Concise Review for Primary-Care Physicians

Treatment of Alcohol Withdrawal in Hospitalized Patients

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Alcoholism can be encountered in many aspects of medicine. Frequently, primary-care physicians are asked to treat patients who are experiencing various stages of alcohol withdrawal while hospitalized for intercurrent illness. A thorough assessment of the patient is important because the symptoms and signs of alcohol withdrawal are nonspecific. Recognizing the patient who is at risk for alcohol withdrawal and initiating appropriate treatment can prevent progression to more serious symptoms and complications. Benzodiazepines are the drugs of choice for pharmacologic treatment of alcohol withdrawal. Their application by means of a symptom-triggered approach based on frequent, objective assessment of the patient is recommended. Adjunctive therapy for specific complications of alcohol withdrawal is discussed. After the acute withdrawal symptoms have been controlled, psychiatric or chemical dependence assessment (or both) is strongly encouraged.

Although primary-care physicians rarely admit patients to the hospital because of a primary diagnosis of alcohol withdrawal, the problem is often mentioned on the list of dismissal diagnoses. Investigators estimate that up to 20% of patients admitted to medical and surgical wards of community teaching hospitals have alcohol dependence. Historically, delirium tremens had an associated mortality rate as high as 20%; however, with appropriate treatment, mortality should now be much lower. This article briefly reviews current management of alcohol withdrawal.

DIAGNOSIS AND SCREENING

Alcoholism is a disease that patients do not readily discuss; thus, the examining physician must identify patients at risk for alcohol withdrawal and initiate treatment early and appropriately. The physician should also be aware of the possibility of withdrawal from multiple drugs, not just alcohol. Asking patients how much they drink may not be helpful in quantifying their actual intake of alcohol. A less confrontational and indirect approach will yield better and more complete information. Several approaches have been developed to establish a diagnosis of alcoholism. The easiest and quickest method is the CAGE mnemonic: (1) Do you feel you should cut down on your alcohol consumption? (2) Have people annoyed you by criticizing your drinking? (3) Have you felt guilty about your drinking? (4) Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (eye-opener)? This tool, used in both inpatient and outpatient settings, has repeatedly been shown to be both reliable and reproducible, and it is applicable at the bedside. A single positive response suggests a problem with alcohol. More than two positive responses correlate highly with severe alcohol abuse and should raise the issue of whether the patient will experience alcohol withdrawal.

PATHOPHYSIOLOGIC ASPECTS AND CLINICAL MANIFESTATIONS

The effects of alcohol on the central nervous system (CNS) are complex, and a comprehensive discussion of the pathophysiologic aspects of alcohol withdrawal is beyond the scope of this article. The primary effect of alcohol on the cell membranes of the CNS is depression of neuronal excitability, impulse conduction, and transmitter release. Patients with alcoholism seem to have a compensation for the depressant effect of alcohol. This phenomenon manifests as withdrawal symptoms when alcohol consumption is terminated or when the alcohol level in the CNS decreases. These symptoms of increased CNS activity, especially autonomic activity, account for the clinical picture of the alcohol withdrawal syndrome.

The precise manner in which the CNS overcomes the depressant effects of alcohol is unknown; however, several biologic mediators have been implicated, including serotonin, γ-aminobutyric acid, and cortisol. The primary mediator may be norepinephrine, although the exact role of multiple potential mediators remains to be determined. A detailed review of the mechanisms of alcohol withdrawal has been previously published. The clinical symptoms of alcohol withdrawal can be classified as early (24 to 48 hours) and late (more than 48 hours).
as well as minor and major. The level of autonomic hyperactivity and the presence of delirium are the main determinants of progression from minor to major symptoms (Fig. 1). The “3 Ts” (temperature, tremor, and tachycardia) of the delirium tremens may be the earliest signs of alcohol withdrawal, although true delirium tremens necessitates the presence of cognitive impairment. Insomnia, restlessness, agitation, nausea and vomiting, myaligias, tremor, systolic hypertension, and tachycardia can progress to disorientation and cognitive impairment. If alcohol withdrawal-related seizures occur, they usually occur early during the course of withdrawal. "Hallucinosis" can also occur early, especially in patients who have consumed alcohol for a prolonged period. These hallucinations can be both visual and auditory, although the patient has an otherwise clear sensorium, a feature that distinguishes such hallucinations from the hallucinations associated with delirium tremens.

