Alcohol Withdrawal Syndrome

MAX BAYARD, M.D., JONAH MCINTYRE, M.D., KEITH R. HILL, M.D., and JACK WOODSIDE, JR., M.D.
East Tennessee State University James H. Quillen College of Medicine, Johnson City, Tennessee

The spectrum of alcohol withdrawal symptoms ranges from such minor symptoms as insomnia and tremulousness to severe complications such as withdrawal seizures and delirium tremens. Although the history and physical examination usually are sufficient to diagnose alcohol withdrawal syndrome, other conditions may present with similar symptoms. Most patients undergoing alcohol withdrawal can be treated safely and effectively as outpatients. Pharmacologic treatment involves the use of medications that are cross-tolerant with alcohol. Benzodiazepines, the agents of choice, may be administered on a fixed or symptom-triggered schedule. Carbamazepine is an appropriate alternative to a benzodiazepine in the outpatient treatment of patients with mild to moderate alcohol withdrawal symptoms. Medications such as haloperidol, beta blockers, clonidine, and phenytoin may be used as adjuncts to a benzodiazepine in the treatment of complications of withdrawal. Treatment of alcohol withdrawal should be followed by treatment for alcohol dependence. (Am Fam Physician 2004;69:1443-50. Copyright© 2004 American Academy of Family Physicians)

In 1992, approximately 13.8 million Americans (7.4 percent of the U.S. adult population)[1] met the criteria for alcohol abuse or dependence as specified in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR).[2] In 2000, 226,000 patients were discharged from short-stay hospitals (excluding Veteran's Affairs and other federal hospitals) with one of the following diagnoses: alcohol withdrawal *(Table 1)*,[2] alcohol withdrawal delirium, or alcohol withdrawal hallucinosis.[3] It is estimated that only 10 to 20 percent of patients undergoing alcohol withdrawal are treated as inpatients,[4] so it is possible that as many as 2 million Americans may experience symptoms of alcohol withdrawal conditions each year.

TABLE 1
Diagnostic Criteria for Alcohol Withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 beats per minute)
   2. Increased hand tremor
   3. Insomnia
   4. Nausea or vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Grand mal seizures
C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Adapted with permission from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed., text revision. Washington, D.C.: American Psychiatric Association, 2000:216.

Pathophysiology

Alcohol withdrawal syndrome is mediated by a variety of mechanisms. The brain maintains neurochemical balance through inhibitory and excitatory neurotransmitters. The main inhibitory neurotransmitter is γ-aminobutyric acid (GABA), which acts through the GABA-alpha (GABA-A) neuroreceptor. One of the major excitatory neurotransmitters is glutamate, which acts through the *N*-methyl-D-aspartate (NMDA) neuroreceptor.

Alcohol enhances the effect of GABA on

See page 1339 for definitions of strength-of-recommendation labels.

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GABA-A neuroreceptors, resulting in decreased overall brain excitability. Chronic exposure to alcohol results in a compensatory decrease of GABA-A neuroreceptor response to GABA, evidenced by increasing tolerance of the effects of alcohol.

Alcohol inhibits NMDA neuroreceptors, and chronic alcohol exposure results in up-regulation of these receptors. Abrupt cessation of alcohol exposure results in brain hyperexcitability, because receptors previously inhibited by alcohol are no longer inhibited. Brain hyperexcitability manifests clinically as anxiety, irritability, agitation, and tremors. Severe manifestations include alcohol withdrawal seizures and delirium tremens.

An important concept in both alcohol craving and alcohol withdrawal is the "kindling" phenomenon; the term refers to long-term changes that occur in neurons after repeated detoxifications. Recurrent detoxifications are postulated to increase obsessive thoughts or alcohol craving.[5] Kindling explains the observation that subsequent episodes of alcohol withdrawal tend to progressively worsen.

