Anticonvulsants may reduce detoxification symptoms, support recovery

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Dr. Spiegel describes when adjunctive anticonvulsants might work best

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ALCOHOL WITHDRAWAL

When to choose an adjunctive anticonvulsant

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Benzodiazepines are the mainstay of alcohol detoxification treatment, with extensive evidence supporting their efficacy and relative safety.[1] The risk of benzodiazepine-alcohol interaction, however, and psychomotor and cognitive impairments associated with benzodiazepine use may limit early rehabilitation efforts in hospitalized patients.[2] Cross-tolerance with alcohol also limits benzodiazepines' potential benefit in outpatients with substance use disorders.

Adding anticonvulsants to acute benzodiazepine therapy has been shown to decrease alcohol withdrawal symptom severity, reduce seizure risk, and support recovery, particularly in patients with multiple alcohol withdrawal episodes. After detoxification, long-term anticonvulsant use may reduce relapse risk by decreasing post-cessation craving, without abuse liability.[3]

Although not all studies endorse adding anticonvulsants to benzodiazepines for managing alcohol withdrawal syndrome (AWS),[4] we present 3 cases in which anticonvulsants were used successfully as adjuncts to lorazepam. Valproic acid, levetiracetam, and gabapentin offer advantages in acute and long-term therapy of alcohol dependence with efficacy in AWS, low abuse potential, benign safety profile, and mood-stabilizing properties.

Neurobiologic rationale

AWS manifests as a cluster of clinical symptoms including delirium tremens (DTs) and seizures (***Table 1, page 28***). Its pathophysiology can be explained by alcohol's agonist effect on the gamma-aminobutyric acid

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Alcohol withdrawal

Table 1

Alcohol withdrawal: Acute vs long-term symptoms

	Alcohol withdrawal syndrome	Protracted withdrawal syndrome
Description	Cluster of symptoms in alcohol-dependent persons after heavy or prolonged alcohol use has lessened or ceased	Constellation of symptoms lasting weeks to months after alcohol use ends
Presentation	Develops during acute detoxification period and lasts 5 to 7 days	Develops after 5- to 7-day acute detoxification period and may persist for 1 year
Symptoms	Mild: insomnia, tremor, anxiety, GI upset, headache, diaphoresis, palpitations, anorexia Severe: alcoholic hallucinosis Seizures (generalized tonic-clonic) occur in up to 25% of withdrawal episodes, usually within 24 hours after alcohol cessation Delirium tremens (characterized by hallucinations, disorientation, tachycardia, hypertension, low-grade fever, agitation, and diaphoresis) occurs in up to 5% of patients undergoing withdrawal, may be delayed 4 to 5 days, and has mortality rates reaching 15%	Sleep disruption; anxiety; depressive symptoms; irritability; increased breathing rate, body temperature, blood pressure, and pulse

GI: gastrointestinal
Source: For a bibliography, see this article at CurrentPsychiatry.com

Clinical Point

Alcohol withdrawal decreases GABA activity and increases glutamate activity, resulting in hyperactivity, anxiety, and seizures

(GABA) system and antagonist effect on the glutamatergic system (***Table 2, page 35***).[5]

Chronic alcohol intake leads to neuroadaptation in the brain in the form of down-regulation of $GABA_A$ receptors and upregulation of *N*-methyl-D-aspartate receptors. During alcohol withdrawal, this neuroadaptation leads to a decrease in central GABA activity and an increase in glutamate activity, resulting in hyperexcitation, anxiety, and seizures.[6]

Little data exist regarding time to relapse after detoxification in alcohol-dependent patients. One theory—called "protracted withdrawal syndrome" (***Table 1***)—suggests that abstinent alcoholics return to drinking because of the same, but attenuated, neuroadaptations that trigger acute AWS.[7]

Advantages of adjunct therapy. Ntais et al[8] evaluated benzodiazepines' effectiveness and safety in treating AWS in a clinical review of 57 randomized, controlled trials totaling 4,051 patients. Benzodiazepines showed similar success rates as other drugs (relative risk [RR] 1.00) or anticonvulsants in particular (RR 0.88), as measured by changes in Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scores at the end of treatment. Benzodiazepines also offered significant benefit for seizure control compared with nonanticonvulsants (RR 0.23), but less when compared with anticonvulsants (RR 1.99).

