# ALCOHOL WITHDRAWAL

**SUMMARY**

Alcohol withdrawal syndrome (AWS) is common in surgical and traumatically injured patients. Patients at risk must be identified and watched carefully for the development of symptoms. The mainstay of treatment is benzodiazepines. Controversy exists as to who should receive treatment, how to administer benzodiazepines, and which benzodiazepine to use. Adjunctive forms of treatment include beta-blockers, clonidine, and others. Other frequently practiced, yet less investigated treatments, include intravenous and oral ethanol.

**RECOMMENDATIONS**

- **Level 1**
  - **None**
- **Level 2**
  - **Benzodiazepines are the agents of choice in preventing alcohol withdrawal seizure activity**
  - **Routine alcohol withdrawal prophylaxis is not necessary**
  - **Ethanol use demonstrates no better outcomes when compared with benzodiazepines**
  - **Alpha-2 agonists are effective adjuncts to benzodiazepine use for AWS**
  - **Short acting agents such as oxazepam may have an increased incidence of seizure activity**
- **Level 3**
  - **Patients with a prior history of alcohol withdrawal seizures should receive prophylaxis**

## INTRODUCTION

Alcohol abuse and dependency remain enormous burdens to the individual and society. It is estimated that eight million American individuals are dependent upon alcohol (1). Death from alcohol abuse claims roughly 85,000 lives annually. Morbidity-related consequences of alcohol abuse are vast, and the estimated annual cost of alcohol abuse exceeds $200 billion dollars. Nearly 40% of individuals in emergency departments have alcohol in their bloodstream, and an estimated 8% of individuals admitted to the hospital will exhibit the constellation of the signs and symptoms known as “alcohol withdrawal syndrome” (AWS). This brief review will provide a focused description of the recognition, prevention, and treatment of AWS. AWS is encountered frequently in the surgical patient population and clinicians can expect that the manifestations may complicate surgical therapy. Thus, it is imperative that control of derangements be swift and effective as the consequences AWS can be deadly.

**EVIDENCE DEFINITIONS**

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

**LEVEL OF RECOMMENDATION DEFINITIONS**

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.



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## HISTORY

Recognition begins with a thorough patient history. Prevention before symptoms arise is paramount (1). At-risk patients should be closely evaluated for signs and symptoms of AWS with the intent to prevent development of the more serious stages of the disease process. Various scales and questionnaires exist to evaluate patients for possible alcohol misuse (CAGE, SMAST) (2). It is vital to identify patients with a history of alcohol-related seizure activity or delirium. Consideration for prophylactic treatment is warranted. Other risk factors include duration of the abuse process (> 6 years), markedly elevated blood alcohol levels, and associated medical illnesses such as alcoholic gastrointestinal disease and elevated liver enzymes which are markers of underlying alcohol abuse. Mechanical ventilation and sedation can mask AWS, making assessment using alcohol abuse prediction scales difficult and delaying care. Friends and family may be reluctant to fully disclose the patient's true daily alcohol intake. Close monitoring and a high index of suspicion are essential.

## PATHOPHYSIOLOGY

It is important for the clinician to understand the manner in which alcohol affects normal homeostasis and how abrupt alcohol cessation can precipitate AWS. The pathophysiology of alcohol dependence and AWS is a broad area of research. The purpose of this review is not to describe the complicated molecular mechanisms involved, but a basic knowledge is important. The excitatory and sympathetic systems are up-regulated in a state of dependence to compensate for the hyperactive GABAergic system stimulated by chronic alcohol use. Abrupt removal of alcohol allows unregulated sympathetic and glutaminergic stimulation. Ethanol suppresses ion flow through NMDA receptors, which manifests as clinical intoxication (3). If that suppression is abruptly removed, the glutaminergic system, previously up-regulated to a new homeostasis, will produce transmission normally dampened by alcohol. Clinically, tachycardia, hypertension, agitation, anxiety, seizures, and excitotoxic neuronal death may ensue. Sellers and Kalant state that AWS results from "acquired tolerance and physical dependence on ethanol with neurophysiologic alteration that offset the depressant effects of alcohol on neuronal excitability, impulse conduction, and transmitter release" (4). This statement encapsulates well the biochemical alterations that occur in the dependent individual and has targeted implications for the prevention and treatment of AWS.

