

Blame it on the Alcohol... withdrawal

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Board Bombs

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Objectives: At the conclusion of this document, the learner will be able to identify what entails alcohol withdrawal, explain complications of alcoholism, diagnose and assess patients withdrawing from alcohol, and treat alcohol withdrawal with correct medications.

Introduction

Alcohol has been around since time immemorial (like, a long time), but with alcohol consumption comes alcohol complications. In America, ~15% of Americans will have alcohol abuse disorder in their lifetime, and nearly half of these patients will experience some withdrawal symptoms upon drinking cessation. Nearly 20% have severe symptoms including hallucinations, seizures, and the infamous delirium tremens.¹

Pathophysiology

Key neuroreceptors involved in alcohol toxicity, withdrawal, and treatment of withdrawal are GABA and NMDA receptors. GABA neuroreceptors are inhibitory. NMDA neuroreceptors have the opposite effect and are excitatory in nature. Alcohol works by binding to both GABA and NMDA neuroreceptors, potentiating GABA while inhibiting the NMDA receptors creating CNS depression.² In chronic alcoholism, the neurons, which don't like to be depressed (who can blame them?), will *downregulate* GABA receptors while *upregulating* NMDA receptors, meaning that those dependent on alcohol will have less overall CNS depression with a given level of alcohol (*tolerance*).² If a patient suffering from alcoholism suddenly stops or reduces the amount of alcohol, they intake, there will be a concomitant increase in CNS stimulation as the NMDA receptors suddenly lose their inhibition and GABA receptors lose their potentiation leading to the symptoms of alcohol withdrawal.²

Symptom Timeline

Mild Symptoms: 6 to 36 hours from the last drink.

Consists of anxiety, tremors, headache, nausea, and sleep disturbances.^{3,4}

The tremors are classically hand or body tremors, including tongue fasciculations which cannot be faked if ever you have doubt.

Seizures: 6 to 48 hours after the last drink.

Rarely do seizures occur after 48 hours; typically generalized tonic-clonic in nature.

Moderate Symptoms: 12 to 48 hours from the last drink.

Alcoholic hallucinosis including visual, auditory, and tactile hallucinations, that can be very frightening (remember the heffalumps and woozles song from Winnie the Pooh). These hallucinations can persist for six days!

Severe Symptoms: 48 to 96 hours from the last drink.

Delirium tremens (DTs) including extreme agitation and altered sensorium.

The hallmark is extreme sympathomimetic symptoms including hypertension, diaphoresis, tachycardia, and hyperthermia.

Historically, up to 30% of patients would die from DTs, but now with modern medical therapy, this rate has fallen to 1-4%. Mortality is related to sympathomimetic complications, respiratory failure secondary to aspiration, and electrolyte abnormalities.

Workup Considerations

Alcoholics, like diabetics, have multisystem pathology and unfortunately very often suffer from poor disease insight. Always look for other acute medical problems that could confound the picture of withdrawal.

"God put alcoholics on this earth to humble physicians."

Our great mnemonic can help: Remember, "**POUR ME A GLASS**"

Pancreatitis	Metabolic changes: hyponatremia, hypomagnesemia, hypoglycemia	GI bleed
Oral cancers (mouth, neck, esophageal)	Encephalopathy (Wernicke, Korsakoff)	Liver cirrhosis
Ulcers	Anemia	Aspiration
Rhythm disorders (A. fib)		Suicide
		Sepsis

What sort of labs you order should largely be dictated by clinical picture and physician gestalt? CBC, CMP, lipase, serum ethanol level, and EKG would likely be justified in most cases. This won't diagnose alcohol withdrawal but will diagnose other complications of alcohol abuse.

If a patient has an elevated serum ethanol level, never assume the pt can't be in alcohol withdrawal. Those who heavily drink and those who drink nearly every day can start withdrawing at non-zero ethanol levels.⁵

If the patient is altered, obvious trauma on exam, or there is a "sketchy" history of a fall, perform a head CT +/- C-spine depending on their alertness.

Assessing level of withdrawal / response to treatment

The best predictor of a significant withdrawal is the PAWSS (Prediction of Alcohol Withdrawal Severity Score). >4.

There are many severity scoring systems for severity of withdrawal, but the most studied and most used is CIWA. CIWA does NOT predict withdrawal (that's PAWSS), but it determines withdrawal severity and can be used to guide therapy.^{6,7}

If using the score:

0-9 is very mild withdrawal, usually does not warrant treatment in the ED

10-15 is mild withdrawal.

16-20 is moderate withdrawal

21-67 is severe withdrawal, usually requiring ICU admission

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The difficulty of using CIWA lies in its length, complexity, and subjectiveness. The score consists of ten items, each with multiple subjective selections. For instance, under auditory disturbances, what's the difference between, "moderate harshness or ability to frighten," "moderately severe hallucinations," "severe hallucinations," and "extremely severe hallucinations"? The variability between providers and nursing staff and the difficulty of using the scale can make guiding therapy challenging.⁸

An alternative approach would be to use the Richmond Agitation-Sedation Scale. The scale is commonly used to guide sedation for intubated patients, making it fairly familiar to use for nursing staff and providers.⁹ The scale is also quicker to use, simplifying assessment of therapy response and guiding additional treatment.