Although the literature does not support anticonvulsant use for monotherapy in AWS, anticonvulsants show potential as adjunctive therapy. Valproic acid, levetiracetam, and gabapentin offer unique mechanisms of action (***Table 3, page 36***) and demonstrate advantages over benzodiazepine monotherapy for AWS. Adjunctive use of valproic acid,[8,9] levetiracetam,[10] and gabapentin[11,12] in detoxification also has demonstrated efficacy in reducing risk of relapse and delaying relapse.

The neurobiologic rationale for using anticonvulsants in acute AWS is speculative, but these agents appear to:

- inhibit "kindling" (neuronal changes that may be associated with repeated intoxications)
- facilitate GABAergic mechanisms.[9]

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Table 2

How alcohol affects GABA and glutamate neurotransmitters

GABA	Glutamate
GABA, the brain's primary inhibitory neurotransmitter, renders nerve cells less sensitive to further signaling	Glutamate, the brain's major excitatory neurotransmitter, renders nerve cells more sensitive to further signaling
Alcohol facilitates the inhibitory function of the $GABA_A$ receptor, allowing more GABA to traverse the receptor, and leading to alcohol's intoxicating effects	Alcohol seems to inhibit the excitatory function of the NMDA glutamate receptor, believed to play a role in memory, learning, and generation of seizures
During alcohol withdrawal, brain GABA concentrations fall below normal and $GABA_A$ receptor sensitivity may be reduced	Long-term alcohol exposure produces an adaptive increase in the function of NMDA receptors and results in development of glutamate-NMDA supersensitivity
In the absence of alcohol, the resulting decrease in inhibitory function may contribute to symptoms of CNS hyperactivity associated with acute and protracted alcohol withdrawal	Acute alcohol withdrawal activates glutamate systems, leading to autonomic nervous system hyperactivity; alcohol withdrawal seizures are associated with increased NMDA receptor function

GABA: gamma-aminobutyric acid; NMDA: *N*-methyl-D-aspartate
Source: For a bibliography, see this article at CurrentPsychiatry.com

CASE REPORT 1

Valproic acid for alcohol overdose

After attempting suicide with an alcohol overdose, Ms. J, age 45, is transferred from the emergency room (ER) to our psychiatry consult service 10 hours after admission. Her symptoms include nausea, tremor, headaches, agitation, disorientation, and auditory hallucinations.

Medical history reveals 25 years of alcohol dependence, multiple hospitalizations for withdrawal, and many failed attempts to quit. Ms. J reports consuming an average of 16 drink equivalents (eg, 12 oz beers) daily but denies illicit drug use.

Lab values on admission include blood alcohol concentration (BAC) 290 mg/dL (0.29%), mean corpuscular volume (MCV) 96 fL, gamma-glutamyltransferase (GGT) 164 U/L, aspartate aminotransferase (AST) 43 U/L, alanine aminotransferase (ALT) 31 U/L, and alkaline phosphatase (ALP) 151 U/L. Urine drug screen, acetaminophen, salicylate, vitamin B1 (thiamine), B12 (cyanocobalamin), B9 (folate), and electrolytes (including magnesium) are normal.

We assess alcohol withdrawal severity using the CIWA-Ar (see this article at Current Psychiatry.com). Ms. J's initial score is 17, indicating a risk of moderate alcohol withdrawal if untreated.

In the ER, Ms. J is placed on a symptom-triggered benzodiazepine detoxification protocol with lorazepam. We add IV valproic acid, 1,250 mg (based on 20 mg/kg body weight)[13] divided into 2 doses over the first 24 hours, then maintain IV valproic acid at 500 mg twice daily ***(Table 4, page 37)***. Within 12 hours of starting combination therapy, Ms. J scores 7 on the CIWA-Ar—indicating mild withdrawal—with subsequent scores <5. She scores 0 with no residual withdrawal symptoms within 36 hours.

