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Alcohol withdrawal syndrome in medical patients

ABSTRACT

The authors provide a critical review focusing on pharmacotherapy of alcohol withdrawal syndrome in hospitalized patients who are not critically ill. They outline recommendations for patient assessment and monitoring.

KEY POINTS

Patients diagnosed with or suspected of having alcohol withdrawal syndrome need a thorough history and physical examination, appropriate laboratory tests, and monitoring using the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) or a similar scale.

For most patients, benzodiazepines should be given in a symptom-triggered fashion, using the CIWA-Ar score as a monitoring tool. Alternatively, scheduled benzodiazepine dosing should be considered for patients with a history of alcohol withdrawal delirium or for patients in whom withdrawal symptoms cannot be easily assessed.

The choice of benzodiazepine should be individualized, based on the half-life of the drug, comorbid diseases, and monitoring plans.

Many patients with alcohol withdrawal syndrome require fluid and electrolyte replacement, as well as adjunctive therapies such as haloperidol for delirium and antihypertensives for cardiac or adrenergic symptoms. No standard currently exists for drug dosing, administration, and assessment protocols in these patients. Therefore, clinicians are adapting study designs and assessment scales to meet patients' individual needs.

D EPRIVED OF ALCOHOL while in the hospital, up to 80% of patients who are alcohol-dependent risk developing alcohol withdrawal syndrome,[1] a potentially life-threatening condition. Clinicians should anticipate the syndrome and be ready to treat and prevent its complications.

Because alcoholism is common, nearly every provider will encounter its complications and withdrawal symptoms. Each year, an estimated 1.2 million hospital admissions are related to alcohol abuse, and about 500,000 episodes of withdrawal symptoms are severe enough to require clinical attention.[1–3] Nearly 50% of patients with alcohol withdrawal syndrome are middle-class, highly functional individuals, making withdrawal difficult to recognize.[1]

While acute trauma patients or those with alcohol withdrawal delirium are often admitted directly to an intensive care unit (ICU), many others are at risk for or develop alcohol withdrawal syndrome and are managed initially or wholly on the acute medical unit. While specific statistics have not been published on non-ICU patients with alcohol withdrawal syndrome, they are an important group of patients who need to be well managed to prevent the progression of alcohol withdrawal syndrome to alcohol withdrawal delirium, alcohol withdrawal-induced seizure, and other complications.

This article reviews how to identify and manage alcohol withdrawal symptoms in noncritical, acutely ill medical patients, with practical recommendations for diagnosis and management.

■ CAN LEAD TO DELIRIUM TREMENS

In people who are physiologically dependent on alcohol, symptoms of withdrawal usu-

TABLE 1

Symptoms of alcohol withdrawal syndrome

Time of appearance after cessation	Symptoms
6–12 hours	Minor withdrawal symptoms: insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia
12–24 hours [a]	Alcoholic hallucinosis: visual, auditory, or tactile hallucinations
24–48 hours [b]	Withdrawal seizures: generalized tonic-clonic seizures
48–72 hours [c]	Alcohol withdrawal delirium (delirium tremens): hallucinations (mainly visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis

[a] Symptoms generally resolve within 48 hours.
[b] Symptoms reported as early as 2 hours after cessation.
[c] Symptoms as late as 5 days.

From Bayard M, McIntyre J, Hill KR, Woodside J, Jr. Alcohol withdrawal syndrome. Am Fam Physician 2004; 69:1443–1450. Reproduced with permission from the American Academy of Family Physicians.

The mortality rate in delirium tremens is 5%–10%

ally occur after abrupt cessation.[4] If not addressed early in the hospitalization, alcohol withdrawal syndrome can progress to alcohol withdrawal delirium (also known as delirium tremens or DTs), in which the mortality rate is 5% to 10%.[5,6] Potential mechanisms of DTs include increased dopamine release and dopamine receptor activity, hypersensitivity to N-methyl-D-aspartate, and reduced levels of gamma-aminobutyric acid (GABA).[7]

Long-term changes are thought to occur in neurons after repeated detoxification from alcohol, a phenomenon called "kindling." After each detoxification, alcohol craving and obsessive thoughts increase,[8] and subsequent episodes of alcohol withdrawal tend to be progressively worse.

