



Indian Health Service
IHS National Pharmacy and Therapeutics Committee
Alternatives to Benzodiazepines in the Management
of Alcohol Withdrawal Syndromes
March 2012



Background:

Currently, a national shortage in the availability of parenteral lorazepam and diazepam exists in the US. Benzodiazepines have been first line therapy in the management of alcohol withdrawal syndromes (AWS), including delirium tremens (DT), since they were first discovered in the 1950s. This shortage has created the need for IHS clinicians to look more closely at adjunctive and alternative approaches to the inpatient management of AWS.

Discussion:

Alcoholism affects an estimated 8 million Americans, with approximately 500,000 episodes of patients requiring pharmacological management of alcohol withdrawal annually¹. The symptoms of alcohol withdrawal occur due to the central nervous system depressant effects of alcohol. It both enhances inhibitory tone by modulating gamma-aminobutyric acid (GABA) activity and inhibits excitatory tone by modulating excitatory amino acid activity (such as glutamate). The constant presence of alcohol maintains this balance. The sudden cessation of alcohol unmasks these adaptive responses leading to central nervous system overactivity.

Benzodiazepines have served as the “gold standard” in treatment of alcohol withdrawal syndromes. Mild withdrawal can be safely managed in an outpatient setting with oral benzodiazepines. Moderate or severe alcohol withdrawal is best managed in an inpatient setting. This often begins with oral benzodiazepines, but many times may require the use of parenteral agents. Prior to the discovery of benzodiazepines, alcohol withdrawal was managed with alcohol infusions, antipsychotics (such as chlorpromazine) or paraldehyde². These therapies are no longer considered safe for use in patients. In more recent times, other alternatives have been evaluated, including anticonvulsants, atypical antipsychotics, centrally acting alpha-2 agonists, beta-blockers, nitrous oxide, propofol and baclofen.

Literature review:*Pharmacotherapy*

A Cochrane review assessing the effectiveness and safety of pharmacologic interventions in treatment of alcohol withdrawal was published in March 2011. Five reviews, 114 studies, and 7333 participants were included in the review. The treatments reviewed included benzodiazepines, anticonvulsants, baclofen, gamma hydrobutyrate (GHB), and psychotropic analgesic nitrous oxide (PAN). Among these agents, benzodiazepines showed a protective benefit against seizures compared to placebo and potentially protective benefit compared to antipsychotics. However, no definite conclusions could be drawn about efficacy or safety due to the heterogeneous nature of the studies. There was not sufficient evidence in favor of the use of anticonvulsants, baclofen or GHB^{3,4}. A 2010 Cochrane review of 48 RCTs involving anticonvulsants in the management of AWS suggested that carbamazepine may be more effective than benzodiazepines in treating some aspects of alcohol withdrawal⁵.

In 2006, Addolorato, et.al. randomized 37 patients with AWS to either receive baclofen 10 mg three times a day for 10 days or diazepam 0.5-0.75 mg/kg/day for 6 days, then tapering the dose by 25% daily from day 7 to day 10. This was conducted in an outpatient setting with daily assessment. The CIWA-Ar was used to evaluate physical symptoms of withdrawal. Both treatment arms experienced significant decreases in CIWA-Ar scores without differences between the two arms⁶.

Lyon, et. al. studied baclofen in a randomized, double-blind, placebo-controlled trial involving 31 patients with AWS symptoms who completed 72 hours of assessment either as inpatients or with outpatient follow-up. The patients received symptom-triggered treatment (utilizing the CIWA-Ar score) with lorazepam and were randomized to receive either baclofen 10 mg or placebo three times a day, orally. The cumulative dose of lorazepam administered in this 72-hr period ranged from 1 to 1035 mg in the placebo group and 0 to 39 mg in

the baclofen group. Eight of the subjects required 20mg or more of lorazepam during the assessment. This included 1 of the 18 subjects in the baclofen arm and 7 of the 13 subjects in the placebo arm ($P=0.0004$). Only 4 subjects required more than 50 mg of lorazepam, all of which were from the placebo arm ($P=0.023$)⁷.