Ms. J requires lorazepam, 7 mg, during the 10 hours before valproic acid is added. She requires only 2 mg lorazepam over the next 3 days and reports no side effects related to IV valproic acid. At discharge, Ms. J begins extended-release oral valproic acid, 1,250 mg (based on 25 mg/kg body weight)[13] once daily for 2 weeks, until she can obtain outpatient follow-up.

Less lorazepam needed

Adjunctive anticonvulsants can reduce the amount of lorazepam required during detoxification.[14,15] Compared with benzodiazepine monotherapy, the advantages of combination therapy—particularly in outpatient alcohol withdrawal treatment and relapse prevention—include:

- minimal interaction with alcohol (avoiding increased psychomotor deficits, cognitive impairment, and intoxication)[15]
- lower abuse potential
- possible efficacy in mood stabilization before, during, and after withdrawal (***Table 5, page 38***).[16]

continued

Clinical Point

Adjunctive valproic acid can reduce the amount of benzodiazepine needed during detoxification

Alcohol withdrawal

Table 3

Mechanisms of action of benzodiazepines vs 3 anticonvulsants

Agent	Mechanism of action
Benzodiazepines	Activate $GABA_A$ chloride ionophore, increasing affinity of $GABA_A$ receptor for GABA and augmenting frequency of chloride channel opening[a]
Valproic acid	GABA modulation and possibly second messenger systems; may inhibit Na^{1+} and/or Ca^{2+} channel, thereby boosting GABA and glutamate action[b]
Levetiracetam	Decreases high voltage activated Ca^{2+} channels; unique binding site (synaptic vesicle protein SV2A) is thought to be involved in calcium-dependent regulation of neurotransmitter vesicle exocytosis[c]
Gabapentin	GABA analog; unique binding site (Ca^{2+} channel subunit in brain) decreases calcium influx and inhibits release of excitatory amino acids and monoamines[d]

GABA: gamma-aminobutyric acid
Source: For references, see this article at CurrentPsychiatry.com

Clinical Point

Anticonvulsants may reduce the frequency and severity of alcohol relapse

Given the risk of seizures during AWS, anticonvulsants seem to make empirical sense. One study reported a 1% incidence of withdrawal-related seizures in 545 alcohol-dependent inpatients treated with valproic acid.[17] Another case series of 37 patients found no acute sequelae when valproic acid was used for AWS.[18]

Anticonvulsants such as valproic acid may reduce the frequency and severity of alcohol relapse, whereas benzodiazepines may increase relapse risk.[19] During a 6-week trial, patients receiving valproic acid maintenance therapy had greater abstinence rates and improved drinking outcomes compared with detoxification-only groups.[9]

One disadvantage of valproic acid is potential hepatotoxicity, an important consideration in patients with liver damage. Fortunately, Ms. J's AST and ALT values remained within normal limits during valproic acid treatment.

CASE REPORT 2

Levetiracetam for withdrawal seizures

Mr. H, age 42, presents to the ER after suffering a seizure. His medical history includes hypertension, alcohol dependence, and seizures during alcohol withdrawal. He denies a history of psychiatric illness, and his family history is unknown. He is noncompliant with hypertension treatment, which includes clonidine. Mr. H reports his usual alcohol consumption as a 6-pack of beer nightly during the week and a 12-pack nightly on weekends. He says his last drink was 4 days before admission.

Mr. H scores 19 on the CIWA-Ar, placing him at risk for moderate withdrawal. Head CT shows diffuse atrophy, without evidence of an acute intracranial process. BAC is zero on admission, and urine drug screen is negative. Amylase, lipase, and lactate dehydrogenase (LDH) levels suggest acute pancreatitis. AST is elevated to 131 U/L, ALT is elevated to 42 U/L, but MCV is within normal limits.

The psychiatric service is consulted on day 2 of admission, and we prescribe levetiracetam, 500 mg IV every 8 hours.[20] IV lorazepam also is available as needed: 1 mg every 8 hours for the first 2 days, then 1 mg every 12 hours for 2 days, then 1 mg every 24 hours. The patient's CIWA-Ar score is 9 on days 2 and 3 of admission, followed by scores consistently between 2 and 3 after scheduled levetiracetam administration. Mr. H requires 3 mg of lorazepam the remainder of his hospitalization. He is discharged on day 7 with a CIWA-Ar score of 2, and reports no adverse effects related to levetiracetam. He leaves the hospital with a 2-week prescription for oral levetiracetam, 500 mg tid.

