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Evidence-Based Education • Practical Application

CLINICAL CHALLENGES:

- How does the timing of alcohol cessation affect withdrawal symptoms?
- What are the most effective medications for management of alcohol withdrawal syndrome?
- What are the criteria for disposition of patients with alcohol withdrawal syndrome?

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Prior to beginning this activity, see "CME Information" on page 2.

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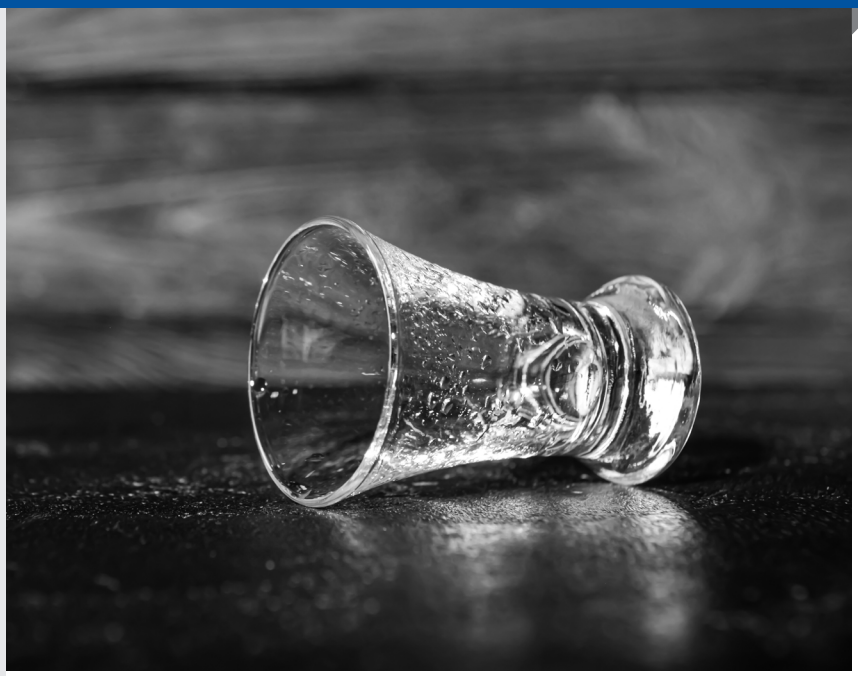

Diagnosis and Management of Emergency Department Patients With Alcohol Withdrawal Syndrome

Abstract

Alcohol withdrawal syndrome is a constellation of symptoms and signs resulting from the abrupt decrease or cessation of heavy alcohol use. Complications of alcohol withdrawal syndrome present significant dangers for patient morbidity and mortality, as well as burdens on emergency department resources. This review presents an overview of the pathophysiology of alcohol withdrawal syndrome and a systematic approach for management in the emergency department. Current evidence on treatment regimens and adjunctive therapies is reviewed, and recommendations for management of patients with alcohol use disorders are discussed.

For online access:

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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) identify areas in practice that require modification to be consistent with current evidence in order to improve competence and performance; (2) develop strategies to accurately diagnose and treat both common and critical ED presentations; and (3) demonstrate informed medical decision-making based on the strongest clinical evidence.
CME Objectives: Upon completion of this activity, you should be able to: (1) differentiate uncomplicated and complicated alcohol withdrawal syndrome; (2) apply a structured approach to treatment of alcohol withdrawal syndrome; and (3) discuss the disposition criteria for patients with alcohol withdrawal syndrome and alcohol use disorder.
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Case Presentations

CASE 1

A 42-year-old man presents to the emergency department by ambulance with a seizure witnessed by bystanders...

- He said he consumes about a fifth (750 mL) of whisky daily, and he says he has a history of alcohol withdrawal seizures. His last drink was about 24 hours ago.
- EMS checked his fingerstick blood glucose, which was normal, and administered 1 liter of IV 0.9% saline.
- His heart rate is 120 beats/min and his blood pressure is 163/92 mm Hg. He is oriented, but tremulous, anxious, and sweating.
- You consider your options to help control his symptoms quickly and prevent a repeat seizure...

CASE 2

52-year-old man presents altered to the ED, but now he is attempting to leave...

- EMS transported him to the ED after reports of a man stumbling into the middle of traffic.
- You see a malnourished-looking man attempting to get out of the stretcher, swaying back and forth.
- His vital signs are unattainable, but he appears diaphoretic, altered, and his extremities are hot to the touch. He is moaning, "No, no, no," and grasping at the air.
- You note in his records that he was seen for alcohol intoxication and a fall 4 days prior. His head and cervical spine CT scans were negative.
- You consider whether this patient has capacity, and what your best next steps would be...

CASE 3

30-year old woman is signed out to you for time to metabolize alcohol ...

- She says she normally imbibes 2 bottles of wine a day, and her last drink was about 12 hours ago.
- She has a history of withdrawal, but no hospitalizations for seizures or hallucinations.
- After 4 hours into your shift, the nurse informs you that the patient's CIWA-Ar is 7, she is feeling anxious, and wishes to discuss detoxification options with you. To prepare for the discussion, you review the options for outpatient care resources you can offer, in order to prevent further withdrawal, and control her cravings...

Introduction

Alcohol is the most-used intoxicant in the world, and alcohol-related emergency department (ED) visits have been increasing steadily over the last decade.[1-3] Alcohol withdrawal syndrome (AWS) is a constellation of physiologic disorders related to central nervous system (CNS) excitability in the setting of cessation of or decreasing alcohol consumption. Symptoms can range from mild nausea and anxiety to altered sensorium and seizures, leading to significant morbidity and mortality. Mortality from severe alcohol withdrawal ranges from 1% to 5.4%.[4] Among heavy alcohol users admitted for hospital management, the incidence of AWS is estimated to be 1.9% to 6.7%.[5] AWS accounts for about 0.25% of all ED visits and presents a significant burden on inpatient and intensive care unit (ICU) resources.[3]

AWS is a clinical diagnosis with presentations that overlap other etiologies, and it can be missed or misdiagnosed.[6] For example, AWS can mimic sepsis or drug intoxication, and may be a concomitant diagnosis to a patient's other presenting complaints in the ED. An understanding of the patient's risk factors, the timeline of their alcohol withdrawal, and the pathophysiology will indicate the likelihood of withdrawal and effective treatment options. Early recognition and aggressive treatment of AWS can prevent unnecessary hospital admissions, decrease a patient's length of stay, and prevent worsening complications.

This issue of *Emergency Medicine Practice* reviews the available literature regarding the pathophysiology of AWS as well as treatment modalities in the ED. Adjunctive and controversial therapeutic interventions are also discussed.

Critical Appraisal of the Literature

Relevant primary literature was identified by searches of the Cochrane Database of Systematic Reviews, PubMed, and Ovid MEDLINE®. Search terms included *alcohol withdrawal syndrome, alcohol withdrawal seizure, alcoholic hallucinosis, alcoholic hallucinations, alcohol withdrawal delirium, delirium tremens, benzodiazepines, phenobarbital, ketamine, dexmedetomidine, gabapentin, alcohol use disorder, antiepileptics,* and *sobriety centers*. Studies available in the English language were reviewed. Using the same search terms, relevant review literature was identified. Select case reports, animal studies, and case series were utilized where clinical trial literature was lacking.

A total of 122 sources were selected for review. Because there have been a limited number of trials in the ED for treatment of AWS, trials and reviews had significant heterogeneity in settings from ICUs to observation units. Challenges pertaining to research of ED diagnosis and management of AWS include difficulty in obtaining informed consent (especially in the setting of delirium) and the lack of homogeneity of AWS cases, settings, and treatment protocols. In addition, the established and proven treatment of AWS is benzodiazepines, making head-to-head single-agent and placebo-controlled trials versus benzodiazepines limited.

There have been 3 guideline papers published in the last 5 years relating to ED management of alcohol use disorder and alcohol withdrawal. The American Society of Addiction Medicine published its initial outpatient and inpatient clinical practice guidelines for alcohol withdrawal in 2020.[7] A 2023 white paper from the American Academy of Emergency Medicine focused on alcohol withdrawal treatment, disposition, and alcohol use disorder in the ED setting.[1] Lastly, the 2024 Guidelines for Reasonable and Appropriate Care in the Emergency Department (GRACE-4) addressed treatment recommendations for AWS and alcohol use disorder.[8]

Etiology and Pathophysiology

Following ingestion, ethanol is rapidly absorbed and distributed, with a volume of distribution near that of total body water (0.6 L/kg). Under typical conditions, approximately 90% of ingested alcohol is absorbed within 60 minutes, though this may be delayed by food in the stomach or by co-ingestants. Absorption may also be impaired by the action of gastric mucosal alcohol dehydrogenase (ADH), the enzyme that oxidizes ethanol and decreases the amount available for absorption.[9] Ethanol has a higher bioavailability in women, compared with men, due to lower ADH activity. There is also higher ethanol bioavailability in patients who have undergone gastric bypass surgery, due to loss of gastric mucosal ADH.[10]

