3 Regimens for alcohol withdrawal and detoxification

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Practice recommendations

- Patients with mild to moderate alcohol withdrawal symptoms and no serious psychiatric or medical comorbidities can be safely treated in the outpatient setting (SOR: **A**).

- Patients with moderate withdrawal should receive pharmacotherapy to treat their symptoms and reduce their risk of seizures and delirium tremens during outpatient detoxification (SOR: **A**).

- Benzodiazepines are the treatment of choice for alcohol withdrawal (SOR: **A**).

- In healthy individuals with mild-to-moderate alcohol withdrawal, carbamazepine has many advantages making it a first-line treatment for properly selected patients (SOR: **A**).

I n our small community hospital—with limited financial and medical resources—we have designed and implemented an outpatient alcohol detoxification clinical practice guideline to provide cost-effective, evidence-based medical care to our patients, in support of their alcohol treatment.

Those patients with mild-to-moderate alcohol withdrawal symptoms and no serious psychiatric or medical comorbidities can be safely treated in the outpatient setting. Patients with history of severe withdrawal symptoms, seizures or delirium tremens, comorbid serious psychiatric or medical illnesses, or lack of reliable support network should be considered for detoxification in the inpatient setting.

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■ THE PROBLEM OF ALCOHOL WITHDRAWAL

Up to 71% of individuals presenting for alcohol detoxification manifest significant symptoms of alcohol withdrawal.[4] Alcohol withdrawal is a clinical syndrome that affects people accustomed to regular alcohol intake who either decrease their alcohol consumption or stop drinking completely.

Physiology

Alcohol enhances gamma-aminobutyric acid's (GABA) inhibitory effects on signal-receiving neurons, thereby lowering neuronal activity, leading to an increase in excitatory glutamate receptors. Over time, tolerance occurs as GABA receptors become less responsive to neurotransmitters, and more alcohol is required to produce the same inhibitory effect. When alcohol is removed acutely, the number of excitatory glutamate receptors remains, but without the suppressive GABA effect.[5] This situation leads to the signs and symptoms of alcohol withdrawal.

Symptoms

Noticeable alcohol withdrawal symptoms may appear within hours of cessation or decreasing alcohol intake. The most common symptoms include tremor, craving for alcohol, insomnia, vivid dreams, anxiety, hypervigilance, agitation, irritability, loss of appetite, nausea, vomiting, headache, and sweating.[5] Even without treatment, most of these relatively benign symptoms resolve within hours to days.

More concerning are hallucinations, delirium tremens (DTs), and seizures. Transient auditory or visual hallucinations may occur within the first 2 days of decreasing or discontinuing alcohol consumption, and can be separate from DTs. DTs, which present within 2 to 4 days of the last drink (and can last up to 3 to 4 days), are characterized by disorientation, persistent visual and auditory hallucinations, agitation and tremulousness, and autonomic signs resulting from the activation of stress-related hormones. These signs include tachycardia, hypertension, and fevers.

DTs are much more serious than the "alcohol shakes"—5% of patients who experience DTs die from metabolic complications.[6] The occurrence of DTs is 5.3 times higher in men than in women;[7] however, women may exhibit fewer autonomic symptoms, making DTs in women more difficult to diagnose.[6]

Grand mal seizures can occur in up to 25% of alcoholics undergoing withdrawal.[4] If alcohol-related seizures do occur, they generally do so within 1 day of cessation of alcohol intake, but can occur up to 5 days later.

Risk factors for prolonged or complicated alcohol withdrawal include duration of alcohol consumption, the number of lifetime prior detoxifications, prior seizures, prior episodes of DTs, and current intense craving for alcohol.[6–10]

■ BEFORE TREATMENT: ASSESS AND STABILIZE

Initial assessment of the patient

Before initiating treatment for alcohol withdrawal, perform a thorough assessment of the patient's medical condition. This evaluation should include an assessment of coexisting medical and psychiatric conditions, the severity of previous withdrawal symptoms, and the risk factors for withdrawal complications. The initial symptoms of alcohol withdrawal are not specific and may mimic other serious disease conditions; therefore, the initial assessment should exclude potentially serious medical and psychiatric comorbidities.