Withdrawal symptoms

Alcohol withdrawal syndrome encompasses a spectrum of symptoms and conditions, from minor (eg, insomnia, tremulousness) to severe (seizures, DTs).[2] The symptoms typically depend on the amount of alcohol consumed, the time since the last drink, and the number of previous detoxifications.[9]

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*,[1] states that to establish a diagnosis of alcohol withdrawal syndrome, a patient must meet four criteria:

- The patient must have ceased or reduced alcohol intake after heavy or prolonged use.
- Two or more of the following must develop within a few hours to a few days: autonomic hyperactivity (sweating or pulse greater than 100 beats per minute); increased hand tremor; insomnia; nausea or vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety; grand mal seizure.
- The above symptoms must cause significant distress or functional impairment.
- The symptoms must not be related to another medical condition.

Some of the symptoms described in the second criterion above can occur while the patient still has a measurable blood alcohol level, usually within 6 hours of cessation of drinking.[10] **Table 1** describes the timetable of onset of symptoms and their severity.[2]

The elderly may be affected more severely

While the progression of the symptoms described above is commonly used for medical inpatients, the timeline may be different in an elderly patient. Compared with younger patients, elderly patients may have higher blood alcohol concentrations owing to lower total body water, so small amounts of alcohol can produce significant effects.[11,12] Brower et al[12] found that elderly patients experienced more withdrawal symptoms, especially cognitive impairment, weakness, and high blood pressure, and for 3 days longer.

In the elderly, alcohol may have a greater impact on the central nervous system because of increased permeability of the blood-brain barrier. And importantly, elderly patients tend to have more concomitant diseases and take more medications, all of which can affect alcohol metabolism.

■ ASSESSMENT SCALES FOR ALCOHOL WITHDRAWAL SYNDROME

A number of clinical scales for evaluating alcohol withdrawal have been developed. Early ones such as the 30-item Total Severity Assess-

ment (TSA) scale and the 11-item Selected Severity Assessment (SSA) scale were limited because they were extremely detailed, burdensome to nursing staff to administer, and contained items such as daily "sleep disturbances" that were not acute enough to meet specific monitoring needs or to guide drug therapy.[13,14]

The **Clinical Institute Withdrawal Assessment for alcohol** (CIWA-A) scale, with 15 items, was derived from the SSA scale and includes acute items for assessment as often as every half-hour.[15]

The **CIWA-Ar scale (Table 2)** was developed from the CIWA-A scale by Sullivan et al.[15] Using both observation and interview, it focuses on 10 areas: nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, headache, disorientation, tactile disturbances, auditory disturbances, and visual disturbances. Scores can range from 0 to 67; a higher score indicates worse withdrawal symptoms and outcomes and therefore necessitates escalation of treatment.

The CIWA-Ar scale is now the one most commonly used in clinical trials[16–20] and, we believe, in practice. Other scales, including the CIWA-AD and the Alcohol Withdrawal Scale have been validated but are not widely used in practice.[14,21]

BASELINE ASSESSMENT AND EARLY SUPPORTIVE CARE

A thorough history and physical examination should be performed on admission in patients known to be or suspected of being alcohol-dependent to assess the patient's affected body systems. The time elapsed since the patient's last alcohol drink helps predict the onset of withdrawal complications.

Baseline laboratory tests for most patients with suspected alcohol withdrawal syndrome should include a basic blood chemistry panel, complete blood cell count, and possibly an alcohol and toxicology screen, depending on the patient's history and presentation.

Hydration and nutritional support are important in patients presenting with alcohol withdrawal syndrome. Severe disturbances in electrolytes can lead to serious complications, including cardiac arrhythmia. Close monitoring and electrolyte replacement as needed are recommended for hospitalized alcoholic patients and should follow hospital protocols.[22]

Thiamine and folic acid status deserve special attention, since long-standing malnutrition is common in alcoholic patients. Thiamine deficiency can result in Wernicke encephalopathy and Korsakoff syndrome, characterized by delirium, ataxia, vision changes, and amnesia. Alcohol withdrawal guidelines recommend giving thiamine intravenously for the first 2 to 5 days after admission.[23] In addition, thiamine must be given before any intravenous glucose product, as thiamine is a cofactor in carbohydrate metabolism.[23] Folic acid should also be supplemented, as chronic deficiencies may lead to megaloblastic or macrocytic anemia.