Advantages of levetiracetam

Levetiracetam is FDA-approved for adjunctive treatment of adults with partial-onset seizures.[21] Successful AWS treatment with adjunctive levetiracetam has been supported by few but promising studies.[10,20] Potential advantages of levetiracetam in detoxification include:

- a lack of GABAergic properties, which limits the risk of intoxication or respiratory insufficiency when combined with alcohol[21]

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Table 4

Benzodiazepines and anticonvulsants for alcohol detoxification

	Benzodiazepines	Valproic acid	Levetiracetam	Gabapentin
Loading dose	None	20 mg/kg of body weight, divided into 2 doses for first 24 hours	1,500 mg IV once daily	400 mg PO qid
Maintenance dose	Day 1: 2 mg tid Day 2: 2 mg morning, 1 mg afternoon, 2 mg evening Day 3: 1 mg tid Day 4: 1 mg bid Day 5: 1 mg Day 6: none	500 mg IV bid	Either 500 mg IV tid or 1,000 mg PO bid after 2 to 3 days of treatment	1,200 mg PO tid
Side effects	Impaired consciousness, respiratory depression, hypotension	Dizziness, drowsiness, hair loss/thinning, nausea, tremor, weight gain	Somnolence, asthenia, dizziness, coordination difficulties	Somnolence, dizziness, ataxia, fatigue
Drug interactions	↑ BZ: cimetidine, oral contraceptives, ethanol (acute), disulfiram, isoniazid, propranolol ↓ BZ: rifampin, ethanol (chronic)	↑ VPA: aspirin, felbamate, fluoxetine, isoniazid ↓ VPA: carbamazepine, lamotrigine, phenobarbital, phenytoin, ritonavir	None	↓ GBP 20%: antacids

BZ: benzodiazepine; GBP: gabapentin; PO: *per os* (by mouth); VPA: valproic acid
Source: For a bibliography, see this article at CurrentPsychiatry.com

Clinical Point

Levetiracetam's advantages include a lack of GABAergic properties and low drug-drug interaction risk

- low drug-drug interaction risk because of nonhepatic metabolism and primary renal excretion.[22,23]

We selected levetiracetam for Mr. H because of his history of alcohol withdrawal seizures and acute pancreatitis. Anticonvulsants may be more effective than lorazepam in reducing the risk of alcohol withdrawal seizures,[24] and we felt valproic acid might not be safe for him because of its low but real risk of pancreatitis.[13] We based our levetiracetam dosing on a small open-label trial[20] and product information for treating adults with partial-onset seizures.[25]

Studies also demonstrate levetiracetam's potential for relapse prevention during outpatient therapy. In a 10-week trial, levetiracetam decreased the number of standard drinks in alcohol-dependent patients from 5.3 to 1.7 per day.[10] This was a small open trial, however, and large controlled trials support the usefulness of other, FDA-approved medications—including disulfiram, naltrexone, and acamprosate—for alcohol relapse prevention.

CASE REPORT 3

Gabapentin for acute withdrawal

Mr. B, age 38, presents to the ER after a 13-day alcohol binge. He has been drinking increasing amounts of alcohol over 6 weeks. Three months earlier, Mr. B was admitted for alcohol withdrawal treatment and received 49 mg of lorazepam over 3 days. This resulted in his transfer from the step-down unit to the intensive care unit for increased agitation, possibly caused by paradoxical disinhibition from excessive lorazepam use.[26]

Mr. B's medical history is significant for alcohol-induced seizures, DTs, traumatic brain injury related to craniotomy, and right arm amputation. Mr. B drinks approximately 24 beers per day. He denies tobacco use but admits to past use of cocaine, marijuana, and heroin.

