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Alcohol Withdrawal Syndrome

Introduction

The National Institutes of Health (NIH) in 2007 estimated that 17.6 million (1 in 12) adults in the United States abuse or are dependent on alcohol. Alcohol withdrawal syndrome (AWS) is a potentially life-threatening condition that can develop as a result of sudden reduction or discontinuation of alcohol use.[1] In heavy drinkers, withdrawal can occur while there are still measurable levels of alcohol in the blood. After as little as one week of excessive alcohol intake, mild withdrawal symptoms can occur upon drinking cessation.[1] Emergency physicians must be proficient at recognizing, evaluating, and treating patients suffering from or at risk for AWS. With the ever-increasing number of admitted patients "boarding" in the emergency department, an understanding of management beyond the initial presentation is necessary. To date, there are many case reports and uncontrolled studies but few randomized controlled studies exploring various treatment modalities for AWS. Clinical decision making, therefore, has to be made based on the literature that is available and on a case-by-case basis. This article aims to provide an evidence-based approach to the evaluation and treatment of these patients in order to minimize the morbidity and mortality associated with AWS.

Overview/Pathophysiology

The level of arousal within the central nervous system (CNS) is determined primarily by two opposing types of neurotransmitters, excitatory and inhibitory, which maintain cerebral homeostasis. An overabundance of excitatory influence can result in seizures, whereas excessive inhibitory influence can result in sedation, incoordination, and coma.[2] Gamma-aminobutyric acid (GABA), which is the primary inhibitory neurotransmitter, acts as a CNS depressant by binding to GABAA receptors embedded in the cell membrane of neurons. Binding of these receptors by GABA activates them, allowing chloride to pass from the extracellular fluid into the cell. This shift of chloride results in a decrease in the cell's excitability.[2] The presence of a large amount of GABA is manifested clinically as sedation and intoxication.

The GABAA receptor complex has highly specific binding sites for ethanol. The effects of ethanol on the CNS are manifested as sedation, motor incoordination, and cognitive dysfunction.[1] With chronic ethanol use, GABA receptor upregulation leads to a progressive insensitivity to both GABA and ethanol, requiring larger and larger doses of either to maintain inhibitory tone. For this reason, alcoholics can remain alert with blood alcohol concentrations (BAC) that normally would cause lethargy or coma in the novice drinker. The GABAA receptor also is modulated by benzodiazepines, hence their role in treating AWS.[3]

Ethanol also causes CNS depression by inhibiting glutamate, the primary CNS excitatory neurotransmitter. N-methyl-D-aspartate receptors (NMDAR) are glutamate receptors expressed in large numbers in the CNS.[4] NMDAR have the highest affinity for ethanol of all the glutamate receptors in the CNS.[4] Increased sensitivity to glutamate via an increase in the number and sensitivity of the NMDAR is a direct result of the constant presence of ethanol.[4] Upregulation of NMDA receptors and increased levels of dopamine develop in response to chronic

Executive Summary

- Consider AWS in adult patients who present with a first seizure.
- Patients with chronic alcohol abuse can develop withdrawal even with detectable alcohol levels.
- Using the CIWA-Ar score guides therapy and determines the risk for AWS.
- Benzodiazepines are the drug of choice for AWS. Haldol has some disadvantages.

ethanol consumption to maintain normal levels of alertness.[5] As a consequence, the brain operates at a new level of "normal." This adaptation of the brain causes problems when the ethanol is withdrawn. The larger number of NMDA receptors is now free to bind with glutamate, leading to enhanced excitatory neurotransmission.[6] Without the counterbalance of the ethanol, the CNS operates at an unopposed level of hyperactivity, leading to the various symptoms of AWS.[7]

The mechanisms by which alcohol withdrawal affects the cardiovascular system are poorly understood. The increased cardiac output, heart rate, peripheral resistance, and arterial hypertension observed in AWS are thought to be related to catecholamine release, beta-adrenergic hypersensitivity, and increased production of cortisol.[8,9] Evidence suggests that nitric oxide (NO) also may play an important role in the cardiovascular changes of AWS.[10] NO is a mediator found in neural cells of the central nervous system and cardiovascular endothelial cells and is involved in the production of cyclic GMP.[10] Cyclic GMP, in turn, initiates vascular smooth muscle relaxation.[10] There is evidence that long-term use of alcohol may interfere with the function of NO and, as a result, impair endothelium-dependent vasodilatation causing increased systolic and diastolic pressures.[10] Because of the multiple mechanisms by which ethanol affects the CNS, the management of AWS with a single agent can be insufficient.

Recognizing Alcohol Withdrawal

If not recognized and treated by the clinician, alcohol withdrawal can be associated with significant morbidity and even mortality. It seems fairly simple to suspect AWS in the "frequent flyer" or the patient who fits what appears to be the typical profile of a chronic alcohol user. Patients who do not fit these stereotypes risk being misdiagnosed. The clinician must maintain an index of suspicion for AWS in those who might not be suspected of chronic alcohol abuse such as the elderly, women, professionals such as healthcare providers, and younger patients. Many times the family will provide this critical portion of the history that the patient will not.

Hypoglycemia, encephalitis, amphetamine/cocaine psychosis, schizophrenia, and anticholinergic toxicity are some of the considerations in the differential diagnosis.[11] Table 1 illustrates some of the distinguishing characteristics of other disorders that may present in a similar fashion to AWS.