The liver is the organ most involved in the elimination of ethanol, though small amounts are excreted unchanged in the kidneys, lungs, and sweat. Ethanol is metabolized, primarily by hepatic ADH, to form acetaldehyde, with the assistance of the cofactor of nicotinamide adenine dinucleotide (NAD+). This is typically the rate-limiting step, and buildup of acetaldehyde can lead to toxic effects, colloquially known as a "hangover." Acetaldehyde is metabolized by aldehyde dehydrogenase to form acetate.[9] 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, water, and adenosine triphosphate. While 90% to 95% of ethanol metabolization undergoes this process, there are minor pathways through CYP2E1 and catalase, and these pathways may play a larger role in patients with chronic alcohol use.[11] Although there is wide individual variation (especially among patients with alcohol use disorder), ethanol is generally metabolized in a manner consistent with Michaelis-Menten kinetics, with a clearance rate of approximately 15 to 20 mg/dL/hr (based on studies of patients presenting to the ED), although the rate is affected by chronic use, genetics, and medications.[9,12,13] In persons with chronic alcohol use, hepatic microsomal enzymes, as CYP2E1, have adapted the metabolism, leading to higher rates of metabolism, approximately 25 to 35 mg/dL/hr.[13]

Alcohol causes profound changes to the neurochemical balance within the brain in persons with chronic alcohol exposure. Alcohol increases the activity of the neurotransmitter gamma-aminobutyric acid (GABA) on the GABA-alpha ($GABA_A$) neuroreceptor. Additionally, alcohol depresses the excitatory effects of the neurotransmitter glutamate's activity on N-methyl-D-aspartate (NMDA) neuroreceptors. With repeated alcohol exposure, there is compensatory downregulation of $GABA_A$ response to GABA and upregulation of excitatory response to glutamate at the NMDA receptor. With abrupt cessation of alcohol use, the adaptive balance is disrupted. GABAergic inhibition rapidly decreases, while glutamatergic excitation is unopposed and thus increases, leading to increased neuroexcitability, in which seizures and psychosis can occur. Peripheral sympathetic adrenergic tone also increases, with hypertension, tachycardia, and tremor resulting.[4,14,15] Executive function may be affected during alcohol withdrawal, due to this imbalance and oxidative stress.[16,17]

Differential Diagnosis

For patients presenting to the ED with signs and symptoms of acute alcohol withdrawal, correct identification of the diagnosis is critical. Clinicians must have a wide differential diagnosis when considering alcohol withdrawal as the primary diagnosis. Evaluation for alternate or concomitant diagnoses should begin at the time of presentation, as coexisting illness may precipitate alcohol withdrawal, and delays in diagnosing the primary pathology may increase risk for significant morbidity or mortality.

The differential diagnosis for alcohol withdrawal is extensive; **Table 1, page 5,** highlights toxicologic and non-toxicologic diagnoses that should be considered. The diagnosis of alcohol withdrawal is primarily historical and is supported by physical examination findings such as tachycardia, hypertension, tremor, diaphoresis, and neuromuscular excitation.

Because symptoms of alcohol withdrawal can begin as soon as 6 hours from the patient's last drink, patients who present to the ED for other

acute reasons may experience cessation of alcohol consumption and begin the process of withdrawal.

AWS is a diagnosis of exclusion, as there is no diagnostic imaging or confirmatory laboratory test for diagnosis. 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 also mimic alcohol withdrawal, with confusion, delirium, anxiety, tachycardia, and diaphoresis.

Prehospital Care

The overall goal for the prehospital care of patients experiencing alcohol withdrawal is rapid transport to an appropriate facility while preventing injury to the patient or prehospital care provider. Approximately 40% of all ED visits for alcohol-related complaints are for patients brought by ambulance.[18] Recognition that AWS is a medical disorder rather than a primary psychiatric disease is paramount. The presence of markedly 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, if these options exist.

Agitation due to suspected AWS should be treated with benzodiazepines in the prehospital setting, when available, in accordance with local emergency medical services protocols. Lorazepam, diazepam, or midazolam should all be effective; midazolam is an ideal intramuscular (IM) option, given its faster onset of action and shorter duration of effect. Drug intoxication from overdose can be difficult to differentiate from alcohol withdrawal, and sedatives for patient and personnel safety may include benzodiazepines, antipsychotic drugs, or ketamine administration until a more complete toxicologic workup can be completed.[19] Other causes of hyperactive delirium syndrome with severe agitation should also be considered. If trauma is suspected, appropriate immobilization and transport to a trauma center are indicated.

Table 1. Differential Diagnosis for Alcohol Withdrawal

Toxicologic Diagnoses
- Sympathomimetic syndrome
- Antimuscarinic syndrome
- Sedative-hypnotic withdrawal
- Severe alcohol intoxication
- Serotonin syndrome

Medical Diagnoses
- Thyrotoxicosis
- Encephalitis
- Acute psychosis
- Hypoglycemia
- Trauma (head injury)
- Sepsis/septic shock

Sobering Centers

As an alternative to management in the ED, prehospital providers can transport patients with alcohol withdrawal to a sobering center, if available. Sobering centers are facilities that assist patients who are currently intoxicated or in mild withdrawal. The patient must meet certain criteria, including a lack of medical or psychiatric conditions that would require care in a hospital.[20]

A 2013 retrospective cohort study evaluated the effectiveness of prehospital providers' use of a triage checklist to determine whether intoxicated patients should be sent to a detoxification facility or to the ED. The study analysis determined that triage in the field can be completed effectively, with few adverse events.[21] A 2019 study found that 4.4% of patients transferred to a sobering center for acute alcohol intoxication required subsequent transfer to an ED, demonstrating that the large majority of patients are transported appropriately to sobering centers. Examples of reasons for ED transfers were worsening clinical conditions such as persistent tachycardia, altered mental status, chest pain, and worsening alcohol withdrawal symptoms and signs.[22]

Care at a sobering center typically includes monitoring of vital signs and nutrition, managing hygiene and activities of daily living, and providing referrals for shelter and detoxification. Patients typically spend 3 to 14 hours in a sobering center.[23] The use of sobering centers can reduce unnecessary ED visits, decrease healthcare costs and overcrowding, as well as provide the patient a dedicated environment to recover rather than a busy ED.[2,23] These benefits must be balanced with the patient's potential need for ready access to the ED in case of occult critical illness or decompensation.[24]

Emergency Department Evaluation

AWS is a clinical diagnosis and one of exclusion, so a thorough history and physical examination and re-evaluations are necessary for the diagnosis. Symptoms and signs of CNS hyperexcitation, along with a clinical suspicion for alcohol withdrawal make the diagnosis of AWS.

History

The studies of indicators that predict increased risk for AWS are limited and not definitive.[25-29] Nonetheless, there is a strong association for a subset of risk factors. **Table 2, page 6,** outlines risk factors for the development of AWS. The most important risk factor is a previous history of alcohol withdrawal,[29] so it is important to ask the patient about a history of withdrawal, hospitalization for withdrawal, and the type of

withdrawal symptoms they experienced (eg, seizures or hallucinations).

Because abrupt cessation of alcohol use can precipitate more-severe withdrawal symptoms than a gradual decrease of use, it is important to ask the patient to report the time of their last drink, as withdrawal can occur as soon as 6 hours from that time. Another important question is about their recent average alcohol consumption (eg, in the last week), compared to their chronic exposure, in order to determine whether their alcohol intake has decreased. Lastly, it is imperative to determine why they stopped drinking alcohol. This may uncover a secondary concern leading to their abstinence. Patients may state that they ceased or reduced alcohol consumption due to a desire to quit, because they were unable to acquire alcohol, or because they were experiencing symptoms of underlying medical complaints, such as pancreatitis or an occult infection.[24]

The patient's symptoms may suggest other underlying medical complaints and help gauge the severity of the patient's withdrawal. Symptoms of nausea and vomiting, headache, anxiety, tactile disturbances, and auditory disturbances are common with AWS. Examples of questions to ask may include, "Do you feel bugs crawling on or under your skin?" or "Are you seeing things you know are not there?"

Physical Examination

The clinical manifestations of AWS range from mild tremor or anxiety to a severe hyperadrenergic state, seizures, or death. After the initial assessment of the patient's airway, breathing, and circulation, ED management of AWS begins with an assessment of the signs and symptoms of alcohol withdrawal.

Withdrawal severity can be observed in the physical examination. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision* (*DSM-5-TR*) has established criteria for diagnosing alcohol withdrawal that occurs following the reduction or cessation of alcohol use that had previously been heavy and prolonged.[6] **(See Table 3.)** According to the *DSM-5-TR* criteria, AWS may be diagnosed in patients exhibiting or developing 2 or more of 8 signs or symptoms that are not attributable to other medical conditions or mental disorders.

Almost invariably, patients with moderate or severe alcohol withdrawal will exhibit autonomic hyperexcitability evidenced by measured tachycardia, hypertension, and observed diaphoresis. **(See Figure 1.)** Tremor represents a prominent sign of alcohol withdrawal, and it is easily identified on physical examination as a coarse, nonfatigable muscle tremor in the outstretched hands, or tongue fasciculations.

However, it is important to note that these effects may be blunted in patients who are taking sympatholytic medications, such as beta-adrenergic blockers (metoprolol, atenolol, labetalol, propranolol, etc) or alpha-2 adrenergic agonists (clonidine, guanfacine, tizanidine, etc).

Table 2. Risk Factors for the Development of Alcohol Withdrawal Syndrome[26,29-31]

- Personal or family history of alcohol withdrawal syndrome
- Metabolic derangements (ALT >50 units/L, serum chloride <96 mEq/L, and serum potassium <3.6 mEq/L)
- Thrombocytopenia (<150,000/mcL)
- Serum ethanol concentration >150 mg/dL on admission

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 delirium tremens.

Abbreviations: ALT, alanine aminotransferase.

