal and that the alcohol use/dependence alone was not responsible for worsening seizure activity. Considering the prior shown effectiveness of Phenobarbital, the authors asked if a benzodiazepine, specifically diazepam, would be effective in reducing alcohol withdrawal seizures in mice.

To answer this question, the authors designed an experiment where rats were to receive 2 days of alcohol intoxication (5 doses of alcohol/day, measured on a scale based on observations on tone, activity level, gait, and other physical characteristics) followed by 5 days of withdrawal in which they observed the subjects for intentional tremor, rigidity, and hyperreactivity/irritability. The diazepam-treated mice received the drug on the first day after cessation of alcohol, whereas the control mice received nothing. This intoxication-withdrawal cycle format occurred for 9 episodes. For an additional 4 cycles, the mice still received 2 days of intoxication, but then were observed for seizure activity, with neither group receiving any diazepam.

The authors noted a significant population loss in both the control and treatment groups, likely due to the high level of alcohol intoxication necessary to precipitate the withdrawal reactions. The most relevant results from this study in an Emergency Medicine context deal with the **significant decrease in seizure frequency during the later episodes in the treatment group** when compared to the control. The authors then go on to discuss this result in the context of a number of other studies showing similar results. One particular study mentioned in the discussion described a positive correlation between the future risk of having a withdrawal seizure and number of prior hospitalizations for alcohol-related seizure activity. Considering these findings, it is important to recognize the utility of benzodiazepines in preventing alcohol withdrawal seizures, not only in the present, but also in the future. This paper shows the applicability (and relative underappreciation) of basic science research in Emergency Medicine

practice. It lends strong support to the importance of a focused, clear history and physical when interviewing patients with suspected alcohol withdrawal symptoms. It also supports early use of benzodiazepines to prevent further, more severe, symptom development. Understanding a patient's prior history of alcohol withdrawal seizures or DT's can help shape clinical decision-making and what a practitioner can anticipate when planning next steps for the patient. As an EM practitioner, keeping disposition in mind is key to successful patient care and ED management.

Reference

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