Symptoms

Alcohol withdrawal can cause a myriad of symptoms, ranging from minor to life threatening. Because the half-life of alcohol is short, the symptoms of AWS will begin within hours and resolve within a few days. In many cases, symptoms will develop within 6 hours of abrupt alcohol cessation and resolve within about 24-48 hours without intervention.[1] As noted above, some patients will manifest symptoms while alcohol levels are still measurable. In other cases, the withdrawal syndrome progresses and requires treatment. Many patients have consistent symptoms over a predictable time course.[5] In general, alcohol withdrawal can be classified into minor, major, and delirium tremens.

Minor Withdrawal. Minor withdrawal symptoms commonly include anxiety, tremor, insomnia, palpitations, headache, and gastrointestinal disturbances. (*See Table 2.*)[1] The symptoms often are relieved by resuming alcohol consumption.[1]

Major Withdrawal. Progression to major withdrawal typically occurs 24-72 hours following the last drink. Major withdrawal symptoms involve heightening of the symptoms seen in minor withdrawal.[1] (*See Table 3.*) Patients commonly are very agitated, diaphoretic, and tremulous. Sinus tachycardia and systolic hypertension are seen, as are vomiting and diarrhea. Confusion is common, and seizures and hallucinations may occur.[1]

Withdrawal Seizures. Approximately 5-10% of patients with AWS will have a seizure.[12] Risk factors include long-term (multiple years) alcohol abuse, co-morbid health conditions such as epilepsy and structural brain lesions, and concomitant drug use.[13] Seizures typically occur as an isolated event 24-48 hours following the cessation or limitation of alcohol use. Multiple seizures are uncommon, and status epilepticus occurs in less than 5%.[9,13] A previous withdrawal seizure is associated with a 10-fold increased risk of repeated withdrawal seizure.[14] An isolated seizure in the adult patient with no previous history of seizure disorder should alert the clinician to the possibility of AWS. If treatment is not instituted, approximately one-third of patients with seizure due to AWS will progress to delirium tremens (DT). The development of withdrawal seizures is associated with a four-fold increase in mortality.[13]

Alcoholic Hallucinations. A special consideration in AWS is alcoholic hallucinosis, a separate entity from DT. The pathophysiology of alcoholic hallucinosis is unclear.[15] Hallucinations typically appear within 24

Table 1: Diagnoses for which Alcohol Withdrawal Symptoms Commonly Can Be Mistaken[6]

Alternative Diagnosis	Distinguishing Features
Hypoglycemia	Symptoms resolve with administration of glucose
Encephalitis	Prodrome of headache, confusion, fever
Drug-induced psychosis	Anorexia, insomnia, physical signs of increased sympathetic tone
Schizophrenia	Adolescent to early adult onset, paranoid delusions, flat affect
Anticholinergic toxicity	Dry mucous membranes, urinary retention
Opioid withdrawal	Normal mental status, abdominal pain, vomiting, diarrhea, seizure uncommon
Thyrotoxicosis	Female predilection, physical findings (lid lag, weight loss)
Sedative-hypnotic withdrawal	Delayed onset of symptoms (> 3 days) due to longer half-life
Trauma	History, physical signs

hours after the last drink, but are short lived and resolve within one to two days. Visual hallucinations are five times more common than auditory hallucinations.[16] Vital signs are usually normal, distinguishing alcoholic hallucinosis from DT. Persistence of hallucinosis beyond the 48-hour time period is uncommon.[1]

Delirium Tremens. The most severe form of AWS is delirium tremens. Current Diagnostic and Statistical Manual of Mental Disorders version 4 (DSM-IV) criteria for DT include disturbance of consciousness, change in cognition or perceptual disturbance developing in a short period (hours to days), and the emergence of the aforementioned symptoms during or after withdrawal from heavy alcohol intake.[17] DT was first described by Pearson and Sutton in 1813.[18] Reports of the number of patients who will experience DT range widely from 1.25–33%.[13] Likely the most accurate estimate of the incidence of DT in patients with AWS is closer to 5%.[18] Delirium tremens previously was associated with a mortality of as high as 35%. Over the past 30 years, mortality has been reduced to < 5%.[14] Early detection and aggressive use of benzodiazepines (BZD) may reduce the mortality rate to 1% or less.[13] Progression from major withdrawal to DT typically occurs 72-96 hours following the last drink, and once it occurs is difficult to treat.[1] Change in mental status, autonomic overdrive, and hallucinations are classic features.[18] (*See Table 4*). A general clouding of sensorium distinguishes the hallucinations of DT from those of alcoholic hallucinosis.[18] Agitation, diaphoresis, and low-grade fever are other common findings.[19] Alcohol withdrawal is one of the most common noninfectious causes of fever.[11] Hyperventilation and subsequent respiratory alkalosis lead to decreased cerebral blood flow (CBF), and this is thought to play a significant role in the development of delirium.[18]