CIWA-Ar scale. To provide consistent monitoring and ongoing treatment, clinicians and institutions are encouraged to use a simple assessment scale that detects and quantifies alcohol withdrawal syndrome and that can be used for reassessment after an intervention.[21] The CIWA-Ar scale should be used to facilitate "symptom-triggered therapy" in which, depending on the score, the patient receives pharmacologic treatment followed by a scheduled reevaluation.[23,24] Most patients with a CIWA-Ar score of 8 or higher benefit from benzodiazepine therapy.[16,18,19]

PRIMARY DRUG THERAPIES FOR MEDICAL INPATIENTS

Benzodiazepines are the first-line agents

Benzodiazepines are the first-line agents recommended for preventing and treating alcohol withdrawal syndrome.[23] Their various pharmacokinetic profiles, wide therapeutic indices, and safety compared with older sedative hypnotics make them the preferred class.[23,25] No single benzodiazepine is preferred over the others for treating alcohol withdrawal syndrome: studies have shown benefits using short-acting, intermediate-acting, and long-acting agents. The choice of drug is variable and patient-specific.[16,18,26]

Benzodiazepines promote and enhance binding of the inhibitory neurotransmitter GABA to $GABA_A$ receptors in the central nervous system.[27] As a class, benzodiazepines are all structurally related and produce the

Symptoms of alcohol withdrawal can arise as early as 6 hours after the last drink

TABLE 2

The CIWA-Ar scale for assessing alcohol withdrawal syndrome

Symptom	Observation	Points
Nausea and vomiting [a] (Ask "Do you feel sick to your stomach? Have you vomited?")	No nausea and vomiting	0
	Intermittent nausea with dry heaves	4
	Constant nausea, frequent dry heaves, vomiting	7
Tremor [a] (Observe with arms extended and apart.)	No tremor	0
	No tremor visible, but can be felt, fingertip to fingertip	1
	Moderate tremor with arms extended	4
	Severe tremor, even with arms not extended	7
Paroxysmal sweats [a]	No sweat visible	0
	Beads of sweat obvious on forehead	4
	Drenching sweats	7
Anxiety [a] ("Do you feel nervous?")	No anxiety (at ease)	0
	Mildly anxious	1
	Moderately anxious or guarded, so anxiety is inferred	4
	Equivalent to acute panic states that occur in severe delirium or acute schizophrenic reactions	7
Agitation [a]	Normal activity	0
	Somewhat more than normal activity	1
	Moderately fidgety and restless	4
	Paces back and forth during most of interview or constantly thrashes about	7
Tactile disturbances ("Do you have any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?")	None	0
	Very mild itching, pins-and-needles sensation, burning, or numbness	1
	Mild itching, pins-and-needles sensation, burning, or numbness	2
	Moderate itching, pins-and-needles sensation, burning, or numbness	3
	Moderately severe hallucinations	4
	Severe hallucinations	5
	Extremely severe hallucinations	6
	Continuous hallucinations	7

[a] If symptoms lie between the point categories listed, it is acceptable to rate as a whole number in between.
CIWA-Ar = revised Clinical Institute Withdrawal Assessment for Alcohol[15]

The CIWA-Ar is now the most commonly used scale to assess for alcohol withdrawal syndrome

Symptom	Observation	Points
Auditory disturbances ("Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?")	Not present	0
	Very mild harshness or ability to frighten	1
	Mild harshness or ability to frighten	2
	Moderate harshness or ability to frighten	3
	Moderately severe hallucinations	4
	Severe hallucinations	5
	Extremely severe hallucinations	6
	Continuous hallucinations	7
Visual disturbances ("Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?")	Not present	0
	Very mild sensitivity	1
	Mild sensitivity	2
	Moderate sensitivity	3
	Moderately severe hallucinations	4
	Severe hallucinations	5
	Extremely severe hallucinations	6
	Continuous hallucinations	7
Headache, fullness in head ("Does your head feel different? Do you feel like there is a band around your head?") *Do not rate for dizziness or lightheadedness. Otherwise, rate severity.*	Not present	0
	Very mild	1
	Mild	2
	Moderate	3
	Moderately severe	4
	Severe	5
	Very severe	6
	Extremely severe	7
Orientation and clouding of sensorium ("What day is this? Where are you? Who am I?")	Oriented and can do serial additions	0
	Cannot do serial additions or is uncertain about date	1
	Date disorientation by no more than 2 calendar days	2
	Date disorientation by more than 2 calendar days	3
	Disoriented to place or person, or both	4
Total CIWA-Ar score	Maximum possible: 67	

Based on Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for alcohol scale (CIWA-Ar). Br J Addict 1989; 84:1353–1357.