Initially, assessment of common alcohol-related medical problems should be conducted. These complications include gastritis, gastrointestinal bleeding, liver disease, cardiomyopathy, pancreatitis, neurological impairment, electrolyte imbalances, and nutritional deficiencies. A physical examination should be performed to assess for arrhythmias, congestive heart failure, hepatic or pancreatic disease, infectious conditions, bleeding, and nervous system impairment.

Initial alcohol level and urine drug screen should be assessed, as recent high levels of alcohol intake and substance abuse place the patient at higher risk for complications. Unstable mood disorders—delirium, psychosis, severe depression, suicidal or homicidal ideation—while potentially difficult to assess during intoxication, need to be considered and ruled out.

Stabilize the patient

After initial assessment, vital signs (eg, heart rate, blood pressure, and temperature) should be stabilized while fluid, electrolyte, and nutritional disturbances are corrected. Some patients undergoing alcohol withdrawal may require intravenous fluids to correct severe dehydration resulting from vomiting, diarrhea, sweating, and fever.

Alcoholics are often deficient in electrolytes or minerals, including thiamine, folate, and magnesium (although replacing magnesium makes no difference in clinically meaningful outcomes) (level of evidence [LOE]: **1**, double-blind randomized controlled trial).[11] All patients being treated for alcohol withdrawal should be given 100 mg of thiamine immediately and daily (LOE: **3**; insufficient evidence from randomized controlled trials

FIGURE 1

The Clinical Institute Withdrawal Assessment for Alcohol—Revised

Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

Patient _____   Date |—|—|—| Time ____:____
                                                              Y m d   (24-hour clock, midnight=00:00)

Pulse or heart rate, taken for one minute: _____   Blood pressure: _____ / _____

NAUSEA AND VOMITING—Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TREMOR—Arms extended and fingers spread apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arm extended
5
6
7 severe, even with arms not extended

PAROXYSMAL SWEATS—Observation.
0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

ANXIETY—Ask "Do you feel nervous?" Observation.
0 no anxiety, at ease
1 mildly anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium
   or acute schizophrenic reactions

AGITATION—Observation.
0 normal scarcity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview,
   or constantly thrashes about

This scale is not copyrighted and may be used freely.

TACTILE DISTURBANCES—Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.
0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

AUDITORY DISTURBANCES—Ask "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?" Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

VISUAL DISTURBANCES—Ask "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?" Observation.
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD—Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM— Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place and/or person

Total CIWA-Ar Score____
Rater's Initials____
Maximum Possible Score 67

TABLE 1		
Pharmacologic treatment of alcohol withdrawal		
Medication	**Comments**	**LOE**
Benzodiazepines	Remain drug of choice for acute alcohol withdrawal[14] Highly significant decrease in seizures and delirium Risk reduction 7.72 seizures/100 patients, 4.9 DTs/100 patients[20] Some abuse potential	A

Carbamazepine	Well-documented anticonvulsant activity; prevents seizures
	    from alcohol Withdrawal
	No abuse potential
	Especially good for those with multiple previously
	    treated withdrawals[22]
	Relative risk of first drink after withdrawal in benzodiazepine
	    group over 3 times higher than carbamazepine[22]
	If carbamazepine-treated patients relapse, they drink less than
	    benzodiazepine-treated patients [absolute risk reduction=4][22]
		A

Valproic acid	Significantly affects the course of acute alcohol withdrawal and
	    reduces need for treatment with a benzodiazepine
	    [absolute risk reduction=4][24]
	Use limited by side effects which mimic alcohol withdrawal
	Wide therapeutic range makes unintentional overdose uncommon
		A

to guide clinicians in the dose, frequency, route, or duration of thiamine treatment for prophylaxis against or treatment of WKS due to alcohol abuse).[4] Thiamine should be given before glucose containing fluids, to avoid the risk of precipitating Wernicke syndrome (LOE: **3**).[12]

Assess the severity of the withdrawal

Once a diagnosis of alcohol withdrawal is made, complete an assessment of the severity of withdrawal and the risk of complications. The best validated tool is the Clinical Institute Withdrawal Assessment for Alcohol–Revised (CIWA-Ar) symptom scale (**Figure 1**).[10] This instrument rates 10 withdrawal features; it takes only a few minutes to administer and may be repeated when re-evaluation is necessary. CIWA-Ar scores of ≤8 are suggestive of mild withdrawal symptoms, while those ≥15 confer an increased risk for confusion and seizures.