Because early detection and prophylaxis of DT reduces morbidity and mortality, identifying patients at risk is a key part of this process.[13] The most important risk factor for the development of DT is a history of previous DT and/or withdrawal seizure.[13] Additional risk factors for DT described by Ferguson et al include history of sustained heavy drinking, age over 30, and greater number of days since last drink.[20] In a prospective study of 334 patients, Palmstierna found that physical as well as historical factors appear to be important predictors of the development of DT. In this study, acute infection had the highest correlation with DT, followed by tachycardia.[21] Five factors readily detected in the ED appear to be strong predictors of DT: presence of infectious disease such as pneumonia or urinary tract infection, tachycardia (on admission), withdrawal symptoms with elevated blood alcohol concentration (BAC), history of seizure, and history of previous DT.[21]

In addition to predicting which patients are at risk for developing DT, identifying risk factors for increased mortality related to DT would aid in clinical management. Unfortunately there is a paucity of data on possible predictors of mortality in DT. Recently, Khan et al conducted a retrospective case-control study of 35 patients who died following hospitalization for DT at two centers.[18] In this small sample size, the researchers found the use of restraints and hyperthermia increased odds of death in patients with DT.[18] While this was a limited study, this paper highlights the critical importance of meticulously monitoring vital signs and aggressively treating agitation to lessen the use of physical restraints.

Table 2: Minor Withdrawal Symptoms

- Anxiety
- Headache
- Insomnia
- Diaphoresis
- Palpitations
- Tremor
- GI upset

Evaluation

Patients present with varying levels of alcohol use, and determining the need for inpatient versus outpatient management can be difficult. Patients who have been symptom-free for more than 4 days without alcohol generally are not at risk for withdrawal and can be referred safely to outpatient centers for management of their alcohol addiction.[1]

A thorough medical evaluation is indicated in patients presenting specifically for detoxification. Other etiologies for altered mental status must be excluded.[22] (*See Table 5.*) Notable findings on physical examination include jaundice, telangietctasia, hepatomegaly, caput medusa,

Table 3: Major Withdrawal Symptoms

- Marked agitation/ tremulousness
- Pronounced paroxysmal diaphoresis
- Tachycardia (> 120 common)
- Systolic hypertension
- Vomiting
- Diarrhea
- Hallucinations
- Seizure

Table 4: Signs and Symptoms of Delirium Tremens

- Disorientation/agitation
- Fever
- Severe tachycardia
- Hypertension
- Hallucinations
- Autonomic instability

petechiae, and guaiac-positive stool. All these signs point to serious underlying medical disorders requiring inpatient treatment. Recommended laboratory studies (helpful in the evaluation, but not required for management) include complete blood count, serum electrolytes, blood glucose concentration, urine hCG, toxicology screen, and liver and renal function tests.[22] In their study of 334 patients, Berggren et al have proposed an association between initial thrombocytopenia and increased risk of AWS, including DT.[13] In select patients, cardiac markers and serum ammonia levels may be indicated.

Electrocardiography should be performed to detect any dysrhythmias.[23] Otero-Anton et al reported prolonged QTc in 46.8% of patients with AWS, although the clinical significance of this finding is unclear.[23] Patients who present with altered mental status may require a lumbar puncture to exclude meningo-encephalitis.

Radiographic studies to consider include plain chest radiography to rule out pneumonia, and a cranial CT scan to exclude intracranial

Table 5: Possible Etiologies of Altered Mental Status[22]

- Trauma
- Infection/sepsis
- Hypertensive emergency
- Psychiatric
- Mass lesion
- Stroke
- Intracranial hemorrhage
- Shock
- Toxic ingestion/overdose
- Hepatic encephalopathy
- Electrolyte disturbance
- Diabetic emergency
- Hypoxia/hypercarbia
- Uremia
- Porphyria

pathology.[22] Clinicians should have a low threshold for ordering a head CT on any patient with seizure.[23] An EEG should be considered in patients with first-time seizure.[24]

Developing theories suggest that homocysteine and prolactin levels may be helpful in the initial evaluation of patients with AWS.[25] It has been found that levels of homocysteine, an excitatory amino acid, are elevated in chronic alcohol users and these levels decrease throughout the withdrawal process. Elevated homocysteine levels on admission may indicate increased risk for withdrawal seizures, but more studies on the subject are needed.[25] In a study by Hillemacher et al, a tentative association was made between the elevation of homocysteine and prolactin levels and an increased risk of withdrawal seizures, although more research into this subject is needed.[25]

Predicting severity of AWS is difficult due to the high variability in patient presentations and responses to treatment. If patients at high risk for developing complicated AWS can be prospectively identified in the ED, determining inpatient versus outpatient detoxification would be easier. The CIWA-Ar (Clinical Institute Withdrawal Assessment) is perhaps the most widely used screening tool to help clinicians predict the need for medication, inpatient detoxification, and efficacy of treatment in AWS. (*See Figure 1.*) Although the predictive power has been proven in just a few studies, it is widely used.[26] The CIWA-Ar score is a clinical tool that can aid in determining who will likely succeed with outpatient detoxification as well as a guide for the administration of medications. It generally is accepted that the use of the CIWA-Ar score leads to more appropriate titration of medications, thereby avoiding excessive sedation. Based on the CIWA-Ar score, guidelines regarding management of AWS have been formulated.[27] (*See Table 6.*) Patients with scores less than 8 generally are safe for ambulatory management, while patients with scores greater than 15 are at high risk for more severe AWS. The disposition of patients with scores between 8 and 15 is evaluated on a case-by-case basis.[1]

Complications

Patients who present for detoxification need treatment not only for AWS, but for the sequelae of their chronic alcohol consumption as well. AWS and the myriad of metabolic dysfunctions due to chronic alcohol use need to be treated simultaneously.