## PREVENTION

Seizure activity and delirium tremens (DT) are two feared morbidities of AWS. Between 5-15% of individuals exhibiting signs of withdrawal will progress to have seizures or DT (1). Quick action on the part of the clinician is imperative. The literature is abundant with strategies aimed at the prevention of AWS, and thus controversy surrounds the "best" manner of action.

The CIWA-Ar (The Clinical Institute Withdrawal Assessment for Alcohol- revised) assessment is a tool to aid the clinician in determining the best course of intervention (5). It has become widely used, and is an example of an instrument to guide treatment once the diagnosis of AWS has been established. The tool consists of ten domains with each domain assigning a score to a particular sign or symptom according to the severity perceived by the patient or observed by the clinician. Each score is added and treatment is tailored to the score. Assessments are repeated on a regular basis during treatment with goal-directed therapy designed to reduce the score.

The mainstay of AWS treatment has been the liberal use of benzodiazepines. Many trials have noted the efficacy of this class of drugs in reducing withdrawal symptoms compared to placebo and other possible agents (6). Controversy exists as to whether these medications should be administered on a routine or as-needed (PRN) basis. The use of one benzodiazepine over another is also a subject of debate. Clonidine, various beta-blockers, and haloperidol have also been advocated. Although these agents may provide symptomatic relief, they can mask the more serious stages of AWS and should be used with caution and in conjunction with a benzodiazepine. Haloperidol may also lower the seizure threshold. The use of ethanol has also been investigated for AWS, but a randomized trial in 2008 failed to show significant benefit over the use benzodiazepines (7). There are rare case reports regarding the use of propofol in refractory delirium tremens (8).


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**TREATMENT**

Benzodiazepines

Benzodiazepines are widely used to treat patients with AWS and are considered to be the drug class of choice. Their use resides in their ability to promote the binding of the major inhibitory neurotransmitter GABA to the GABA receptor, a ligand-gated chloride channel (9). In cases of overdose, flumazenil is an effective GABA receptor antagonist that competes with benzodiazepines for binding. Respiratory depression and hypoxia is minimal in normal patients, but can be marked in patients with hepatic dysfunction and COPD. Caution should be exercised in patients who snore or those with obstructive sleep apnea as benzodiazepines can relax the upper airway musculature. Cardiovascular effects are of minor consequence in normal patients, but may produce decreased blood pressure and increased heart rate in the critically ill. Volume of distribution is large and increased in elderly patients. Benzodiazepines cross the placenta and are secreted in breast milk. Anterograde amnesia is common and beneficial. When used for the short-term treatment of delirium, physical dependence is rare. All of the agents listed below have been used to treat and ameliorate the symptoms of AWS. Optimal treatment with benzodiazepines is controversial, but there is some evidence that longer-acting benzodiazepines may prevent seizures more effectively than the shorter-acting formulations (10). Lipophilic agents enter the central nervous system more quickly and seem more effective in controlling acute seizure activity.

Prolonged sedation may be cumbersome or unwanted in some patients. The method of metabolism is also important in choosing the optimal agent. An agent with a simpler hepatic degradation process (glucuronide conjugation) may be beneficial in certain patient populations. Benzodiazepines that have a rapid onset are thought to have an increased abuse potential, however, this is probably more of a concern in a less acute, outpatient setting.

| DRUG | EQUIPOTENT DOSE | HALF LIFE | ONSET | TIME TO PEAK ACTION | DURATION | ACTIVE METABOLITES |
|---|---|---|---|---|---|---|
| Chlordiazepoxide | 20 mg | 5-30 hrs | Intermediate | 0.5-4.0 | Short | Yes<br>t½=5-30 hrs |
| Diazepam | 5 mg | 20-100 hrs | Very fast | 0.5-2.0 | Short | Yes<br>t½=30-200 hrs |
| Lorazepam | 1 mg | 10-20 hrs | Intermediate | 1.0-6.0 | Intermediate | None |
| Midazolam | 2.5 mg | 1-4 hrs | Very fast | 0.5-1.0 | Very short | None |