Although the significance of kindling in alcohol withdrawal is debated, this phenomenon may be important in the selection of medications to treat withdrawal. If certain medications decrease the kindling effect, they may become preferred agents.

The Authors

MAX BAYARD, M.D., is assistant professor in the Department of Family Medicine at the East Tennessee State University James H. Quillen College of Medicine, Johnson City, and program director of the university's family medicine residency program. Dr. Bayard received his medical degree from East Tennessee State University and completed a family practice residency at Bristol (Tenn.) Family Practice.

JONAH MCINTYRE, M.D., is a third-year resident in the Department of Family Medicine at the East Tennessee State University James H. Quillen College of Medicine. He received his medical degree from the University of South Alabama College of Medicine, Mobile.

KEITH R. HILL, M.D., is a third-year resident in the Department of Family Medicine at the East Tennessee State University James H. Quillen College of Medicine. He graduated from Saba University School of Medicine, The Bottom, Saba, Netherlands-Antilles.

JACK WOODSIDE, JR., M.D., is associate professor in the Department of Family Medicine at the East Tennessee State University James H. Quillen College of Medicine. Dr. Woodside received his medical degree from Jefferson Medical College of Thomas Jefferson University, Philadelphia. He completed a family medicine residency at East Tennessee State University, Kingsport.

Address correspondence to Max Bayard, M.D., East Tennessee State University James H. Quillen College of Medicine, Department of Family Medicine, Box 70621, Johnson City, TN 37614 (e-mail: bayard@mail.etsu.edu) Reprints are not available from the authors.

Withdrawal Symptoms

The spectrum of withdrawal symptoms and the time range for the appearance of these symptoms after cessation of alcohol use are listed in *Table 2*. Generally, the symptoms of alcohol withdrawal relate proportionately to the amount of alcoholic intake and the duration of a patient's recent drinking habit. Most patients have a similar spectrum of symptoms with each episode of alcohol withdrawal.

Minor withdrawal symptoms can occur while the patient still has a measurable blood alcohol level. These symptoms may include insomnia, mild anxiety, and tremulousness. Patients with alcoholic hallucinosis experience visual, auditory, or tactile hallucinations but otherwise have a clear sensorium.

Withdrawal seizures are more common in patients who have a history of multiple episodes of detoxification. Causes other than alcohol withdrawal should be considered if seizures are focal, if there is no definite history of recent abstinence from drinking, if seizures occur more than 48 hours after the patient's last drink, or if the patient has a history of fever or trauma.

Alcohol withdrawal delirium, or delirium tremens, is characterized by clouding of consciousness and delirium. Episodes of delirium tremens have a mortality rate of 1 to 5 percent.[6] Risk factors for developing alcohol withdrawal delirium include concurrent acute medical illness, daily heavy alcohol use, history of delirium tremens or withdrawal seizures, older age, abnormal liver function, and more severe withdrawal symptoms on presentation.

Evaluation of the Patient in Alcohol Withdrawal

The history and physical examination establish the diagnosis and severity of alcohol withdrawal. Important historical data include quantity of alcoholic intake, duration of alcohol use, time since last drink, previous alcohol withdrawals, presence of concurrent medical or psychiatric conditions, and abuse of other agents. In addition to identifying withdrawal symptoms, the physical examination should assess possible complicating

TABLE 2
Symptoms of Alcohol Withdrawal Syndrome

Symptoms	*Time of appearance after cessation of alcohol use*
Minor withdrawal symptoms: insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia	6 to 12 hours
Alcoholic hallucinosis: visual, auditory, or tactile hallucinations	12 to 24 hours*
Withdrawal seizures: generalized tonic-clonic seizures	24 to 48 hours†
Alcohol withdrawal delirium (delirium tremens): hallucinations (predominately visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis	48 to 72 hours‡

*—*Symptoms generally resolve within 48 hours.*
†—*Symptoms reported as early as two hours after cessation.*
‡—*Symptoms peak at five days.*

medical conditions, including arrhythmias, congestive heart failure, coronary artery disease, gastrointestinal bleeding, infections, liver disease, nervous system impairment, and pancreatitis. Basic laboratory investigations include a complete blood count, liver function tests, a urine drug screen, and determination of blood alcohol and electrolyte levels.

The revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale is a validated 10-item assessment tool that can be used to quantify the severity of alcohol withdrawal syndrome, and to monitor and medicate patients going through withdrawal[7,8] *(Figure 1)*.[7] CIWA-Ar scores of 8 points or fewer correspond to mild withdrawal, scores of 9 to 15 points correspond to moderate withdrawal, and scores of greater than 15 points correspond to severe withdrawal symptoms and an increased risk of delirium tremens and seizures.

In using the CIWA-Ar, the clinical picture should be considered because medical and psychiatric conditions may mimic alcohol withdrawal symptoms. In addition, certain medications (e.g., beta blockers) may blunt the manifestation of these symptoms.

Differential Diagnosis

Alcohol withdrawal syndrome can be confused with other conditions. Thyrotoxicosis, anticholinergic drug poisoning, and amphetamine or cocaine use can result in signs of increased sympathetic activity and altered mental status. Central nervous system infection or hemorrhage can cause seizures and mental status changes. Withdrawal from other sedative-hypnotic agents causes symptoms similar to those occurring in alcohol withdrawal syndrome.

Goals of Treatment

The American Society of Addiction Medicine lists three immediate goals for detoxification of alcohol and other substances: (1) "to provide a safe withdrawal from the drug(s) of dependence and enable the patient to become drug-free"; (2) "to provide a withdrawal that is humane and thus protects the patient's dignity"; and (3) "to prepare the patient for ongoing treatment of his or her dependence on alcohol or other drugs."[6]

General Care

Abnormalities in fluid levels, electrolyte levels, or nutrition should be corrected. Intravenous fluids may be necessary in patients with severe withdrawal because of excessive fluid loss through hyperthermia, sweating, and vomiting. Intravenous fluids should not be administered routinely in patients with less severe withdrawal, because these patients may become overhydrated.

Routine administration of magnesium sulfate has not been shown to improve withdrawal symptoms,[9] but supplementation is appropriate if a patient is hypomagnesemic. Multivitamins and thiamine (100 mg per day) should be provided during treatment for alcohol withdrawal. If intravenous fluids are administered, thiamine (100 mg intravenously) should be given before glucose is administered, to prevent precipitation of Wernicke's encephalopathy.

Medication Regimens

Medication can be administered using fixed-schedule or symptom-triggered regimens *(Table 3)*.[10] With a fixed-schedule regimen, doses of a benzodiazepine are admin-

Assessment of Alcohol Withdrawal

Patient: _____ Date: _____ Time: _____:_____

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. Ask patient to extend arms and spread fingers apart.

Observation:

0—No tremor
1—Tremor not visible but can be felt, fingertip to fingertip
2—
3—
4—Moderate tremor with arms extended
5—
6—
7—Severe tremor, 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 occur in severe delirium or acute schizophrenic reactions

Agitation

Observation:

0—Normal activity
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

Tactile disturbances. Ask "Do you have you any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?"

Observation:

0—None
1—Very mild itching, pins-and-needles sensation, burning, or numbness
2—Mild itching, pins-and-needles sensation, burning, or numbness
3—Moderate itching, pins-and-needles sensation, 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 lightheadness; 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?"

Observation:

0—Orientated and can do serial additions
1—Cannot do serial additions or is uncertain about date
2—Date disorientation by no more than two calendar days
3—Date disorientation by more than two calendar days
4—Disorientated for place and/or person

Total score: _____ (maximum = 67) Rater's initials _____

FIGURE 1. Revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale.

Adapted from 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;84:1353-7.