- Hypokalemia results in weakness, myopathy, and can predispose to sudden death due to cardiac dysrhythmia.[6]
- Hypomagnesemia results in hypokalemia, hypocalcemia, and hypophosphatemia, and may predispose to withdrawal seizures.[6]
- Hypophosphatemia: Due to malnutrition, it causes WBC and platelet dysfunction and may predispose to cardiac failure and rhabdomyolysis. Acute repletion of glucose has been associated with severe reduction in serum phosphate levels. Respiratory failure, myocardial dysfunction, and CNS irritability can result.[20]
- Thiamine deficiency: A deficit of thiamine in combination with direct neurotoxic effects from ethanol can lead to polyneuropathy. Pain and paresthesias, mostly in the lower extremities, are the most common symptoms.[28]
- Wernicke's encephalopathy (WE) is classically described as a triad of oculomotor dysfunction (nystagmus, palsy), abnormal mentation, and ataxia (related to thiamine

deficiency).[6] The presence of all three components of the triad is found in only approximately 12% of patients, and therefore the syndrome tends to be under-recognized.[28] In more recent years, criteria for diagnosis include two of the following: dietary deficiency, oculomotor disturbances, cerebellar dysfunction, and impaired memory or mental status.[29] It is thought that a genetic deficiency of transketolase, a thiamine-requiring enzyme, may be associated with the development of WE.[12] The mortality associated with WE is estimated to be 10-20% and is considered a true medical emergency.[6]

• Korsakoff's syndrome: A late neuropsychiatric manifestation of WE characterized by antegrade and retrograde amnesia.[6] Classic symptoms of this disorder include recent memory difficulties, the inability to learn new information, and confabulation.[6] Most commonly, patients are older, with a long history of heavy drinking. The onset of Korsakoff's syndrome can be gradual or acute.[6]

• Cerebellar degeneration results in ataxia, mostly in the lower extremities. Physical signs include a wide-based stance and uncoordinated gait. Severe, disproportionate cerebellar atrophy will be seen on imaging studies.[6]

• Central pontine myelinolysis (CPM) usually is observed as a complication of the electrolyte imbalances due to chronic alcohol abuse. The mechanism of CPM is not well understood but is thought to be related to osmotic insults to the vascular endothelium in the basal ganglia.[30] Vasogenic edema and generation of toxic free radicals cause separation of the myelin from the axons, resulting in cellular disruption. Clinically this is manifested as cognitive dysfunction and behavioral disturbances (psychosis).[30] CPM also has been reported after alcohol withdrawal in the absence of hyponatremia and should be considered in the differential of psychosis in the alcoholic patient.[30]

• Dysrhythmias: The prevalence of dysrhythmias in AWS is not well documented. The high percentage of patients with prolonged QTc intervals reported by Otero-Anton and Cuculi et al theoretically would be clinically significant.[23,31] A prolonged QTc, which represents dysfunction of cardiac repolarization, is a risk factor in the development of torsade de pointes.[31] Avoiding medications that prolong the QTc (neuroleptics) is important in patients with this ECG abnormality. The retrospective studies by Otero-Anton et al and Cuculi et al both indicated that there is an elevated risk of sudden death in patients with severe AWS and prolonged QTc.[23,31] Dysrhythmias related to electrolyte abnormalities also are observed.

• Aspiration and respiratory compromise/arrest may occur due to over sedation.

• Rhabdomyolysis may occur due to agitation.

Treatment

Treatment of the patient with AWS must first address the basics. An airway must be established, breathing assessed, and circulatory status evaluated (ABCs). Oxygen, intravenous access, and cardiac monitoring should be administered.

Benzodiazepines. The treatment of AWS is centered on the use of benzodiazepine sedatives and anti-epileptic medications. Benzodiazepines (BZD) are the only drugs that have been shown conclusively to decrease the complications associated with AWS.[32,33] Like ethanol, BZD (e.g. diazepam) are GABAA receptor agonists, and binding of BZD to these receptors counteracts the CNS hyperactivity induced by withdrawal of ethanol. Several meta-analyses have established that the use of BZD decreased the incidence of delirium and seizures compared to placebo.[1] BZD are considered agents of choice supported by randomized trials.[34] There are no conclusive advantages of one BZD over another, although it is thought that the longer-acting agents have less potential for abuse.[19] Diazepam and chlordiazepoxide are the most commonly used long-acting drugs. The half life of diazepam is 20-100 hours, and the half life of chlordiazepoxide is 5-30 hours. Each of these drugs is converted to its own active metabolite, and each of these has a half life of 36-200 hours, allowing for very smooth tapering in serum levels and fewer withdrawal symptoms. IV diazepam appears to provide the fastest control of agitation in DT.[34] The half lives of lorazepam and oxazepam are 10-20 and 4-15 hours, respectively.

The mean time to achieve adequate sedation (an awake but calm patient) is three hours.[34] The two most common short-acting BZD are lorazepam and oxazepam, which are not metabolized by the liver, an important consideration in the treatment of those with liver dysfunction and the elderly.[1] Isolated case reports have described withdrawal seizures continuing to occur with the use of shorter-acting BZD, making the long-acting BZD the agents of choice in most cases.[33] The use of drugs that can induce respiratory depression is commonly discouraged in the treatment of patients who present requiring detoxification but still have BAC >100 mg/dL.[6] Adverse effects of the BZD include amnesia, sedation, and dependence. When used for less than seven days, the risk of dependence appears to be low.[35]

Anti-epileptic Medications. Various anti-epileptic drugs (AEDs) have been studied in the treatment of AWS and prevention of withdrawal seizures.