Most patients with a CIWA-Ar score ≥ 8 benefit from benzodiazepine therapy

TABLE 3
Pharmacokinetic characteristics of benzodiazepines

	Chlordiazepoxide	Diazepam	Lorazepam	Oxazepam
Dosage forms	Oral	Oral, gel, intramuscular, intravenous	Oral, intramuscular, intravenous	Oral
Equivalent dosages	25 mg	5 mg	1 mg	15 mg
Half-life	5–15 hours with active metabolites > 100 hours	30–60 hours with active metabolites >100 hours	10–20 hours	5–20 hours
Active metabolites	Desmethylchlordiazepoxide, desmoxepam, desmethyldiazepam	Desmethyldiazepam	None	None
Lipid solubility	Less lipophilic than diazepam; slower onset of action	Highly lipophilic; quick onset of action	Less lipophilic than diazepam; slower onset of action	Less lipophilic than diazepam; slower onset of action
Effect of hepatic disease	Half-life increases in patients with cirrhosis	Half-life increases in patients with cirrhosis, acute viral hepatitis, chronic active hepatitis	Half-life increases in patients with cirrhosis	Half-life increases in patients with cirrhosis
Effect of renal disease	No effect	Decreases protein binding	Half-life increases; impaired elimination	No effect
Effect of older age	Slower absorption; half-life increases	Half-life increases; decreased protein binding	No effect on half-life; decreased protein binding	No effect on half-life; decreased protein binding

same effects—namely, sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity.[27]

The most studied benzodiazepines for treating and preventing alcohol withdrawal syndrome are chlordiazepoxide, oxazepam, and lorazepam,[16–20] whereas diazepam was used in older studies.[23]

Diazepam and chlordiazepoxide are metabolized by oxidation, each sharing the long-acting active metabolite desmethyldiazepam (half-life 72 hours), and short-acting metabolite oxazepam (half-life 8 hours).[27] In addition, the parent drugs also have varying pharmacokinetic profiles: diazepam has a half-life of more than 30 hours and chlordiazepoxide a half-life of about 8 hours. Chlordiazepoxide and diazepam's combination of both long- and short-acting benzodiazepine activity provides long-term efficacy in attenuating withdrawal symptoms, but chlordiazepoxide's shorter parent half-life allows more frequent dosing.

Lorazepam (half-life 10–20 hours) and oxazepam (half-life 5–20 hours) undergo glucuronide conjugation and do not have metabolites.[27,28] **Table 3** provides a pharmacokinetic summary.[27,28]

Various dosage regimens are used in giving benzodiazepines, the most common being symptom-triggered therapy, governed by assessment scales, and scheduled around-the-clock therapy.[29] Current evidence supports symptom-triggered therapy in most inpatients who are not critically ill, as it can reduce both benzodiazepine use and adverse drug events and can reduce the length of stay.[16,19]

TABLE 4

Trials comparing inpatient symptom-triggered vs fixed-dosing benzodiazepine therapy in alcohol withdrawal syndrome

