Management of moderate and severe alcohol withdrawal syndromes

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Literature review current through: Nov 2015. | This topic last updated: Nov 12, 2015.

INTRODUCTION — Alcoholism is such a common condition that virtually every clinician is confronted with its complications. There are an estimated 8 million alcohol dependent people in the United States. Approximately 500,000 episodes of withdrawal severe enough to require pharmacologic treatment occur each year [1].

The in-patient management of syndromes associated with moderate and severe alcohol withdrawal is reviewed here. The ambulatory management of mild alcohol withdrawal, the initial diagnosis and treatment of alcohol dependence, and specific conditions due to alcohol-related organ damage (eg, cirrhosis, pancreatitis) are discussed elsewhere. (See "Medically supervised alcohol withdrawal in the ambulatory setting" and "Psychosocial treatment of alcohol use disorder" and "Pharmacotherapy for alcohol use disorder" and "Clinical manifestations and diagnosis of alcoholic fatty liver disease and alcoholic cirrhosis" and "Etiology and pathogenesis of chronic pancreatitis in adults" and "Hematologic complications of alcohol use" and "Screening for unhealthy use of alcohol and other drugs in primary care" and "Brief intervention for unhealthy alcohol and other drug use").

PATHOPHYSIOLOGY

Overview — It is not entirely clear why some individuals suffer from more severe withdrawal symptoms than others, but genetic predisposition may play a role [2]. Experiments in 1955 demonstrated that alcohol-naive volunteers given continual alcohol for longer periods developed more severe withdrawal than those who drank for shorter periods [3]. These results imply that most people are vulnerable to the effects of the abrupt cessation of prolonged, sustained ethanol intake. However, withdrawal usually does not occur in the general population because most people drink in an episodic fashion that does not lead to the sustained high blood concentrations of alcohol necessary to develop tolerance and withdrawal.

Symptoms of alcohol withdrawal occur because alcohol is a central nervous system depressant. Alcohol simultaneously enhances inhibitory tone (via modulation of gamma-aminobutyric acid activity) and inhibits excitatory tone (via modulation of excitatory amino acid activity). Only the constant presence of ethanol preserves homeostasis. Abrupt cessation un_masks the adaptive responses to chronic ethanol use resulting in overactivity of the central nervous system.

Gamma-aminobutyric acid — Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. Highly specific binding sites for ethanol are found on the GABA receptor complex [4]. Chronic ethanol use induces an insensitivity to GABA such that more inhibitor is required to maintain a constant inhibitory tone [5]. As alcohol tolerance develops, the individual retains arousal at alcohol concentrations which would normally produce lethargy or even coma in relatively alcohol naive individuals. Cessation of alcohol or a reduction from chronically elevated concentrations results in decreased inhibitory tone.

Excitatory amino acids — Glutamate is one of the major excitatory amino acids. When glutamate binds to the N-methyl-D-aspartate (NMDA) receptor, calcium influx leads to neuronal excitation. Ethanol inhibits glutamate induced excitation [6,7]. Adaptation occurs by increasing the number of glutamate receptors in an attempt to maintain a normal state of arousal. Cessation of alcohol or a reduction from chronically elevated concentrations results in unregulated excess excitation.

MINOR WITHDRAWAL SYMPTOMS — Minor withdrawal symptoms are due to central nervous system
hyperactivity, and can include:

- Insomnia
- Tremulousness
- Mild anxiety
- Gastrointestinal upset; anorexia
- Headache
- Diaphoresis
- Palpitations

Symptoms are usually present within six hours of the cessation of drinking and may develop while patients still have a significant blood alcohol concentration (table 1) [8]. If withdrawal does not progress, these findings resolve within 24 to 48 hours. The specific minor withdrawal symptoms in a given patient typically are consistent from one episode to the next. The ambulatory management of mild alcohol withdrawal, including criteria to determine which patients are suitable for out-patient management, is discussed elsewhere. (See "Medically supervised alcohol withdrawal in the ambulatory setting".)

**WITHDRAWAL SEIZURES** — Withdrawal-associated seizures are generalized tonic-clonic convulsions that usually occur within 12 to 48 hours after the last drink, but may occur after only two hours of abstinence (table 1) [9]. The seizures occur predominantly in patients with a long history of chronic alcoholism.

Withdrawal seizures are usually singular or occur as a brief flurry of seizures over a short period. Recurrent or prolonged seizures or status epilepticus should prompt an investigation into possible structural or infectious etiologies, generally guided by the findings of cranial computed tomography (CT) and/or lumbar puncture. Benzodiazepines and phenobarbital can be used to treat status epilepticus while investigations proceed. Several studies have demonstrated that phenytoin is ineffective in the treatment of alcohol withdrawal seizures and the drug should not be used for this purpose [10-12]. (See "Evaluation of the first seizure in adults".)

While some authors use other anticonvulsants such as carbamazepine and levetiracetam in the therapy of alcohol withdrawal, the role of these medications in alcohol withdrawal related seizures is incompletely evaluated.