- Chlordiazepoxide (Librium®): The oldest of the benzodiazepines (introduced in 1960). Largely supplanted by the newer agents as it cannot be given intramuscularly (IM) due to its slow and erratic absorption. It should be used with caution as its metabolites have long half-lives (see diazepam below) and its hepatic oxidation requires caution in patients with hepatic insufficiency.
- Diazepam (Valium®): A lipophilic agent with a very fast onset of action (1-5 minutes) making it attractive for the acute control of seizure activity. As with chlordiazepoxide, IM use is discouraged due to its erratic absorption. It is metabolized in the liver by hepatic microsomal oxidation producing active metabolites with long half-lives that may extend the sedative and anxiolytic effects (desmethyldiazepam, half-life = 200 hrs.). Metabolism may be impaired in the elderly and those with hepatic insufficiency. Coronary blood flow appears to be increased.
- Lorazepam (Ativan®): The least lipid soluble of the benzodiazepines making it a less desirable alternative for acute seizure control due to its intermediate onset of action. Attractive qualities include its intermediate half-life and its lack of active metabolites. It does not undergo hepatic oxidation making it a safer alternative in patients with significant alcoholic liver disease. It also has intrinsic anti-emetic properties that may be helpful in the postoperative patient. It may be administered sublingually.
- Midazolam (Versed®): A short half-life, rapid onset, and brief duration of action together with water soluble properties make this agent suitable for continuous intravenous (IV) infusion.

Gabapentin

Gabapentin is currently FDA approved for the treatment of neuropathic pain. There is some evidence it may be an effective adjunctive treatment for AWS (11). Regarding pharmacokinetics and pharmacodynamics, the medication is not metabolized in the liver, thus making it attractive for the cirrhotic patient. It has no known plasma protein binding, nor does it induce hepatic enzyme production. Gabapentin exhibits renal excretion in an unchanged form.

Baclofen

Baclofen is typically utilized as a centrally acting muscle relaxant. It is an analogue of GABA and functions as a GABA-B receptor agonist. There is some evidence it may be helpful in conjunction with benzodiazepines, but other studies have shown it to be no better than placebo when used alone. It can cause drowsiness and may lower the seizure threshold in patients with seizure disorder (12).

Alpha-2 Agonists

As outlined above, sympathetic overdrive is an important pathophysiologic mechanism precipitating many of the signs and symptoms of AWS. Clonidine has been a useful tool to attenuate norepinephrine release (13). Reports have shown clonidine to be a helpful adjunct in the treatment of AWS. Evidence supports the use of clonidine to safely and effectively reduce symptoms of sympathetic overdrive. Clonidine can cause sedation and abrupt withdrawal of clonidine can induce profound hypertension. It should be used with extreme caution in patients with intravascular volume depletion.

Dexmedetomidine (Precedex®) is a highly selective alpha-2 agonist approved for short term sedation in non-intubated patients. Dexmedetomidine causes a decrease in blood pressure and heart rate. Caution should be used in surgical patients. Minimal respiratory depression is associated with its use. Randomized controlled trials have been completed, which are discussed below.

Haloperidol (Haldol®)

Haloperidol is a neuroleptic agent whose use in treating delirium in the critical care setting is well described, safe, and effective. It is frequently used in combination with other agents, especially the benzodiazepines. Neuroleptic agents are non-addictive with very little development of tolerance to their beneficial effects. Potential complications include extrapyramidal effects, which may be acute in onset and are not dose-related. These reactions appear to be related to oral administration of the agent. Such reactions usually require either lowering the dose of the neuroleptic agent or discontinuing its use altogether. These agents have also been associated with tardive dyskinesia and neuroleptic malignant syndrome (NMS).

Haloperidol may be given orally, IV or IM. For the rapid control of acute delirium, the IV route is preferred. Onset of action after an IV dose is 10-30 minutes. This agent minimally impairs respiratory and cardiovascular function, making it attractive in the unstable critically ill patient. It is a central dopamine receptor antagonist although its exact mechanism of action is unclear. Dosages depend on the degree of agitation and are typically 0.5-2 mg for mild agitation, 5 mg for moderate agitation and 10-20 mg for severe agitation, repeated as necessary until agitation is controlled. Reports of the safe use of massive dosages of haloperidol are common. Haloperidol may be safely used concomitantly with the various benzodiazepines.

Intravenous Ethanol

The use of intravenous ethanol in the management is AWS is controversial and practiced sporadically. Opponents to its use cite its narrow margin of safety, short duration of action, potential toxicity and drug interactions, possibility of irritation at the infusion site, the need to continuously monitor levels, the possibility for gastric irritation, and its interaction with many medications. Ethical concerns also exist.