	Saitz et al[16]	Jaeger et al[17]	Daeppen et al[18]	Weaver et al[19]	Reoux and Miller[20]
No. of patients	101	216	117	183	40
Type of program	Alcohol withdrawal inpatient treatment program	Retrospective, adult medicine patients	Alcohol withdrawal inpatient treatment program	Prospective, adult medicine patients	Addiction unit vs medical and psychiatric services
Duration and monitoring	4 days; CIWA-Ar scores every 8 hours and 1 hour after medication dose	Up to 7 days; CIWA-Ar scores every 1–2 hours	3 days; CIWA-Ar scores every 30 minutes	CIWA-Ar every 4 hours	2 to 8 days; CIWA-Ar scores every 8 hours
Symptom-triggered protocol	If CIWA-Ar ≥ 8, chlordiazepoxide 20–100 mg every hour	If CIWA-Ar > 10, chlordiazepoxide 50–100 mg with repeated doses	Placebo every 6 hours If CIWA-Ar 8–15, oxazepam 15 mg If CIWA-Ar > 15, oxazepam 30 mg	If CIWA-Ar 6–9, lorazepam 0.5 mg intravenously or orally; If 10–19, 2 mg If 20–29, 3 mg if 30–39, 4 mg	If CIWA-Ar ≥ 10, oxazepam 30 mg or chlordiazepoxide 50 mg every hour until < 10
Fixed schedule	Chlordiazepoxide 50 mg every 6 hours for 4 doses, then 25 mg every 6 hours for 8 doses	Usual care: tapering, fixed-dose regimen, or sporadic dosing by medical staff	Oxazepam 30 mg every 6 hours	Lorazepam 2 mg every 4 hours for 48 hours, then 1 mg every 4 hours for 24 hours, then 0.5 mg every 4 hours for 24 hours	As ordered by attending physician
Total dose[a]	100 vs 425 mg ($P < .001$)	Benzodiazepine equivalents 20.1 vs 20.1 mg	37.5 vs 231.4 mg ($P < .001$)	Lower with symptom-triggered protocol	Benzodiazepine equivalents 82.7 vs 367.5 mg ($P < .01$)
Duration of therapy (hours)[a]	9 vs 68 ($P < .001$)	44.9 vs 55.5	20 vs 62.7 ($P < .001$)	—	10.7 vs 20.7 ($P < .01$)
CIWA-Ar score differences[a]	Not significant	Not reported	$P < .01$	$P < .01$	Not reported
Outcomes[a]	Delirium tremens (DTs) 2% vs 6% Readmission in 30 days 6% vs 8%	DTs 6.9% vs 20.5% ($P < .04$)	No DTs One seizure in symptom-triggered group	No DTs or seizures in either group Median length of stay 3 days in both groups	No DTs, seizures, or adverse drug events in either group Oversedation and hypotension in one patient in usual-care group

[a] Symptom-triggered group vs fixed-schedule group.
CIWA-Ar = revised Clinical Institute Withdrawal Assessment for Alcohol scale (Table 1)

Trials of symptom-triggered benzodiazepine therapy

Most inpatient trials of symptom-triggered therapy (**Table 4**)[3,16–20] used the CIWA-Ar scale for monitoring. In some of the studies, benzodiazepines were given if the score was 8 or higher, but others used cut points as high as 15 or higher. Doses:

- Chlordiazepoxide (first dose 25–100 mg)
- Lorazepam (first dose 0.5–2 mg)
- Oxazepam (30 mg).

After each dose, patients were reevaluated at intervals of 30 minutes to 8 hours.

Most of these trials showed no difference in rates of adverse drug events such as seizures, hallucinations, and lethargy with symptom-triggered therapy compared with scheduled therapy.[16,18,20] They also found either no difference in the incidence of delirium tremens, or a lower incidence of delirium tremens with symptom-triggered therapy than with scheduled therapy.[16–18,20]

Weaver et al[19] found no difference in length of stay between scheduled therapy and symptom-triggered therapy, but Saitz et al[16] reported a median benzodiazepine treatment duration of 9 hours with symptom-triggered therapy vs 68 hours with fixed dosing. Thus, the study by Saitz et al suggests that hospitalization might be shorter with symptom-triggered therapy.

Many of the trials had notable limitations related to the diversity of patients enrolled and the protocols for both symptom-triggered therapy and fixed dosing. Some trials enrolled only inpatients in detoxification programs; others focused on inpatients with acute medical illness. The inpatient alcohol treatment trials[16,18] excluded medically ill patients and those with concurrent psychiatric illness,[16,18] and one excluded patients with seizures.[16] One of the inpatient alcohol treatment program trials[16] excluded patients on beta-blockers or clonidine because of concern that these drugs could mask withdrawal symptoms, whereas trials in medically ill patients allowed these same drugs.[17,19,20]

Most of the patients were men (approximately 75%, but ranging from 74% to 100%), and therefore the study results may not be as applicable to women.[16–20] Most participants were middle-aged, with average ages in all

studies between 46 and 55. Finally, the studies used a wide range of medications and dosing, with patient monitoring intervals ranging from every 30 minutes to every 8 hours.[16–20]

In a 2010 Cochrane analysis, Amato et al[29] concluded that the limited evidence available favors symptom-triggered regimens over fixed-dosing regimens, but that differences in isolated trials should be interpreted very cautiously.