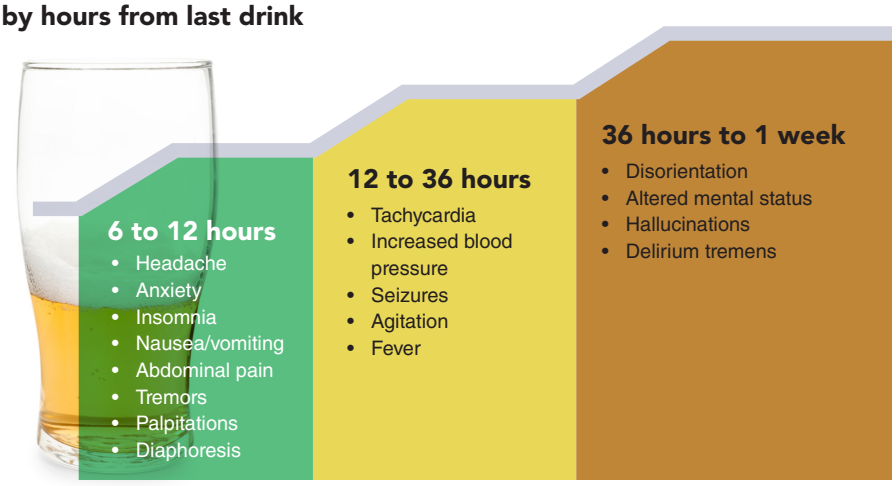
Table 3. *DSM-5-TR* Criteria for Alcohol Withdrawal Syndrome[6]

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

Abbreviation: *DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision.*

Figure 1. Alcohol Withdrawal Syndrome Timeline

Signs and symptoms of alcohol withdrawal, by hours from last drink



Scoring the Severity of Alcohol Withdrawal

After diagnosing a patient with AWS, the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) criteria can be used to score the severity of alcohol withdrawal. As an externally validated scoring criteria, it is among the most widely used scoring criteria for alcohol withdrawal.[8] **(See Figure 2, page 8.)**

The CIWA-Ar can be used to categorize severity and can be repeated to determine effectiveness of treatments. However, it is not appropriate for sedated/intubated patients, as 7 of the items require interview with the patient. Other limitations are its subjectiveness in items and the time required to perform a CIWA-Ar.[32] Alternative and more convenient scoring methods, such as the Brief Alcohol Withdrawal Scale (BAWS), Prediction of Alcohol Withdrawal Severity Scale (PAWSS), and Severity of Ethanol Withdrawal Scale (SEWS), are available, though these require additional investigation for use in the ED.[14,33-35]

Online tools for calculating severity of alcohol withdrawal are available at MDCalc.com:

- CIWA-Ar for Alcohol Withdrawal: www.mdcalc.com/calc/1736/ciwa-ar-alcohol-withdrawal
- Brief Alcohol Withdrawal Scale (BAWS): www.mdcalc.com/calc/10446/brief-alcohol-withdrawal-scale-baws
- Prediction of Alcohol Severity Scale (PAWSS): www.mdcalc.com/calc/10102/prediction-alcohol-withdrawal-severity-scale

Complicated Alcohol Withdrawal

With increasing neurotoxicity, neuropsychiatric complications can occur. Complicated alcohol withdrawal encompasses alcohol withdrawal hallucinosis, seizures, and alcohol withdrawal delirium (also known as *delirium tremens*). Risk factors for complicated alcohol withdrawal include a history of alcohol withdrawal hallucinosis, seizures, numerous prior withdrawal episodes, comorbid medical or surgical illness, age >65 years, long duration of heavy and regular alcohol consumption, seizure during current withdrawal, autonomic hyperactivity, and dependence on GABAergic agents, such as benzodiazepines and barbiturates.

Alcohol Withdrawal Hallucinosis

Alcohol withdrawal hallucinosis (visual, auditory, or tactile) is noted in 0.2% to 12% of patients hospitalized with AWS.[36,37] The hallucinations are most often tactile, and the patient's level of consciousness, awareness, and attention should largely remain intact. Altered sensorium with hallucinations—particularly visual—should raise concern for progression to delirium tremens. Nonetheless, a very small percentage of patients with alcoholic withdrawal hallucinosis progress to delirium tremens.[38] Patients with comorbid psychiatric conditions, such as schizophrenia, are at increased risk for alcohol withdrawal hallucinosis.[38]

Alcohol Withdrawal Seizures

Alcohol withdrawal seizures occur most commonly within 12 to 36 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, complicating <3% of alcohol withdrawal seizures.[39,40] Patients with alcohol use disorder are at increased risk for multiple CNS conditions, including infection, subdural hemorrhage, and metabolic derangements, so additional diagnoses as well as alternative causes of seizures and status epilepticus should be considered in patients presenting to the ED with AWS.

Delirium Tremens

Delirium tremens represents a severe form of AWS, typically manifesting about 24 to 72 hours after last alcohol intake, with duration lasting 1 to 8 days thereafter.[1,15,38] The signs and symptoms of delirium tremens include the symptoms of alcohol withdrawal, as well as alteration in mentation, such as inattention or disorientation. It is imperative to evaluate for other causes of delirium, especially in a patient population that is at high risk for coexisting pathology. Estimated mortality of delirium tremens in modern series is 1% to 4%, but can be decreased to 0% to 1% with timely ED diagnosis and adequate management.[15,41,42]

Diagnostic Studies

Because alcohol withdrawal is a clinical diagnosis and one of exclusion, a thorough history as to the patient's last drink, their risk factors, social history, and physical examination for a hyperadrenergic state guide diagnosis. Nonetheless, diagnostic studies can be helpful to exclude other etiologies of a hyperadrenergic state, seizures, hallucinations, and/or delirium. In addition, patients experiencing AWS can have relevant electrolyte derangements and concomitant disease processes.

Laboratory Studies

A fingerstick blood glucose should be performed for any altered patient, regardless of suspected alcohol use or withdrawal. A complete blood cell count, basic serum chemistries, and magnesium and ethanol levels should be collected for patients experiencing moderate or severe alcohol withdrawal symptoms. Although leukocytosis may suggest an underlying infection, it is a nonspecific finding that can also occur in otherwise healthy individuals with alcohol withdrawal.[43] Conversely, thrombocytopenia, anemia, or leukopenia

Figure 2. The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

Clinical Insitutue Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

Patient:_____ Date: _____ Time: _____ (24 hour clock, midnight = 00:00)

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

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

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

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

ANXIETY — Ask "Do you feel nervous?" Observation.
0 no anxiety, at ease
1 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

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

TACTILE DISTURBANCES — Ask "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 ornumbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

AUDITORY DISTURBANCES — Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

VISUAL DISTURBANCES — Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD — Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 no present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

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

Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). *British Journal of Addiction* 84:1353-1357, 1989.

Patients scoring less than 10 do not usually need additional medication for withdrawal.

Total CIWA-Ar Score _____

Rater's Initials _____

Maximum Possible Score 67

Mild: CIWA <10
Moderate: CIWA 10-18
Severe: CIWA ≥19
Available at: https://www.ci2i.research.va.gov/paws/pdfs/ciwa-ar.pdf

can be the result of alcohol-induced bone marrow suppression, decreased thrombopoietin synthesis, and splenic sequestration in cirrhosis. An anemia with high mean corpuscular volume could be indicative of folic acid deficiency. An anion gap acidosis could be the result of alcohol ketoacidosis, toxic alcohol ingestion, or lactic acidosis from seizures, hypovolemia, underlying infection, or cirrhosis itself.[44] Also, sequelae from poor absorption and intake of nutrition in patients with alcohol use disorder may present with common electrolyte derangements such as hypokalemia, hyponatremia, hypomagnesemia, and hypocalcemia.

Determining an ethanol level may be helpful, because alcohol intoxication can mimic alcohol withdrawal. Also, withdrawal at a higher ethanol level portends more severe alcohol withdrawal.[31] While an elevated alcohol level cannot be used to exclude alcohol withdrawal, from the author's experience and a case report,[45] alcohol withdrawal rarely occurs at ethanol levels >150 mg/dL.

A serum salicylate, acetaminophen level, and urine drug screen are indicated in cases suggestive of overdose. While there are limitations to a basic urine drug screen, the presence of cocaine or amphetamines may provide evidence for a hyperadrenergic state.

Electrocardiogram

An electrocardiogram can be considered if there is concern for atrial arrythmias unresponsive to intravascular volume repletion or a prolonged QTc interval secondary to electrolyte deficiencies, especially if therapy with QT-prolonging agents is being considered.

Imaging Studies

A chest x-ray is indicated for patients in whom hypoxia or fever are present. Computed tomography (CT) of the head may be warranted in the setting of alteration in mental status, seizure, evidence or history of head trauma, or delirium, as patients with alcohol use disorder are at high risk for subdural hematoma and other traumatic neurologic insults.

Treatment

Treatment of AWS is focused on decreasing CNS hyperexcitation, primarily through GABA receptor agonism, and adjunctively decreasing glutamate activity. It is important to note a "kindling" effect,[7] in which, with repeated cycles of withdrawal and intoxication, there is heightened CNS hyperexcitability, resulting in longer duration and severity of withdrawal symptoms.[46] Treatment of withdrawal symptoms may become more difficult with each subsequent alcohol withdrawal episode, and the astute clinician should be vigilant in aggressive and mindful management to control symptoms, rather than automatically resorting to a previous regimen for that patient's withdrawal.[7]

Treatment Strategies for Alcohol Withdrawal Syndrome

Treatment strategies center around aggressive front-loading and symptom-triggered benzodiazepine administration to achieve symptom control and normalization of vital signs.[7] Symptom-triggered benzodiazepine treatment entails intermittent re-evaluations of patient symptoms and signs to guide re-dosing. For example, CIWA-Ar scores can be obtained every 1 to 4 hours, or more often, to determine initial and repeat dosing and frequency of benzodiazepine treatment. In comparison, a fixed-dosing protocol employs a gradually tapered dose of benzodiazepines over several days. An established body of evidence suggests that symptom-driven dosing of benzodiazepines based on validated withdrawal assessment tools is superior to fixed dosing.