CIWA-Ar is reliable, brief, uncomplicated, and clinically useful scale that can also be used to monitor response to treatment. It offers an increase in efficiency over the original CIWA-A scale, while retaining clinical usefulness, validity, and reliability. It can be incorporated into the usual clinical care of patients undergoing alcohol withdrawal and into clinical drug trials of alcohol withdrawal (strength of recommendation [SOR]=**A**).[5,13]

■ PHARMACOTHERAPY

Patients experiencing more serious withdrawal (with CIWA-Ar scores >8) should receive pharmacotherapy to treat their symptoms and reduce their risk of seizures and DTs (SOR=**A**).[14]

Benzodiazepines

Benzodiazepines are the mainstay of treatment in alcohol withdrawal (number needed to treat [NNT]=17; data from large meta-analysis of 6 prospective, placebo-controlled trials) (SOR=**A**).[10,14–16] Like alcohol, these agents magnify GABA's effect on the brain. Benzodiazepines are cross-tolerant with alcohol; during

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Alcohol detoxification in a community hospital

The problem. In our small community hospital, prior to the development of a clinical practice guideline, admissions for "inpatient alcohol detoxification" were among our top 5, with a select few patients making multiple, repeat visits. Additionally, we had no standardized, consistent strategy for initial emergency room evaluation; frequent early discharges against medical advice; multiple readmissions; infrequent and inconsistent entry into our outpatient Alcohol and Substance Abuse Program; and no existing process for primary care outpatient follow-up. We found ourselves in a situation where we were essentially enabling our patients in a destructive behavior. With no formal policy or guidelines, physicians tended to follow the path of least resistance: repeated short-stay admissions with limited therapeutic benefit.

The process. Our initial goal was to develop a standardized policy in an attempt to minimize the number of admissions of mild-to-moderate, uncomplicated alcohol withdrawal patients. Many of our patients are at low risk for serious complications, and we hoped to triage such individuals to an outpatient treatment setting. To organize the thought process, a flowchart was developed and refined. By incorporating current evidence, a clinical practice guideline was developed.

Evidence-based algorithm. We developed an evidence-based algorithm, Outpatient Treatment for Alcohol Detoxification (**Figure 2**), which uses a gradually tapering regimen, and allows providers to prescribe the medication they feel most appropriate given the clinical situation.

Results. In the 12 months since implementation of our clinical practice guideline, total alcohol-related admission decreased from 4 to 5 per month to only 1 during the entire period; furthermore, no patients treated with our guidelines were subsequently hospitalized for complications of alcohol withdrawal.

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withdrawal from 1 agent, the other may serve as a substitute. Benzodiazepines also reduce the incidence of DTs and seizures (**Table 1**).[5,14]

The most commonly used benzodiazepines are diazepam (Valium), chlordiazepoxide (Librium), and lorazepam (Ativan). All appear to be equally efficacious in treating alcohol withdrawal symptoms (LOE: **1**; randomized controlled trial).