Therapeutic ethanol

Aside from the lack of evidence to support its use in alcohol withdrawal syndrome, prescribing oral ethanol to alcoholic patients clearly poses an ethical dilemma. However, giving ethanol intravenously has been studied, mostly in surgical trauma patients.[30]

Early reports described giving intravenous ethanol on a gram-to-gram basis to match the patient's consumption before admission to prevent alcohol withdrawal syndrome. But later studies reported prevention of alcohol withdrawal syndrome with very small amounts of intravenous ethanol.[30,31] While clinical trials have been limited to ICU patients, ethanol infusion at an initial rate of 2.5 to 5 g per hour and titrated up to 10 g per hour has appeared to be safe and effective for preventing alcohol withdrawal syndrome.[30,31] The initial infusion rate of 2.5 to 5 g per hour is equivalent to 4 to 10 alcoholic beverages per 24 hours.

Nevertheless, ethanol infusion carries the potential for toxicities (eg, gastric irritation, precipitation of acute hepatic failure, hypoglycemia, pancreatitis, bone marrow suppression, prolonged wound healing) and drug interactions (eg, with anticoagulants and anticonvulsants). Thus, ethanol is neither widely used nor recommended.[25,31]

■ ADJUNCTIVE THERAPIES

Many medications are used adjunctively in the acute setting, both for symptoms of alcohol withdrawal syndrome and for agitation.

Haloperidol

No clinical trial has yet examined haloperidol monotherapy in patients with alcohol withdrawal syndrome in either general medical units or intensive care units. Yet haloperidol remains important and is recommended as an

Current evidence supports symptom-based therapy in most inpatients who are not critically ill

adjunct therapy for agitation.[23,32] Dosing of haloperidol in protocols for surgical patients ranged from 2 to 5 mg intravenously every 0.5 to 2 hours, with a maximum dosage of 0.5 mg per kg per 24 hours.[7,33]

Alpha-2 agonists

Alpha-2 agonists are thought to reduce sympathetic overdrive and the autonomic symptoms associated with alcohol withdrawal syndrome, and these agents (primarily clonidine) have been studied in the treatment of alcohol withdrawal syndrome.[34,35]

Clonidine. In a Swedish study,[34] 26 men ages 20 to 55 who presented with the tremor, sweating, dysphoria, tension, anxiety, and tachycardia associated with alcohol withdrawal syndrome received clonidine 4 µg per kg twice daily or carbamazepine 200 mg three to four times daily in addition to an antiepileptic. Adjunctive use of a benzodiazepine was allowed at night in both groups. No statistically significant difference in symptom reduction was noted between the two groups, and there was no difference in total benzodiazepine use.

Dexmedetomidine, given intravenously, has been tested as an adjunct to benzodiazepine treatment in severe alcohol withdrawal syndrome. It has been shown to decrease the amount of total benzodiazepine needed compared with benzodiazepine therapy alone, but no differences have been seen in length of hospital stay.[36–39] However, research on this drug so far is limited to ICU patients.

Beta-blockers

Beta-blockers have been used in inpatients with alcohol withdrawal syndrome to reduce heart rate and potentially reduce alcohol craving. However, the data are limited and conflicting.

Atenolol 50 to 100 mg daily, in a study in 120 patients, reduced length of stay (4 vs 5 days), reduced benzodiazepine use, and improved vital signs and behavior compared with placebo.[40]

Propranolol 40 mg every 6 hours reduced arrhythmias but increased hallucinations when used alone in a study in 47 patients.[41] When used in combination with chlordiazepoxide, no benefit was seen in arrhythmia reduction.[41]

Barbiturates and other antiepileptics

Data continue to emerge on antiepileptics as both monotherapy and adjunctive therapy for alcohol withdrawal syndrome. Barbiturates as monotherapy were largely replaced by benzodiazepines in view of the narrow therapeutic index of barbiturates and their full agonist effect on the GABA receptor complex. However, phenobarbital has been evaluated in patients presenting with severe alcohol withdrawal syndrome or resistant alcohol withdrawal (ie, symptoms despite large or repeated doses of benzodiazepines) as an adjunct to benzodiazepines.[42,43]

In addition, a newer trial[44] involved giving a single dose of phenobarbital in the emergency department in combination with a CIWA-Ar–based benzodiazepine protocol, compared with the benzodiazepine protocol alone. The group that received phenobarbital had fewer ICU admissions; its evaluation is ongoing.