In a retrospective study of 100 patients with AWS who were treated in an ED clinical decision unit, the total dose of benzodiazepines administered was nearly 50% lower with a symptom-triggered protocol compared to a fixed-schedule protocol. The length of stay for the symptom-triggered group was 50% shorter when compared with the fixed-schedule group (2 days vs 3 days, respectively).[47] More recently, in a retrospective cohort study of 175 patients with alcohol withdrawal in an ED clinical decision unit, symptom-triggered therapy was successful in keeping median length of stay to 22 hours in the clinical decision unit, with only 5 patients ultimately needing general hospital admission.[48] Lastly, the 2020 ASAM clinical practice guidelines recommend symptom-triggered benzodiazepine over fixed-dosing regimens in short-term observational settings.[7]

Benzodiazepines

Benzodiazepines have traditionally been the cornerstone of treatment for alcohol withdrawal. A seminal study in 1969 comparing chlordiazepoxide, hydroxyzine, thiamine, chlorpromazine, and placebo found that chlordiazepoxide was associated with the lowest incidence of delirium tremens and alcohol withdrawal seizures.[49] Subsequent studies and meta-analyses have confirmed the effectiveness of benzodiazepines in decreasing the incidence of withdrawal seizures, lower CIWA-Ar scores at 48 hours, and delirium control, with minimal life-threatening side effects.[22,50-53]

Studies are inconclusive regarding the optimal benzodiazepine for treatment of alcohol withdrawal.[51] The unique characteristics of each benzodiazepine, local practice patterns, and logistics should be considered, as outlined in **Table 4, page 10**. Diazepam and chlordiazepoxide have longer half-lives, with active metabolites that are advantageous in

preventing worsening withdrawal, with less titration needed than a shorter-acting benzodiazepine, such as lorazepam.[54] Intravenous (IV) diazepam reaches peak clinical effect in 1 to 5 minutes, whereas lorazepam may take 5 to 20 minutes. A faster onset of action can prevent inadvertent dose-stacking (administration of additional medication doses before previous doses have reached peak effect, potentially causing oversedation).[55,56]

Conversely, because both of these longer-acting benzodiazepines (diazepam and chlordiazepoxide) are hepatically metabolized, in a patient with severe liver disease, the effects of the drugs could, theoretically, be markedly prolonged past the point that the withdrawal has abated, resulting in ongoing sedation. Lorazepam undergoes only phase II hepatic metabolism to an inactive metabolite and is then eliminated by the kidneys.[57-59] Midazolam is absorbed predictably via the IM route, while diazepam has high lipophilicity, making it inadvisable to be given via the IM route. Although lorazepam is less lipophilic than diazepam, it is more lipophilic than midazolam, with longer onset of action and more unpredictable absorption when given IM, compared with midazolam. Chlordiazepoxide can be given only orally.[54,58]

Midazolam may be the preferred IM medication when a rapid onset of action is necessary, such as during a seizure; however, its shorter duration of action makes it less suitable for ongoing management of alcohol withdrawal.

In many EDs, especially those directly associated with psychiatric or inpatient alcohol detoxification units, the management of AWS 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. Repeated and adequate dosing of treatments should be a mainstay of alcohol withdrawal management. An example of escalating doses of benzodiazepines is discussed in "The Complicated Withdrawal Patient" on page 11 and in the Clinical Pathway, page 23.

Phenobarbital

Phenobarbital has re-emerged as a popular treatment for AWS in the last decade.[3,61-63] Barbiturates have a distinct binding site on the $GABA_A$ receptor. Phenobarbital increases chloride influx by prolonging channel opening, raising the threshold for the action potential because it directly activates the $GABA_A$ receptor, versus enhancing the effect of GABA, as with benzodiazepines.[64] In addition, phenobarbital has a "dual mechanism," as it also suppresses glutamate activity. Proponents of phenobarbital use point to its long half-life of 120 hours and tapering effect, which provides ongoing protection from recurrent withdrawal and its complications.

Phenobarbital may cause respiratory depression and oversedation, given its narrow therapeutic window. However, under established phenobarbital protocols, treatment of AWS with phenobarbital only and phenobarbital plus benzodiazepine protocols appear safe.[65-69] **(See Table 5.)** In a prospective randomized trial of 44 patients that compared lorazepam to phenobarbital for treatment of mild to moderate AWS, there was no difference in admission rate and follow-up CIWA-Ar scores at 48 hours from discharge.[70] In a meta-analysis of 12 studies including 1934 patients comparing benzodiazepines to phenobarbital, there were no differences in the rate of intubation, seizures, hospitalizations, and ICU length of stay.[71] When combined with benzodiazepines, adjunctive phenobarbital may further improve outcomes. In a double-blind, randomized, placebo-controlled trial, patients receiving standard symptom-triggered lorazepam dosing

Table 5. Example of Phenobarbital-Only Dosing for Alcohol Withdrawal[66,70]

Loading Dose

- 10 mg/kg (ideal body weight) IV, over 30 minutes

OR

- 260 mg IV over 5 minutes for moderate symptoms

Subsequent Dosage

- 130-260 mg every 30 minutes as needed for symptom relief (up to 1040 mg total in 24 hours)

Abbreviation: IV, intravenous.

Table 4. Pharmacologic Properties of Diazepam, Lorazepam, Midazolam, and Chlordiazepoxide for Management of Alcohol Withdrawal Syndrome[60]

Drug	Properties			
	Time to Onset	Active Metabolites?	Initial Dose*	Half-Life (Approximate)
Diazepam	1-5 min IV	Yes	10-20 mg IV or PO	20-80 hours
Lorazepam	10-30 min IM/IV	No	2-4 mg IV or IM or PO	10-20 hours
Midazolam	5-15 min IM/IV	Yes	2-4 mg IM or IV	6 hours
Chlordiazepoxide	2-3 hours PO	Yes	50-100 mg PO	24-84 hours

*For management of alcohol withdrawal syndrome in a 70-kg adult.
Abbreviations: IM, intramuscular; IV, intravenous; PO, orally.

for alcohol withdrawal were given either phenobarbital (10 mg/kg) or placebo. Those treated with phenobarbital had significantly lower rates of ICU admission compared to placebo, highlighting its potential role as a beneficial adjunct in selected patients.[61]

While there is still no high-quality evidence of randomized controlled trials comparing benzodiazepines to phenobarbital alone, it appears safe in experienced and monitored settings. Observational studies suggest that phenobarbital, whether used alone or with benzodiazepines, may reduce 72-hour ED return visits and hospital admission rates compared with benzodiazepines alone.[68,72] It is supported as a reasonable alternative and/or adjunct to first-line benzodiazepines based on clinical practice guidelines from ASAM, GRACE4, and SAEM.[7,8,73]

Adjunctive Therapy

Individuals with alcohol use disorder frequently have metabolic derangements on presentation, often with marked electrolyte abnormalities. These patients are often significantly dehydrated, nutritionally deficient, and require IV crystalloid fluid resuscitation. Any electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, contraction alkalosis, alcoholic ketoacidosis) should be corrected. Alcoholic ketoacidosis is typically reversed with dextrose-containing IV fluids and thiamine.[74]

It is estimated that thiamine (vitamin B1) deficiency is present in 15% to 80% of patients experiencing alcohol use disorder, and its administration is associated with improved cognitive function.[75,76] In the ED, initiation of thiamine 100 mg IV or orally is reasonable in the absence of Wernicke encephalopathy.

Wernicke encephalopathy may cause or contribute to altered mental status and gait disturbance in these patients. Nystagmus, ataxia, and confusion is the hallmark triad of Wernicke encephalopathy, but all 3 clinical findings are seen in only approximately 10% of cases.[77] It is imperative to have a low threshold to administer high doses of thiamine (500 mg IV) if signs of Wernicke encephalopathy are present, even in the absence of the classic clinical triad.[1] IV thiamine is preferred, as absorption of oral thiamine is erratic.[74] Depending on the patient's severity, symptoms may improve slowly over several days to weeks, but they may not improve at all. Ideally, thiamine should be administered prior to dextrose-containing fluid; however, dextrose should not be withheld or delayed in the setting of hypoglycemia, and it can be administered simultaneously with thiamine.

Prevention and Prophylaxis

There are no known prospective studies comparing the use of a benzodiazepine or a barbiturate to placebo for the prevention of AWS. There are retrospective studies that, in part, advocate for such practice.[78-81] Notably, the inclusion criteria for whom to offer treatment for prevention of alcohol withdrawal is inconsistent in the literature. A retrospective observational study of 582 admitted patients with a history of alcohol withdrawal or positive CAGE (Cut, Annoyed, Guilty, Eye-Opener) questionnaire who were enrolled into an alcohol withdrawal pathway of scheduled lorazepam demonstrated a decreased overall hospital length of stay by about 1.5 days.[80] Another retrospective study that utilized phenobarbital for the prevention and treatment of alcohol withdrawal reported a sedation rate of 12.3% but without any readmissions for adverse drug events, concluding that phenobarbital was safe in that cohort of patients.[81]

An online calculator for the CAGE score is available at MDCalc.com: www.mdcalc.com/calc/1729/cage-questions-alcohol-use

The 2020 ASAM clinical practice guidelines recommend front-loading the following patients with at least a single dose of preventative medication: those with a history of severe or complicated alcohol withdrawal; an acute medical, psychiatric, or surgical illness; severe coronary artery disease; and those with signs or symptoms of alcohol withdrawal and a positive blood alcohol content.[7]

The single most predictive factor for developing AWS is prior episodes of alcohol withdrawal; other factors are not adequately predictive or sufficiently studied to advocate for empiric use of potentially deliriogenic medications. Thus, in the author's opinion, preventative dosing should be a risk/benefit assessment for each individual patient, based on their history of withdrawal and the potential risks of administration of preventative medications.