Although seemingly benign, alcohol withdrawal seizures left untreated progress to delirium tremens in nearly one-third of patients [9]. (See 'Delirium tremens (DT)' below.)

**ALCOHOLIC HALLUCINOSIS** — Despite a tendency to equate alcoholic hallucinosis with delirium tremens, the two terms are NOT synonymous. Alcoholic hallucinosis refers to hallucinations that develop within 12 to 24 hours of abstinence and typically resolve within 24 to 48 hours (which is the earliest point at which delirium tremens typically develops) (table 1) [13]. Hallucinations are usually visual, although auditory and tactile phenomena may also occur. In contrast to delirium tremens, alcoholic hallucinosis is not associated with global clouding of the sensorium but with specific hallucinations, and vital signs are usually normal. (See "Approach to the patient with visual hallucinations", section on 'Alcohol and drug use'.)

**DELIRIUM TREMENS (DT)**

**Clinical manifestations of severe withdrawal and DT** — Delirium tremens (DT) is defined by hallucinations, disorientation, tachycardia, hypertension, hyperthermia, agitation, and diaphoresis in the setting of acute reduction or abstinence from alcohol. In the absence of complications, symptoms of DT typically persist for up to seven days.

Patients with DT have significantly elevated cardiac indices, oxygen delivery, and oxygen consumption [14]. Arterial pH rises due to hyperventilation, which may be a rebound effect related to the respiratory depressant properties of alcohol. Hyperventilation and consequent respiratory alkalosis in this setting result in a significant decrease in cerebral blood flow [15]. There is a correlation between the length of the preceding alcohol binge,
the degree of clouding of the sensorium, and the size of the average decrease in cerebral hemispheric blood flow, although there is no association between blood flow parameters and hallucinations or tremors [15].

Severe alcohol withdrawal may have an important impact on fluid and electrolyte status. Almost all patients in acute withdrawal are hypovolemic as a result of diaphoresis, hyperthermia, vomiting, and tachypnea. Hypokalemia is common due to renal and extrarenal potassium losses, alterations in aldosterone levels, and changes in potassium distribution across the cell membrane [16,17]. Hypomagnesemia is common in patients with DT and may predispose to dysrhythmias and seizures [18]. Hypophosphatemia may occur due to malnutrition, may be symptomatic, and if severe, may contribute to cardiac failure and rhabdomyolysis.

**Risk factors** — Approximately 5 percent of patients who undergo withdrawal from alcohol suffer from DT. DT typically begins between 48 and 96 hours after the last drink and lasts one to five days (table 1). DT and alcoholic hallucinosis are NOT synonymous and symptoms that occur a few hours after the cessation of drinking, even if severe, are usually not manifestations of DT. (See ‘Alcoholic hallucinosis’ above.)

Risk factors for the development of DT include [19-21]:

- A history of sustained drinking
- A history of previous DT
- Age greater than 30
- The presence of a concurrent illness
- The presence of significant alcohol withdrawal in the presence of an elevated alcohol level
- A longer period since the last drink (ie, patients who present with alcohol withdrawal more than two days after their last drink are more likely to experience DT than those who present within two days)

**Mortality** — DT is associated with a mortality rate of up to 5 percent. This figure has diminished from a 37 percent mortality rate reported in the early 20th century, probably as a result of earlier diagnosis, improvements in supportive and pharmacologic therapies, and improved treatment of comorbid illnesses [2,22-26]. Death usually is due to arrhythmia, complicating illnesses, such as pneumonia, or failure to identify an underlying problem that led to the cessation of alcohol use, such as pancreatitis, hepatitis, or central nervous system injury or infection. Older age, preexisting pulmonary disease, core body temperature greater than 40°C (104°F), and coexisting liver disease are associated with a greater risk of mortality [27].

**MANAGEMENT**

**Ruling out alternative diagnoses** — Alcohol withdrawal remains a clinical diagnosis. It may be necessary to perform extensive testing, including lumbar puncture and cranial CT, to rule out other diagnostic considerations with confidence. This is particularly true when the presentation includes altered mental status and fever. Conditions, such as infection (eg, meningitis), trauma (eg, intracranial hemorrhage), metabolic derangements, drug overdose, hepatic failure, and gastrointestinal bleeding, can mimic or coexist with alcohol withdrawal [28]. A premature diagnosis of alcohol withdrawal can lead to inappropriate use of sedatives, which can further delay accurate diagnosis [29].

**Symptom control and supportive care** — Once comorbid illnesses have been excluded or adequately treated, the management of alcohol withdrawal is directed at alleviating symptoms and identifying and correcting metabolic derangements. Benzodiazepines are used to control psychomotor agitation and prevent progression to more severe withdrawal. Supportive care, including intravenous fluids, nutritional supplementation, and frequent clinical reassessment including vital signs, is important. Clinicians must avoid complacency when treating patients with alcohol withdrawal. (See ‘Treatment of psychomotor agitation with benzodiazepines’ below and ‘Symptom-triggered therapy’ below.)