TABLE 3
Examples of Treatment Regimens for Alcohol Withdrawal

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istered at specific intervals, and additional doses of the medication are given as needed based on the severity of the withdrawal symptoms. In a symptom-triggered regimen, medication is given only when the CIWA-Ar score is higher than 8 points.

Symptom-triggered regimens have been shown to result in the administration of less total medication and to require a shorter duration of treatment.[11,12] In one randomized, double-blind controlled trial,[11] patients in the symptom-triggered group received an average of 100 mg of chlordiazepoxide, whereas patients in the fixed-schedule group received an average of 425 mg. The median duration of treatment in the symptom-triggered group was nine hours, compared with 68 hours in the fixed-schedule group. Patients were excluded from the study if they had concurrent medical or psychiatric illness requiring hospitalization or seizures from any cause.[11]

In most patients with mild to moderate withdrawal symptoms, outpatient detoxification is safe and effective, and costs less than inpatient

Another trial[12] yielded similar results, with patients in the fixed-schedule group receiving an average of 231.4 mg of oxazepam and those in the symptom-triggered group receiving an average of 37.5 mg. Of the patients in the symptom-triggered group, 61 percent did not receive any oxazepam. This trial excluded persons with major psychiatric, cognitive, or medical comorbidities.

The use of symptom-triggered therapy requires training of the clinical staff. If this training has not been provided, fixed-schedule pharmacotherapy should be used.[10]

Choice of Treatment Setting

In most patients with mild to moderate withdrawal symptoms, outpatient detoxification is safe and effective, and costs less than inpatient treatment.[4,13-15] However, certain patients should be considered for inpatient treatment regardless of the severity of their symptoms. Relative indications for inpatient alcohol detoxification are as follows: history of severe withdrawal symptoms, history of withdrawal seizures or delirium tremens, multiple previous detoxifications, concomitant psychiatric or medical illness, recent high levels of alcohol consumption, pregnancy, and lack of a reliable support network.[16]

If outpatient treatment is chosen, the patient should be assessed daily. The patient and support person(s) should be instructed about how to take the withdrawal medication, the side effects of the medication, the expected withdrawal symptoms, and what to do if symptoms worsen.[6,17] Small quantities of the withdrawal medication should be prescribed at each visit; thiamine and a multivitamin also should be prescribed. Because close monitoring is not

available in ambulatory treatment, a fixed-schedule regimen should be used.

Pharmacologic Treatment of Withdrawal

benzodiazepines

Pharmacologic treatment of alcohol withdrawal syndrome involves the use of medications that are cross-tolerant with alcohol. Benzodiazepines have been shown to be safe and effective, particularly for preventing or treating seizures and delirium, and are the preferred agents for treating the symptoms of alcohol withdrawal syndrome.[10]

The choice of agent is based on pharmacokinetics. Diazepam (Valium) and chlordiazepoxide (Librium) are long-acting agents that have been shown to be excellent in treating alcohol withdrawal symptoms. Because of the long half-life of these medications, withdrawal is smoother, and rebound withdrawal symptoms are less likely to occur. Lorazepam (Ativan) and oxazepam (Serax) are intermediate-acting medications with excellent records of efficacy. Treatment with these agents may be preferable in patients who metabolize medications less effectively, particularly the elderly and those with liver failure. Lorazepam is the only benzodiazepine with predictable intramuscular absorption (if intramuscular administration is necessary).

Rarely, it is necessary to use extremely high dosages of benzodiazepines to control the symptoms of alcohol withdrawal. Dosages of diazepam as high as 2,000 mg per day have been administered.[18] Because clinicians often are reluctant to administer exceptionally high dosages, undertreatment of alcohol withdrawal is a common problem.