Managing withdrawal symptoms

Supportive care is a must including intravenous fluids, nutrition and avoiding stimulation (can be difficult depending on your operating environment).

Our usual "go to" nutrition supplement in alcoholic dependent patients is thiamine and folate (a good ole banana bag, not named after a "Dr. Banana," but because the fluids appear yellow). Alcoholic patients can also have a concomitant hypoglycemia, and there is a theoretical (and board testable!) risk of worsening Wernicke encephalopathy if glucose is given prior to thiamine.¹⁰ This risk is likely untrue in real life, and honestly is likely being phased out of board exams. However, still be familiar with it. When giving glucose, intravenous is expensive. Unless the patient demonstrates inability to tolerate oral medications or is clearly in Wernicke encephalopathy, oral glucose (grab a snickers!) is preferred and its effects last longer.

The heart of the management of alcohol withdrawal is activating their GABA receptors and suppressing their NMDA receptors, most commonly with benzodiazepines, although there is increasing evidence for phenobarbital monotherapy. Antipsychotics should NEVER be used as they lower the seizure threshold, prolong the Qtc, and do not address GABA receptor depletion.¹¹

Benzodiazepines

The most commonly used benzodiazepines used in acute withdrawal are lorazepam and diazepam.¹² There has not been any studies showing any benzodiazepine superior in the treatment of alcohol withdrawal.¹³ Diazepam does have a faster onset, taking one to five minutes to take effect, while lorazepam is slightly slower at five to twenty minutes; however, diazepam has active metabolites that are metabolized by the liver. In liver failure, these metabolites can remain in circulation, increasing sedation by almost five times.

Whichever choice of benzodiazepine you decide to use, the key to management is regular and frequent reevaluation of the patient. You may need to escalate the dose, titrating to a goal RASS of -1 or CIWA <8, and heart rate <120.

- Diazepam every 5-10 minutes starting with 10mg IV, increasing by 10mg every other recheck (ie, 10-10-20-20-30-30-40-40)
- Lorazepam every 20-30 minutes starting with 2mg IV, increasing by 2mg every other recheck (ie, 2-2-4-4-6-6-8-8)

Refractory Alcohol Withdrawal

There is no clear definition of refractory alcohol withdrawal, but some suggest no response to lorazepam more than 10mg in one hour or diazepam more than 200mg in 3 hours.^{14,15}

Phenobarbital is a drug gaining notoriety and popularity in the FOAMed/Pulmcrit world. When used as a rescue agent in conjunction with benzodiazepines, patients have had lower rates of ICU admission, as well as decreased ICU stays.^{16,17} There are many potential reasons why phenobarbital can be effective in alcohol withdrawal.

Benzodiazepines increase frequency of GABA channel opening, while barbiturates increase the duration of opening, making them act synergistically. Also, phenobarbital not only acts on the GABA receptor, but can also inhibit some of the other excitatory neuroreceptors.¹⁸ Additionally, treatment with large amounts of benzodiazepines can cause a paradoxical delirium which is not as common a reaction with barbiturates.¹⁹

While evidence mounts regarding phenobarbital's efficacy in alcohol withdrawal, widespread use of the drug has been slow to be adopted. Perhaps people are just more comfortable giving benzodiazepines than barbiturates. There have been long term worries regarding respiratory depression and need for intubation. However, studies have found patients treated with phenobarbital were *less* likely to require intubation.²⁰

Most resources we've seen recommend phenobarbital in refractory withdrawal, but others are more aggressive with it and if they see clear-obvious signs of withdrawal phenobarbital might be started earlier. This is where clinical preference plays a large role... and it's at this intersection our review stops.

Most of the more successful studies using phenobarbital as monotherapy started with a loading dose of 10 mg/kg over 1 hour, but some other sources recommend using 130mg every 15 minutes, again titrating appropriate RASS/CIWA and vital improvement.²¹ Another alternative is ketamine, which can augment your benzodiazepines as ketamine is an NMDA antagonist. Lastly, propofol can also be used in the refractory alcohol withdrawal.¹²

Whichever agent you reach for next, you will likely need to intubate them at this point given the levels of sedative medications the patient is receiving, and that decision point may depend on the patient's medical comorbidities as well as their ability to protect their airway.

Disposition

Many patients in alcohol withdrawal require ICU admission. There is no set criteria on ICU admission, however clinical gestalt is paramount. One must consider their initial presentation, their medical comorbidities, their response to therapy, if they have been refractory to treatment. We prefer ICU for all alcohol withdrawal patients, as they can frequently be reassessed and the potential for "sneaky" decline on the floor is too great a risk.