Longer-acting agents, such as chlordiazepoxide or diazepam, contribute to an overall smoother withdrawal course with lessened breakthrough or rebound symptoms, but they may also lead to excess sedation for patients with hepatic dysfunction.[17–20] Shorter-acting benzodiazepines, such as oxazepam (Serax), may result in greater discomfort and more discharges against medical advice, because alcohol withdrawal symptoms tend to recur when serum benzodiazepine levels drop.
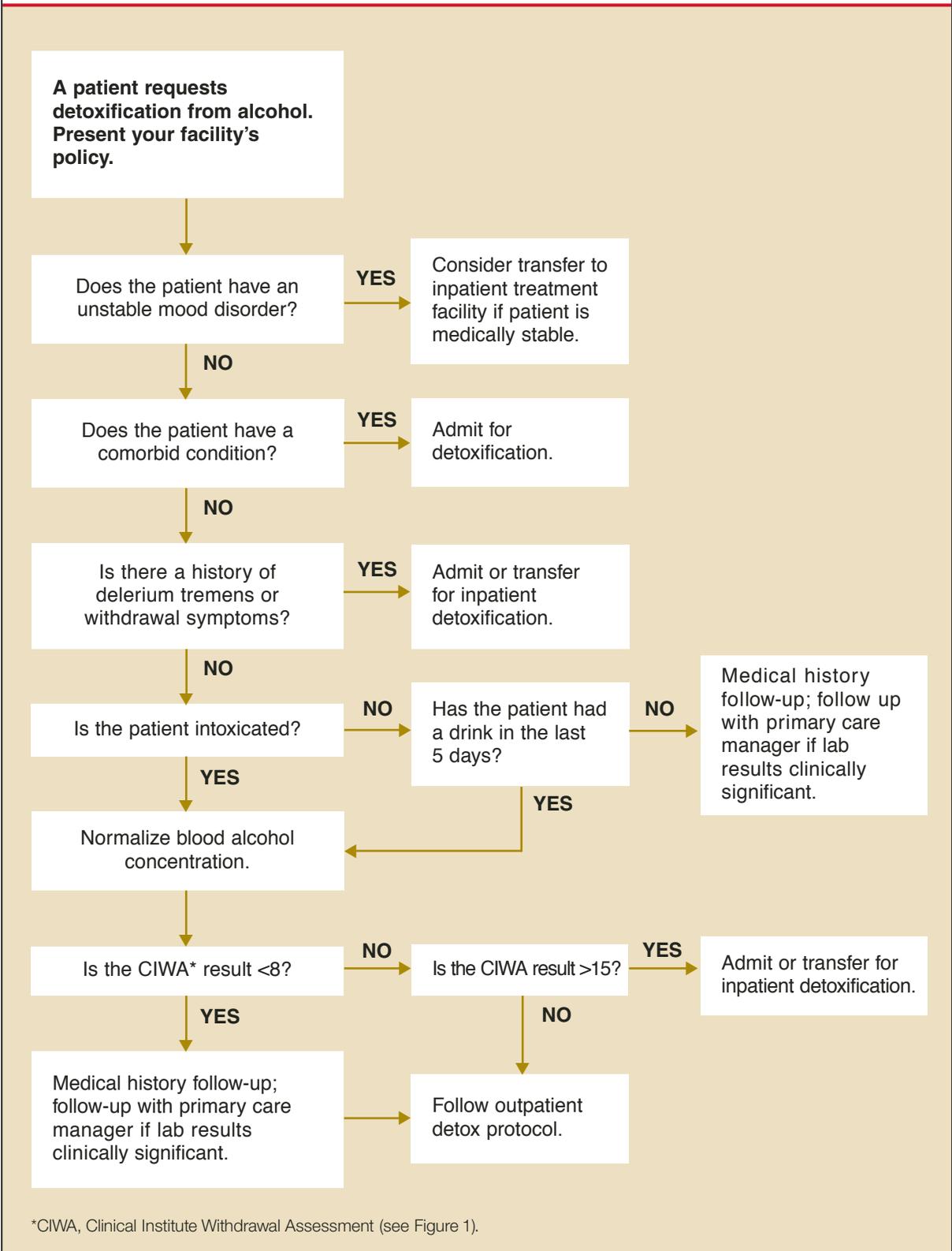
Anticonvulsants

Attractive alternatives to benzodiazepines include the anticonvulsants carbamazepine (Tegretol) and valproic acid (Depakote).

Carbamazepine. Carbamazepine has been used successfully for many years in Europe,[21] but has not been used widely in the US due to the safety, efficacy, and familiarity of benzodiazepines (**Table 1**). The use of anticonvulsants, however, has several advantages. They are not as sedating as benzodiazepines and do not have the abuse potential, making them particularly useful in the outpatient setting.

The use of anticonvulsant medication decreases the possibility of seizures, one of the more serious complications of alcohol withdrawal (NNT=36) (LOE: **1**, 2 double-blind randomized controlled trials). The brain cell kindling-like phenomenon—in which repeated episodes of alcohol withdrawal is associated with increasing severity

FIGURE 2

Guiding a patient through alcohol detoxification

A patient requests detoxification from alcohol. Present your facility's policy.

Does the patient have an unstable mood disorder? — **YES** → Consider transfer to inpatient treatment facility if patient is medically stable.