One randomized controlled trial (RCT)[19] affirmed previous findings that carbamazepine is an effective alternative to benzodiazepines in the treatment of alcohol withdrawal syndrome in patients with mild to moderate symptoms. Patients in the study received 800 mg of carbamazepine on the first day, with the dosage tapered to 200 mg by the fifth day. Carbamazepine (Tegretol) also appears to decrease the craving for alcohol after withdrawal. It is not sedating and has little potential for abuse. Although carbamazepine is used extensively in Europe, its use in the United States has been limited by lack of sufficient evidence that it prevents seizures and delirium.

ADJUNCTIVE AGENTS

Several medications may be helpful adjuncts to benzodiazepines in the treatment of alcohol withdrawal syndrome. However, these medications should not be used as monotherapy.

Haloperidol (Haldol) can be used to treat agitation and hallucinations, although it can lower the seizure threshold. The use of atenolol (Tenormin) in conjunction with oxazepam has been shown to improve vital signs more quickly and to reduce alcohol craving more effectively than the use of oxazepam alone.[20]

Adjunctive treatment with a beta blocker should be considered in patients with coronary artery disease, who may not tolerate the strain that alcohol withdrawal can place on the cardiovascular system. Clonidine (Catapres) also has been shown to improve the autonomic symptoms of withdrawal.[10] Although phenytoin (Dilantin) does not treat withdrawal seizures, it is an appropriate adjunct in patients with an underlying seizure disorder.

Patient Follow-Up

Treatment of alcohol withdrawal syndrome should be followed by treatment for alcohol dependence. Treatment of withdrawal alone does not address the underlying disease of addiction and therefore offers little hope for long-term abstinence.

In the outpatient setting, brief interventions are helpful in patients with alcohol abuse,[21] but more intense interventions are required in patients with alcohol dependence. The anticonvulsant topiramate (Topamax) has been shown to be an effective adjunctive medication to decrease alcohol consumption and increase abstinence in alcohol-dependent patients.[22]

Some patients achieve dramatic results by joining 12-step groups such as Alcoholics Anonymous and Narcotics Anonymous. Other patients benefit from stays in comprehensive treatment facilities, which offer a combination of a 12-step model, cognitive-behavior therapy, and family therapy. The treatment of alcohol withdrawal syndrome should be supplemented by an individualized, comprehensive treatment program, or at least as many elements of such a program as the patient can tolerate

Strength of Recommendations

Key clinical recommendation	*Strength of recommendation*	*References*
The revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale is a validated 10-item assessment tool that can be used to quantify the severity of alcohol withdrawal syndrome, and to monitor and medicate patients going through withdrawal.	A	7,8
Symptom-triggered regimens have been shown to result in the administration of less total medication and to require a shorter duration of treatment.	A	11, 12
In most patients with mild to moderate withdrawal symptoms, outpatient detoxification is safe and effective, and costs less than inpatient treatment.	A	4, 13, 14, 15
Benzodiazepines have been shown to be safe and effective, particularly for preventing or treating seizures and delirium, and are the preferred agents for treating the symptoms of alcohol withdrawal syndrome.	A	10

and afford.

Future Directions

Several medications have shown early promise in the treatment of alcohol withdrawal. In one case report[23] involving five patients, a single 10-mg dose of baclofen resulted in relief of severe withdrawal symptoms. In a preliminary RCT,[24] baclofen also reduced craving in alcohol-dependent patients.

Gabapentin, which is structurally similar to GABA, has been effective in the treatment of alcohol withdrawal in small studies.[25,26] The low toxicity of gabapentin makes it a promising agent. In another study,[27] the anticonvulsant agent vigabatrin, which irreversibly blocks GABA transaminase, improved withdrawal symptoms after only three days of treatment.

Prevention

Early identification of problem drinking allows prevention or treatment of complications, including severe withdrawal. The U.S. Preventive Services Task Force[28] recommends screening patients for problem drinking through a careful history or standardized screening questionnaire. Patients undergoing preoperative evaluation also should be screened, because alcohol withdrawal can complicate recovery from surgery.[29] Elective surgery should be postponed until the dependent patient has not had alcohol for seven to 10 days.

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