Alcohol Withdrawal Syndrome: Improving Outcomes Through Early Identification And Aggressive Treatment Strategies

Abstract

Alcoholism is a prevalent medical and psychiatric disease, and, consequently, alcohol withdrawal is encountered frequently in the emergency department. This issue reviews the pathophysiology of the alcohol withdrawal syndrome, describes the 4 manifestations of alcohol withdrawal, and looks at the available evidence for optimal treatment of alcohol withdrawal in its diverse presentations. Patients commonly manifest hyperadrenergic signs and symptoms, necessitating admission to the intensive care unit, intravenous benzodiazepines, and, frequently, adjunctive pharmacotherapy. An aggressive front-loading approach with benzodiazepines is proposed and the management of benzodiazepine-resistant disease is addressed.

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Critical Care Issue
Case Presentations

A 56-year-old alcoholic woman presents to the ED seeking detoxification from alcohol. Her reported consumption is 750 mL of vodka daily. Her last drink was 15 hours prior, at 4:30 PM the previous afternoon. Upon presentation to the ED, she is found to be tachycardic, with a heart rate of 139 beats/min; and hypertensive, with blood pressure of 172/84 mm Hg. She is diaphoretic and has a severe tremor. She is unable to hold a glass of water without spilling its contents. The patient denies any history of illicit drug use and states that she has no history of alcohol withdrawal seizures or delirium tremens. She receives 1 liter of intravenous normal saline and an intravenous dose of 5 mg of diazepam. Fifteen minutes later, her tremor is worsening and her vital signs have failed to improve. What treatment modalities should you choose for her worsening symptoms?

As you are returning to her room, a nurse asks for your assistance in an adjacent room where EMS has brought in a 62-year-old man with agitated delirium. You find a disheveled, malnourished-appearing man being restrained by 2 security guards. He is tachycardic, with a heart rate of 162 beats/min; and hypertensive, with blood pressure of 165/92 mm Hg. He is attempting to sit up in the stretcher and appears to be miming turning a key in a car ignition, repeating over and over, “I have to go.” He does not attend to you or the staff, and he appears to look off into space, tracking objects that are not there. He is diaphoretic and tremulous. The paramedics tell you they know him as a local alcoholic. He has a history of pancreatitis, and his wife told the paramedics that he has complained of abdominal pain and has been vomiting for the past 2 or 3 days. The paramedics were initially called for seizure-like activity. What are your priorities in the initial diagnosis and management of this patient?

Introduction

Alcohol withdrawal syndrome (AWS) is a major cause of morbidity and mortality among alcoholics, and, for many medical centers, it creates a significant burden on resource utilization. Several studies have reported that alcohol withdrawal increases the morbidity and mortality of coexisting illness and prolongs the duration of hospital admissions. Alcoholic withdrawal has been recognized since ancient times. Marked strides in recognition and management have occurred over the past century. The mortality rate of delirium tremens (DT), the most severe manifestation of AWS, was 52% in 1912, and had decreased to 10% to 12% by the 1930s. Mortality due to DT is now estimated to be 2% to 3%. Nonetheless, complications due to alcohol abuse remain important clinical problems, accounting for 21% of medical intensive care unit (ICU) admissions at one urban hospital. Alcohol withdrawal was the most common of these diagnoses.

While seemingly straightforward, the diagnosis of AWS is often missed, or its signs and symptoms are erroneously attributed to another cause, such as sepsis or drug intoxication. The differential diagnosis is broad. There is no single laboratory or imaging test that can diagnose AWS, and the criteria are strictly historical and clinically based. An understanding of risk factors for progression to severe AWS as well as basic knowledge of the pathophysiology of alcohol withdrawal will aid the emergency clinician in the prompt recognition of AWS. Recognition of risk factors will allow for early empiric treatment as well as optimal choices for therapeutic interventions. In turn, unnecessary hospital and ICU admissions can be avoided and hospital lengths of stay shortened when alcohol withdrawal is recognized promptly and aggressive treatment is initiated early. This review will evaluate the limited available literature regarding the management of AWS in the emergency department (ED). It will also address the underlying pathophysiology of AWS and the treatment modalities available to emergency clinicians. Finally, it will introduce adjunctive and controversial therapeutic interventions.

Critical Appraisal Of The Literature

Relevant primary literature was identified by a search of the Cochrane Database of Systematic Reviews, PubMed, and Ovid MEDLINE. Search terms included “alcohol withdrawal syndrome,” “alcohol withdrawal seizure,” “alcoholic hallucinosis,” “alcoholic hallucinations,” and “delirium tremens.” We reviewed only reports available in the English language and excluded outpatient studies. Using the same search terms, relevant review literature was identified. Select case reports and case series were utilized where clinical trial literature was lacking. The bibliographies of major toxicology textbooks and review articles were also queried to ensure relevant literature was not overlooked.

A total of 87 randomized controlled studies of drug-versus-drug trials or drug-versus-placebo trials were identified. However, there was a paucity of trials pertaining directly to the ED management of AWS. The settings of most clinical trials were inpatient psychiatric alcohol detoxification units, predominantly in Europe, and the numbers of participants in these studies were small. In addition, the patient populations in these inpatient detoxification unit trials did not necessarily parallel the patient population seen in the ED with acute, severe alcohol withdrawal. The challenges of research directly pertaining to the ED diagnosis and management of AWS are numerous and include difficulty in obtaining informed consent (especially in the setting of delirium) and the lack of homogeneity of alcohol withdrawal. While the underlying principles of the
management of the 4 stages of AWS are similar, studies focusing on a single presentation (such as alcohol withdrawal seizure) cannot necessarily be applied to alcohol withdrawal as a whole.

**Etiology And Pathophysiology**

AWS represents a complex collection of signs and symptoms that occur as a direct result of the acute cessation or reduction of alcohol intake. The syndrome is best understood as a state of central nervous system (CNS) hyperexcitation, with clinical manifestations ranging from mild tremor to DT, seizure, severe autonomic dysfunction, and death.

**Ethanol Pharmacology**

Following ingestion, ethanol is rapidly absorbed and distributed, with a volume of distribution near that of total body water \((V_w, 0.6 \text{ L/kg})\). Under typical conditions, approximately 90% of ingested alcohol is absorbed by 60 minutes, though this may be delayed by food in the stomach or co-ingestants. Absorption may also be prevented by the action of gastric mucosal alcohol dehydrogenase (ADH) which oxidizes ethanol and decreases the amount available for absorption.22

The liver is the primary means of elimination of ethanol, though small amounts are excreted unchanged in the kidneys, lungs, and sweat. Ethanol is metabolized primarily by ADH to form acetaldehyde and, secondarily, by aldehyde dehydrogenase (ALDH) to form acetate.22 Acetate is then converted to acetyl coenzyme A (acetyl-CoA), which enters the Krebs cycle in a thiamine-dependent conversion, where it is metabolized to carbon dioxide and water. Although there is wide individual variation (especially among alcoholics), ethanol is generally metabolized with a clearance rate of approximately 20 mg/dL/h, based on a study of patients presenting to the ED.22 There are additional minor hepatic metabolic pathways that are involved in ethanol metabolism, but these are of little clinical significance.