## LITERATURE REVIEW

Several reports demonstrate the effectiveness of benzodiazepines over placebo for the prevention of seizures and delirium. A meta-analysis by Mayo et al. demonstrated a risk reduction of 7.7 seizures per 100 patients treated (p=0.003) and a risk reduction of 4.9 cases of delirium per 100 patients treated (p=0.04) (6). Benzodiazepines are the agents of choice in preventing alcohol withdrawal seizure activity (Class I). No consensus exists as to which benzodiazepine should be considered first line therapy in the surgical and

trauma patient population. Miller et al. performed a double-blind comparison between lorazepam and diazepam in the treatment of AWS (14). There were no statistical differences between the two agents with regard to efficacy. Solomon et al. completed a double-blind comparison of lorazepam and chlordiazepoxide (15). Again, no significant differences were found between the two agents. However, both authors indicate "lorazepam may have therapeutic advantages" and that "because of its simpler and more predictable metabolic pathway and its insignificant accumulation in the plasma during multiple-dose therapy, lorazepam may be the drug of choice." Ritson and Chick also compared diazepam to lorazepam in a randomized, double-blind manner (16). The lorazepam group demonstrated greater depression ($p<0.01$) and anxiety ($p<0.05$) as well as increased tachycardia ($p<0.05$). Withdrawal symptoms were significantly less in the diazepam group ($p<0.05$). In a meta-analysis comparing numerous studies, analysis failed to show statistically significant differences between different benzodiazepines. (17).

Investigators have also studied symptom-triggered benzodiazepine dosing versus scheduled benzodiazepine dosing. In a randomized controlled trial, Maldonado et al. could not identify an advantage of one strategy over the other. After 72 hours, 69% of the loading group participants were free of symptoms and only 42% of symptom-triggered participants were free of symptoms. The study failed to show a statistical significance (18). In a related study, Saitz et al. performed a randomized double-blind controlled trial to compare the effectiveness of a "standard" dosing schedule of benzodiazepines vs. dosing on a PRN basis (19). Those patients treated with symptom-triggered therapy completed treatment courses sooner and required less benzodiazepine. Symptom-triggered therapy was considered to be as efficacious as routine therapy as there were no significant differences between the groups with regard to CIWA-Ar scores, delirium tremens, hallucinations or seizures. Conversely, Amato et al., in a Cochrane meta-analysis, indicated that in the comparison of fixed-schedule vs. symptom-triggered regimens, symptom-triggered regimens should be utilized (16).

Class II data suggests that the longer-acting benzodiazepines may be more effective in preventing withdrawal seizures (10,15). Mayo-Smith et al. observed eleven seizures in 1044 admissions (1.1%) for alcohol withdrawal treated with a standardized protocol of short-acting benzodiazepines (oxazepam). 82% of the seizure activity occurred 12-48 hours after cessation of the oxazepam. They hypothesized that the rapid fall in benzodiazepine blood levels with discontinuation of the short-acting agent contributed to the seizures. Hill et al. reported three cases of major seizure activity within 24 hours of completing detoxification with oxazepam (20). In another study, although not statistically significant, seizures occurred in 8% of those treated with lorazepam compared to 0% among those receiving chlordiazepoxide (15). Ritson identified a 5% seizure incidence with lorazepam compared to 0% with diazepam (16). Mayo-Smith et al. subsequently substituted chlordiazepoxide for oxazepam and did not witness any seizure activity in the subsequent 1030 patients.

Studies comparing benzodiazepines to other agents have been performed. Anticonvulsants have been reviewed from many randomized controlled trials (17), and no specific advantages have been noted in comparison to benzodiazepines in regards to lessening AWS symptoms (RR -1.04 (-1.89 to -0.20). Baclofen is a newer agent utilized in the treatment of AWS. Addolorato et al. compared baclofen to diazepam and although diazepam was slightly more rapid, efficacy was otherwise comparable (21). Liu and Wang make no definitive recommendations regarding the use of baclofen based on their meta-analysis of RCT (12). Amato et al. identified that benzodiazepines performed better for the prevention of seizures than antipsychotics (4 studies, 633 participants, 633 participants, RR 0.24 (95% CI 0.07 to 0.88) with high quality of the evidence) (12). Alpha-2 agonists have served as adjunctive measures to benzodiazepines. Dobrydnjov et al. conducted a randomized controlled trial and concluded that clonidine given either intrathecally or orally performed slightly better than diazepam in controlling AWS signs and symptoms (22). Muzyk et al. reviewed the use of alpha-2 agonists and concluded that clonidine and dexmedetomidine should be used as adjuncts to benzodiazepines at this time until further controlled trials can be conducted (13). Mueller et al. concluded that dexmedetomidine was effective in lowering the dosage of Ativan needed over the course of 24 hours, but failed to show the same effect when observed over seven days (23). A recent article from the Journal of Emergency Medicine conducted a RCT to determine whether a single dose of phenobarbital alongside standard lorazepam treatment may decrease the rate of ICU admissions.