Special Populations

The Complicated Withdrawal Patient

Initial management of the complicated alcohol withdrawal patient experiencing seizures, hallucinosis, or alcohol withdrawal delirium (delirium tremens) will address airway, breathing, and circulation with consideration of concomitant disorders. After stabilization, benzodiazepines and/or barbiturates are the mainstay of therapy. Early, aggressive, and titrated dosing, ideally to somnolence with arousability to minimal tactile stimulus, reduces progression to seizures, delirium tremens, and the need for mechanical ventilation.[82]

Studies have evaluated the efficacy of antiseizure medications compared with benzodiazepines or placebo for the treatment and prevention of AWS seizures.[55,83] In the setting of significant alcohol withdrawal, antiseizure medications uniformly fail when compared with benzodiazepines. This is due to the etiology of AWS seizures, namely a diffuse neuroexcitatory state caused by decreased GABA

tone and increased NMDA tone.[84] There is no role for traditional antiseizure medications (such as phenytoin and carbamazepine), except benzodiazepines or barbiturates, in the management of alcohol withdrawal seizures. Typical starting doses of 5 to 10 mg IV diazepam, 2 to 4 mg IV lorazepam, 5 mg IV midazolam, or 5 to 10 mg IM midazolam doses can be given for actively seizing AWS patients.[85]

A paucity of literature exists regarding the use of antipsychotic medications or other medications for isolated alcohol withdrawal hallucinosis. Because hallucinations associated with alcohol withdrawal are distinct from those typically associated with schizophrenia (eg, visual or tactile rather than auditory), the underlying pathophysiology is likely different. However, patients with AWS may have underlying psychiatric disease, and discerning the etiology of the hallucinations is often difficult.[38] Continuation of antipsychotic medications that the patient may have already been taking is advised.

For patients experiencing alcohol withdrawal delirium (delirium tremens), multiple escalating doses of benzodiazepines and/or barbiturates may be needed. In an observational study of 54 patients, higher individual and total doses of diazepam (86 mg vs 32 mg per individual dose and 562 mg vs 248 mg total dose) 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.[86] Diazepam can be given at an initial IV dose of 5 mg with repeated evaluation and readministration every 10 minutes. If further administration of diazepam is needed, the dose can be doubled every 2 doses.[15,42]

The Intubated Patient

In some cases, the agitation associated with delirium tremens, the need for airway protection, and respiratory failure from iatrogenic sedative administration necessitate intubation and mechanical ventilation. After intubation, propofol is an ideal adjunct medication.[87] In addition to its GABA-agonist effects, propofol is thought to reduce glutamate activity through NMDA antagonism.[88] The use of propofol should be reserved for intubated patients only, due to respiratory depression and loss of protective airway reflexes. Additionally, prolonged use of propofol, especially at high doses, is associated with metabolic derangements, such as propofol infusion syndrome.[89]

Because CIWA-Ar scoring is not appropriate for the intubated patient, use of the Richmond Agitation-Sedation Scale (RASS) may be more appropriate.[90,91] **(See Table 6.)** For these critically ill patients, symptom-triggered therapy has been shown to be effective, with a RASS goal of 0 to -3. Other scoring scales, such as the modified Minnesota Detoxification Scale (mMinds) and Severity of Ethanol Withdrawal Scale (SEWS) have been studied in the ICU population, with correlation to the CIWA-Ar.[92,93]

An online calculator for the Richmond Agitation-Sedation scale is available at MDCalc.com: www.mdcalc.com/calc/1872/richmond-agitation-sedation-scale-rass

The use of benzodiazepine infusions may not be ideal for these patients, as those intubated for AWS generally require significant benzodiazepine doses given as a continuous IV infusion. Lorazepam infusions carry a risk for lactic acidosis from the propylene glycol diluent, and prolonged high-dose midazolam infusions may cause hyperchloremia metabolic acidosis or benzyl alcohol-induced metabolic acidosis. Benzodiazepine continuous infusions in combination with propofol may lead to increased incidence of hypotension and delirium.[94] In addition, there may be other sedative agents, such as dexmedetomidine and ketamine, that could be more appropriate.

The Patient With End-Stage Liver Disease

Patients with alcohol use disorder present with varying degrees of hepatic dysfunction, from mild to severe. Symptoms of severe liver disease may include lethargy, jaundice, ascites, edema of the legs, sequelae of gastric or esophageal varices, hepatic encephalopathy, and pruritus. The Model for End-Stage Liver Disease (MELD) score considers sodium, international normalized ratio, bilirubin, and creatinine to predict 3-month mortality. Those with higher scores (6 to 40) have more severe liver disease.

An online calculator for the MELD score is available at MDCalc.com: www.mdcalc.com/calc/78/meld-score-model-end-stage-liver-disease-12-older

It may be difficult to distinguish withdrawal-related delirium from hepatic encephalopathy. The presence and/or absence of recent alcohol use and

Table 6. Richmond Agitation-Sedation Scale[91]

Patient Condition	Score
Combative	+4
Very agitated	+3
Agitated	+2
Restless	+1
Alert and calm	0
Drowsy	-1
Light sedation	-2
Moderate sedation	-3
Deep sedation	-4
Unarousable sedation	-5

timing can help guide diagnosis. In addition, hepatic encephalopathy is typically hypoactive, whereas AWS is hyperactive, with dysautonomia. To treat AWS in those with end-stage liver disease, consider benzodiazepines that have inactive metabolites, such as lorazepam, to prevent oversedation. Considering other medications to reduce craving (eg, acamprosate, gabapentin) over naltrexone, which is hepatically metabolized, may be more reasonable.[1]

The Pregnant Patient

Pregnant patients with AWS are particularly vulnerable and should be strongly considered for inpatient management, regardless of AWS severity.[95] Benzodiazepines and barbiturates have potentially teratogenic effects, but the short-term risk is small, especially when used later in pregnancy, and generally outweighed by risks of untreated AWS.[7] Untreated AWS in pregnant patients leads to higher risk for placental abruption, preterm delivery, and fetal distress.

Controversies and Cutting Edge

N-Methyl-D-Aspartate Receptor Antagonists

Receptors other than the $GABA_A$ 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.[96-98] Ethanol is an NMDA-receptor antagonist, and chronic antagonism of the NMDA receptor results in upregulation of neurotransmission.[99] Similar to the $GABA_A$ receptor, this increase in neurotransmission is likely related to alteration of receptor subunits rather than an increase in the absolute number of NMDA receptors.[99] In the acute alcohol withdrawal state, NMDA receptor activity is uninhibited, resulting in CNS hyperstimulation. This process offers a biologically plausible approach to combating the underlying pathophysiology of CNS hyperexcitability seen in AWS.

Ketamine

Ketamine is an NMDA receptor antagonist familiar to the ED setting. While a systematic review of 634 participants found no sufficient evidence for ketamine use in decreasing withdrawal severity and cravings,[100] the subset of retrospective ICU studies in the review and other retrospective studies in the ICU suggested a significant difference associated with those receiving subdissociative ketamine infusions as an adjunct for decreasing withdrawal severity, risk for intubation, and benzodiazepine use.[100-103] More prospective trials are needed to evaluate ketamine's efficacy, but given its safety profile, it may be considered as a reasonable adjunct for refractory alcohol withdrawal or complicated alcohol withdrawal not fully controlled with benzodiazepines or phenobarbital.[7] Subdissociative dosing of ketamine would be up to a 0.35 mg/kg IV bolus, followed by an infusion of 0.3 mg/kg/hr for symptom control.[103,104]

Acamprosate

Acamprosate, which is structurally similar to GABA, also decreases NMDA receptor activity, decreasing glutamate activity in the CNS.[105] While theoretically viable to treat alcohol withdrawal, there are no published studies, to date, on treatment for alcohol withdrawal with acamprosate. However, acamprosate is studied in the treatment of alcohol use disorder to decrease and prevent recurrence of drinking alcohol.[8] A systematic review of 20 trials of over 6000 participants demonstrated a number needed to treat of 11 to prevent 1 person from returning to drinking.[106]

Magnesium

Magnesium is a voltage-dependent blocker of NMDA receptors, decreasing nitric oxide synthase production, important in the neural transmission in glutamatergic pathways. It is postulated that magnesium could decrease neuron excitability, thus decreasing symptoms of withdrawal. In addition, many patients with alcohol use disorder and alcohol withdrawal are often hypomagnesemic due to increased magnesium urinary excretion and poor nutritional intake. A 2013 Cochrane review did not find any benefit with giving magnesium.[107,108] There is insufficient evidence to recommend its routine use in ED patients with AWS.[7]