**Pathophysiology Of Alcohol Withdrawal**

Though there is no specific ethanol receptor, ethanol produces generalized CNS depression by multiple and incompletely understood mechanisms. Ethanol potentiates the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, at GABA\(_A\) receptors and antagonizes the effect of glutamate, an excitatory amino acid, at N-methyl-D-aspartate (NMDA) receptors. Chronic ethanol potentiation of GABA activity results in conformational changes to the GABA\(_A\) receptor and desensitization of the GABA\(_A\) receptor to ethanol. A similar phenomenon occurs at the NMDA receptor; chronic NMDA receptor antagonism by ethanol leads to either an upregulation in the number of receptors or a con-formational change of the receptor subunits. This alteration of receptor structure and function results in resistance to the antagonistic effects of ethanol, requiring higher blood alcohol levels to achieve similar effect. In acute ethanol withdrawal, a hyper-excitatory state exists due to the loss of GABA inhibitory effect and potentiation of NMDA-mediated excitatory neurotransmission. This is the underlying pathophysiologic mechanism of acute AWS and the CNS hyperexcitable state.

By mechanisms not completely understood, repeated episodes of AWS lead to increasingly difficult-to-treat withdrawal symptoms known as “kindling.” Data suggest that these GABA receptor alterations may become permanent, leading to benzodiazepine resistance.23

**Differential Diagnosis**

For patients presenting to the ED with signs and symptoms of acute alcohol withdrawal, correct identification of the diagnosis is critical. A wide differential diagnosis must be considered when entertaining alcohol withdrawal as the primary diagnosis. It is imperative that evaluation for alternate or concomitant diagnoses begins at the time of presentation, because coexisting illness may precipitate alcohol withdrawal, and delay in diagnosing the primary pathology may cause significant morbidity or mortality.

The differential diagnosis for alcohol withdrawal is extensive. Table 1 highlights many of the toxicologic and nontoxicologic diagnoses to consider. The diagnosis of alcohol withdrawal is primarily historical and is supported by physical examination findings including tachycardia, hypertension, tremor, diaphoresis, and neuromuscular excitation. Commonly, there is underlying disease, and both may cause a patient to present to the ED and lead to the cessation of alcohol consumption. Thus, the emergency clinician must also investigate why the patient has stopped consuming alcohol. Often, underlying pancreatitis or severe gastritis should be considered and treated appropriately.

As there is no diagnostic imaging or laboratory test to confirm AWS, it should be considered a diag-

<table>
<thead>
<tr>
<th>Table 1. Differential Diagnoses Of Alcohol Withdrawal Syndrome</th>
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<tbody>
<tr>
<td><strong>Toxicologic Differential</strong></td>
<td><strong>Medical Differential</strong></td>
</tr>
<tr>
<td>• Sympathomimetic syndrome (cocaine, amphetamines, etc)</td>
<td>• Thyrotoxicosis</td>
</tr>
<tr>
<td>• Antimuscarinic syndrome</td>
<td>• Encephalitis</td>
</tr>
<tr>
<td>• Antidepressant withdrawal</td>
<td>• Acute psychosis</td>
</tr>
<tr>
<td>• Severe alcohol intoxication</td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td>• Serotonin syndrome</td>
<td>• Trauma (head injury)</td>
</tr>
<tr>
<td>• Neuroleptic malignant syndrome</td>
<td>• Sepsis and septic shock</td>
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</tbody>
</table>

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nosis of exclusion. Drug intoxication, predominantly sympathomimetic or antimuscarinic syndromes, should be considered and ruled out either historically, clinically, or by laboratory confirmation. Importantly, severe alcohol intoxication can mimic alcohol withdrawal. Severe alcohol intoxication can lead to confusion, delirium, tachycardia, and diaphoresis. A serum ethanol level may be considered in cases where the history is inconclusive. There is no single ethanol level at which withdrawal is impossible; however, withdrawal does become increasingly unlikely at higher ethanol levels. Alcoholics may experience ethanol withdrawal at serum ethanol levels that are intoxicating to the naïve drinker.

Prehospital Care

The overall goal for the prehospital care of patients with alcohol withdrawal is rapid transport to an appropriate facility while preventing injury to the patient or prehospital care provider. Recognition that alcohol withdrawal is an underlying medical disorder rather than a primary psychiatric disease is paramount. The presence of abnormal vital signs or severe agitation should prompt the prehospital care provider to transport the patient to a medical facility rather than a psychiatric facility. Agitation due to suspected alcohol withdrawal should be treated with benzodiazepines, when available, in the prehospital setting. Lorazepam, diazepam, or midazolam should all be effective. Midazolam is an ideal intramuscular option. There are no data regarding the prehospital administration of sedatives to patients with alcohol withdrawal. Antipsychotics should be avoided, as these may lower the seizure threshold.

Drug intoxication from overdose can be difficult to differentiate from alcohol withdrawal, and due to the complex receptor pharmacology of antipsychotic agents, benzodiazepines are a safer choice until a more complete toxicologic workup can be completed. Appropriate consideration of other causes of agitated delirium should be considered. (See Table 1, page 3.) If trauma is suspected, appropriate immobilization and transport to a trauma center are indicated.

Emergency Department Evaluation

The underlying pathophysiology of AWS is CNS hyperexcitation. As such, tachycardia and hypertension are manifestations of the underlying pathology and these conditions generally respond to standard therapies targeting CNS hyperexcitation. If a patient’s symptoms and objective parameters fail to improve with escalating doses of GABA_\_ receptor agonists (ie, benzodiazepines or barbiturates), the patient’s worsening condition may be due to benzodiazepine-resistant alcohol withdrawal or an alter-

Table 2. Risk Factors For The Development Of Alcohol Withdrawal

- Personal history of AWS or DT^24
- Family history of AWS or DT^24
- Metabolic derangements (ALT > 50 units/L, serum chloride < 96 mEq/L, and serum potassium < 3.6 mEq/L)^25
- Serum ethanol concentration > 150 mg/dL on admission^26

Note: Factors for development of severe alcohol withdrawal are poorly identified; no single characteristic or combination of the above characteristics can reliably predict development of severe withdrawal or DT.

Abbreviations: ALT, alanine aminotransferase; AWS, alcohol withdrawal syndrome; DT, delirium tremens.
or developing 2 or more of the 8 signs or symptoms that are not attributable to other medical conditions or mental disorders. The 8 signs include:

- Autonomic hyperactivity
- Tremor
- Insomnia
- Nausea/vomiting
- Hallucinations
- Psychomotor agitation
- Anxiety
- Seizures

**Autonomic Hyperactivity**
Almost invariably, patients with moderate or severe alcohol withdrawal will exhibit autonomic hyperexcitability evidenced by tachycardia, hypertension, and diaphoresis. These effects may be blunted in patients taking sympatholytics, such as beta-adrenergic blockers or alpha-2 adrenergic agonists, for hypertension, migraine, anxiety, musculoskeletal disorders (tizanidine), or attention deficit disorder (clonidine, guanfacine).

