What treatments are effective for acute alcohol withdrawal syndrome (AWS) not adequately controlled with benzodiazepines?

**Bottom line**

Phenobarbital, divalproex sodium, or dexmedetomidine decrease benzodiazepine requirements in patients with AWS. Phenobarbital decreases intensive care unit (ICU) admission when administered in the emergency department, and divalproex sodium decreases progression of withdrawal symptoms (SOR: B, for phenobarbital and C for others, single RCT for each adjunct).

**Evidence summary**

A 2013 RCT (N=102) compared initial level of hospital admission (ICU, telemetry, or floor status) in adults (89% male, mean age 47 years) with AWS who were randomized to receive 1 dose of intravenous phenobarbital (10 mg/kg) or placebo in the emergency department. All patients also received symptom-triggered lorazepam utilizing the Alcohol Withdrawal Clinical Assessment (AWCA) scale.

Phenobarbital reduced ICU admission (8% vs 25%; risk difference [RD] 17%; 95% CI, 4–32), need for continuous lorazepam infusion (4% vs 31%; RD 27%; 95% CI, 14–41), and total lorazepam administration (26 vs 49 mg; mean difference 23 mg; 95% CI, 7–40) compared with placebo. No differences were noted in other secondary outcomes (maximum AWCA, overall length of stay [LOS], or ICU LOS) or adverse outcomes (intubation, seizure, or mechanical restraints).

Limitations included the use of an unvalidated scoring system and a lack of formal criteria guiding ICU admission or continuous lorazepam infusion.

A 2001 RCT (N=36) evaluated withdrawal severity and oxazepam requirements in adults (97% male; mean age 48 years) admitted for AWS with revised Clinical Institute Withdrawal Assessment (CIWA) for Alcohol Scale (CIWA-Ar) scores of ≥10. Patients with significant comorbidities, illicit drug use, or use of anticonvulsants or benzodiazepines at enrollment were excluded. Patients received divalproex sodium (500 mg 3 times a day for 7 days) or placebo plus CIWA-Ar-triggered oxazepam. Scoring was continued until withdrawal resolution (36 consecutive hours with CIWA-Ar <10).

Divalproex decreased total oxazepam administration (85 vs 112 mg; P=.033) and decreased progression of AWS (defined as a 1-point increase in CIWA-Ar score above baseline) vs placebo (6% vs 40%; P<.05). Divalproex increased somnolence more than placebo (94% vs 61%; P<.05). No other differences in adverse effects were noted.

A 2014 RCT (N=24) evaluated dexmedetomidine as an adjunctive treatment to lorazepam for severe AWS in ICU patients (92% male, mean age 49 years) with CIWA scores of 15 or more (despite 16 mg lorazepam in 4 hours). Exclusion criteria included severe medical comorbidities, benzodiazepines not prescribed for AWS, or dexmedetomidine treatment at time of enrollment. Patients were randomized to dexmedetomidine infusion (0.4 or 1.2 µg/kg per hour; n=16) or placebo (n=8) until AWS resolution (5 days maximum).

Compared with placebo, dexmedetomidine decreased dose of lorazepam needed in the 24 hours after intervention compared with the 24 hours before intervention (–56 vs –8 mg; P=.037). The cumulative lorazepam dose postrandomization was lower with dexmedetomidine versus placebo, but the difference was not statistically significant (59 vs 109 mg; P=.23). No difference was noted in the proportion of patients with severe agitation, overall LOS, or ICU LOS. Bradycardia occurred more frequently in the dexmedetomidine group than in the placebo group (50% vs 0%; P=.02), with no other difference in adverse outcomes.

Limitations included lorazepam titration via the Riker sedation scale in intubated patients, concomitant use of potentially confounding medications (propofol, haloperidol, phenobarbital), and including patients intubated at randomization.

**REFERENCES**