Carbemazepine. Carbemazepine (CBZ), studied in the prevention of withdrawal seizures, has been found to be effective in reducing psychomotor agitation.[36] It has been theorized that CBZ also may have a tempering effect on the increasing severity of symptoms that can be observed with repeated episodes of withdrawal (the kindling phenomenon).[6] Advantages of CBZ use include the lack of sedation, abuse potential, and interaction with alcohol.[37] Unfortunately, CBZ is converted in the liver by the cytochrome P450 oxidase system to an active metabolite that is associated with a myriad of adverse effects, including dizziness, ataxia, diplopia, nausea, and vomiting.[37] The results of many studies comparing the efficacy of AEDs such as CBZ support its use in the treatment of AWS.[38] The

Figure 1: Addiction Research Foundation Clinical Institute Withdrawal Assessment—Alcohol (CIWA-Ar)

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

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 Mildly 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.

Tactile Disturbances. Ask "Do you have 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 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

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 you? Are you hearing things you know are not there?"
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 you? Are you seeing things that 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 you 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

(*Continued.*)

Figure 1: Addiction Research Foundation Clinical Institute Withdrawal Assessment—Alcohol (CIWA-Ar) (*Continued*)

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 nor more than 2 calendar days
3 Disoriented for date by more than 2 calendar days
4 Disoriented for place and/or person

Total CIWA-A Score _____
Rater's initials _____
Maximum Possible Score: 67

This scale is not copyrighted and may be used freely. Adapted from: Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: The Revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA–Ar). *Br J Addiction* 1989;84:1353-1357.

Table 6: CIWA–Ar Guidelines[1]

- **Score < 8:** Detoxification may not be needed, use caution in patients who have ingested alcohol within the past 8 hours
- **Score 8-15:** If the patient meets specific criteria, ambulatory detoxification may be good option
- **Score > 15:** Inpatient treatment recommended

Cochrane review of 48 randomized trials was unable to establish a clear advantage of CBZ over other drugs in the treatment of AWS due to "heterogeneity of the trials both in interventions and the assessment of outcomes."[39] While no specific evidence-based recommendations can be made, CBZ may be helpful as an adjunctive medication in the treatment of AWS.

Divalproex Sodium. Divalproex sodium (Valproate, valproic acid) also has shown some promise as an alternative to BZD in open trials, but there has been little "methodologically rigorous" research conducted.[6] Because divalproex sodium is well tolerated in most patients and has a wide therapeutic window, it theoretically would be a safe alternative to BZD in the prevention of withdrawal seizures.[7] Side effects include gastrointestinal upset, tremor, and confusion, although these tend to be dose-related. In a small double-blind study by Reoux et al, 36 patients were randomized to receive either divalproex sodium 500 mg or placebo three times daily. These authors found that the divalproex sodium group had a reduced need for benzodiazepines, lower severity of symptoms (evaluated with CIWA-Ar scores), and were less likely to progress to a more severe stage of withdrawal than those treated with placebo.[7] Somnolence was observed more often in the divalproex sodium group than in the placebo group.[7] The use of divalproex sodium in the ambulatory setting would be useful in that it has less potential for abuse than BZD.

Phenytoin. Phenytoin has demonstrated no benefit over placebo in the prevention of withdrawal seizures.[40] To date, phenytoin plays no role in treatment of AWS.

Miscellaneous Medications Studied in the Treatment of AWS. Baclofen, which is a $GABA_B$ receptor agonist, is commonly used to treat spasticity. There have been case reports of rapid suppression of AWS using baclofen in humans.[41] In the first study to compare baclofen and BZD in the treatment of AWS, Addolorato et al randomly assigned patients to receive either 30 mg/kg baclofen per day divided into three doses or oral diazepam 0.5-0.75 mg/kg divided into six doses. This study found that baclofen performed as well as and, in some cases, better than diazepam in the reduction of the severity of diaphoresis, tremors, anxiety, and agitation.[42] On discontinuation of treatment, no withdrawal or adverse symptoms were reported. Baclofen has long been established as a safe medication without addiction potential. This study and other case reports provide evidence that baclofen may be considered as efficacious as BZD in the treatment of AWS.[41] There have been no double-blind controlled trials to attempt to establish the efficacy of baclofen vs. BZD.[43,44]

Beta-blockers are thought to offset some of the autonomic symptoms associated with AWS. Their use has not been studied in any randomized controlled trials. Due to the inherent potential of beta-blockers to induce delirium and hallucinations, if used they should only be administered in

conjunction with BZD.[45] Beta-blockers have no role in the prevention of withdrawal seizures.[19]

Alpha-2-blockers such as clonidine have been used effectively in the treatment of narcotic withdrawal. Because the signs and symptoms of AWS are interpreted as responses to sympathetic hyperactivity, the use of clonidine to offset these responses was investigated.[46] Although clonidine was found to suppress tachycardia and hypertension in patients with AWS, there are no data to suggest benefit in prevention of withdrawal seizure. Rebound hypertension and nightmares were common.[35] In a small double-blind study by Baumgartner and Rowan, clonidine performed favorably in comparison to chlordiazepoxide with respect to reducing tremor, diaphoresis, and restlessness.[47] No specific recommendations were made, but the use of clonidine to ameliorate the adverse effects of sympathetic hyperactivity appears to be a safe option.[47]