Patients should be placed in a quiet, protective environment. Mechanical restraint may be necessary temporarily for patients suffering from delirium tremens (DT) in order to protect both the patient and caretakers. Clinicians should follow their facility’s guidelines for documentation and implementation of physical restraints. Once
adequate chemical sedation is achieved, physical restraints should be removed, as resistance against restraints can increase temperature, produce rhabdomyolysis, and cause physical injury.

Volume deficits can be calculated and replaced accordingly, or, if there are no contraindications, isotonic intravenous fluid can be infused rapidly until patients are clinically euvolemic. Thiamine and glucose should be administered in order to prevent or treat Wernicke's encephalopathy [30,31]. Multivitamins containing or supplemented with folate should be given routinely, and deficiencies of glucose, potassium, magnesium, and phosphate should be corrected as needed. Initially (first day or two), treatment should be intravenous as gastrointestinal absorption is impaired in many patients who abuse alcohol chronically. The details of these supportive treatments are discussed separately. (See "Wernicke encephalopathy", section on 'Treatment' and "Overview of the chronic neurologic complications of alcohol" and "Clinical manifestations and treatment of hypokalemia in adults" and "Evaluation and treatment of hypophosphatemia".)

Some clinicians treat alcohol withdrawal patients with an intravenous infusion of a combination of thiamine, folate, and a multivitamin in isotonic saline with 5 percent dextrose. The multivitamin makes the fluid appear yellow, and thus, this treatment combination is sometimes referred to as a "banana bag". Use of this treatment has not been well studied, and it may not meet the specific requirements for fluid, glucose, and other substrates of many patients with alcohol withdrawal.

During the early phases of withdrawal alcoholic patients are often given nothing by mouth (ie, NPO) to prevent aspiration [32]. However, nutritional support is essential as alcoholic patients are frequently malnourished and have high metabolic needs due to their excited autonomic state. Initially, parenteral glucose supplementation is sufficient, but additional nutrition may be needed for patients who remain unable to eat for more than a day or two. Patients considered at high risk for complications should be monitored in an intensive care unit (table 2). (See "Nutrition support in critically ill patients: An overview").

**Treatment of psychomotor agitation with benzodiazepines**

**Drug selection** — Benzodiazepines are used to treat the psychomotor agitation most patients experience during withdrawal and to prevent progression from minor withdrawal symptoms to major ones [22-25,28,32-35]. Diazepam (Valium), lorazepam (Ativan), and chlordiazepoxide (Librium) are used most frequently to treat or prevent alcohol withdrawal, but other benzodiazepines may be used [36]. In general, long-acting benzodiazepines with active metabolites (eg, diazepam) are preferred because they seem to result in a smoother course with less chance of recurrent withdrawal or seizures. We recommend a symptom-triggered approach to treatment with benzodiazepines. (See 'Symptom-triggered therapy' below.)

We prefer lorazepam (Ativan) or oxazepam (Serax) for the treatment of patients with advanced cirrhosis or acute alcoholic hepatitis. The shorter half-life of lorazepam and the absence of active metabolites with oxazepam may prevent prolonged effects if oversedation occurs. In contrast, chlordiazepoxide has a relatively long half-life and may lead to oversedation in patients with severe liver disease. Treatment with agents available in parenteral form (eg, lorazepam, diazepam) may be necessary in patients who cannot receive oral medications.

Given the recent trend of drug shortages, preferred agents may not always be available. A treatment algorithm for clinicians managing moderate or severe alcohol withdrawal without access to diazepam is provided (algorithm 1).

Benzodiazepines exert their effect via stimulation of gamma-aminobutyric acid (GABA) receptors, causing a decrease in neuronal activity and relative sedation. (See 'Gamma-aminobutyric acid' above.)

**Route** — All patients with seizures or DT require intravenous (IV) therapy with benzodiazepines. IV therapy is appropriate for the initial management of most patients with tremulousness from alcohol withdrawal because of guaranteed absorption and rapidity of onset. It is important to have IV access in all patients at risk of severe withdrawal.

Intramuscular administration should be avoided because of variable drug absorption. Oral formulations are
preferred in most outpatient settings, for the prevention of withdrawal in asymptomatic patients known to be at risk, and for those with mild and minimal symptoms. (See 'Prophylaxis' below and "Medically supervised alcohol withdrawal in the ambulatory setting".)

**Dosing** — Titration of medications should be based upon a given patient's risk factors for and ability to tolerate DT. As an example, a patient younger than 45 years with no comorbid illnesses should be lightly sedated to a degree that insures safety and comfort but does not obscure the neurologic examination. In contrast, an older patient with preexisting cardiopulmonary disease may benefit from heavier sedation, but must be closely monitored due to the greater risk imposed by the high systemic stress of major withdrawal or oversedation. Explicit criteria for ICU admission are provided (table 2).

A variety of dosing schedules can be used. We generally give IV diazepam, 5 to 10 mg IV every 5 to 10 minutes, until the appropriate level of sedation is achieved. Lorazepam, 2 to 4 mg IV every 15 to 20 minutes, can also be used. Equivalent doses of oral chlordiazepoxide may be on the order of 25 to 100 mg, which can be repeated hourly. In severe withdrawal, select patients may require massive doses (>500 mg diazepam) to achieve initial control of symptoms, and continued aggressive use of benzodiazepines thereafter (>2000 mg diazepam over 48 hours).

