American Journal of Emergency Medicine 35 (2017) 1005–1011

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Review

The emergency medicine management of severe alcohol withdrawal

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ARTICLE INFO

Article history:
Received 13 July 2016
Received in revised form 31 January 2017
Accepted 3 February 2017

Keywords:
Alcohol
Withdrawal
Delirium tremens
Benzodiazepine
Propofol
Phenobarbital
Ketamine
Dexmedetomidine

ABSTRACT

Introduction: Alcohol use is widespread, and withdrawal symptoms are common after decreased alcohol intake. Severe alcohol withdrawal may manifest with delirium tremens, and new therapies may assist in management of this life-threatening condition.
Objective: To provide an evidence-based review of the emergency medicine management of alcohol withdrawal and delirium tremens.
Discussion: The underlying pathophysiology of alcohol withdrawal syndrome (AWS) is central nervous system hyperexcitation. Stages of withdrawal include initial withdrawal symptoms, hallucinations, seizures, and delirium tremens. Management focuses on early diagnosis, resuscitation, and providing medications with gamma-aminobutyric acid (GABA) receptor activity. Benzodiazepines with symptom-triggered therapy have been the predominant medication class utilized and should remain the first treatment option with rapid escalation of dosing. Treatment resistant withdrawal warrants the use of phenobarbital or propofol, both demonstrating efficacy in management. Propofol can be used as an induction agent to decrease the effects of withdrawal. Dexmedetomidine does not address the underlying pathophysiology but may reduce the need for intubation. Ketamine requires further study. Overall, benzodiazepines remain the cornerstone of treatment. Outpatient management of patients with minimal symptoms is possible.
Conclusions: Alcohol withdrawal syndrome can result in significant morbidity and mortality. Physicians must rapidly diagnose these conditions while evaluating for other diseases. Benzodiazepines are the predominant medication class utilized, with adjunctive treatments including propofol or phenobarbital in patients with withdrawal resistant to benzodiazepines. Dexmedetomidine and ketamine require further study.
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1. Introduction

Alcohol use is widespread throughout developed countries, with over 8 million people in the U.S. dependent on alcohol [1]. Approximately 20% of men and 10% of women will suffer an alcohol-use disorder, and approximately half will experience withdrawal symptoms following decreased alcohol consumption [2,3]. Extreme complications, including seizures and delirium tremens, may occur in 3–5% [3]. The objective of this review is to summarize the current literature concerning emergency medicine management of alcohol withdrawal and delirium tremens (DT).

1.1. Pathophysiology

Alcohol is a central nervous system (CNS) depressant through potentiation of gamma-aminobutyric acid (GABA) receptors, enhancing central inhibitory tone [1,4]. Chronic ethanol use leads to down-regulation and conformational changes of the GABA receptor. Additionally, in chronic alcoholics, *N*-methyl-D-aspartate (NMDA) receptors undergo conformational changes and up-regulation [1,5-7]. After discontinuation of alcohol consumption, patients lose the GABA inhibitory effect with potentiation of NMDA excitatory effects, leading to CNS hyperstimulation [6,8].

1.2. Stages of withdrawal

The diagnosis of alcohol withdrawal is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), displayed in Table 1 [3]. Acute reduction in serum alcohol concentration leads to symptoms that begin within 6–8 h, peak at 72 h, and diminish by days 5 to 7 of abstinence [1,7]. Broad withdrawal signs and symptoms include insomnia, anxiety, nausea/vomiting, tremulousness, headache, diaphoresis, palpitations, increased body temperature, tachycardia, and hypertension [1,3]. Patients taking beta blockers or alpha-2 agonists may display blunted vital signs [5,8]. If the patient's withdrawal does not progress, these withdrawal symptoms may resolve within 24 to 48 h, but more

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http://dx.doi.org/10.1016/j.ajem.2017.02.002
0735-6757/Published by Elsevier Inc.

Table 1
Diagnostic criteria of alcohol withdrawal [3].

Diagnostic and statistical manual of mental disorders (DSM-5) criteria for alcohol withdrawal
A. Cessation or reduction in alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A.
– Autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual/auditory/tactile hallucinations or illusions, psychomotor agitation, anxiety, generalized tonic-clonic seizures

Table 3
Development of DT [17-19]

Factors associated with DT development
– History of previous DT
– Recent withdrawal seizures, specifically if left untreated
– Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA--Ar) ≥ 15
– History of sustained drinking
– Patients with SBP > 150 mm Hg, or patients with HR > 100 beats/min
– Last alcohol intake >2 days
– Age > 30 years
– Recent misuse of other depressants such as benzodiazepines
– Concurrent medical illness such as pneumonia or active ischemia

commonly 5–7 days [9]. Alcohol withdrawal syndromes (AWS) are demonstrated in Table 2. Severe withdrawal with seizures or delirium tremens occurs in approximately 5% of patients [5,8].