Phenothiazines have been used with BZD as an adjunct, but great caution must be exercised due to lowering of seizure threshold.[45]

Barbiturates (phenobarbital) work synergistically with BZD and were expected to relieve withdrawal symptoms and prevent seizures and DTs. Although there have been no controlled studies to evaluate the efficacy of barbiturates in the treatment of AWS, some reports strongly support the use of phenobarbital as an excellent adjunctive therapy to BZD in the treatment of refractory DT.[48] Barbiturates are known to interfere with clearance of medications requiring hepatic metabolism, and their narrow therapeutic index requires meticulous monitoring.[49] Phenobarbital 130-260 mg IV every 15-20 minutes may be used, knowing that endotracheal intubation may be necessary.[50]

Antipsychotics (haloperidol) historically have been used to treat refractory agitation and hallucinations. Despite trials demonstrating the inferiority of neuroleptic medications compared to sedative-hypnotics in the treatment of DT, their use remains common.[45] Most often, haloperidol is used in combination with BZD to control agitation.[45] The risk of serious adverse effects seen with the high doses of neuroleptics commonly required is significant; these medications have been associated with increased mortality and prolonged duration of delerium.[45] These medications should be used only in conjunction with BZD, if used at all.[45]

Gamma-hydroxybutyric acid (GHB) is an analog of gamma-aminobutyric acid found in the human brain. In the study by Korninger et al, 299 patients were medicated with 50 mg/kg GHB daily in three divided doses at the onset of withdrawal symptoms. As reported by the authors, GHB appeared to be well tolerated, provided relief from symptoms of the AWS, and may be "an attractive alternative to tranquilizers in the management of the alcohol withdrawal syndrome in the hospital."[51] GHB is a Schedule III Controlled Substance in the United States and, because of its potential for abuse, it is not yet recommended for use in the treatment of AWS.[45]

Gabapentin (GP) is structurally related to GABA and readily transported across the blood brain barrier. The mechanism of action of GP is unclear, but it has been used as therapy in the treatment of partial complex seizures as well as some psychiatric disorders.[52] GP is an attractive therapeutic option, as it does not affect liver enzymes and has a good safety profile.[52] In the placebo-controlled two-center trial by Bonnet et al, 400 mg GP was administered four times daily to 61 patients with AWS. This small study did not find any benefit associated with the administration of GP in AWS.[52]

Nutritional Support. Patients who consume alcohol often have poor nutrition. However, it is important to note that most patients will have adequate stores. Further, patients seen on a very frequent basis will not need replacement therapy on every visit. Thiamine (vitamin B1) 100 mg IV should be administered to appropriate patients in the ED to prevent and/or treat WE and KS. The dogma handed down through the generations that glucose preceding thiamine can precipitate acute thiamine deficiency and WE is unproven.[53] Thiamine, when given within minutes to hours of dextrose, is considered safe.[53]

Potassium, in addition to playing a critical role in the cardiovascular and neurologic systems (among others), also may aid in thiamine absorption. Potassium should be repleted as indicated.[45]

Magnesium 1-2 g administered over an hour or two may improve electrolyte balance and facilitate the absorption of thiamine.[11] Magnesium may reduce neuromuscular activity, although this has not been proven in any controlled trials.[45] The administration of magnesium carries little risk or cost and has potential benefit.[45]

Glucose should be repleted as indicated.[45]

Phosphate levels should be maintained for optimal respiratory and cardiac function.[45]

Folate, a coenzyme in amino acid metabolism and DNA synthesis, should be administered 1 mg IV to appropriate patients.[45]

Niacin (vitamin B3), critical to multiple enzymatic functions including the oxidation of alcohol, is administered at a dose of 100 mg IV in the ED.[45]

Multivitamins should be administered to appropriate patients due to the chronic malnutrition suffered by most alcoholics.[45]

Future Possibilities

Studies involving NMDA receptor antagonists, such as memantine, are ongoing. In animal studies, these drugs have been very effective at suppressing the neurotoxicity and seizures associated with alcohol withdrawal.[3] The side effect profiles of NMDA receptor antagonists are significant. Memantine however, has been well tolerated in the treatment of Alzheimer's dementia.[3] In a recent animal study by Stepanyan et al, memantine performed well in the reduction of neurotoxicity (in vitro) and seizures.[3] Further investigation into the use of memantine in human subjects with AWS is needed but holds promise.

Oxcarbazepine (OXC), a newer anti-epileptic drug, is being studied as a better alternative to CBZ in the treatment of AWS.[37] OXC was shown to significantly alleviate AWS symptoms and alcohol cravings in studies by Schik et al and others.[54] In the randomized, double-blind placebo study performed by Koethe et al, however, OXC was found to be no more efficacious than placebo.[37] More studies are needed to support using OXC rather than CBZ.