The description of alcohol withdrawal by Sir William Osler in 1892 still applies today:

Delirium tremens (mania a potu) is really only an incident in the history of chronic alcoholism, and results from the long-continued action of the poison on the brain....A spree in a temperate person, no matter how prolonged, is rarely if ever followed by delirium tremens; but in the case of an habitual drinker a temporary excess is apt to bring on an attack. It sometimes develops in consequence of the sudden withdrawal of the alcohol....At the outset of the attack the patient is restless and depressed and sleeps badly....The patient talks constantly and incoherently; he is incessantly in motion, and desires to go out and attend to some imaginary business. Hallucinations of sight and hearing develop. He sees objects in the room, such as rats, mice, or snakes, and fancies that they are crawling over his body. The terror inspired by these imaginary objects is great, and has given the popular name "horrors" to the disease....There is much muscular tremor; the tongue is covered with a thick white fur, and when protruded is tremulous. The pulse is soft, rapid, and readily compressed. There is usually fever, but the temperature rarely registers above 102° or 103°....Insomnia is a constant feature. On the third or fourth day in favorable cases the restlessness abates, the patient sleeps, and improvement gradually sets in. The tremor persists for some days, and hallucinations gradually disappear, as the appetite returns.

Alcohol withdrawal has been formally defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV):

1. Cessation (or reduction) in alcohol use that has been heavy and prolonged.
2. Two (or more) of the following developing within several hours to a few days after criterion 1: autonomic hyperactivity (for example, sweating or pulse greater than 100); increased hand tremor; insomnia; transient visual, tactile, or auditory hallucinations or illusions; nausea or vomiting; psychomotor agitation; anxiety; and grand mal seizures.

3. The symptoms in criterion 2 cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
4. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Several assessment tools have been developed to help health-care professionals determine the need to treat alcohol withdrawal with more than a supportive environment. The Clinical Institute Withdrawal Assessment for Alcohol scale (revised) (CIWA-Ar) (Fig. 2) is currently recommended and is easy to use. In general, a score of less than 10 requires no pharmacologic treatment; a score of 10 to 20 requires at least later assessment, if not treatment; and a score of more than 20 usually merits pharmacologic treatment or a gradual increase to a higher dosage for a person receiving treatment. This tool can also help to identify patients with underlying complications because they may not respond in the usual manner—for example, their scores may not decrease as treatment progresses. Moreover, it can help to select patients who might need treatment in the intensive-care unit and intravenously administered therapy.

TREATMENT WITH BENZODIAZEPINES
The goals of treatment are amelioration of symptoms and prevention of complications. Mild alcohol withdrawal can be managed with a quiet, supportive environment, reorientation, and one-to-one contact. If patients progress symptomatically despite a supportive environment, pharmacologic treatment should be instituted. As previously noted, the
symptoms of withdrawal are primarily the manifestations of autonomic hyperactivity, and the cornerstone of treatment is benzodiazepines.

All benzodiazepines are effective. They can be used safely to replace the alcohol-depressant effects on the CNS, and their use can be rapidly tapered as symptoms abate. Multiple randomized controlled trials have shown the superiority of benzodiazepines to placebo in the treatment of alcohol withdrawal. Using the shorter-acting formulations may be advantageous, especially in elderly persons and in patients with hepatic dysfunction. In otherwise healthy patients, the longer-acting formulations are acceptable. Famil-

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**Fig. 2. Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-A).** (See text for scoring details.) (From Sullivan and colleagues.18)
iarity with the intravenous dose administered to a critically ill patient or to a patient in whom oral intake has been restricted is important. Intramuscular absorption is unpredictable and probably should be avoided. The preferred modes of administration are oral and intravenous (Table 1).

A key point in treating alcohol withdrawal is to begin with a larger dose of benzodiazepines than is commonly used when these drugs are prescribed for anxiety. This approach is necessary to overcome the patient’s autonomic hyperactivity. The patient’s response should then be observed, and the dosage adjusted accordingly. Many treatment centers have used fixed-dose schedules for withdrawal. Recent studies, however, have promoted a “symptom-triggered approach” that involves repeated assessments of the patient. This important advance in the treatment of alcohol withdrawal results in less total drug use and seems to be as efficacious as the fixed-dose schedules. The following illustrative case describes the symptom-triggered treatment approach.

ILLUSTRATIVE CASE
A 48-year-old man is hospitalized because of pneumonia. He admits to drinking one or two martinis a day. On the second hospital day, an increased heart rate, some tremulousness and restlessness, and increased blood pressure are noted. On physical examination, the patient is alert, somewhat agitated, tremulous, and oriented to person only, findings that definitely differ from those on examination at admission. No history of liver disease or previous alcohol withdrawal is evident. His respiratory status seems stable, and a repeated examination reveals no new signs of trauma or changes from the admission assessment other than disorientation and restlessness. Results of blood gas studies, glucose testing, electrocardiography, and electrolytes are stable. On the basis of the CIWA-Ar, the patient has a score of 40, an indication of a definite need for pharmacologic treatment. He is given an oral dose of diazepam (20 mg) and reexamined in 1½ to 2 hours, at which time his score is 32. He is not overly sedated, and an additional dose of diazepam (20 mg) is administered; he is reassessed in about 2 hours. Again, he is not sedated, although he is somewhat calm; his score has decreased to 24. A third dose of diazepam (10 mg) is given, and he is reexamined in 2 to 4 hours; his score is 19. He is given 5 mg of diazepam and is reassessed in about 4 hours.