NO

Does the patient have a comorbid condition? — **YES** → Admit for detoxification.

NO

Is there a history of delerium tremens or withdrawal symptoms? — **YES** → Admit or transfer for inpatient detoxification.

NO

Is the patient intoxicated? — **NO** → Has the patient had a drink in the last 5 days? — **NO** → Medical history follow-up; follow up with primary care manager if lab results clinically significant.

YES (Is the patient intoxicated?)

YES (Has the patient had a drink in the last 5 days?)

Normalize blood alcohol concentration.

Is the CIWA* result <8? — **NO** → Is the CIWA result >15? — **YES** → Admit or transfer for inpatient detoxification.

YES (Is the CIWA result <8?)

NO (Is the CIWA result >15?)

Medical history follow-up; follow-up with primary care manager if lab results clinically significant.

Follow outpatient detox protocol.

*CIWA, Clinical Institute Withdrawal Assessment (see Figure 1).

of withdrawal—is decreased with the anticonvulsant carbamazepine.[14]

In a double-blind controlled trial comparing carbamazepine with oxazepam, carbamazepine was shown to be superior in ameliorating global psychological distress and reducing aggression and anxiety.[21] Stuppaeck et al showed that for alcohol withdrawal longer than 5 days, carbamazepine was statistically superior ($P<.05$) to oxazepam in reduction of CIWA scores.[22,23] Carbamazepine is also superior to benzodiazepines in preventing rebound withdrawal symptoms and reducing post-treatment drinking, especially in those with a history of multiple repeated withdrawals (SOR=**A**).[22] It has been shown that patients treated with carbamazepine were less likely to have a first drink following detoxification, and if they did drink, they drank less. This difference was especially evident for those patients with a history of multiple withdrawal attempts.[22]

A limitation of carbamazepine use, however, is its interaction with multiple medications that undergo hepatic oxidative metabolism, making it less useful in older patients or those with multiple medical problems. In summary, in generally healthy individuals with mild-to-moderate alcohol withdrawal, carbamazepine is just as efficacious as benzodiazepines, but has many advantages making it the drug of choice for properly selected patients (SOR=**A**).[21–23]

Valproic acid. Another widely used anticonvulsant, valproic acid, significantly affects the course of alcohol withdrawal and reduces the need for treatment with a benzodiazepine (LOE: **1**).[24] Two double-blind, randomized studies showed that patients treated with valproic acid for 4 to 7 days had fewer seizures, dropped out less frequently, had less severe withdrawal symptoms, and require less oxazepam than those treated with placebo or carbamazepine.[24,25]

Although effective, valproic acid use may be limited by side effects—somnolence, gastrointestinal disturbances, confusion, and tremor—that mimic the symptoms of alcohol withdrawal, making it difficult to assess improvement.

TABLE 2
Outpatient treatment for alcohol detoxification
Thiamine – 100 mg orally per day (for 5 days)
Consider folate (1 mg) and multiple vitamin injection
One of the following regimens:
3-day supply (only) of the following:
Chlordiazepoxide   50–100 mg every 6 hours for 4 doses, then 25–50 mg every 6 hours for 8 doses
Diazepam   10–20 mg every 6 hours for 4 doses, then 5–10 mg every 6 hours for 8 doses
Lorazepam   2–4 mg every 6 hours for 4 doses, then 1–2 mg every 6 hours for 8 doses (consider this choice if significant hepatic dysfunction)

Carbamazepine (Tegretol) — ***5-day supply***
  200 mg 4 times on day 1,
  200 mg 3 times on day 2,
  200 mg 2 times on day 3,
  200 mg daily for 2 more days (5 days total)

Other types of medications
Alpha-adrenergic agonists,[24–30] beta-blockers,[31–33] and calcium channel blockers[34,35] have been used to control symptoms of acute alcohol withdrawal, but have demonstrated little efficacy in prevention of seizures or DTs (LOE: **1**).[5,36]

■ TREATMENT REGIMENS

The acceptable medication regimens for treating alcohol withdrawal are the gradually tapering dose approach, the fixed-schedule approach, and the symptom-triggered approach. The first 2 regimens are appropriate for the pharmacological treatment of outpatient alcohol detoxification.