The three other medications with the most data are carbamazepine, valproic acid, and gabapentin.[45,46] However, the studies were small and the benefit was modest. Although these agents are possible alternatives in protracted alcohol withdrawal syndrome, no definite conclusion can be made regarding their place in therapy.[46]

■ RECOMMENDATIONS FOR DRUG THERAPY AND SUPPORTIVE CARE

Which benzodiazepine to use?

No specific benzodiazepine is recommended over the others for managing alcohol withdrawal syndrome, but studies best support the long-acting agent chlordiazepoxide.[16,17,20] Other benzodiazepines such as lorazepam and oxazepam have proved to be beneficial, but drugs should be selected on the basis of patient characteristics and drug metabolism.[18,19,27]

Patients with severe liver dysfunction and the elderly may have slower oxidative metabolism, so the effects of medications that are primarily oxidized, such as chlordiazepoxide and diazepam, may be prolonged. Therefore, lorazepam and oxazepam would be preferred in these groups.[47] While most patients with alcohol withdrawal syndrome and liver dysfunction do not have advanced cirrhosis, we recommend liver function testing (serum

No specific benzodiazepine is recommended, but studies best support the long-acting drug chlordiazepoxide

TABLE 5

Examples of symptom-triggered dosing and CIWA-Ar scores

CIWA-Ar score	Chlordiazepoxide dose (oral)[a]	Lorazepam dose (oral or intravenous)[a]	Reassess CIWA-Ar and vital signs, and redose
0–7	No medication necessary	No medication necessary	Every 2 hours
8–10	25–50 mg	1–2 mg	Every 2 hours
11–15	50–75 mg	2–3 mg	Every 1–2 hours
16–19	75–100 mg	3–4 mg	Every 1–2 hours
20 or greater	Evaluation for patient transfer to intensive care unit		
CIWA-Ar < 8 for three consecutive checks	Reassess or redose to every 4 hours. If score remains < 8 every 4 hours on three checks, reassess or redose every 8 hours. If CIWA-Ar score is ≤ 8 for 48 hours, discontinue monitoring.		

[a] Patients with liver failure and elderly patients should be started on lower doses.
CIWA-Ar = revised Clinical Institute Withdrawal Assessment for Alcohol scale (Table 1)

Based on references 15,16, and 19.

aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels) and screening for liver disease, given the drug metabolism and package insert caution for use in those with impaired hepatic function.[48]

Patients with end-stage renal disease (stage 5 chronic kidney disease) **or acute kidney injury** should not receive parenteral diazepam or lorazepam. The rationale is the potential accumulation of propylene glycol, the solvent used in these formulations.

In the elderly, the Beers list of drugs to avoid in older adults includes benzodiazepines, not differentiating individual benzodiazepines in terms of risk.[49] However, chlordiazepoxide may be preferable to diazepam due to its shorter parent half-life and lower lipophilicity.[27] Few studies have been done using benzodiazepines in elderly patients with alcohol withdrawal syndrome, but those published have shown either equivalent dosing required compared with younger patients or more severe withdrawal for which they received greater amounts of chlordiazepoxide.[9,12] Lorazepam and oxazepam have less potential to accumulate in the elderly compared with the nonelderly due to the drugs' metabolic profiles; lorazepam is the preferred agent because of its faster onset of action.[47] Ultimately, the choice of benzodiazepine in elderly patients with alcohol withdrawal syndrome should be based on patient-specific characteristics.

> **Symptom-triggered therapy works best when a hospital has a protocol and staff are trained**

How should benzodiazepines be dosed?

While the CIWA-Ar thresholds and subsequent dosing of benzodiazepines varied in different studies, we recommend starting benzodiazepine therapy at a CIWA-Ar score of 8 or higher, with subsequent dosing based on score reassessment. Starting doses of benzodiazepines should be chlordiazepoxide 25 to 50 mg, lorazepam 1 to 2 mg, or oxazepam 15 mg.[16–20]

Subsequent doses should be titrated upward, increasing by 1.5 to 2 times the previous dose and monitored at least every 1 to 2 hours after dose adjustments. Once a patient is stable and the CIWA-Ar score is less than 8, monitoring intervals can be extended to every 4 to 8 hours. If the CIWA-Ar score is more than 20, studies suggest the need for patient reevaluation for transfer to the ICU; however, some health systems have a lower threshold for this intervention.[7,14,50]

Dosing algorithms and CIWA-Ar goals may vary slightly from institution to institution, but it has been shown that symptom-triggered therapy works best when hospitals have a protocol for it and staff are adequately trained to assess patients with alcohol withdrawal syndrome.[7,50,51] Suggestions for dose ranges and symptom-triggered therapy are shown in **Table 5**.