On admission, Mr. B's BAC is 360 mg/dL (0.36%), AST is elevated at 72 U/L, ALT at 42 U/L, and LDH significantly elevated at 384 U/L. Urine drug screen is negative, and his CIWA-Ar score is 23. His score of −1 on the

Alcohol withdrawal

Clinical Point

By increasing the number of abstinent days, gabapentin may help patients maintain abstinence

Table 5

Pharmacologic profiles of benzodiazepines vs 3 anticonvulsants

	Benzodiazepines	Valproic acid	Levetiracetam	Gabapentin
Metabolism	CYP 2C19: diazepam CYP 3A3/4: alprazolam, clonazepam, diazepam, triazolam Phase II only: lorazepam, temazepam, oxazepam	>95% hepatic, of which <20% occurs via CYP isoenzymes	Not extensively metabolized; renal clearance; not involved with hepatic CYP isoenzymes	Not metabolized; secreted via kidneys as unchanged drug
Sedation	Mild to moderate	Mild to moderate	Mild to moderate	Moderate to severe
Synergistic effects with alcohol	Yes	No	No	No
Paradoxical disinhibition	Yes	No	No	No
Risk of addiction in outpatient therapy	Yes	No	No	No

CYP: cytochrome P450
Source: For a bibliography, see this article at CurrentPsychiatry.com

Richmond Agitation and Sedation Scale (RASS)[27] correlates with very mild sedation.

Guided by Bonnet et al[28] and clinical experience, we start Mr. B on gabapentin, 1,200 mg tid, and IV lorazepam, 2 mg every 8 hours as needed for breakthrough withdrawal. We decrease lorazepam by 50% every other day until Mr. B is discharged. On days 2, 3, and 4, Mr. B's CIWA-Ar scores are 6, 9, and 2, respectively. His RASS score drops from –1 on days 1 and 2 to 0 until discharge, indicating an alert and calm state.

Mr. B requires a total of 2 mg of lorazepam throughout hospitalization. He finishes alcohol detoxification on day 4 and is discharged with a prescription for gabapentin, 1,200 mg tid. Two weeks later, when he is admitted to a 28-day inpatient alcohol rehabilitation unit, Mr. B has not relapsed.

More abstinent days

Gabapentin is FDA-approved as adjunctive therapy for partial seizures. Off-label, it has been generally efficacious as an adjunct in alcohol detoxification.[29-32] We chose adjunctive anticonvulsant therapy for Mr. B because of his history of alcohol-induced seizures. We chose gabapentin instead of valproic acid because of Mr. B's liver damage and gabapentin's lack of hepatic metabolism.

Gabapentin may reduce alcohol consumption and craving in alcohol-dependent patients. By increasing the number of abstinent days, gabapentin may help patients maintain abstinence.[33] Gabapentin does not appear to interact clinically with alcohol, causing neither sedation nor synergistic effects.[34] Its relative lack of abuse potential may be valuable in outpatient alcohol withdrawal treatment and in maintaining alcohol abstinence after detoxification.

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Related Resource

- Asplund CA, Aaronson JW, Aaronson HE. 3 regimens for alcohol withdrawal and detoxification. J Fam Pract. 2004;53(7):545-554. www.jfponline.com/Pages.asp?AID=1730.

Drug Brand Names

Acamprosate • Campral
Alprazolam • Xanax
Carbamazepine • Carbatrol
Cimetidine • Tagamet
Clonazepam • Klonopin
Clonidine • Catapres
Diazepam • Valium
Disulfiram • Antabuse
Felbamate • Felbatol
Fluoxetine • Prozac
Gabapentin • Neurontin
Isoniazid • Nydrazid
Lamotrigine • Lamictal
Levetiracetam • Keppra
Lorazepam • Ativan
Naltrexone • ReVia, Vivitrol
Oxazepam • Serax
Phenobarbital • Luminal
Phenytoin • Dilantin
Propranolol • Inderal
Rifampin • Rifadin
Ritonavir • Norvir
Temazepam • Restoril
Triazolam • Halcion
Valproic acid • Depakote, Depakene

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Bottom Line

Adjunctive anticonvulsants in treating alcohol withdrawal syndrome can reduce the amount of benzodiazepine required during detoxification. Potential advantages include anticonvulsants' minimal interaction with alcohol, lower abuse potential, efficacy in improving psychiatric symptoms before, during, and after withdrawal, and reduced risk of relapse while awaiting substance abuse rehabilitation.

Clinical Point

Gabapentin does not appear to interact clinically with alcohol