**Alcoholic Tremor**
Tremor represents the mildest form of alcohol withdrawal, and it is easily identified on physical examination as a coarse muscle tremor in outstretched hands or protruding tongue. Patients may feign the extended hand tremor in an attempt to obtain treatment with benzodiazepines or other sedative-hypnotic agents; however, the tongue tremor is more difficult to feign and is probably a more sensitive confirmation of alcoholic tremor.

**Alcoholic Hallucinosis**
Hallucinations (visual, auditory, or tactile) develop in 7% to 8% of patients with AWS. The hallucinations are most often tactile, but they may be visual. The sensorium remains otherwise normal, which distinguishes alcoholic hallucinosis from DT. While hallucinations may portend impending DT, a very small percentage of patients with alcoholic hallucinosis progress to DT.

**Seizures**
Alcohol withdrawal seizures occur most commonly within 24 hours after cessation of alcohol consumption. Typically, alcohol withdrawal seizures are isolated, of short duration, and with little to no postictal period. Status epilepticus is rare and complicates <3% of alcohol withdrawal seizures. Since alcoholics are at increased risk for multiple CNS problems, including infection, subdural hemorrhage, and metabolic derangements, additional diagnoses should be entertained in patients presenting to the ED with AWS, and alternative causes of seizures and status epilepticus must be considered.

**Delirium Tremens**
DT represents the most severe form of AWS. The signs and symptoms of DT are a continuation of the symptoms of milder forms of alcohol withdrawal but they are accompanied by alteration in mentation, including inattention or disorientation. As mentioned previously, it is imperative to evaluate for other causes of delirium, especially in a patient population that is at high risk for coexisting pathology.

**Diagnostic Studies**

There are no particular diagnostic studies that will show a patient is in withdrawal from alcohol. Rather, AWS is a clinical diagnosis of exclusion. Diagnostic studies are useful to rule out other causes of tremor, tachycardia, hypertension, seizures, hallucinations, and delirium.

All patients with suspected moderate or severe alcohol withdrawal should have basic laboratory studies obtained, including basic serum chemistries and a complete blood count (CBC). The CBC may show leukocytosis, which may be indicative of a hyperadrenergic state or underlying infection. An elevated mean corpuscular volume (MVC) may be indicative of pernicious anemia secondary to vitamin B12 deficiency. Serum pH and osmolality tests may be indicated based on the results of the patient’s chemistries; alcoholic ketoacidosis may present with an elevated anion gap. The serum pH may be low or normal due to concomitant ketoacidosis and contraction alkalosis. Alcoholics commonly have severe electrolyte abnormalities including hypokalemia, hypomagnesemia, hyponatremia, and alcoholic ketoacidosis.

A urine immunoassay for drugs of abuse is usually indicated. There are limitations to the basic urine drug screen, but the presence of cocaine or amphetamines may provide diagnostic clues to the patient’s hyperadrenergic state. Serum salicylate and acetaminophen levels are indicated in cases where the history of present illness may suggest drug overdose. Abdominal pain in an alcoholic should prompt evaluation for pancreatitis.

Obtaining an ethanol level is also recommended; as severe alcohol intoxication can mimic alcohol withdrawal in some individuals. Additionally, individuals who have alcohol withdrawal with an elevated ethanol level are more likely to develop severe alcohol withdrawal. In cases where laboratory studies are being obtained, a serum ethanol level is preferred; however, in cases of mild alcohol withdrawal (ie, alcoholic tremor with normal vital signs) measurement of the expired ethanol in breath (breathalyzer) will suffice.

A chest x-ray is indicated in cases where hypoxia or fever is present. Computed tomography of the head is warranted in cases with alteration in mental
Treatment

GABA<sub>α</sub> Agonists

Benzodiazepines

The cornerstone of the management of AWS is administration of sedative-hypnotic xenobiotics, most notably, benzodiazepines. The use of sedative-hypnotics in AWS is logical, given the psychomotor agitation that develops with severe symptoms. As central GABA<sub>α</sub> agonists, benzodiazepines directly address the underlying pathophysiology of the GABA<sub>α</sub> receptor driving alcohol withdrawal. A landmark study in 1969 compared chlordiazepoxide, hydroxyzine, thiamine, chlorpromazine, and placebo. Chlordiazepoxide was associated with the lowest incidence of DT and alcohol withdrawal seizures. Two Cochrane reviews concluded that benzodiazepines are effective in the management of alcohol withdrawal.

The first-line pharmaceutical class for the management of mild, moderate, and severe alcohol withdrawal symptoms is benzodiazepines. They have stood the test of time. Multiple studies have promoted one xenobiotic after another against benzodiazepines, but no other drug class has been demonstrated to be superior. A 1997 meta-analysis further supported the use of benzodiazepines as first-line agents over alternative regimens, showing decreased withdrawal severity, decreased rates of delirium, and decreased incidence of seizure.

Benzodiazepines are effective for the management of early alcohol withdrawal in oral, intramuscular, and intravenous forms. Oral therapy affords the advantages of avoiding intravenous access as well as the potential option of outpatient treatment. Intravenous administration allows for rapid titration. Intravenous benzodiazepines should always be used in the treatment of severe alcohol withdrawal due to their rapid onset of action and ease of rapid titration.

There is much debate regarding the optimal benzodiazepine for AWS. One must balance the ease of dose titration and the duration of action to control symptoms quickly with avoiding unnecessary and prolonged sedation. With intravenous administration, lorazepam reaches peak cerebrospinal fluid (CSF) concentration in 7 minutes, whereas diazepam reaches peak CSF concentration in 3.7 minutes.

The time to effects of diazepam occurs in 1 to 5 minutes, whereas the time to effects of lorazepam occur in 5 to 20 minutes. The more rapid achievement of peak concentrations (and thus peak effect) of diazepam allows for easy, rapid titration and avoidance of dose-stacking. Dose-stacking is the administration of additional medication doses before previous doses have reached peak effect. This clinical scenario often results in oversedation.

There is no correlation between CSF concentration and clinical effect for AWS, but experience and consensus recommend diazepam for these reasons. For AWS refractory to 200 mg of diazepam in 4 hours or requiring a single dose of diazepam ≥ 40 mg, escalating doses of 20 mg, 50 mg, and 100 mg per dose every 15 minutes is recommended and supported by case-control literature.

While there is no randomized controlled trial comparing the efficacy of diazepam versus lorazepam for early control of alcohol withdrawal symptoms, case series and case control literature support the use of escalating diazepam dosing over lorazepam.