They did see a reduction of admissions to the ICU (8% vs. 25%, 95% confidence interval 4-32%), but failed to see a difference in the number of adverse events (24).

The use of ethanol has been thoroughly studied. Craft et al. studied 37 trauma patients treated for AWS with IV ethanol (25). Patients with signs of AWS were started on a 10% ethanol in D5W (vol/vol) IV drip at 50 cc/hr. Treatment was continued for 48 hours and then weaned over the next 48 hours. The average time to amelioration of symptoms was 14 hours and the duration of treatment averaged 4 days. The effectiveness of the ethanol drip was rather subjective and graded from 1 to 5 (1=poor, 5=very good). Five of the 37 patients had a poor or no response. Patients were said to have remained calm, alert, oriented and able to participate in treatment. There were no serious complications. Hansbrough et al. studied 22 alcoholic burn patients treated with IV ethanol (26). Infusions were continued for a 3-8 day period. A similar alcohol drip was started as described in the previous study. Patients studied were those “suspected” to be heavy drinkers and the authors readily admit that perhaps some of them were not. Patients did not experience clear signs of alcohol withdrawal nor did they appear sedated. DiPaula et al. performed a retrospective review of their experience with IV ethanol. They stressed the need for reliable documentation with regard to the patient's past history, risk factors, and admission blood alcohol levels (BAL) in guiding which patients should receive IV ethanol therapy (27). They also stressed the need for serial BAL’s when the patient is receiving IV ethanol therapy. They recognized the great degree of variation of ethanol-prescribing within their institution and the need to develop clear and effective guidelines. Dissanaike compared their results with the use of IV ethanol before and after development of a protocol and found that protocol driven therapy decreased the failure rate of IV ethanol therapy as well as the treatment time and concluded that IV ethanol therapy was a viable option for AWS prophylaxis when administered according to a systematic protocol (28).

A recent randomized trial compared IV ethanol versus diazepam. Trauma patients admitted to the ICU with a history of chronic daily alcohol consumption of greater than or equal to five beverages per day were prospectively randomized to IV ethanol infusion vs. scheduled-dose diazepam and were evaluated with the Riker Sedation-Agitation Scale. A significant number of patients treated with IV ethanol deviated within the scale and required rescue treatment with diazepam and haloperidol (p=0.002). The authors concluded that IV ethanol offered no advantage over diazepam with respect to efficacy or adverse sedative effects (7).

Numerous small series and case reports document experience with less commonly used pharmacological agents. Perhaps the drugs most studied in this regard are the anti-epileptic drugs, namely carbamazepine. Malcolm et al. compared the effects of carbamazepine and lorazepam and found that both drugs were equally efficacious at treating the symptoms of alcohol withdrawal (29). The carbamazepine group had less post–treatment relapses and a greater reduction in anxiety symptoms. This particular work studied patients treated as outpatient, and may not be applicable to the acute symptoms of alcohol withdrawal treated in the more acute setting. Schik et al. studied the use of oxcarbazepine and carbamazepine in the inpatient treatment of alcohol withdrawal (30). The oxcarbazepine group was found to have less of a “craving for alcohol.” Mariani et al. studied gabapentin in the treatment of alcohol withdrawal and suggested further study (31). Myrick et al. compared the anticonvulsant tiagabine to benzodiazepines and saw equal reduction in alcohol withdrawal symptoms (32). Although the numbers are small and firm recommendations cannot be made at this time, there is promise that some of these agents with less addiction potential and reduced sedative side effects could be valuable adjuncts in the future.

A 2009 study represents the first randomized control trial detailing the use of gabapentin as an agent in the treatment of alcohol withdrawal (11). The study compared its use with the commonly used agent lorazepam. It should be noted that the study was performed in an outpatient setting. Three arms of study were presented. Two arms received different doses of tapered gabapentin while a third arm received tapered lorazepam. Results indicated a decrease in the CIWA-Ar scores of all groups over the course of the taper. High dose gabapentin was statistically significant, but clinically similar to lorazepam (p=0.009).

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