Dexmedetomidine, an alpha 2 adrenergic antagonist used as a sedative in the treatment of AWS, has shown promise in case reports as a safe adjunctive therapy to BZD.[55]

Topiramate (AED) suppresses glutaminergic input and, in open-label studies, has performed similarly to BZD in reducing AWS symptoms.[49] Topiramate also appears to have a good safety profile and shows promise in the treatment of AWS.[49]

Medication Dosing

Studies have compared medication regimens in an attempt to determine the optimal dosing schedule in the pharmacologic treatment of AWS. A common approach uses fixed doses of long-acting BZD at regularly scheduled intervals regardless of symptoms. Typically, BZD are given every six hours for two to three days, with additional medications given as needed based on symptom severity.[6] As discussed below, this approach is no longer recommended in the inpatient setting.[10,56]

The bulk of the evidence supports the use of symptom-triggered therapy in the inpatient setting, i.e., the administration of subsequent medications only when the patient experiences significant symptoms after an initial bolus of BZD.[34] The CIWA-Ar score then is calculated on an hourly basis, and the patient is medicated only when the score is elevated.[9] Patients who are symptom-free are given no medications. In the randomized, double-blind, controlled trial by Saitz et al in 1994, 100 patients were randomized to receive either a standard four-time daily course of chlordiazepoxide or an as-needed course of the medication. The median duration of treatment reported in this study was 9 hours for the symptom-triggered group vs. 68 hours for the fixed schedule group. No significant difference was reported in either severity of symptoms or incidence of seizure or DT.[34] Spies et al found similar results in their randomized double-blind controlled study of 44 patients admitted to the intensive care unit with AWS. This study observed a median stay in the ICU of 6 days less in the bolus-treated group vs. the continuous-infusion group.[56] The CIWA-Ar scores continued to rise in the infusion group but not in the bolus group. The total amount of medication required also was observed to be significantly lower in the bolus group.[56] Evidence strongly supports that the symptom-triggered approach appears to allow for a reduction in the total amount of medication and time needed for treatment.[6,34,56] Symptom-triggered therapy has been studied only in the treatment of inpatients, and studies are needed to determine whether it may be feasible in the ambulatory setting.[34]

Disposition

Many factors must be considered in the determination of the best disposition for patients in or at risk for withdrawal. Patients who have symptoms of withdrawal with elevated BAC are at high risk for severe symptoms.[1] Patients who have had several (more than three) alcohol binges over the past two weeks are also at high risk for more severe symptoms.[1]

Determining which patients are appropriate for ambulatory detoxification is a clinical judgment that must be made taking numerous factors into consideration. The CIWA-Ar score can be used as a tool in making this judgment. Ambulatory treatment can be considered in patients with mild withdrawal with all of the following characteristics:[57]

- able to take medications by mouth;
- reliable support from a close contact who can stay with and monitor the patient for several days;
- resources to attend daily outpatient medical evaluations;
- no unstable medical or psychiatric condition;
- not pregnant;
- no concurrent substance abuse from which the patient may withdraw;
- no history of DT or withdrawal seizure.

Once the patient has been deemed safe for outpatient detoxification, treatment with either BZD or carbamazepine is recommended.[1] Patients with a CIWA score less than 8 are expected to do well with symptom-triggered therapy and close follow-up. Symptom-triggered therapy is thought to be safe in this group due to the mild nature of their symptoms.[1] Chlordiazepoxide, 50 mg every 6-12 hours as needed for the first 24 hours, is a common medication regimen.[1] Beyond this period, the patient should be receiving daily outpatient evaluations and medications. According to some sources, patients with a CIWA score between 8 and 15 can be carefully selected for outpatient management, but this should be considered on a case-by-case basis, erring on the side of caution.[1] For these patients, a fixed-dose schedule may be more appropriate, since symptom-triggered therapy still has not been formally studied in the outpatient setting.[1] Carbamazepine 200 mg every 6 hours or chlordiazepoxide 50 mg every 6-12 hours are reasonable choices.[1] Nutritional support with multivitamins and thiamine 100 mg daily for three days also should be considered.

Patients in moderate to severe withdrawal require close monitoring, often in the intensive care unit.

Summary Recommendations

Patients who present with AWS require complex evaluation and management, including the diagnosis and treatment of underlying medical conditions.[11]

AWS should be suspected in adult patients presenting with first-time seizure.[11]

Risk factors for AWS include history of withdrawal seizure or DT, prolonged heavy drinking, and age over 30.[19]

The CIWA-Ar score may be helpful

in determining risk of serious AWS and guiding therapy.[25]

Aggressive use of BZD is recommended. Literature supports the use of oral or IV diazepam as first-line BZD due to more rapid onset of action, long duration of action, and decreased breakthrough symptoms.[45] The use of shorter-acting BZD in patients with severe liver disease, other serious illness, and the elderly should be considered.[45]

Symptom-triggered therapy seems to be superior to continuous-dose therapy, although it has not been formally studied in the outpatient setting.[55]

Evolving evidence supports considering the use of CBZ, valproate, or baclofen in combination with BZD for severe AWS.[49] Modest evidence supports the use of gabapentin and topiramate; however, the use of these agents is still controversial.[49]

Phenothiazines alone should not be used due to risk of seizure.[45]

Phenytoin plays no role in the prevention of withdrawal seizures.[40]

Clonidine may be a safe option in the treatment of hypertension and tachycardia.[46]

Neuroleptic medications should not be the only agents used in the management of alcohol withdrawal delirium. If considered at all, they should be used in conjunction with BZD.[45]