Other pharmacokinetic factors of diazepam make it ideal for the expected clinical course of alcohol withdrawal. Table 3 compares the pharmacoki-

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Table 3. Pharmacologic Properties Of Diazepam, Lorazepam, Midazolam, And Chlordiazepoxide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lipid Solubility</th>
<th>V&lt;sub&gt;D&lt;/sub&gt; (L/kg)</th>
<th>Time to Onset</th>
<th>Active Metabolites?</th>
<th>Initial Dose*</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>+++</td>
<td>0.9</td>
<td>1-5 min IV</td>
<td>Yes</td>
<td>10-20 mg IV</td>
<td>• 5 mg/mL injectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-20 mg PO</td>
<td>• Rectal gel 5 mg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 2 mg, 5 mg, and 10 mg tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 1 mg/mL, 5 mg/mL oral solution</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>+++</td>
<td>1.3</td>
<td>5-20 min IV</td>
<td>No</td>
<td>2-4 mg IV</td>
<td>• 2 mg/mL and 4 mg/mL injectable</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-4 mg PO</td>
<td>• 0.5 mg, 1 mg, and 2 mg tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 2 mg/mL oral solution</td>
</tr>
<tr>
<td>Midazolam</td>
<td>+++</td>
<td>0.8</td>
<td>2-5 min IM/IV</td>
<td>Yes</td>
<td>2-4 mg IM/IV</td>
<td>• 1 mg/mL and 5 mg/mL injectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 2 mg/mL oral syrup</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>+++</td>
<td>0.3</td>
<td>2-3 hours PO</td>
<td>Yes</td>
<td>50-100 mg PO</td>
<td>• 5 mg, 10 mg, and 25 mg capsules</td>
</tr>
</tbody>
</table>

*For 70 kg adult, for alcohol withdrawal syndrome.
Abbreviations: IM, intramuscular; IV, intravenous; PO, by mouth; V<sub>D</sub>, volume of distribution.
Chloral hydrate and its inactive metabolites are excreted in urine; however, there is potential for hepatic injury, hypoglycemia, and caustic vascular injury when administered intravenously, and possible adverse effects on wound healing. Due to these shortcomings, most studies have deemed ethanol to be an ineffective means of managing acute alcohol withdrawal. Ethanol has been reported as a potential treatment for AWS. It seems logical to replace what is missing: at first glance, ethanol appears as the perfect treatment for alcohol withdrawal. However, the use of ethanol (oral or intravenous) in the hospital is fraught with difficulties, including the need for frequent monitoring of blood alcohol levels, potential for hepatic injury, hypoglycemia, and possible adverse effects on wound healing. Due to these shortcomings, most studies have deemed this an ineffective means of managing acute alcohol withdrawal. Ethanol has an exceedingly narrow and variable therapeutic index, and it is difficult to titrate due to zero-order elimination kinetics. The use of ethanol for the treatment of acute alcohol withdrawal is strongly discouraged.

**Treating Uncomplicated Alcohol Withdrawal**

The ED management of AWS begins with an assessment of the severity of alcohol withdrawal. This occurs promptly after the initial assessment of airway, breathing, and circulation. The emergency clinician may obtain an excellent sense of withdrawal severity from simple observation. The presence of tachycardia, hypertension, diaphoresis, agitation, and/or seizure activity (or history) suggests severe withdrawal. Patients deemed to have severe alcohol withdrawal should be treated with intravenous benzodiazepines to control symptoms and prevent progression to life-threatening withdrawal.

Patients with mild withdrawal symptoms are candidates for ED discharge. (See the “Disposition” section, page 15.) Outpatient management of mild withdrawal is fraught with difficulties, including the need for frequent monitoring of blood alcohol levels, potential for hepatic injury, hypoglycemia, and possible adverse effects on wound healing. Due to these shortcomings, most studies have deemed this an ineffective means of managing acute alcohol withdrawal. Ethanol has an exceedingly narrow and variable therapeutic index, and it is difficult to titrate due to zero-order elimination kinetics. The use of ethanol for the treatment of acute alcohol withdrawal is strongly discouraged.

**Barbiturates**

Phenobarbital has been used both in uncomplicated alcohol withdrawal and in DT. Studies regarding its use are limited. One study compared lorazepam/chlordiazepoxide and phenobarbital for the management of patients with uncomplicated withdrawal who were discharged from the ED. The authors found that lorazepam given in the ED and oral chlordiazepoxide given at discharge were equivalent to phenobarbital given in the ED and placebo given at discharge. For DT, a Dutch study comparing phenobarbital to diazepam found the 2 treatments equivalent; however, there was a slightly higher rate of respiratory depression in the phenobarbital group (4% vs 1%). A 2013 study showed that a single 10 mg/kg dose of intravenous phenobarbital decreased the probability of ICU admission in a population admitted for alcohol withdrawal. Barbiturates have a distinct binding site on the GABA receptor. While phenobarbital increases chloride influx by prolonging channel opening in the presence of GABA, at high doses, it does not require the presence of GABA for chloride channel opening and chloride influx. Escalating doses of 65 mg, 130 mg, and 260 mg intravenously every 20 to 30 minutes are often effective, and are well below the status epilepticus dose of 15 mg/kg (about 1000 mg in a 70-kg adult). Care must be taken to avoid dose-stacking, as the peak effects of intravenous phenobarbital are seen in 20 to 40 minutes.

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alcohol withdrawal is cost-effective and has similar success rates to inpatient treatment. Patients who are not intoxicated, have no history of complicated AWS (withdrawal seizures or DT), no significant underlying medical or psychiatric comorbidities, and a Clinical Institute Withdrawal of Alcohol Scale, Revised (CIWA-Ar) score of < 8 can be safely managed as outpatients, provided close outpatient follow-up with an addiction specialist or an outpatient alcohol detoxification program is available. See Figure 1 for links and QR codes for an online tool for administering the CIWA-Ar and a PDF of the CIWA-Ar. Figure 2, page 9, displays the complete CIWA-Ar.

Oral benzodiazepines are appropriate for this patient population. Chlordiazepoxide is an ideal choice, as it is long-acting and has less abuse potential than diazepam or lorazepam, due to its slower onset of action. Reasonable chlordiazepoxide dosing would be 50 to 100 mg every 6 hours for 4 doses, then 25 to 50 mg every 6 hours. Patients should be provided with only a short supply (2 to 3 days) due to the abuse potential of benzodiazepines and to encourage follow-up. Diazepam and lorazepam are also suitable for outpatient management in doses of 10 to 20 mg and 2 to 4 mg every 6 hours as needed, respectively.

**Treating More-Severe Withdrawal Symptoms**

Management of more-severe alcohol withdrawal symptoms should consist of aggressive early treatment. Initial attention to airway, breathing, and circulation are mandatory. The emergency clinician must also consider other disorders in the differential diagnosis for alcohol withdrawal. Initial control of symptoms is best done with intravenous benzodiazepines. As stated previously, intravenous diazepam offers the advantages of rapid onset of action for easy titration and long-acting metabolites, allowing for self-tapering of the GABA-agonist effect.