Fixed schedule therapy, in which a benzodiazepine is given at fixed intervals even if symptoms are absent, is often administered despite evidence against this strategy [37-40]. A fixed dose schedule strategy is most useful for preventing withdrawal in patients at risk, but asymptomatic or minimally symptomatic. The only advantage of this strategy is for the provider, as frequent reassessment is not required.

**Symptom-triggered therapy** — We favor a symptom-triggered approach to the treatment of alcohol withdrawal that involves providing medication only when a patient has symptoms.

To use this approach, a regular systematic assessment should be made of the patient's status using a validated instrument, such as the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar), a measure of withdrawal severity (table 3) [41], or some equivalent assessment. A calculator to determine the CIWA-Ar score is provided (calculator 1). Evaluation intervals as frequent as every 10 to 15 minutes are appropriate for patients with more severe symptoms being treated with IV benzodiazepines. Once severe symptoms are controlled, hourly reassessment of such patients is reasonable. In contrast, an interval of four to six hours is reasonable for stable patients with mild symptoms receiving oral benzodiazepines.

When the score is elevated, additional medication is given. For acute withdrawal, we give diazepam 5 to 10 mg IV for any score of 8 or greater on the CIWA-Ar.

In some patients with severe alcohol withdrawal, including those who require tracheal intubation and mechanical ventilation, assessment scales such as the CIWA-Ar that rely upon patients being able to answer specific questions cannot be used effectively. In these patients, we suggest using a sedation scale more appropriate for the intensive care setting such as the Richmond Agitation-Sedation Scale (RASS) (table 4). We aim for a score of 0 to -2 when using the RASS to manage such patients. (See "Sedative-analgesic medications in critically ill adults: Selection, initiation, maintenance, and withdrawal", section on 'Monitoring'.)

Multiple randomized and observational studies support this simple concept of giving the patient the therapy they need, only when they need it [37-40,42]. Taken collectively, these studies demonstrate that symptom-triggered therapy achieves equivalent or superior clinical endpoints while requiring lower total doses of sedatives and shorter periods of hospitalization.

In the landmark study of this approach, 101 patients admitted to an inpatient alcohol detoxification unit were randomly assigned to treatment with chlordiazepoxide using a fixed schedule or a symptom-triggered therapy [37]. Patients in the symptom-triggered group required less medication (median 100 versus 425 mg) and a shorter treatment period (median 9 versus 68 hours).

**Disposition and monitoring** — Patients being treated for moderate or severe alcohol withdrawal must be
closely monitored and many require admission to an intensive care unit (ICU). A table of ICU admission criteria is provided (table 2). Older patients are at greater risk for delirium tremens and may not tolerate the systemic stress of major withdrawal. Standard monitoring includes continual assessment of vital signs, pulse oximetry, fluid status, and neurological function. (See 'Delirium tremens (DT)' above.)

Refractory delirium tremens — Some patients have refractory delirium tremens (DT) despite treatment with high-dose benzodiazepines, possibly because of low endogenous GABA levels or acquired conformational changes in the GABA receptor [43,44]. Refractory DT is not clearly defined. It may be present if more than 50 mg of diazepam or 10 mg of lorazepam is required to control the symptoms of severe withdrawal during the first hour of treatment, or if doses greater than 200 mg of diazepam or 40 mg of lorazepam fail to adequately control symptoms during the initial three to four hours of treatment [45]. As with any dangerous intoxication, we recommend obtaining assistance from a medical toxicologist or poison control center in such instances. (See 'Additional resources' below.)

In patients with refractory DT, barbiturates (specifically phenobarbital) can be very effective when given with benzodiazepines [45]. We give phenobarbital 130 to 260 mg IV, repeated every 15 to 20 minutes, until symptoms are controlled. While one recent study provides support for early use of phenobarbital, we feel that this study needs to be replicated before it can be adopted into mainstream practice [46]. In addition, some preliminary evidence supports the use of dexmedetomidine in refractory patients [47]. While this approach appears promising, we advise caution until well performed controlled trials of safety and efficacy are available.

Benzodiazepines, which increase the frequency of GABA chloride channel opening and barbiturates, which increase the duration of channel opening, may work synergistically.

Another reasonable alternative treatment for refractory DT is propofol, which can act to open chloride channels in the absence of GABA, and may also antagonize the excitatory amino acids that are upregulated during alcohol withdrawal [48,49]. Endotracheal intubation and mechanical ventilation are frequently necessary if phenobarbital or propofol are used.

