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## Q/ Which detoxification regimens are effective for alcohol withdrawal syndrome?

### EVIDENCE-BASED ANSWER

**A/** **BENZODIAZEPINES** remain the first-line regimen for alcohol withdrawal syndrome (AWS) and are the only class more effective than placebo for reducing seizure (strength of recommendation [SOR]: **B**, based on 3 medium-quality randomized controlled trials [RCTs]). Anticonvulsants are no more effective than placebo at reducing seizures (SOR: **B**,

based on 10 moderate-quality RCTs). Gabapentin reduces withdrawal symptoms and is less sedating than benzodiazepines (SOR: **B**, based on 1 medium-quality RCT). Carbamazepine also reduces withdrawal symptoms (SOR: **B**, based on 3 RCTs). Evidence of benzodiazepine superiority to other drugs with respect to safety is lacking (SOR: **A**, based on a meta-analysis).

### Evidence summary

#### Benzodiazepines work— but how do they compare?

A 2010 Cochrane meta-analysis of 64 RCTs and controlled clinical trials (CCTs; N = 4309) evaluated the use of benzodiazepines for treatment of AWS in adults.<sup>1</sup> This systematic review compared benzodiazepines

- vs placebo (10 studies)
- vs other drugs, including phenobarbital, carbamazepine, topiramate, lamotrigine, gabapentin, haloperidol, clonidine, hydroxyzine, propranolol, and baclofen (42 studies)
- to other benzodiazepines, including chlordiazepoxide, alprazolam, diazepam, and lorazepam (18 studies)
- in combination with other drugs vs other drugs alone (3 studies)
- administered on a fixed schedule vs symptom-triggered administration (3 studies).

Primary outcomes included efficacy (alcohol withdrawal seizures, alcohol withdrawal delirium, alcohol withdrawal symptoms, global improvement), safety (adverse events

and severe, life-threatening adverse events), and acceptability (dropouts and dropouts due to adverse events).

Benzodiazepines performed better than placebo for seizures in 3 studies (N = 324), with a relative risk (RR) of 0.16 (95% confidence interval [CI], 0.04-0.69). Studies assessing the described outcomes between benzodiazepines and other drugs were often of small sample size and heterogeneous in interventions and outcomes, limiting the ability to draw clear conclusions regarding benzodiazepine superiority. Comparisons of different benzodiazepines with each other and comparisons of benzodiazepines combined with other drugs vs other drugs alone did not reach statistical significance. Data on harms of benzodiazepines were lacking.

#### Anticonvulsants are not better than placebo for AWS

Another 2010 Cochrane meta-analysis of 56 RCTs and CCTs (N = 4076) evaluated the use of anticonvulsants for AWS.<sup>2</sup> This systematic review compared anticonvulsants

- vs placebo (17 studies)
- vs other drugs, such as bromocriptine,

piracetam, gamma-hydroxybutyric acid, trifluoperazine, clonidine, and various benzodiazepines (32 studies)

- to other anticonvulsants (10 studies)
- in combination with other drugs vs other drugs alone (6 studies)
- in combination with other drugs vs different anticonvulsants (1 study).

Primary outcomes included reductions in alcohol withdrawal seizures, adverse events, and acceptability of medication as indicated by participant dropouts.

Anticonvulsants were not superior to placebo for any outcome. Three studies (N = 260) favored carbamazepine over benzodiazepine (oxazepam or lorazepam) for 1 secondary outcome: a reduction of Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-Ar) score (maximum score of 7; mean difference [MD] = -1 [95% CI, -1.9 to -0.2]).

### **Gabapentin is effective; less sedating than chlordiazepoxide**

A 2013 RCT of US veterans with AWS (N = 26; 25 men; average age, 53.5 years) compared gabapentin and chlordiazepoxide.<sup>3</sup> Endpoints were ratings on the Epworth Sleepiness Scale (ESS; maximum score = 24), Penn Alcohol Craving Scale (PACS; maximum score, 30), and CIWA-Ar.

In the early treatment period (Days 1-4), ESS and PACS scores did not differ significantly between groups. At end of treatment (Days 5-7), ESS and PACS scores were lower in gabapentin-treated patients (ESS: MD = -3.7; 95% CI, -7.2 to -0.19; *P* = .04; PACS: MD = -6.05; 95% CI -12.82 to 0.72; *P* = .08). CIWA-Ar did not differ between treatment groups.

### **Recommendations from others**

In January 2020, the American Society of Ad-

diction Medicine (ASAM) published a clinical practice guideline for alcohol withdrawal management. Protocols for diagnosis, assessment, level of care determination, and management are delineated.<sup>4</sup>

Benzodiazepines are the first-line treatment for moderate-to-severe AWS, or when there is risk for severe AWS. In the ambulatory setting, when AWS is mild and there is no risk for worsening, AWS can be managed with supportive care or with either benzodiazepines, gabapentin, or carbamazepine as monotherapy. ASAM recommends long-acting benzodiazepines (eg, chlordiazepoxide or diazepam) over short-acting benzodiazepines (eg, alprazolam or lorazepam), except in the elderly and those with liver or lung disease.<sup>5</sup>

### **Editor's takeaway**

Dozens of small trials and meta-analyses confirm the benefits (sometimes marginal) of sedation to treat alcohol withdrawal. Given that the evidence fails to point to the superiority of 1 agent over another, it seems reasonable to make treatment decisions based on physician and perhaps patient preference. This review does not support a change in clinical practice. **JFP**

### **References**

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