Repeating escalating doses of intravenous diazepam (20 mg, 50 mg, 100 mg) or lorazepam (2 mg, 4 mg, 8 mg, 16 mg) are recommended until symptoms are controlled. Escalating doses of diazepam can be given every 10 to 15 minutes, while doses of lorazepam should be spaced out every 15 to 20 minutes to avoid oversedation. Benzodiazepines should be titrated based on the clinical appearance of the patient as well on correction of vital sign abnormalities. For severe withdrawal, titration to a state of somnolence with arousal to minimal tactile stimulus is ideal. The use of escalating diazepam dosing in this fashion and diazepam front-loading has been shown to reduce the frequency of a number of important markers of alcohol withdrawal including seizure, DT, and the need for mechanical ventilation.

In the absence of coadministered sedatives (such as opioids), benzodiazepines rarely interfere with respiratory drive except in the very young, the obese, and the elderly. Bedside titration of benzodiazepines by the treating clinician is strongly recommended in order to prevent oversedation, especially when large and frequent doses of benzodiazepines are used.

**Alcohol Withdrawal Seizures**

As with early alcohol withdrawal, the pharmacologic cornerstone of withdrawal seizure management is benzodiazepines. Numerous studies have evaluated the efficacy of antiepileptic drugs (AEDs) compared to benzodiazepines or placebo for the prevention of recurrent alcohol withdrawal seizures. In the setting of significant alcohol withdrawal, AEDs uniformly fail, compared to benzodiazepines. This is easily explained by the etiology of alcohol withdrawal seizures, namely a neuroexcitatory state due to decreased GABA tone and increased NMDA tone. There is no role for traditional AEDs – except benzodiazepines or barbiturates – in the prevention of alcohol withdrawal seizure.

Alcohol withdrawal seizures are typically self-limited. The presence of status epilepticus would be highly unusual and concomitant pathology should be investigated in such cases. Thus, the administration of benzodiazepines is for prevention of recurrent seizure and for the treatment of active withdrawal. There are insufficient data pertaining to alcohol withdrawal seizure to recommend diazepam over lorazepam. However, extrapolating from the pharmacology literature, the electroencephalographic effects of a single dose of lorazepam may outlast those of a single dose of diazepam.

**Alcoholic Hallucinosis**

The management of alcoholic hallucinosis mimics that of uncomplicated alcohol withdrawal. Benzodi-
### Figure 2. Clinical Institute Withdrawal Assessment Of Alcohol Scale, Revised (CIWA-Ar)

<table>
<thead>
<tr>
<th>Patient:</th>
<th>Date:</th>
<th>Time:</th>
<th>Pulse or heart rate, taken for one minute:</th>
<th>Blood pressure:</th>
</tr>
</thead>
<tbody>
<tr>
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#### 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

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

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

#### 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

#### 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

#### 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

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

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

#### 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

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

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The CIWA-Ar is not copyrighted and may be reproduced freely. This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer. The maximum score is 67 (see instrument). Patients scoring less than 10 do not usually need additional medication for withdrawal.

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Clinical Pathway For Emergency Department Management Of Alcohol Withdrawal Syndrome

Patient presents with signs of AWS
- Autonomic hyperactivity
- Agitation
- Tremor
- Seizure
- Delirium

- Send basic laboratory tests, including ethanol level
- Obtain further workup as clinically indicated
- Rule out other diagnoses
- Administer IV fluids, thiamine, glucose, folate, as needed

Administer benzodiazepine:
- Diazepam 10 mg IV
- Lorazepam 2 mg IV

Re-evaluate in 10-15 min. Symptoms controlled? (Normalization of vital signs, improvement of tremor, resolution of agitation)

Any of the following:
- History of complicated withdrawal?
- Severe underlying psychiatric or medical comorbidities?
- Clinical alcohol or drug intoxication?
- Initial CIWA-Ar score > 8 (or other comparable, validated tool)?

Discharge with addiction or outpatient detoxification follow-up (Class II)

- Monitored unit or inpatient detoxification admission
- Benzodiazepine administration (diazepam or lorazepam) based on CIWA-Ar score (or other validated tool) (Class I)

Administer escalating doses of benzodiazepines:
- Diazepam 20 mg, 50 mg, 100 mg IV every 15 min
- Lorazepam 4 mg, 8 mg, 16 mg IV every 20-30 min

Re-evaluate every 10-15 min. Symptoms controlled?

- Continue high-dose benzodiazepines (Class I)
- Consider adjunct phenobarbital, 500 mg IV x 1 (Class I)
- Adjunctive ketamine 0.3 mg/kg IV bolus, 0.3 mg/kg/h infusion (Class III)

Admit to ICU

Abbreviations: AWS, alcohol withdrawal syndrome; CIWA-Ar, Clinical Institute Withdrawal Assessment Of Alcohol Scale, Revised; ICU, intensive care unit; IV, intravenous.

For class of evidence definitions, see page 11.
A paucity of literature exists regarding the use of antipsychotics or other medications for hallucinosis. Because the hallucinations associated with alcohol withdrawal are distinct from those typically associated with schizophrenia (ie, visual or tactile rather than auditory), the underlying pathophysiology is likely different. There are limited data to suggest antipsychotic use is actually detrimental in acute alcohol withdrawal. However, patients with alcohol withdrawal may also have underlying psychiatric disease, and discerning hallucinations from alcohol withdrawal or underlying psychiatric pathology is often difficult. Continuation of home antipsychotics is advised, but benzodiazepines should remain first-line treatment of alcohol withdrawal-related hallucinations.

Delirium Tremens And Benzodiazepine-Resistant Alcohol Withdrawal

Despite optimal pharmacologic management, there is a subset of patients who develop severe benzodiazepine-resistant alcohol withdrawal and DT. An early, aggressive approach improves outcomes in these cases. In one observational study, higher individual and total doses of diazepam (86 mg vs 32 mg per dose and 562 mg vs 248 mg, respectively) were associated with a statistically significant decrease in the need for mechanical ventilation, and trends were noted in shorter ICU stays and a lower incidence of nosocomial pneumonia. In our experience, it is not unusual to administer in excess of 400 to 500 mg of intravenous diazepam over several hours for severe alcohol withdrawal without the need for mechanical ventilation. For patients in whom extreme benzodiazepine resistance is present, barbiturates (notably, phenobarbital) are reasonable adjuncts. Phenobarbital use has been associated with a decrease in ICU admissions when given early in the course of disease and it has been associated with decreases in mechanical ventilation when administered to patients in the ICU.

In many cases, the agitation associated with DT or respiratory failure from iatrogenic sedative administration necessitates intubation and mechanical ventilation. After intubation, propofol is an ideal adjunct. In addition to its GABA-agonist effects, propofol is an NMDA antagonist, and it inhibits the neuroexcitation from increased NMDA receptor-mediated glutamate activity. Propofol, however, does have a narrow therapeutic index and can be difficult to titrate in patients without a protected airway. Prolonged use, especially at high doses, is associated with metabolic derangements. While the use of propofol for alcohol withdrawal has been reported in the absence of mechanical ventilation, we strongly recommend the use of this drug only in intubated patients, due to respiratory depression and loss of airway protective reflexes. Dosing of propofol for ICU sedation is typically 1 to 6 mg/kg/h.