Alternative and contraindicated agents — Drugs other than phenobarbital and propofol have been used with benzodiazepines or, rarely, alone to treat alcohol withdrawal. These agents are less well studied than benzodiazepines and may mask the hemodynamic signs of withdrawal, which can precede seizures. We believe they should not be used routinely in the treatment of moderate or severe alcohol withdrawal. Such drugs include:

- Ethanol
- Antipsychotics (eg, haloperidol)
- Anticonvulsants (eg, carbamazepine)
- Centrally acting alpha-2 agonists (eg, clonidine)
- Beta blockers (eg, propranolol)
- Baclofen

All of these agents can reduce the frequency and intensity of minor withdrawal symptoms, but more data support the efficacy and safety of benzodiazepines in reducing the risk of seizures and delirium tremens.

- Ethanol – Ethanol should not be used as therapy in the setting of acute alcohol withdrawal. It is difficult to titrate, associated with many adverse metabolic and end-organ effects, and clearly inferior to benzodiazepines [50]. Of note, the metabolism and kinetics of ethanol have not been well studied in the critically ill.

- Antipsychotics – Phenothiazines and butyrophenones (including haloperidol) lower the seizure threshold and should not be used routinely in the withdrawing alcoholic [51]. These drugs may also interfere with heat dissipation and do not exhibit cross-tolerance with ethanol.
Treatment with antipsychotics would only be appropriate when a decompensated thought disorder (such as schizophrenia) coexists with ethanol withdrawal and any symptoms associated with ethanol withdrawal have been definitively treated with benzodiazepines. In our experience, such occurrences are rare, even in patients with known thought disorders.

If a clinician determines that antipsychotic therapy is indicated, we recommend an ECG to screen for QT prolongation (a contraindication to many antipsychotic medications) and the correction of electrolyte abnormalities (such as hypokalemia and hypomagnesemia, which are common in alcoholics) before any medication is administered.

- Anticonvulsants – Sustained anticonvulsant therapy has no role in patients with isolated alcohol withdrawal seizures. The overwhelming majority of seizures from withdrawal are self-limited and do not require treatment with anticonvulsants. If status epilepticus ensues, phenobarbital or propofol may be used for short-term management in conjunction with benzodiazepines, while an underlying cause is investigated. (See 'Withdrawal seizures' above.)

While carbamazepine may have a role in the outpatient management of mild alcohol withdrawal, convincing evidence that the drug effectively treats patients with delirium tremens or other severe symptoms is lacking [52]. (See "Medically supervised alcohol withdrawal in the ambulatory setting".)

- Centrally acting alpha-2 agonists – Some clinicians report using centrally acting alpha-2 agonists (eg, dexametadomidine) as adjunct therapy for alcohol withdrawal, and these agents may reduce some symptoms of withdrawal. However, there are no controlled trials showing that they prevent the development of seizures or DT. Pending more convincing studies, we believe centrally acting alpha-2 agonists should not be used as a primary treatment for acute severe alcohol withdrawal.

- Beta blockers – Beta blockers may reduce minor symptoms of withdrawal, but they have not been shown to prevent the development of seizures or DT. We believe they should not be used for the treatment of acute severe alcohol withdrawal. However, patients with known cardiovascular disease should be given their maintenance medications after sedation and volume resuscitation, as sustained tachycardia and hypertension may contribute to cardiovascular morbidity especially in the elderly.

- Baclofen – Baclofen, a selective agonist of the gamma-aminobutyric acid (GABA)-B receptor used to treat reversible spasticity, has been studied as a therapy for acute alcohol withdrawal, but its effectiveness in controlling severe symptoms remains unproven [53-56]. We believe baclofen should not be used for the treatment of acute severe alcohol withdrawal.

**PROPHYLAXIS** — Patients with a history of seizures, delirium tremens, or prolonged, heavy alcohol consumption, who are minimally symptomatic or asymptomatic and are admitted to the hospital for other reasons, can be prophylactically treated with oral chlordiazepoxide. Should more severe symptoms develop, the patients are managed in standard fashion. (See 'Management' above.)

For prophylaxis, we give 25 to 100 mg every six hours for one day, followed by 25 to 50 mg every six hours for an additional two days. Monitoring is no different from patients in active withdrawal. Patients should be reassessed frequently and additional 25 to 50 mg doses of chlordiazepoxide administered each hour if a score of 8 or greater is achieved on the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) (table 3) [41].

Asymptomatic or minimally symptomatic patients at lower risk for seizures or delirium tremens who are being admitted to the hospital for other reasons should be closely monitored and may be treated with oral chlordiazepoxide 25 to 50 mg every hour as needed when a score of 8 or greater is achieved on the CIWA-Ar.

After acute treatment, all patients should be screened for alcohol dependence and should be considered at risk for recurrent episodes of withdrawal. In-hospital evaluation and long-term follow-up are recommended. (See
"Psychosocial treatment of alcohol use disorder."

ADDITIONAL RESOURCES — Regional poison control centers in the United States are available at all times for consultation on patients who are critically ill, require admission, or have clinical pictures that are unclear (1-800-222-1222). In addition, some hospitals have clinical and/or medical toxicologists available for bedside consultation and/or inpatient care. Whenever available, these are invaluable resources to help in the diagnosis and management of ingestions or overdoses. The World Health Organization provides a listing of international poison centers at its website: [www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html](http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)


SUMMARY AND RECOMMENDATIONS — A table summarizing the emergent management of alcohol withdrawal is provided ([table 5](http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html)).