Gradually tapering regimen. With the gradual-dosing plan, patients receive medication according to a predetermined dosing schedule for several days as the medication is gradually discontinued (**Table 2**).

TABLE 3

Criteria for inpatient alcohol detoxification

Consider transfer for inpatient detoxification if the patient:

- Has current symptoms of moderate to severe alcohol withdrawal (CIWA ≥15)

- Has a known history of delirium tremens (DTs) or alcohol withdrawal seizure
  - If the patient has a remote history of seizures or DTs, but has detoxified previously without complications, they may be offered outpatient treatment.

- Needs and is unable to tolerate oral medication

- Is in imminent risk of harm to self or others

- Has had recurrent unsuccessful attempts

- Has had multiple past detoxifications

- Has a reasonable likelihood that he will not complete the ambulatory detoxification

- Has active psychosis or severe cognitive impairment

- Has concomitant medical or psychological illness

- Has recent high levels of alcohol consumption

- Has lack or reliable support network

- Is pregnant

Fixed-schedule regimen. In the fixed-schedule dosing regimen, the patient receives a fixed dose of medication every 6 hours for 2 to 3 days regardless of severity of symptoms.

Symptom-triggered regimen. For the symptom-triggered approach, the patient's CIWA-Ar score is determined hourly or bihourly and the medication is administered only when the score is elevated. Typically, benzodiazepines are used in a symptom-triggered regimen, although either benzodiazepines or anticonvulsants may be used in a fixed-schedule plan.

The main advantage to the symptom-triggered approach is that much less medication is used to achieve the same withdrawal state (LOE: **1**).[37–39] The symptom-triggered approach has also shown a possible decrease in DTs and may lead to less oversedation.[38,39]

We favor a symptom-based approach whenever adequate periodic assessment of CIWA-Ar can be performed, such as in an inpatient setting. For those patients who require pharmacological treatment during outpatient detoxification (CIWA-Ar score 8–15), we prefer the gradually tapering or fixed dosing plan, to provide a margin of safety, simplify the dosing schedule, and maximize compliance (SOR: **C**, expert opinion).[14]

■ INPATIENT VS OUTPATIENT TREATMENT

Most patients undergoing alcohol withdrawal may be treated safely in either an inpatient or outpatient setting (SOR=**A**).[40] Treatment professionals should assess whether inpatient or outpatient treatment would contribute more therapeutically to an alcoholic's recovery process.[41]

Patients with severe alcohol withdrawal symptoms (CIWA-Ar ≥15), previous history of DTs or seizures, or those with serious psychiatric or medical comorbidities should be considered for detoxification in an inpatient setting (SOR=**B**) (**Table 3**).[10,42] The main advantage of inpatient detoxification is

the availability of constant medical care, supervision, and treatment of serious complications.

A major disadvantage is the high cost of inpatient treatment. Hayashida and colleagues found inpatient treatment to be significantly more costly than outpatient treatment ($3,319–$3,665 vs $175–$388).[43] Additionally, while inpatient care may temporarily relieve people from the social stressors that contribute to their alcohol problem, repeated inpatient detoxification may not provide an overall therapeutic benefit.

Most alcohol treatment programs find that <10% of patients need admission to an inpatient unit for treatment of withdrawal symptoms.[44] For patients with mild-to-moderate alcohol withdrawal symptoms (CIWA-Ar <15), and no serious psychiatric or medical comorbidities, outpatient detoxification has been shown to be as safe and effective as inpatient detoxification (SOR=**A**).[40] Additionally, most patients in an outpatient setting experience greater social support, and maintain the freedom to continue working or maintaining day-to-day activities with fewer disruptions, and incur fewer treatment costs.[41] When assessing a patient for suitability for outpatient detoxification, it is important to ascertain motivation to stay sober, ability to return for daily nursing checks, and presence of a supportive observer at home.

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Look for these Clinical Inquiries

Are inhaled beta-agonists effective in controlling cough in patients with upper respiratory infections or acute bronchitis?

Is methylphenidate useful for treating adolescents with ADHD?

What is the best approach for managing recurrent bacterial vaginosis?

Does yoga speed healing for patients with low back pain?

Should we screen women for hypothyroidism?

What is the best approach to managing recurrent bacterial vaginitis?