Symptom-Driven Dosing Versus Fixed Dosing

In many EDs, especially those directly associated with psychiatric or inpatient alcohol detoxification units, the management of alcohol withdrawal may be prolonged while patients await inpatient bed assignment. In these instances, it becomes important to understand benzodiazepine dosing beyond the initial control of withdrawal symptoms. An increasing body of evidence suggests that symptom-driven dosing of benzodiazepines based on validated withdrawal assessment tools is superior to fixed dosing. With symptom-driven dosing of benzodiazepines, less total benzodiazepines are administered, hospital lengths of stay are shorter, and complication rates are similar.

Fixed-dosing regimens are often protocol-driven and involve tapering a benzodiazepine, regardless of the severity of withdrawal symptoms or consideration of the patient’s withdrawal history. Symptom-driven therapy utilizes a validated withdrawal assessment tool (such as the CIWA-Ar), and benzodiazepine dosing is based on a score achieved

Class Of Evidence Definitions

Each action in the clinical pathways section of Emergency Medicine Practice receives a score based on the following definitions.

**Class I**
- Always acceptable, safe
- Definitively useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

**Class II**
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies:
  - historic, cohort, or case control studies
  - Less robust randomized controlled trials
- Results consistently positive

**Class III**
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

**Indeterminate**
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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in that assessment. For example, appropriate dosing regimens may include diazepam 10 to 20 mg orally, lorazepam 2 to 4 mg orally every 2 to 4 hours, or chloralhydrate 50 to 100 mg orally every 6 hours if CIWA-Ar scores are > 8 to 10.

The use of such assessment tools and the dosage of benzodiazepines based on the patient’s score is appropriate only for uncomplicated alcohol withdrawal. Patients with severe withdrawal symptoms, seizures, or DT are best served by aggressive bedside administration of intravenous benzodiazepines, ideally diazepam, using the front-loading technique, until symptoms are adequately controlled.

**Adjunctive Therapy**

Alcoholics frequently have significant metabolic derangements on presentation, often with marked electrolyte abnormalities. These patients are often significantly dehydrated, requiring intravenous fluid resuscitation. Electrolyte abnormalities (including alcoholic ketoacidosis and hypokalemia) and hypomagnesemia may be present and should be addressed with dextrose-containing fluids and judicious replacement of potassium and magnesium.

Alcoholic ketoacidosis is typically reversed with glucose-containing intravenous fluids and thiamine. Wernicke encephalopathy is a common cause of altered mental status and gait disturbance among alcoholics. Nystagmus, ataxia, and confusion are the hallmark triad of Wernicke encephalopathy, or dry beriberi.

However, in the authors’ experience, rarely are all 3 clinical findings seen concurrently. It is imperative to have a low threshold to use high thiamine doses if signs of Wernicke encephalopathy are present, even in the absence of the classic clinical triad. We suggest 500 mg of intravenous thiamine every 8 hours. Intravenous thiamine is preferred, as the absorption of oral thiamine is erratic.

Depending upon the patient’s severity, symptoms may slowly improve over several days to weeks, but they may not improve at all. The convention that thiamine ought to be administered before glucose in that assessment. For example, appropriate dosing regimens may include diazepam 10 to 20 mg orally, lorazepam 2 to 4 mg orally every 2 to 4 hours, or chloralhydrate 50 to 100 mg orally every 6 hours if CIWA-Ar scores are > 8 to 10.

The use of such assessment tools and the dosage of benzodiazepines based on the patient’s score is appropriate only for uncomplicated alcohol withdrawal. Patients with severe withdrawal symptoms, seizures, or DT are best served by aggressive bedside administration of intravenous benzodiazepines, ideally diazepam, using the front-loading technique, until symptoms are adequately controlled.

1. “The patient was hallucinating, so I gave him an antipsychotic.”

   While antipsychotics are certainly indicated for psychotic hallucinations, the use of antipsychotics in alcohol withdrawal is associated with poorer outcomes. It is best to address the underlying pathophysiology of CNS hyperexcitability and utilize a GABA<sub>Α</sub> receptor agonist such as a benzodiazepine.

2. “The patient’s withdrawal looked mild, so I discharged her with benzodiazepines.”

   There are criteria for safe discharge of an alcoholic patient presenting with withdrawal or requesting detoxification: CIWA-Ar score < 8, no history of complicated alcohol withdrawal, no clinical alcohol or drug intoxication, no significant underlying medical or psychiatric comorbidities. Even in patients who develop DT, early symptoms may be mild.

3. “The patient was tachycardic; I presumed it was from alcohol withdrawal.”

   Alcoholics are at high risk for multiple acute and chronic medical comorbidities. Furthermore, there is commonly an acute medical ailment that causes an alcoholic patient to decrease or cease alcohol consumption. Pulmonary embolus, myocardial infarction, sepsis, dehydration, and a number of other diagnoses should be considered in the tachycardic alcoholic patient.

4. “I thought the patient had straightforward alcohol withdrawal, so I didn’t check any labs.”

   Alcoholics commonly present with a range of metabolic derangements, some of which can be life threatening. These generally stem from malnutrition and dehydration. All intoxicated patients or patients with altered mental status should have a capillary glucose checked. Alcoholics who require inpatient admission (for withdrawal or otherwise) should have basic chemistries performed (including checking the magnesium level), and should be checked for severe abnormalities such as hyponatremia or alcoholic ketoacidosis.

5. “The patient presented with alcohol withdrawal and was confused, but looked okay, so I admitted him to the floor.”

   Even in the absence of agitation, the presence of confusion in the setting of alcohol withdrawal suggests DT and necessitates admission to a higher level of care such as the ICU or, at minimum, a step-down unit. Furthermore, the treating emergency clinician should consider Wernicke encephalopathy or an underlying concomitant medical cause.
is pharmacologically illogical, as thiamine acts on enzyme pathways (eg, as a cofactor in the conversion of pyruvate to acetyl-CoA) while the effects of glucose are nearly immediate.63

The emergency clinician must be cognizant of alternative underlying pathology either masquerading as or coexisting with alcohol withdrawal, including, but not limited to, drug intoxication, trauma, or sepsis. External evidence or history of trauma should prompt appropriate radiologic evaluation. The presence of fever and leukocytosis, while potentially due to severe alcohol withdrawal, should be considered infectious until proven otherwise.