- Alcohol withdrawal remains a clinical diagnosis. It may be necessary to perform extensive testing (eg, lumbar puncture and cranial CT) to rule out other diagnoses as many patients with alcoholism do not stop drinking spontaneously and present with overt withdrawal symptoms that may mask other disorders. Conditions such as infection, trauma, metabolic derangements, drug overdose, hepatic failure, and gastrointestinal bleeding can mimic or coexist with alcohol withdrawal. (See [Ruling out alternative diagnoses](http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html) above.)


- Delirium tremens (DT) is a syndrome characterized by agitation, disorientation, hallucinations, and autonomic instability (tachycardia, hypertension, hyperthermia, and diaphoresis) in the setting of acute reduction or abstinence from alcohol. DT is associated with a mortality rate of up to 5 percent, but the rate can be substantially higher if the condition goes untreated. Alcoholic hallucinosis and DT are distinct clinical entities. Patients at risk and those who fail to respond appropriately to initial doses of sedatives should be monitored closely and treated aggressively ([table 2](http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html)). (See [Delirium tremens (DT)](http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html) above.)

- Risk factors for delirium tremens include:
  - A history of sustained drinking
  - A history of previous DT
  - Age greater than 30
  - The presence of a concurrent illness
  - The presence of significant alcohol withdrawal in the presence of an elevated ethanol level
A longer period (more than two days) between the last drink and the onset of withdrawal

- Patients in alcohol withdrawal require medical treatment and observation. We suggest that patients who present with signs and symptoms of moderate or severe alcohol withdrawal be treated with benzodiazepines (Grade 2B). We give diazepam 5 to 10 mg IV, repeated every 5 to 10 minutes until symptoms are controlled. Lorazepam may also be used (2 to 4 mg IV, repeated every 15 to 20 minutes). The general goal of sedation is a calm but alert state. Patients at greater risk for adverse outcomes may need heavier sedation. IV benzodiazepines should be continued until it is clear that the patient is no longer delirious and at high risk for aspiration, and that absorption from the gut is reliable. (See 'Treatment of psychomotor agitation with benzodiazepines' above.)

- We recommend that benzodiazepines be dosed and administered using a validated assessment tool, such as the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) (table 3) (Grade 1A). This requires formally assessing patients at regular intervals. Evaluation intervals as frequent as every 10 to 15 minutes are appropriate for patients with severe symptoms; an interval of four to six hours is reasonable for stable patients with mild symptoms. For acute withdrawal, we give diazepam 5 to 10 mg IV for any score of 8 or greater on the CIWA-Ar. (See 'Symptom-triggered therapy' above.)

- Patients with moderate or severe alcohol withdrawal need close monitoring, some in an intensive care setting (table 2). (See 'Disposition and monitoring' above.)

- For delirium tremens refractory to aggressive treatment with high-dose benzodiazepines, we suggest treatment with phenobarbital or propofol (Grade 2C). Patients receiving these agents require ICU admission and will likely require mechanical ventilation (table 5). (See 'Refractory delirium tremens' above.)

- Asymptomatic or minimally symptomatic patients at risk for alcohol withdrawal, but admitted to the hospital for other reasons, should be closely monitored and may be treated prophylactically with oral benzodiazepines. We use chlordiazepoxide. (See 'Prophylaxis' above.)

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REFERENCES


Topic 323 Version 26.0
# Timing of alcohol withdrawal syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical findings</th>
<th>Onset after last drink</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor withdrawal</td>
<td>Tremulousness, mild anxiety, headache, diaphoresis, palpitations, anorexia, GI upset; Normal mental status</td>
<td>6 to 36 hours</td>
</tr>
<tr>
<td>Seizures</td>
<td>Single or brief flurry of generalized, tonic-clonic seizures, short post-ictal period; Status epilepticus rare</td>
<td>6 to 48 hours</td>
</tr>
<tr>
<td>Alcoholic hallucinosis</td>
<td>Visual, auditory, and/or tactile hallucinations with intact orientation and normal vital signs</td>
<td>12 to 48 hours</td>
</tr>
<tr>
<td>Delirium tremens</td>
<td>Delirium, agitation, tachycardia, hypertension, fever, diaphoresis</td>
<td>48 to 96 hours</td>
</tr>
</tbody>
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**Suggested criteria for ICU admission of patients with alcohol withdrawal**