Magnesium should be considered empirically in patients with normal renal function and in whom magnesium levels will be monitored. Magnesium should be repleted in patients with hypomagnesemia on laboratory evaluation.[45]

Administer thiamine in appropriate patients to treat and prevent WE and KS.[45]

Select patients who meet specific criteria may be considered for ambulatory detoxification.[56]

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Physician CME Questions

21. Which inhibitory neurotransmitter does ethanol mimic?
    A. NMDA
    B. GABA
    C. Glutamate
    D. Prolactin

22. Minor withdrawal symptoms include all of the following *except*:
    A. Tremulousness
    B. Seizure
    C. Anxiety
    D. Headache

23. Risk factors for the development of AWS include all of the following *except*:
    A. History of seizure or DT
    B. Prolonged, heavy drinking
    C. Age > 30
    D. Previous admission for detoxification

24. Progression to major withdrawal occurs within how many hours following the last drink ingested?
    A. 6-12 hours
    B. 12-24 hours
    C. 24-72 hours
    D. Greater than 72 hours

25. Which of the following are critical actions in the management of DT?
    A. Constant monitoring of vital signs
    B. Aggressive treatment of agitation
    C. Avoiding the use of restraints
    D. All of the above

26. How should thiamine and glucose be administered in the patient with AWS?
    A. Thiamine should always be given before glucose
    B. Thiamine should always be given after glucose
    C. Thiamine and glucose should be given together
    D. As long as thiamine and glucose are given within a few hours of each other, it does not matter.

27. The triad of Wernicke's encephalopathy includes all of the following *except*:
    A. Oculomotor dysfunction
    B. Abnormal mentation
    C. Fever
    D. Ataxia

28. Which class of drugs should be avoided in patients with a prolonged QTc?
    A. Benzodiazepines
    B. Antiepileptic drugs
    C. Neuroleptics
    D. Barbiturates

29. All of the following are true about symptom-triggered therapy *except*:
    A. It has been studied extensively in the outpatient setting
    B. It is associated with a decreased amount of medication needed
    C. It is associated with decreased total time spent in the hospital
    D. Patients receive an initial bolus of medication, followed by subsequent doses only if they are symptomatic

30. Criteria for outpatient management include:
    A. Ability to take oral medications
    B. Supervision by a family member or close contact
    C. Ability to attend daily medical evaluations
    D. All of the above

CME Answer Key

21.B; 22. B; 23. D; 24. C; 25. D; 26. D; 27. C; 82. C; 29. A; 30. D

In Future Issues

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Alcohol Withdrawal Syndrome

Diagnoses for which Alcohol Withdrawal Symptoms Commonly Can Be Mistaken

Alternative Diagnosis	Distinguishing Features
Hypoglycemia	Symptoms resolve with administration of glucose
Encephalitis	Prodrome of headache, confusion, fever
Drug-induced psychosis	Anorexia, insomnia, physical signs of increased sympathetic tone
Schizophrenia	Adolescent to early adult onset, paranoid delusions, flat affect
Anticholinergic toxicity	Dry mucous membranes, urinary retention
Opioid withdrawal	Normal mental status, abdominal pain, vomiting, diarrhea, seizure uncommon
Thyrotoxicosis	Female predilection, physical findings (lid lag, weight loss)
Sedative-hypnotic withdrawal	Delayed onset of symptoms (> 3 days) due to longer half-life
Trauma	History, physical signs

CIWA–Ar Guidelines

- **Score < 8:** Detoxification may not be needed, use caution in patients who have ingested alcohol within the past 8 hours
- **Score 8-15:** If the patient meets specific criteria, ambulatory detoxification may be good option
- **Score > 15:** Inpatient treatment recommended

Major Withdrawal Symptoms

- Marked agitation/ tremulousness
- Pronounced paroxysmal diaphoresis
- Tachycardia (> 120 common)
- Systolic hypertension
- Vomiting
- Diarrhea
- Hallucinations
- Seizure

Minor Withdrawal Symptoms

- Anxiety
- Headache
- Insomnia
- Diaphoresis
- Palpitations
- Tremor
- GI upset

Signs and Symptoms of Delirium Tremens

- Disorientation/agitation
- Fever
- Severe tachycardia
- Hypertension
- Hallucinations
- Autonomic instability

Possible Etiologies of Altered Mental Status

- Trauma
- Infection/sepsis
- Hypertensive emergency
- Psychiatric
- Mass lesion
- Stroke
- Intracranial hemorrhage
- Shock
- Toxic ingestion/overdose
- Hepatic encephalopathy
- Electrolyte disturbance
- Diabetic emergency
- Hypoxia/hypercarbia
- Uremia
- Porphyria

Addiction Research Foundation Clinical Institute Withdrawal Assessment—Alcohol (CIWA–Ar)

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

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 Mildly 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 "Do you have 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 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

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 you? Are you hearing things you know are not there?"
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 you? Are you seeing things that 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 you 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

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 nor more than 2 calendar days
3 Disoriented for date by more than 2 calendar days
4 Disoriented for place and/or person

Total CIWA-A Score _____
Rater's initials _____
Maximum Possible Score: 67

This scale is not copyrighted and may be used freely. Adapted from: Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: The Revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA–Ar). *Br J Addiction* 1989;84:1353-1357.

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