### Controversies And Cutting Edge

#### NMDA Receptor Antagonists

Receptors other than the GABA\textsubscript{A} receptors are affected by chronic alcohol consumption. The NMDA receptor is a glutamatergic excitatory receptor that is thought to be involved in the development of alcohol dependence.64-66 Ethanol is an NMDA receptor antagonist, and chronic antagonism of the NMDA receptor results in upregulation of neurotransmission.67 Like the GABA\textsubscript{A} receptor, this increase in neurotransmission is likely related to alteration of receptor subunits rather than an increase in the absolute number of NMDA receptors.68 In the acute alcohol withdrawal state, there is uninhibited NMDA receptor activity, resulting in CNS hyperstimulation. This scenario offers a biologically plausible approach to combating the underlying pathophysiology of CNS hyperexcitability seen in alcohol withdrawal.

NMDA receptor antagonists have been studied in alcohol-related disorders and have been shown to decrease the severity of symptoms in AWS, prevent ethanol withdrawal seizures, and sustain alcohol abstinence after detoxification.69-71 Acamprosate is one such NMDA receptor antagonist and GABA\textsubscript{A} agonist studied extensively in alcohol-related disorders. It has been shown to be both safe and effective in maintaining alcohol abstinence after detoxification.

### Risk Management Pitfalls For Alcohol Withdrawal

(Continued from page 12)

6. **“The patient is an alcoholic; I assumed his delirium was from alcohol withdrawal.”**
   Alcohol withdrawal is a diagnosis of exclusion; there is no available test that confirms a diagnosis of alcohol withdrawal delirium. Consideration must be taken for other causes of delirium including structural CNS pathology (eg, stroke, intracranial hemorrhage), metabolic derangements (eg, uremia, hyperammonemia), infectious sources (eg, sepsis, meningitis), and toxicologic causes (eg, antimuscarinic syndrome, sympathomimetic syndrome).

7. **“I was afraid benzodiazepines would cause her to stop breathing.”**
   In the absence of structural airway abnormalities or drug co-intoxication, benzodiazepines should not have a significant effect on ventilation. While patients will become sedated with high-dose benzodiazepines, their respiratory drive should be maintained, provided they are not also toxic on opioids or other sedating medications and they are without obstructive upper airway pathology.

8. **“The patient is an alcoholic; I assumed the seizure was from alcohol withdrawal.”**
   While alcohol withdrawal seizures are relatively uncommon, alcoholics are at high risk for structural CNS injury, putting them at high risk for the development of epilepsy. Furthermore, antecedent trauma and subsequent intracranial hemorrhage places that patient at high risk for seizure. A seizure in an adult alcoholic without a history of withdrawal seizures and without other objective signs of withdrawal should prompt a more complete neurologic workup and cranial imaging.

9. **“The patient told me he only drink 2 beers per day, so I didn’t think his presentation could be alcohol withdrawal.”**
   Alcoholics commonly minimize their alcohol consumption, portraying to the clinician a vast underestimation of actual alcohol consumption. In the right clinical context, a social history of daily drinking or periodic heavy alcohol consumption should prompt the emergency clinician to further consider alcohol withdrawal in the presentation of the tachycardic tremulous patient and/or new-onset seizure.

10. **“The patient was requesting detoxification, but had no history of severe withdrawal and had no symptoms in the ED, so I discharged her with outpatient follow-up.”**
    Psychiatric comorbidities, including depression, are common among alcoholics. Some drink alcohol due to an underlying psychiatric disorder, and others have a mood disorder due to alcohol consumption. It is imperative that patients presenting with alcohol-related complaints are screened for suicidality.
tion in the outpatient setting. Krupitsky and Krystal suggest that lamotrigine (an inhibitor of glutamate release) and memantine are equally efficacious to benzodiazepines in treating AWS. The authors’ institution has presented data previously that support the use of intravenous subdissociative ketamine as adjunctive therapy in treating severe alcohol withdrawal in both the ED and the ICU. In light of these data suggesting uninhibited NMDA receptor agonism in the acute alcohol withdrawal state, we initiated an institutional guideline with intravenous subdissociative ketamine for severe alcohol withdrawal. (Note: this is off-label use.) In the authors’ clinical experience, ketamine has been well tolerated, safe, and effective in reducing benzodiazepine requirements, normalizing vital signs, and decreasing the duration of delirium. At the present time, we utilize intravenous ketamine only as adjunctive treatment for severe alcohol withdrawal, most often after 200 mg of diazepam or equivalent benzodiazepine has failed to control symptoms or decrease delirium. Our recommended dosing is 0.3 mg/kg IV bolus and an infusion of 0.3 mg/kg/h for 24 hours followed by 0.15 mg/kg/h for 24 hours. Multiple studies in the chronic pain literature suggest that oral ketamine is safe when administered in the setting of a hospital guideline or in the context of a research protocol. The authors believe that in the future this may prove to be an essential component of treatment of AWS.

**Neuromodulators**

**Gamma-hydroxybutyric Acid**

Gamma-hydroxybutyric acid (GHB) is a GHB receptor and GABA<sub>B</sub> receptor agonist produced endogenously as a metabolite of GABA. It is also available as an FDA-approved treatment for narcolepsy, and it can be a drug of abuse. Multiple studies demonstrate the efficacy of GHB in the prevention and treatment of alcohol withdrawal. Though GHB is not commonly used in the United States, it appears to be safe in the treatment of AWS.

**Baclofen**

Baclofen is a GABA<sub>B</sub> receptor agonist that has been studied in acute alcohol withdrawal. Data from a prospective randomized controlled trial of patients with mild to moderate withdrawal demonstrated comparable efficacy between baclofen and diazepam. A second study compared baclofen and placebo in addition to standard therapy and found a reduction in benzodiazepine requirements among patients treated with low-dose baclofen. At this time, though several studies have favorable results with baclofen, there is insufficient evidence to recommend its routine use in ED patients with AWS.

**Adrenergic Antagonists**

Beta-adrenergic antagonists are effective in reducing the autonomic effects of ethanol withdrawal syndrome. While this has not been extensively studied, the selective treatment of tachycardia and hypertension without treating CNS hyperexcitation is not expected to reduce delirium or prevent convulsions. It is imperative to understand that the underlying pathophysiology of AWS is a state of CNS hyperactivity. Masking the peripheral effects of this hyperactive state overlooks the underlying pathological mechanism. Clonidine and dexmedetomidine, both centrally acting selective alpha-2 adrenergic agonists, may have an additive benefit when used in conjunction with benzodiazepines, but there is insufficient evidence to recommend using these agents as primary treatments in controlling alcohol withdrawal symptoms. Lofexidine, also a selective alpha-2 adrenergic agonist, was used as adjunctive treatment to chloralazine and compared to placebo, but no benefit was identified and lofexidine-treated patients experienced more severe withdrawal symptoms and hypotension. A prospective randomized placebo-controlled study of dexmedetomidine as an adjunctive therapy for patients in alcohol withdrawal did not decrease long-term benzodiazepine exposure, and it was associated with bradycardia.