<table>
<thead>
<tr>
<th>Age &gt;40</th>
</tr>
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<tbody>
<tr>
<td>Cardiac disease (heart failure, arrhythmia, angina, myocardial ischemia, recent myocardial infarction)</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td>Marked acid-base disturbances</td>
</tr>
<tr>
<td>Severe electrolyte abnormalities (hypokalemia, hypophosphatemia, hypomagnesemia, hypocalcemia)</td>
</tr>
<tr>
<td>Respiratory insufficiency (hypoxemia, hypercapnia, severe hypocapnia, pneumonia, asthma, COPD)</td>
</tr>
<tr>
<td>Potentially serious infections (wounds, pneumonia, trauma, urinary tract infection)</td>
</tr>
<tr>
<td>Signs of gastrointestinal pathology (pancreatitis, GI bleeding, hepatic insufficiency, suspected peritonitis)</td>
</tr>
<tr>
<td>Persistent hyperthermia (T &gt;39°C [103°F])</td>
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<tr>
<td>Evidence of rhabdomyolysis</td>
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<tr>
<td>Renal insufficiency or increased fluid requirements</td>
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<tr>
<td>History of prior alcohol withdrawal complications (eg, delirium tremens, alcohol withdrawal seizures)</td>
</tr>
<tr>
<td>Need for frequent or high doses of sedatives or an intravenous infusion to control symptoms</td>
</tr>
<tr>
<td>Withdrawal despite an elevated ethanol concentration</td>
</tr>
</tbody>
</table>

COPD: Chronic obstructive pulmonary disease; GI: Gastrointestinal; ICU: Intensive care unit

*Adapted from Carlson, RW, Keske, B, Cortez, D, J Crit Illness 1998; 13:311.*

Graphic 73377 Version 2.0
Treatment of severe alcohol withdrawal when IV diazepam is not available*

AWS: alcohol withdrawal syndrome; CIWA: clinical institute withdrawal assessment for alcohol scale; RASS: richmond agitation sedation scale.

* Doses are for adults. Medications and doses may need adjustment based upon comorbidities (eg, liver disease), patient age, or other factors (eg, coadministered medications).

¶ Lorazepam infusion is titrated to effect, and additional symptom-based bolus doses, 2-4 mg IV, are given when titrating the infusion up.

Courtesy of Robert S. Hoffman, MD.

Graphic 53322 Version 2.0
# Clinical Institute Withdrawal Assessment Scale for Alcohol, revised (CIWA-Ar)

<table>
<thead>
<tr>
<th>Nausea and vomiting</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No nausea or vomiting</td>
<td>0 Not present</td>
</tr>
<tr>
<td>1</td>
<td>1 Very mild</td>
</tr>
<tr>
<td>2</td>
<td>2 Mild</td>
</tr>
<tr>
<td>3</td>
<td>3 Moderate</td>
</tr>
<tr>
<td>4 Intermittent nausea with dry heaves</td>
<td>4 Moderately severe</td>
</tr>
<tr>
<td>5</td>
<td>5 Severe</td>
</tr>
<tr>
<td>6</td>
<td>6 Very severe</td>
</tr>
<tr>
<td>7 Constant nausea, frequent dry heaves and vomiting</td>
<td>7 Extremely severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paroxysmal sweats</th>
<th>Auditory disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No sweats visible</td>
<td>0 Not present</td>
</tr>
<tr>
<td>1 Barely perceptible sweating, palms moist</td>
<td>1 Very mild harshness or ability to frighten</td>
</tr>
<tr>
<td>2</td>
<td>2 Mild harshness or ability to frighten</td>
</tr>
<tr>
<td>3</td>
<td>3 Moderate harshness or ability to frighten</td>
</tr>
<tr>
<td>4 Beads of sweat obvious on forehead</td>
<td>4 Moderately severe hallucinations</td>
</tr>
<tr>
<td>5</td>
<td>5 Severe hallucinations</td>
</tr>
<tr>
<td>6</td>
<td>6 Extremely severe hallucinations</td>
</tr>
<tr>
<td>7 Drenching sweats</td>
<td>7 Continuous hallucinations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Visual disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No anxiety, at ease</td>
<td>0 Not present</td>
</tr>
<tr>
<td>1</td>
<td>1 Very mild photosensitivity</td>
</tr>
<tr>
<td>2</td>
<td>2 Mild photosensitivity</td>
</tr>
<tr>
<td>3</td>
<td>3 Moderate photosensitivity</td>
</tr>
<tr>
<td>4 Moderately anxious, guarded</td>
<td>4 Moderately severe visual hallucinations</td>
</tr>
<tr>
<td>5</td>
<td>5 Severe visual hallucinations</td>
</tr>
<tr>
<td>6</td>
<td>6 Extremely severe visual hallucinations</td>
</tr>
<tr>
<td>7 Acute panic state, consistent with severe delirium or acute schizophrenia</td>
<td>7 Continuous visual hallucinations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agitation</th>
<th>Tactile disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Normal activity</td>
<td>0 None</td>
</tr>
<tr>
<td>1 Somewhat more than normal activity</td>
<td>1 Very mild paresthesias</td>
</tr>
<tr>
<td>2</td>
<td>2 Mild paresthesias</td>
</tr>
<tr>
<td></td>
<td>3 Moderate paresthesias</td>
</tr>
<tr>
<td></td>
<td>4 Moderately severe hallucinations</td>
</tr>
<tr>
<td>Tremor</td>
<td>Orientation and clouding of sensorium</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>3</td>
<td>5 Severe hallucinations</td>
</tr>
<tr>
<td>4 Moderately fidgety and restless</td>
<td>6 Extremely severe hallucinations</td>
</tr>
<tr>
<td>5</td>
<td>7 Continuous hallucinations</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7 Paces back and forth during most of the</td>
<td><strong>Orientation and clouding of sensorium</strong></td>
</tr>
<tr>
<td>interview or constantly thrashes about</td>
<td></td>
</tr>
<tr>
<td><strong>Tremor</strong></td>
<td></td>
</tr>
<tr>
<td>0 No tremor</td>
<td>0 Oriented and can do serial additions</td>
</tr>
<tr>
<td>1 Not visible, but can be felt at fingertips</td>
<td>1 Cannot do serial additions</td>
</tr>
<tr>
<td>2</td>
<td>2 Disoriented for date by no more than 2 calendar days</td>
</tr>
<tr>
<td>3</td>
<td>3 Disoriented for date by more than 2 calendar days</td>
</tr>
<tr>
<td>4 Moderate when patient's hands extended</td>
<td>4 Disoriented for place and/or patient</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7 Severe, even with arms not extended</td>
<td><strong>Total score is a simple sum of each item score (maximum score is 67).</strong></td>
</tr>
</tbody>
</table>