Gabapentin

Gabapentin is a voltage-gated calcium channel modulator with an unclear exact mechanism of action and, while not a direct $GABA_A$ analogue, causes increases in central GABA levels.[109] Gabapentin has a paucity of evidence regarding prospective randomized controlled trials on its use for treating AWS for hospitalized patients. However, a systematic review and meta-analysis of gabapentin that included 8 retrospective studies of 2030 patients found that there were significant decreases in length of stay and benzodiazepine administration. The authors concluded there is not enough evidence to support its use, given the types of studies found, confounding variables, and need for randomized controlled trials.[110-112] In 2019, a benzodiazepines-sparing protocol (clonidine and gabapentin) for trauma patients at risk for AWS was implemented at a Level I trauma site. In a before-and-after comparison, there was a significantly lower lorazepam equivalents per day in the benzodiazepine-sparing protocol versus conventional protocol, with similar outcome variables as mortality, hospital length of stay, and CIWA-Ar scores.[113] An open-label randomized controlled trial of 88 patients found no statistically significant difference in the mean amount of benzodiazepine administered in the fixed-dose gabapentin taper plus

benzodiazepine group versus the benzodiazepine-only group, but the study had under-enrollment and was not powered sufficiently.[114] According to ASAM guidelines, gabapentin may be a reasonable option as an adjunct medication to benzodiazepines to treat mild to moderate alcohol withdrawal in outpatient settings.[7] A recommended regimen would be a loading dose of 1200 mg, then 600 mg every 6 hours for 1 to 3 days, tapered to 300 to 600 mg/day up to 4 to 7 days.[7]

Antiseizure Medications

A 2010 Cochrane review of 56 studies of 4076 participants evaluating the effectiveness of anticonvulsants in treatment of alcohol withdrawal, found insufficient evidence in favor of anticonvulsants for the treatment of AWS. Carbamazepine had some favorable outcomes when compared to benzodiazepines, but these were in outpatient populations with mild withdrawal.[115] It is difficult to extrapolate these results into the ED setting.

Dexmedetomidine

Dexmedetomidine is an alpha-2 adrenoreceptor agonist, providing sedative effects with little effect on respiratory function. Given its advantage of preserving respiratory function with sedative effects, it has been suggested as an adjunct therapy to benzodiazepines for treatment of AWS. Dexmedetomidine does not address the underlying pathophysiology but has been theorized to decrease the incidence of intubation that may occur with the sedative effects of benzodiazepines. Two systematic reviews and meta-analyses found low-quality evidence that did not demonstrate a difference in likelihood of intubation or ICU length of stay compared with benzodiazepines alone for AWS.[116,117] The only retrospective review of continuous infusions of dexmedetomidine versus propofol and lorazepam infusions found a decreased incidence of intubation; however, the numbers were small, and it is unclear whether the patients received intermittent doses of push-dose benzodiazepines in both groups.[94]

Baclofen

Baclofen is a $GABA_B$ receptor agonist that has been studied for management of acute alcohol withdrawal. A 2019 Cochrane review found low-quality and insufficient evidence for its efficacy and safety in treating patients with AWS.[51,118-120] Currently, there is insufficient evidence to recommend its routine use in ED patients with AWS.[7]

Disposition

AWS represents a spectrum of illness, and accurately identifying the patient's place on this spectrum is critical in determining the treatment and level of care required. Patients with AWS present complicated clinical scenarios, and a thorough understanding of the underlying pathophysiology, the typical progression of the disease, and associated illnesses are required for effective treatment. Refer to **Table 7** for disposition criteria for AWS. Patients with CIWA-Ar scores ≥19 should receive inpatient treatment, given a high risk for recurrence of withdrawal and complications.[1,7]

Patients planned for discharge require a thorough neurocognitive function assessment to determine their understanding of their circumstances, ability to care for themselves, and any degree of psychomotor impairment (ie, gait). If symptoms are controlled, the CIWA-Ar score is <10, and there is a safe disposition plan, the patient is appropriate for discharge. Consideration of alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT) should be engaged to provide the patient with evidence-based pathways to

Table 7. Disposition for Patients With Alcohol Withdrawal Syndrome[121]

Disposition	Criteria
Discharge with detoxification referral	• Initial CIWA-Ar score <10 (or equivalent score from other validated withdrawal assessment tool) • No clinical alcohol or drug intoxication • No history of complicated AWS (seizures, hallucinosis, delirium tremens) • No significant underlying medical or psychiatric comorbidities
Admit for inpatient detoxification or care in the medical unit	• No underlying medical or surgical condition requiring ICU-level care • Normalization or near-normalization of vital signs with emergency department management • Clear sensorium • Responsive to 10-20 mg of diazepam or equivalent • Tolerates 2-4 hours between benzodiazepine or phenobarbital doses • Presence of medical or psychiatric condition requiring inpatient admission
Admit to ICU	• Underlying medical or surgical condition requiring ICU-level care, including mechanical ventilation • Requires >100-200 mg of diazepam or equivalent to control symptoms in the emergency department • Requires benzodiazepines or phenobarbital more frequently than every 2 hours • Requires use of adjunctive therapies to control acute withdrawal • Hyperthermia due to alcohol withdrawal • Presence of altered sensorium or recurrent seizures

Abbreviations: AWS, alcohol withdrawal syndrome; CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol, revised; ICU, intensive care unit.

alcohol use disorder treatment resources. Nurse care managers, peer navigators, substance use disorder navigators, and outpatient clinic resources can provide the patient with resources to make a successful and safe transition to outpatient programs.[122]

Medications for discharge should be considered. Outpatient benzodiazepine tapers should be prescribed only for patients with mild to moderate withdrawal, reliable follow-up, and low risk for relapse or misuse. An example taper of diazepam is 10 mg orally every 6 hours for the first 24 hours, then 5 mg orally every 6 to 12 hours for the following 3 days; or chlordiazepoxide 50 to 100 mg orally every 6 hours for 4 doses, then 25 to 50 mg orally every 6 hours for 2 to 3 days.

Medications to reduce cravings that are United States Food and Drug Administration (FDA)-approved for alcohol use disorder (acamprosate and naltrexone) can be prescribed. **(See Table 8.)** Gabapentin can be an alternative. Gabapentin's efficacy for decreasing cravings is promising. A randomized controlled trial of 90 individuals randomized to oral gabapentin (1200 mg/day) versus placebo found a number needed to treat of 5.4 for no heavy drinking days and number needed to treat of 6.2 for total abstinence.[123] Gabapentin has shown benefit in reducing cravings and promoting abstinence in alcohol use disorder, though it is not FDA-approved for this indication and carries a risk for misuse, and it should therefore be prescribed with caution for select patients.[73,112]

Summary

AWS is a complex and sometimes difficult diagnosis to make, as it can present subtly and/or develop over the course of an ED visit. Using a stepwise approach with high clinical suspicion and prompt response is imperative. When AWS is identified, front-loading benzodiazepines with symptom-triggered treatment or phenobarbital are the best options. Other adjunctive medications show promise, but there is a lack of sufficient evidence for widespread use in an inpatient setting. Disposition requires a knowledge of appropriate medications for outpatient treatment of AWS, resources for alcohol use disorder and treatment, and adjunctive medications to decrease cravings.

Time- and Cost-Effective Strategies

- Front-loading benzodiazepines or phenobarbital may prevent complications of severe AWS in the ED and the resulting increased length of stay.
- Symptom-driven benzodiazepine dosing is preferred over scheduled dosing therapy for AWS, given its proven benefits to reduce hospital length of stay, complications, and decreased total benzodiazepine use.
- Patients who meet discharge criteria should be considered for a benzodiazepine taper, referral to substance use resources, and a prescription for a medication that reduces craving, which may decrease the incidence of complications and return visits.

5 Things That Will Change Your Practice

1. Front-loading and aggressive early therapy for AWS can prevent complications and progression of symptoms.
2. Benzodiazepines are still first-line therapy, but phenobarbital has shown promising results as both monotherapy and an adjunct to benzodiazepines.
3. Symptom-based treatment is more effective than fixed-schedule treatment for AWS.
4. For carefully selected patients with mild to moderate AWS managed in the outpatient setting, carbamazepine or gabapentin may be considered as alternatives or adjuncts to benzodiazepines.
5. Anticraving medications such as naltrexone, acamprosate, and gabapentin should be considered to prevent alcohol relapse in eligible discharged patients.

Table 8. Medications for the Treatment of Alcohol Use Disorder[1,8]

Medication	Dosing	Notes
Naltrexone	50 mg PO per day (may increase to 100 mg PO per day after 3 days)	• Avoid in patients with end-stage liver disease, acute hepatitis, severe renal impairment, opioid dependence • Adverse effects: nausea/vomiting, headache, dizziness, fatigue
Acamprosate	666 mg PO 3 times per day	• Requires renal dosing and adjustment for patients weighing <60 kg • Adverse effects: diarrhea, insomnia, depression, anorexia, dry mouth
Gabapentin	300-600 mg 3 times per day	• Use caution in elderly patients and patients with fall risk • Requires renal dosing • Not FDA-approved for alcohol use disorder • Adverse effects: dizziness, somnolence, fatigue, diarrhea

Abbreviations: FDA, United States Food and Drug Administration; PO, orally.

Risk Management Pitfalls for Emergency Department Patients With Alcohol Withdrawal Syndrome

1. **"The patient had alcohol use disorder with an elevated blood alcohol level. I assumed she was intoxicated."** In patients with chronic alcohol use, withdrawal can occur even with an elevated blood alcohol level. While there is a paucity of evidence for a particular blood alcohol level, withdrawal has been noted in levels as high as 150 mg/dL.[45] The higher the ethanol level with development of alcohol withdrawal, the greater the likelihood for severe alcohol withdrawal.