ALTERNATIVES TO BENZODIAZEPINE TREATMENT
Several alternatives to benzodiazepines are available that can be used adjunctively and, occasionally, independently. β-Adrenergic blockers are useful for controlling blood pressure and tachyarrhythmias. Most of the arrhythmias that patients experience are responsive to β-blockade; however, the usual contraindications, including bronchospasm, heart block, and congestive heart failure, must be considered. Atenolol has been used widely and is helpful for single-day dosing; associated CNS side effects are minimal. The β-blockers, however, do not prevent progression to more serious symptoms of withdrawal and should not be used alone but should be used in conjunction with benzodiazepines. Moreover, they may mask symptoms of alcohol withdrawal. α-Blockers have been used to treat the hypertension associated with alcohol withdrawal. Clonidine hydrochloride, which has been studied extensively, is available in a patch preparation that is helpful for patients in whom oral intake has been restricted. As with β-blockers, the α-blockers should not be used alone but should be used in conjunction with benzodiazepines. They also can mask symptoms of alcohol withdrawal. Thus, some experts warn against the use of both α- and β-blockers.

Phenobarbital has the advantage of being long acting (half-life is 96 to 99 hours, similar to that of diazepam metabolites). Occasionally, only one or two doses are necessary, and the seizure threshold is increased in patients experiencing alcohol withdrawal. This drug has been used widely in Europe but infrequently in the United States, inasmuch as American physicians seem more comfortable and familiar with the benzodiazepines. Carbamazepine and valproic acid have also been used in Europe to treat alcohol withdrawal and are effective; however, North American experience with these agents is minimal. Similar to phenobarbital, they increase the seizure threshold. All three of these drugs (phenobarbital, carbamazepine, and valproic acid) can be used alone rather than in conjunction with benzodiazepines.

Magnesium can be used to increase the seizure threshold if the magnesium level is low. If, however, the initial magnesium level is normal, magnesium supplementation has probably little associated benefit. In addition, renal function must be normal before magnesium supplementation can be considered.

Table 1.—Equivalent, Potential Initial Doses of Benzodiazepines Frequently Used for Treatment of Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Administration (mg)</th>
<th>Intravenous Administration (mg)</th>
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<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td>Oxazepam*</td>
<td>120</td>
<td>...</td>
</tr>
<tr>
<td>Lorazepam*</td>
<td>4</td>
<td>1-2</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20</td>
<td>5-10</td>
</tr>
</tbody>
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*Shorter-acting formulations with fewer active metabolites.
Use of thiamine should always be considered. As subsequently discussed, administration of thiamine is the main method for preventing Wernicke’s encephalopathy and Korsakoff’s psychosis. It is safe and easy to administer (intramuscularly, intravenously, and orally) at 100 mg/day during the first few days of withdrawal. The only caveat is that, if a patient has a thiamine deficiency, administration of high-concentration glucose solutions without thiamine can precipitate acute Wernicke’s encephalopathy. In patients with oculogyric crises, high doses (up to 1,000 mg/day) have been used.

Multivitamins are useful if the patient is clinically malnourished. If, however, the patient seems to have a relatively normal state of nourishment on examination and routine laboratory tests (albumin and total protein), multivitamins have probably little associated benefit.

**COMPLICATIONS**

**Seizures.**—Alcohol withdrawal-related seizures have been reported to occur in up to 33% of patients who have consumed alcohol 48 to 87 days before hospitalization. \(^{15}\) Seizures generally occur during the first 48 hours and before delirium develops. \(^{4,5}\) They are usually generalized, self-limited, and single or occur in a short series. Intravenous administration of diazepam can be used to stop an acute episode. The use of phenytoin and the need for a loading dose of long-term anticonvulsant therapy are two issues that frequently arise. In general, the physician should consider anticonvulsant therapy if the patient has (1) a history of alcohol withdrawal-related seizures, (2) recurrent seizures after admission, or (3) a history of a prior seizure disorder unrelated to intake of alcohol.

Because of the varied histories in patients, both an anatomic and a metabolic assessment are important in determining the cause of the seizure. Imaging of the head and neurologic consultation should be strongly considered, particularly if the seizure occurs after delirium has begun or if the patient has multiple seizures. In addition, in a febrile patient who is having a seizure, a lumbar puncture is almost always necessary.