Delirium tremens occurs in 3–5% of patients who are hospitalized for alcohol withdrawal [7,13,14]. DT usually begins 3 days after the appearance of withdrawal symptoms and lasts for 1 to 8 days, though symptoms may appear as quickly as 8 h from the last drink [7,8,15,16]. The mortality of hospitalized patients with DT is currently estimated to be 1–4%; however, prior to the era of benzodiazepine use and intensive care, mortality reached 35% [7,8,14-16]. DT can be predicted by several factors, demonstrated in Table 3. If seizures remain untreated, up to one third of patients progress to DT. Other common factors include history of prior DT and Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar) score ≥ 15 [17-19].

2. Discussion

Patients with alcohol withdrawal require immediate evaluation for life-threatening DT, as well as other conditions that may mimic withdrawal. The first aspect of management is resuscitation and stabilization, while evaluating for life-threatening conditions. Alcohol withdrawal is a clinical diagnosis, as well as a diagnosis of exclusion.

Table 2
Alcohol withdrawal syndromes (AWS).

Syndrome	Timeline	Characteristics
Initial Withdrawal Symptoms [1,3]	Begins 6–8 h after last drink	– Includes tachycardia, hypertension, increased body temperature, tremulousness, anxiety, nausea/vomiting, headache, diaphoresis, and palpitations
Alcohol hallucinations [10,11]	12–24 h after last drink	– 7–8% of patients with AWS – Tactile hallucinations common, visual less likely – Auditory hallucinations possible (sometimes persecutory) – May present with tremors and other withdrawal symptoms, though some do not – Normal sensorium
Withdrawal seizures [6,8,12]	12–48 h after last drink	– Generalized tonic-clonic, though often isolated, short in duration, short post-ictal period – 1/3 of patients with withdrawal seizures will progress to delirium tremens
Delirium tremens [5]	Begins 3 days after the appearance of withdrawal symptoms and lasts for 1 to 8 days	– Rapid-onset, fluctuating disturbance of attention and cognition plus alcohol withdrawal symptoms – Diagnosis requires autonomic instability

Once other conditions have been considered and the emergency provider has diagnosed withdrawal, management of symptoms is required. A pitfall to avoid in the management of AWS is attributing complications from AWS to another condition and administering the incorrect treatment. For example, in alcoholic hallucinosis, the management is benzodiazepines, with limited data showing that antipsychotics are detrimental in acute AWS [8,22]. For withdrawal seizures, there is no role for outpatient antiepileptic medications such as phenytoin, and benzodiazepines are the treatment of choice [8,23].

Additionally, it is important to consider the reason for cessation of alcohol ingestion. While patients may admit ceasing alcohol consumption for multiple reasons, it is important to consider acute illnesses. Alcoholic patients may develop diseases such as pneumonia, pancreatitis, hepatitis, alcoholic gastritis, sepsis, acute coronary syndrome, meningitis/encephalitis, and many other pathologic processes leading to alcohol withdrawal. Other conditions such as trauma, infection, metabolic derangement, drug overdose, gastrointestinal bleeding, and hepatic failure may coexist with withdrawal. A concise and focused history and physical examination are necessary to evaluate for other co-existing disease processes. Any suspicion of another disease process requires immediate treatment and stabilization [24,25]. For example, patients with fever, altered mental status, and signs of alcohol withdrawal should be assessed for other conditions. In particular, meningitis and encephalitis may present in a similar manner, with lumbar puncture and neuroimaging warranted for further evaluation, while the patient receives antimicrobials. Intracerebral hemorrhage may also cause similar symptoms, with noncontrast head computed tomography (CT) required for diagnosis. If these investigations are not conducted in a rapid manner, patients may experience severe morbidity and mortality. An electrocardiogram (ECG) is warranted to assess for signs of acute ischemia and evidence of QT interval prolongation. In practice, an ethanol level is often obtained in these patients. A patient experiencing withdrawal symptoms with an elevated ethanol level will worsen with continued metabolism of ethanol, thus requiring immediate management.

2.1. Standard treatment

Management for any patient with suspected alcohol withdrawal is initial resuscitation and rehydration. Classic treatment of mild, moderate, and severe alcohol withdrawal is to administer GABA agonists [7,8,15,20]. Benzodiazepines act as central $GABA_A$ agonists, increasing the frequency of GABA-receptor channel opening. Benzodiazepines treat the psychomotor agitation experienced by withdrawing alcoholics in addition to preventing progression to more serious withdrawal symptoms [7,8]. While benzodiazepines are one treatment option, there is debate regarding which benzodiazepine is most efficacious.

Several benzodiazepines available for treatment include diazepam, lorazepam, midazolam, oxazepam, and chlordiazepoxide. Table 4 compares these agents in the treatment of AWS. For acute symptom control, many clinicians prefer intravenous (IV) diazepam or lorazepam, though oral medications are acceptable for non-severe symptoms [5-9]. Diazepam has a faster onset of action compared to lorazepam, which may