2. **"The patient's withdrawal appeared to be mild, so I discharged them."** While withdrawal may be mild, it can progress after discharge. It is important to note any underlying medical conditions that contribute to the alcohol withdrawal in the first place. Aggressive treatment, referral to resources, and adjunct care are needed. Safe discharge criteria are a CIWA-Ar score <10, no history of complicated alcohol withdrawal, and no clinical evidence of alcohol or drug intoxication. If the patient will not return to alcohol consumption, a benzodiazepine taper should be prescribed to prevent worsening withdrawal.

3. **"The patient presented with AWS and was confused, but he seemed stable, so I admitted him to the floor."** Delirium tremens can present without agitation and will not always have autonomic dysregulation. Given the high chance for morbidity and mortality in these patients, they should be admitted to a step-down, monitored setting.

4. **"The patient will just go out to start drinking again. I won't prescribe him any medications."** Although prescribing tapered benzodiazepines outpatient may not be appropriate for a patient who will continue alcohol use, referral to resources and offering anticraving medications should still be strongly considered.

5. **"I was afraid benzodiazepines would cause her to stop breathing."** Patients with AWS typically require higher doses of benzodiazepines due to downregulated GABAergic receptors. Aggressive and early treatment of AWS, with frequent evaluations and monitoring, should be done to prevent worsening withdrawal and complications.

6. **"I thought I should use the same dosing as his previous admission for alcohol withdrawal."** Patients who experience frequent alcohol withdrawal episodes can have a "kindling" effect, with increasing difficulty treating alcohol withdrawal symptoms with each subsequent episode of withdrawal.[7] There may be increased treatment dosing needs for subsequent visits for alcohol withdrawal.

7. **"The presentation can't be alcohol withdrawal because the patient told me he drinks only 2 drinks a day."** Patients with alcohol use disorder may minimize their alcohol consumption. Obtaining collateral information and/or monitoring the patient for withdrawal is still warranted, particularly if there is history of withdrawal.

8. **"The patient is altered because of alcohol withdrawal."** While delirium tremens is a medical emergency, many patients with alcohol use disorder can have complicating comorbid conditions, such as hepatic encephalopathy, electrolyte abnormalities, and epilepsy. In addition, there can be concomitant pathology, such as traumatic brain injury from falls, sepsis, or other intoxicants.

9. **"The patient is presenting to the ED in alcohol withdrawal again. We don't need to check labs."** Patients with alcohol use disorder can present with complicating electrolyte derangements and/or metabolic derangements, including alcoholic ketoacidosis, that should be considered.

10. **"The patient requested detoxification, but she had no history of severe withdrawal and had no symptoms in the ED, so I discharged her."** Alcohol use disorder is associated with significant morbidity and mortality, particularly in patients presenting to the ED. Patients may have psychiatric comorbidities, and suicidality must be screened for. If a patient has a wish to seek treatment, connecting and helping that patient with resources can prevent repeat visits and complications and can be life-saving.

Case Conclusions

CASE 1

For the 42-year-old man who presented to the ED by ambulance with a seizure witnessed by bystanders…

After ensuring his stability and evaluating for other etiologies, you diagnosed this patient with a withdrawal seizure, in the setting of his history of withdrawal seizures and current seizure episode. You decided to administer 10 mg/kg of IV phenobarbital. One hour later, his CIWA-Ar score was 6, with significant improvement in his symptoms and vital signs. His laboratory results demonstrated hypokalemia and hypomagnesemia, so you repleted his electrolytes while checking an electrocardiogram, which showed a normal QTc. You administered adjunctive thiamine and admitted him to the step-down unit for continued monitoring for AWS. While inpatient, he required a subsequent phenobarbital 130 mg IV dose.

CASE 2

For the 52-year-old man who presented altered to the ED, but was attempting to leave…

After determining his lack of capacity and danger to self and others, you decided to give medication for symptom management. He was given droperidol IM, placed on monitors, and IV access was obtained. His vital signs were: temperature, 39.6°C; heart rate, 140 beats/min; blood pressure, 184/83 mm Hg; and respiration rate, 34 breaths/min on 95% room air. He was still thrashing against restraint. After escalating doses of diazepam for a total of 140 mg and 1 liter crystalloid fluid bolus IV in 1 hour, his vital signs improved, but he was still delirious and severely agitated, fighting against the physical restraints. You wanted to avoid intubation, but with his continued delirium, threat to safety, and need for continued workup, you decided to intubate him, utilizing propofol for induction, and succinylcholine for paralysis. For postintubation sedation, you started a propofol infusion. Despite adequate propofol dosing, his vital signs remained hypertensive, tachycardic, and febrile, prompting dexmedetomidine infusion and continued intermittent dosing of diazepam IV for a RASS score of -1. After evaluating for other etiologies of his altered mental status, he was admitted to the ICU for further treatment of delirium tremens.

CASE 3

For the 30-year old woman who was signed out to you for time to metabolize alcohol …

After talking with and evaluating the patient, you recognized that she was seeking detoxification. Her screening for suicide was negative. You engaged your peer recovery team, who would seek local inpatient detoxification centers. In the meantime, you administered oral chlordiazepoxide 50 mg, oral thiamine 100 mg, and oral naltrexone 50 mg to help with her symptoms. After a couple of hours, her CIWA-Ar score was 3, she felt comfortable, and the peer recovery team had found an accepting inpatient treatment center. She was transported safely to continue her treatment.

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 author, are noted by an asterisk (*) next to the number of the reference.

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1. **How soon can alcohol withdrawal present after the patient's last drink of ethanol?**
   a. 2 hours
   b. 6 hours
   c. 24 hours
   d. 48 hours

2. **Which of the following is the most significant risk factor for development of alcohol withdrawal?**
   a. Thrombocytopenia
   b. Serum ethanol level >150 mg/dL
   c. Metabolic or electrolyte derangements
   d. Previous history of alcohol withdrawal

3. **Which of the following is a validated tool for assessing the severity of alcohol withdrawal and response to treatment in non-intensive care unit patients?**
   a. CIWA-Ar
   b. CAGE questionnaire
   c. MELD scoring
   d. SBIRT screening

4. **How does alcohol withdrawal hallucinosis differ from delirium tremens?**
   a. Delirium tremens includes visual hallucinations, whereas alcohol withdrawal hallucinosis is limited to tactile hallucinations.
   b. Alcohol withdrawal hallucinosis is a more serious condition than delirium tremens.
   c. Delirium tremens has alteration of sensorium and disorientation, compared to alcohol hallucinosis.
   d. Delirium tremens occurs earlier than alcohol hallucinosis, with normal vital signs.

5. **Which of the following statements concerning the diagnosis of alcohol withdrawal is FALSE?**
   a. The diagnosis is often missed, or signs and symptoms are erroneously attributed to another cause.
   b. The presence of hypokalemia can be used to confirm the diagnosis.
   c. Diagnostic criteria are strictly historical and clinical.
   d. The differential diagnosis for alcohol withdrawal is broad.

6. **As used in the alcohol withdrawal literature, "kindling" refers to which of the following?**
   a. Increasing difficulty treating alcohol withdrawal symptoms with each subsequent episode of withdrawal
   b. Increased tolerance to the effects of alcohol with prolonged alcohol consumption
   c. Increased sedation with higher serum or blood alcohol levels
   d. Ability to metabolize alcohol more quickly with chronic alcohol use

7. **Which of the following benzodiazepines does not have active hepatic metabolites?**
   a. Lorazepam
   b. Diazepam
   c. Chlordiazepoxide
   d. Midazolam

8. **Why is phenobarbital considered a reasonable adjunct or alternative to benzodiazepines?**
   a. Phenobarbital has a theoretical dual benefit of both decreasing glutamate activity and its $GABA_A$ agonism.
   b. Phenobarbital has an extended half-life of up to 120 hours, making frequent redosing less necessary.
   c. Studies have demonstrated similar efficacy and a benzodiazepines-sparing effect when phenobarbital is used as a single agent or adjunctive benzodiazepine therapy.
   d. All of the above.

9. **In addition to $GABA_A$ receptors, what other receptor is altered in chronic alcohol use and may be an appropriate source of pharmacotherapy for alcohol withdrawal patients who are resistant to large benzodiazepine doses?**
   a. Serotonin receptors
   b. $GABA_B$ receptors
   c. NMDA receptors
   d. Beta adrenergic receptors

10. **Which of the following medications is used to decrease cravings in alcohol use disorder?**
    a. Baclofen
    b. Acamprosate
    c. Naltrexone
    d. Both b and c

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
- Definitely 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