**Antiepileptic Agents**

Antiepileptic agents are often used to treat AWS. Carbamazepine is the most widely studied and has been used extensively and effectively in Europe because of availability of an intravenous formulation. In a Cochrane review of anticonvulsants for alcohol withdrawal published in 2010, only carbamazepine showed a favorable outcome when compared to benzodiazepines. However, the patients in the carbamazepine studies had less-severe alcohol withdrawal, and extrapolating treatment to the ED patient population is difficult. Carbamazepine may be a good adjunct in the outpatient setting, but the authors do not recommend its use in moderate to severe withdrawal in the ED patient due to the lack of evidence and availability of better alternatives. Oxcarbazepine performed no better than placebo in a randomized, placebo-controlled trial published in 2007. Valproic acid has been studied and is safe and effective in reducing auditory hallucinations. Comparison studies between carbamazepine and valproic acid as adjunctive therapies showed slight benefit of valproic acid over carbamazepine in the prevention of withdrawal seizures. Multiple other studies demonstrate the safety and efficacy of valproic acid in the treatment of AWS. In spite of this, a Cochrane review found insufficient evidence to support the use of any antiepileptic drug in the treatment of AWS.
Nonpharmacologic Therapies
Acupuncture as an adjunctive treatment and aromatherapy have been suggested as beneficial treatments of substance-related disorders. Neuroelectric therapy involves administration of low-voltage currents to the patient’s head; at this time there is a lack of evidence to recommend its use, especially in the ED patient. Data related to these therapies are mixed and we mention these only for information’s sake.

Disposition
As mentioned previously, AWS represents a spectrum of illness. Accurately identifying the patient’s place on this spectrum is critical for determining the treatment and level of care required. Patients with AWS represent complicated clinical scenarios, and a thorough understanding of the underlying pathophysiology, the typical progression of the disease, and associated illnesses is required for effective treatment. (See Table 4.)

Must-Do Markers Of Quality Emergency Department Care
- Early recognition of alcohol withdrawal based on presentation and history
- Consideration of differential diagnoses, including head trauma, sepsis, and drug intoxication
- Early and aggressive titration of benzodiazepines
- Evaluation for and treatment of metabolic comorbidities
- Appropriate selection of level of care

Summary
AWS is a complex diagnosis that requires thorough evaluation, given the risk of precipitating or coexisting illness. When the diagnosis is established, early and aggressive front-loading with benzodiazepines is appropriate. A stepwise approach to management of AWS will improve symptoms and decrease morbidity and mortality. DT represents the most severe form of AWS and merits aggressive therapy and ICU admission. Several novel therapies such as intravenous ketamine are being studied and warrant consideration as adjunctive therapy in patients with severe alcohol withdrawal. AWS represents a spectrum of illness, and accurately identifying a patient’s place on the spectrum is imperative for determining treatment and disposition of the patient.

Case Conclusions
After examining the first patient, you correctly diagnose the patient with severe AWS. You decide to administer 20 mg of intravenous diazepam followed by 50 mg of diazepam 15 minutes later after she experiences no clinical improvement. The patient’s heart rate and tremor failed to improve with these doses, so you gave her 100 mg of intravenous diazepam, which resulted in significant improvement in her symptoms. One hour later, her tremor increased significantly, her heart rate increased to 124 beats/min, and her subjective level of anxiety returned. You gave her a second 100-mg dose of intravenous diazepam. After you gained initial control of her symptoms, she was admitted to the ICU for further treatment of severe AWS. She was administered folic acid, thiamine, and multivitamins for nutritional replacement.

After receiving the history from EMS and evaluating the second patient, you suspected that his withdrawal was more severe and would be more difficult to treat than your first patient. After intravenous access is obtained, you sent blood to the lab for evaluation and administered escalating doses of diazepam. After giving 270 mg of intravenous diazepam in 2 hours, you administered 260 mg of phenobarbital. The patient remained...

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<th>Disposition</th>
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<tr>
<td>Discharge with detoxification referral</td>
<td>Initial CIWA-Ar score &lt; 8 (or equivalent of other validated withdrawal assessment tool)</td>
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<tr>
<td>Inpatient detoxification or medical unit</td>
<td>No underlying medical or psychiatric comorbidities</td>
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<tr>
<td>Intensive care unit</td>
<td>Underlying medical or surgical condition requiring ICU-level care, including mechanical ventilation</td>
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Table 4. Disposition Criteria For Alcohol Withdrawal

Abbreviations: AWS, alcohol withdrawal syndrome; CIWA-Ar, Clinical Institute Withdrawal Assessment Of Alcohol Scale, Revised; DT, delirium tremens; ED, emergency department; ICU, intensive care unit.
agitated, with hypertension and tachycardia; he still did not attend to you or follow commands. He continued to mime turning a key in an ignition and voicing a desire to leave. You administered a second bolus of phenobarbital 260 mg. The patient’s hypertension and tachycardia improved, but did not completely resolve. After 30 minutes, the patient’s vital signs again worsened, and he was severely agitated and delirious. You wanted to avoid intubation and its attendant complications, if possible. You administered a ketamine bolus (0.3 mg/kg IV) followed by initiation of a ketamine infusion at 0.3 mg/kg/h. The patient’s tachycardia and hypertension again improved, he became somnolent, with normal respirations, and he was admitted to the ICU for further treatment of DT.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


Time- and Cost-Effective Strategies

- Discharge patients who meet discharge criteria with a prescription for 2 to 3 days of an oral benzodiazepine. (See Table 4, page 15.)
- Any patient with alcohol withdrawal seizure or DT should be treated with intravenous benzodiazepines.
- Utilize symptom-triggered therapy (rather than scheduled or protocol-driven) for uncomplicated or controlled alcohol withdrawal.
- Early and aggressive front-loading of benzodiazepines may prevent a prolonged hospitalization.
4. Which of the following should be considered in the differential diagnosis of alcohol withdrawal?
   a. Head trauma
   b. Psychosis
   c. Encephalitis
   d. Sympathomimetic toxicity
   e. All of the above

5. Patients with alcohol withdrawal seizures
   a. Almost always present more than 24 hours after cessation of alcohol consumption
   b. Often present with status epilepticus
   c. Most often progress to DT
   d. Should have a careful consideration for meningitis, head trauma, and metabolic derangements in addition to alcohol withdrawal

6. All of the following statements concerning DT are true, EXCEPT:
   a. DT is the most severe form of alcohol withdrawal
   b. Patients with DT always have associated confusion
   c. Patients with DT usually have hypotension and bradycardia
   d. Patients with DT will require an ICU admission
   c. Patients with DT may have increased sedation with higher serum or blood alcohol levels

7. Which of the following drugs is the least-preferred first-line treatment for alcohol withdrawal in the ED?
   a. Midazolam
   b. Lorazepam
   c. Diazepam
   d. Chlordiazepoxide

8. Which of the following is appropriate adjunctive therapy in patients with alcohol withdrawal?
   a. Electrolyte replacement
   b. Intravenous fluid hydration
   c. Intravenous thiamine replacement
   d. Parenteral glucose administration
   e. All of the above
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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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