**Delirium Tremens.**—The later, more serious phases of alcohol withdrawal are characterized by clouding of the sensorium, profound autonomic hyperactivity, and hallucinations. Haloperidol and phenothiazines can be used to help control hallucinations. These drugs, however, can lower the seizure threshold and should be used cautiously, either alone or with benzodiazepines. Although the dose should be individualized, initiation of a low dose is prudent, especially if the patient has already received benzodiazepines, and subsequent doses can be increased as necessary.

**Arrhythmias.**—As previously noted, most cardiac arrhythmias associated with alcohol withdrawal are tachyarrhythmias. Although such arrhythmias respond well to \(\beta\)-blockers, the treatment regimen should be as that for any patient with arrhythmias.

**Wernicke-Korsakoff Syndrome.**—The Wernicke-Korsakoff syndrome is manifested by ataxia, cognitive impairment, and oculogyric crises attributed to thiamine deficiency. Korsakoff’s psychosis, a confabulatory psychosis, is believed to be related to a thiamine deficiency that may or may not follow typical Wernicke’s encephalopathy. Accordingly, thiamine should be considered for all patients who are undergoing treatment of alcohol withdrawal to prevent these complications. Chronic and recurring episodes of Wernicke’s encephalopathy can lead to chronic and irreversible dementia.

**Psychiatric.**—Some patients experiencing alcohol withdrawal have underlying psychiatric diagnoses, especially depression. \(^1\) After the acute treatment period has been completed, both chemical dependence counseling and psychiatric assessment can be initiated. Patients admitted to medical and surgical wards who have not heretofore recognized their difficulties with alcohol may be willing to discuss long-term treatment options. The opportunity for counseling should not be overlooked, and the skills of the chemical dependence counselor should be used.

**General.**—Dehydration, fluid and electrolyte disturbances, infection, pancreatitis, and alcoholic ketoacidosis are commonplace in patients experiencing alcohol withdrawal; a thorough initial examination and treatment are necessary. Management of these conditions is similar to that in other patients and thus will not be specifically addressed.

**CONCLUSION**

In patients experiencing alcohol withdrawal during hospitalization, the physician must perform a thorough physical examination. Occult infection, trauma, or the possibility of withdrawal from multiple drugs must be considered. Criteria from the DSM-IV can be used to help with the diagnosis.

Benzodiazepines are the drugs of choice. After administration of a trial load, the patient’s response should be noted. A symptom-triggered approach is recommended. The drug should be rapidly tapered as symptoms abate. Fixed-dose schedules should be avoided. The CIWA-Ar should be used to help adjust dosage, detect complications, and identify patients who require more intensive therapy. \(\alpha\)- or \(\beta\)-Blockers should be considered for autonomic hyperactivity that is not controlled with the benzodiazepines; however, such intervention cannot be used alone. Haloperidol can be used for hallucinations; however, administer cautiously if used alone. Complications, including seizures, arrhythmias, and infection, can be treated as usual. The skills and expertise of the available chemical dependence services should be used.
REFERENCES

Questions About Alcohol Withdrawal
(See article, pages 777 to 782)

1. Which one of the following is true regarding drug therapy for alcohol withdrawal?
   a. Any benzodiazepine can be used to treat alcohol withdrawal, usually beginning with a higher than usual (for anxiety) dose
   b. Intramuscular administration is preferred
   c. Isoniazid is useful
   d. Shorter-acting benzodiazepines are usually preferred
   e. ~-Blockers should be used alone (without benzodiazepines)

2. Which one of the following best describes the symptoms of alcohol withdrawal?
   a. All patients require pharmacologic therapy
   b. The degree of autonomic hyperactivity and the absence or presence of delirium help determine whether symptoms should be considered major or minor
   c. Alcoholic hallucinosis is associated with a cloudy sensorium
   d. The degree of tachycardia predicts the onset of seizures
   e. Symptoms considered major or minor are distinctly different

3. Which one of the following is true of alcohol withdrawal-related seizures?
   a. Usually occur late during the course of withdrawal (more than 48 hours) and after delirium develops
   b. Always require anticonvulsant therapy
   c. Are usually generalized and self-limited
   d. Occur multiple times during an episode of withdrawal
   e. Can be prevented with the use of ~-blockers

4. Which one of the following is useful in treating alcohol withdrawal without benzodiazepines?
   a. Thiamine
   b. Haloperidol
   c. Atenolol
   d. Clonidine hydrochloride
   e. Phenobarbital

5. Which one of the following is true regarding treatment of alcohol withdrawal?
   a. Fixed-dose schedules of benzodiazepines are best
   b. A score of 15 on the Clinical Institute Withdrawal Assessment for Alcohol scale (revised) suggests that the physician should gradually increase the dose of benzodiazepine
   c. Frequent assessment of the patient is rarely needed
   d. Symptom-triggered administration of benzodiazepines results in less total drug use
   e. Magnesium supplementation should always be used

Correct answers: [ ] [ ] [ ] [ ] [ ]