**Score:**

- <10: Very mild withdrawal
- 10-15: Mild withdrawal
- 16-20: Modest withdrawal
- >20: Severe withdrawal


Graphic 64835 Version 2.0
## Richmond agitation-sedation scale (RASS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Overtly combative or violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls on or removes tubes or catheters, aggressive behavior toward staff</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequent nonpurposeful movement or patient-ventilator dyssynchrony</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious or apprehensive but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Not fully alert, sustained (&gt;10 seconds) awakening, eye contact to voice</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Briefly (&lt;10 seconds) awakens with eye contact to voice</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>Any movement (but no eye contact) to voice</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice, any movement to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

### Procedure

1. Observe patient. Is patient alert and calm (score 0)?
2. Does patient have behavior that is consistent with restlessness or agitation?
   Assign score +1 to +4 using the criteria listed above.
3. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
   - Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score -1).
   - Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score -2).
   - Patient has any movement in response to voice, excluding eye contact (score -3).
4. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response.
   - Patient has any movement to physical stimulation (score -4).
   - Patient has no response to voice or physical stimulation (score -5).


Graphic 57874 Version 1.0
Moderate and severe alcohol withdrawal: Rapid overview

To obtain emergent consultation with a medical toxicologist, call the United States Poison Control Network at 1-800-222-1222, or access the World Health Organization's list of international poison centers (www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html).

### Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol tremulousness</td>
<td>Occurs early, characterized by hypertension, tachycardia, tremors, and anxiety, with normal mental status</td>
</tr>
<tr>
<td>Alcohol withdrawal seizures</td>
<td>Occurs early, usually single or brief flurry of seizures with short post-ictal period</td>
</tr>
<tr>
<td>Alcoholic hallucinosis</td>
<td>Occurs early, no evidence of autonomic instability</td>
</tr>
<tr>
<td>Delirium tremens</td>
<td>Occurs late, characterized by delirium and autonomic instability</td>
</tr>
</tbody>
</table>

### History

Pattern of alcohol use, history of withdrawal symptoms; inquire about reasons for cessation of alcohol

### Physical examination

Vital signs, mental status, presence of tremor; examine for signs of trauma, abdominal tenderness, other findings consistent with complications of chronic alcohol use

### Laboratory testing

No test truly assesses withdrawal; ancillary data (eg, serum ethanol concentration, lumbar puncture (CSF), head CT, lipase) frequently needed to assess patient and rule out coexistent illness

### Treatment

#### Benzodiazepines

First line therapy for ALL alcohol withdrawal syndromes

Most patients with symptoms require IV therapy initially

**Give:**

- Diazepam, 5 to 10 mg IV, repeat every 5 to 10 minutes, **OR**
- Lorazepam, 2 to 4 mg IV, repeat every 15 to 20 minutes

Massive doses (>2000 mg diazepam in 48 hours) may be required

Clinically stable patients with minimal symptoms may be treated with oral medications

#### Barbiturates

Synergistic with benzodiazepines; give if patient refractory to high-dose benzodiazepines

- Phenobarbital 130 to 260 mg IV, repeat every 15 to 20 minutes

Intubation frequently required with concurrent benzodiazepine and barbiturate use

ALL patients requiring barbiturates are monitored in an intensive care unit

#### Propofol

- [Link to related content]
<table>
<thead>
<tr>
<th>Excellent agent if patient refractory to benzodiazepines and barbiturates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation almost always required</td>
</tr>
<tr>
<td>1 mg/kg IV push as induction agent for intubation; titrate continuous infusion for sedation</td>
</tr>
</tbody>
</table>

**Supportive care**

- Assure adequate fluid and electrolyte replacement
- Give parenteral thiamine 100 mg and glucose daily
- Give multivitamin supplements
- Ensure adequate caloric support

Graphic 64745 Version 7.0
Disclosures


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