A NICE Clinical Guideline (2010) on diagnosis and clinical management of alcohol-related physical complications recommends offering either a benzodiazepine or carbamazepine following a symptom-triggered regimen for inpatient treatment of acute alcohol withdrawal. For patients with DT not controlled with oral lorazepam, they recommend parenteral lorazepam, haloperidol or olanzapine⁸.

Symptom-triggered therapy

In 1994, Saitz, et. al. performed a randomized, double-blind, controlled trial of 101 patients admitted for inpatient treatment of alcohol withdrawal. The patients were randomized to either receive chlordiazepoxide four times a day (fixed-schedule therapy) or treatment with chlordiazepoxide in response to CIWA-Ar scores. The median duration of treatment in the symptom-triggered group was 9 hours, compared with 68 hours in the fixed-schedule group ($P<0.001$) The symptom-triggered group received 100 mg of chlordiazepoxide compared to 425 mg in the fixed-schedule arm ($P<0.001$)⁹.

Jaeger, et. al. published a retrospective analysis of 216 admissions at Saint Mary's Hospital in Rochester, MN who experienced AWS during the admission. Patients were compared before and after the implementation of symptom-triggered therapy. No significant differences were seen in duration of treatment, benzodiazepine use, total dose of benzodiazepine, or total complication rate. However, there was a significantly lower rate of DT development post-implementation, particularly for those patients with no prior history of DT ($P=0.04$)¹⁰.

The *Archives of Internal Medicine* published a Swiss prospective, randomized, double-blind, controlled trial of 117 patients with alcohol dependence entering an alcohol treatment program. Fifty-six were treated with oxazepam in a symptom-triggered arm and 61 were treated with oxazepam every 6 hours in a fixed-schedule arm. Thirty-nine percent of the patients in the symptom-triggered group received oxazepam vs. 100% in the fixed-treatment arm ($P<0.001$). The mean oxazepam dose was 37.5 mg for the first group vs. 231.4 mg in the fixed-schedule group ($P<0.001$). The symptom-triggered group had a mean duration of treatment of 20.0 hours vs. 62.7 hours ($P<0.001$). There were no differences in measures of comfort between the two groups¹¹.

Clinical guidance:

In the face of shortages in the supply of parenteral benzodiazepines, there are several strategies that could be implemented to provide an alternative to or reduce the use of available parenteral benzodiazepines:

- 1) Utilize oral benzodiazepines for alcohol withdrawal syndrome whenever possible.
- 2) The use of a symptom-triggered rather than a fixed-schedule management plan has been shown to significantly reduce the cumulative dose of benzodiazepines utilized, reducing the duration of therapy, progression to delirium tremens, and with similar measures of patient comfort.
- 3) Several classes of medications could be considered to either augment therapy with parenteral benzodiazepines or as alternative to their use.
 - a. Anticonvulsants- Carbamazepine has been shown to be comparable to oxazepam and lorazepam for the suppression of moderate alcohol withdrawal. It may have advantages to benzodiazepines, as it appears to ameliorate comorbid psychological symptoms and does not interact with alcohol¹². Phenobarbital has been used in the management of AWS, but due to risk of sedation should only be administered in the inpatient setting. Sodium valproate and gabapentin may have a role, esp. as adjuncts, but data on their use is limited.
 - b. Baclofen- Growing evidence supports a role for baclofen in the acute management of AWS. It has been shown to decrease the amount of benzodiazepines utilized in inpatient and outpatient settings.
 - c. Antipsychotics- Some guidelines support the use of antipsychotics in the management of AWS. These should be used with caution. Phenothiazines and butyrophenones lower the seizure threshold. These agents also make it more difficult to shed excess body heat, complicating

management of DT. If utilized, an ECG to screen for prolonged QT and correction of electrolyte abnormalities should precede use.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

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