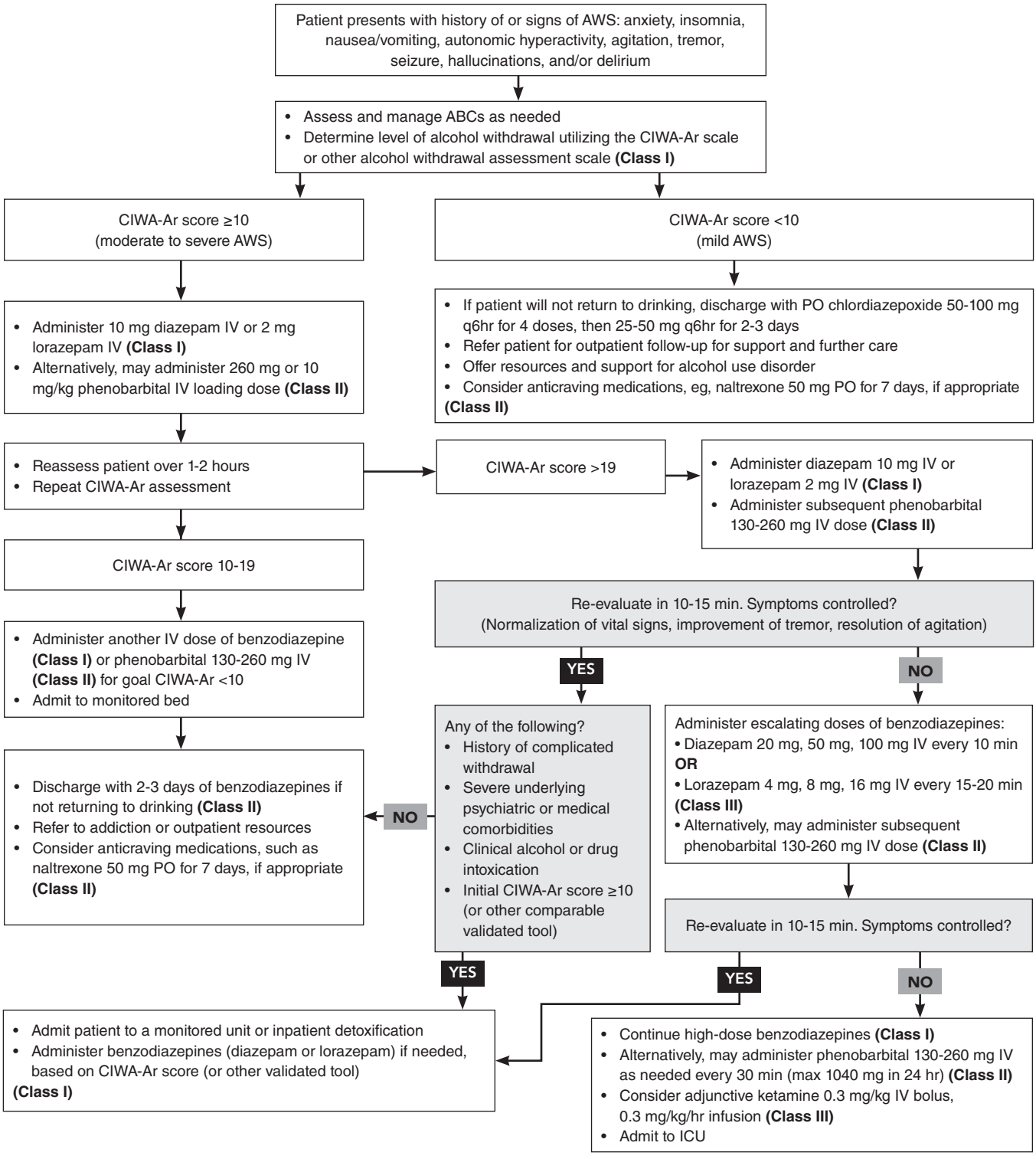
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

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

Clinical Pathway for Emergency Department Management of Alcohol Withdrawal Syndrome

Click here or scan for interactive pathway



Abbreviations: ABCs, airway, breathing, circulation; AWS, alcohol withdrawal syndrome; CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, revised; ICU, intensive care unit; IV, intravenous; PO, orally; q, every.

For Class of Evidence definitions, see page 22.

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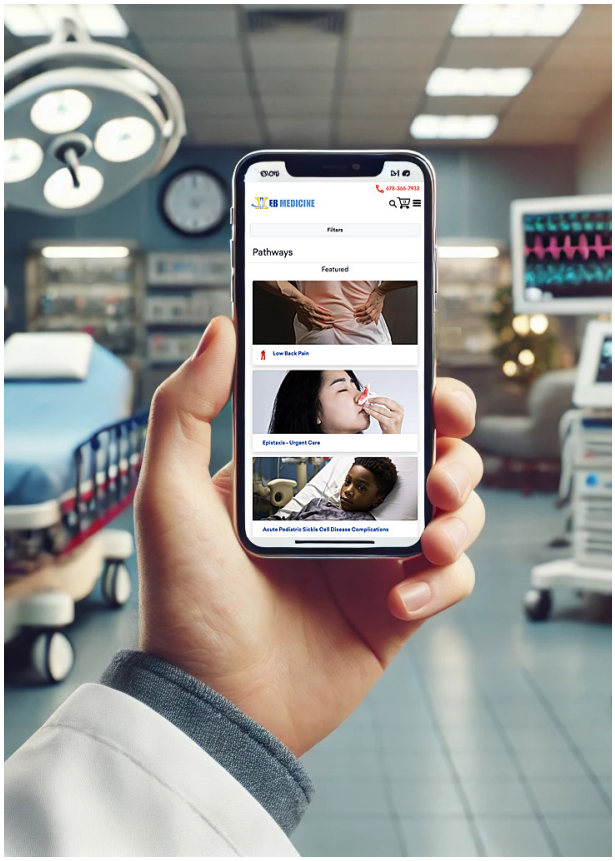

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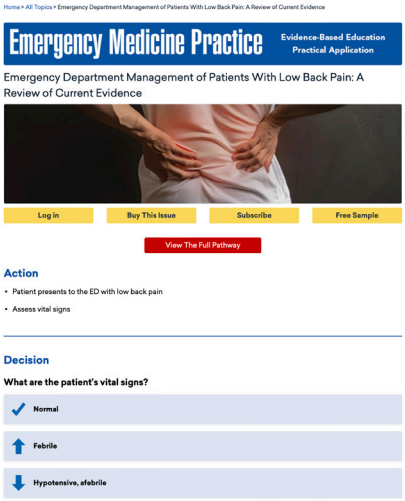

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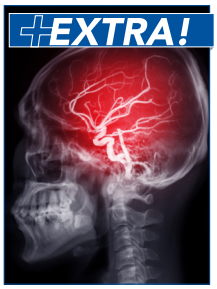

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QUICK READ

Points & Pearls

NOVEMBER 2025 | VOLUME 27 | ISSUE 11

Diagnosis and Management of Emergency Department Patients With Alcohol Withdrawal Syndrome

Points

- Alcohol withdrawal syndrome (AWS) represents a spectrum of illness and presents with a constellation of disorders related to central nervous system excitability in the setting of decreased or ceased alcohol consumption.
- AWS symptoms can begin as soon as 6 hours from decreased or ceased alcohol use, and may occur in patients who present to the ED with other acute reasons.
- Coexisting illness may precipitate AWS, and evaluation for alternate or concomitant diagnoses should begin at presentation. **Table 1** outlines toxicologic and medical diagnoses on the differential for AWS.
- Agitation due to suspected AWS should be treated with benzodiazepines in the prehospital setting, according to local EMS protocols.
- **Table 2** lists risk factors for development of AWS. The most important risk factor is a previous history of AWS.[29]
- AWS is a clinical diagnosis. Two or more of the 8 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision (DSM-5-TR)* criteria for AWS confirms diagnosis. **See Table 3**.
- **Figure 1** illustrates common symptoms and signs of AWS according to the timing since the patient's last alcoholic drink.
- Early symptoms include headache, nausea/vomiting, tremors, diaphoresis, and anxiety. Symptoms may be blunted in those taking sympatholytic medications or alpha-2 adrenergic agonists.
- Moderate to severe AWS symptoms occuring in the first 12 to 36 hours include autonomic hyperexcitability, eg, tachycardia, hypertension, diaphoresis, agitation, and seizures.
- Patients with AWS may present with electrolyte and nutritional derangements such as hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia, and thiamine deficiency.
- Any electrolyte abnormalities should be corrected. Alcoholic ketoacidosis is typically reversed with dextrose-containing IV fluids and thiamine.[74]
- Alcohol intoxication can mimic AWS, so determining an ethanol level may be helpful. It is possible for a patient with a positive blood alcohol content to present with AWS.
- For patients with end-stage liver disease, consider benzodiazepines that have inactive metabolites (eg, lorazepam), to prevent oversedation.
- Outpatient benzodiazepine tapers should be prescribed only for patients with mild to moderate withdrawal, reliable follow-up, and low risk for relapse or misuse.
- When discharging a patient with AWS, consider an anticraving medication, benzodiazepine taper (if appropriate), vitamins, and addiction resources to ensure safety and follow-up. (**See Table 8.**)

Pearls

- Abrupt cessation of alcohol use can precipitate more-severe withdrawal symptoms than gradual decrease, so it is important to question patients regarding their chronic exposure, cessation history, and why they ceased alcohol use.
- When AWS is diagnosed, the severity should be scored using a validated tool such as the CIWA-Ar (**see Figure 2**). Repeat scoring with patient re-assessment during treatment will assist in determining disposition.
- The "kindling effect" occurs with repeated cycles of withdrawal, leading to longer duration of symptoms and severity.[46]
- Aggressive front-loading and symptom-triggered benzodiazepine administration is the primary treatment for AWS.[7]
- In choosing benzodiazepine for treatment, the patient's condition, local practice patterns, and logistics should be considered. **See Table 4**.
- Phenobarbital has emerged in the last decade as a treatment for AWS.[3,61-63] Phenobarbital can be given alone or with benzodiazepines.[65-69] **See Table 5** for phenobarbital-only dosing.[66,70]
- Maintain a low threshold for administration of high doses of thiamine (500 mg IV) if signs of Wernicke encephalopathy are present, even in the absence of the classic clinical triad.[1]
- **Table 7** lists disposition criteria for patients with AWS.[121]