In case of benzodiazepine overdose or potential benzodiazepine-induced delirium, flu-

mazenil could be considered.[52]

Patients who should not receive symptom-triggered therapy include immediate postoperative patients in whom clinicians cannot properly assess withdrawal symptoms and patients with a history of DTs.[51] While controversy exists regarding the use of symptom-triggered therapy in patients with complicated medical comorbidities, there are data to support symptom-triggered therapy in some ICU patients, as it has resulted in less benzodiazepine use and reduced mechanical ventilation.[53,54]

There are limited data to support phenobarbital in treating resistant alcohol withdrawal syndrome, either alone or concurrently with benzodiazepines, in escalating doses ranging from 65 to 260 mg, with a maximum daily dose of 520 mg.[42,55,56]

Haloperidol

For patients exhibiting agitation despite benzodiazepine therapy, giving haloperidol adjunctively can be beneficial.

Haloperidol can be used in medical patients as an adjunctive therapy for agitation, but caution is advised because of the potential for a lowering of the seizure threshold, extrapyramidal effects, and risk of QTc prolongation leading to arrhythmias. Patients considered at highest risk for torsades de pointes may have a QTc of 500 msec or greater.[57]

Patients should also be screened for factors that have been shown to be independent predictors of QTc prolongation (female sex, diagnosis of myocardial infarction, septic shock or left ventricular dysfunction, other QT-prolonging drugs, age > 68, baseline QTc ≥ 450 msec, and hypokalemia).[58] If combined predictors have been identified, it is recommended that haloperidol be avoided.

If haloperidol is to be given, a baseline electrocardiogram and electrolyte panel should be obtained, with daily electrocardiograms thereafter, as well as ongoing review of the patient's medications to minimize drug interactions that could further increase the risk for QTc prolongation.

Suggested haloperidol dosing is 2 to 5 mg intravenously every 0.5 to 2 hours with a maximum dose of 0.5 mg/kg/24 hours.[8,33] A maximum of 35 mg of intravenous haloperidol should be used in a 24-hour period to avoid QTc prolongation.[57]

Antihypertensive therapy

Many patients receive symptomatic relief of autonomic hyperreactivity with benzodiazepines. However, some may require additional antihypertensive therapy for cardiac adrenergic symptoms (hypertension, tachycardia) if symptoms do not resolve by treating other medical problems commonly seen in patients with alcohol withdrawal syndrome, such as dehydration and electrolyte imbalances.[7]

Published protocols suggest giving clonidine 0.1 mg orally every hour up to three times as needed until systolic blood pressure is less than 140 mm Hg (less than 160 mm Hg if the patient is over age 60) and diastolic pressure is less than 90 mm Hg.[51] Once the patient is stabilized, the dosing can be scheduled to a maximum of 2.4 mg daily.[59] However, we believe that the use of clonidine should be restricted to patients who have a substantial increase in blood pressure over baseline or are nearing a hypertensive urgency or emergency (pressures > 180/120 mm Hg) and should not be used to treat other general symptoms associated with alcohol withdrawal syndrome.[42]

In addition, based on limited evidence, we recommend using beta-blockers only in patients with symptomatic tachycardia or as an adjunct in hypertension management.[40,41]

Therapies to avoid
in acutely ill medical patients

Ethanol is not recommended. Instead, intravenous benzodiazepines should be given in patients presenting with severe alcohol withdrawal syndrome.

Antiepileptics, including valproic acid, carbamazepine, and pregabalin, lack benefit in these patients either as monotherapy or as adjunctive therapy and so are not recommended.[45,60–62]

Magnesium supplementation (in patients with normal serum magnesium levels) should not be given, as no clinical benefit has been shown.[63] ■

Cautions with haloperidol: seizures, extrapyramidal effects, QTc prolongation

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