Review Article

Alcohol Withdrawal

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Abstract: Alcohol withdrawal is a common clinical condition that has a variety of complications and morbidities. The manifestations can range from mild agitation to withdrawal seizures and delirium tremens. The treatments for alcohol withdrawal include benzodiazepines, anticonvulsants, beta-blockers and antihypertensives. Although benzodiazepines are presently a first-line therapy, there is controversy regarding the efficacies of these medications compared with others. Treatment protocols often involve one of two contrasting approaches: symptom-triggered versus fixed-schedule dosing of benzodiazepines. We describe these protocols in our review and examine the data supporting symptom-triggered dosing as the preferred method for most patients in withdrawal.

The Clinical Institute Withdrawal Assessment for Alcohol scoring system for alcohol withdrawal streamlines care, optimizes patient management, and is the best scale available for withdrawal assessment. Quality improvement implications for inpatient management of alcohol withdrawal include increasing training for signs of withdrawal and symptom recognition, adding new hospital protocols to employee curricula, and ensuring manageable patient-to-physician and patient-to-nurse ratios.

Key Words: alcohol withdrawal symptoms, alcohol withdrawal treatment, benzodiazepine, Clinical Institute Withdrawal Assessment for Alcohol, fixed-schedule dosing, symptom-triggered dosing

In the United States, alcohol is the most commonly abused substance.[1] Approximately one in four patients admitted to general hospitals meets the criteria for alcohol dependence.[2] In 2009, approximately $185 billion were spent as a result of excessive alcohol consumption.[3]

The sequelae of alcohol abuse include loss of trust of friends and family, inability to secure employment, legal consequences, physical debilitation, and permanent mental deterioration. The manifestations of alcohol withdrawal range from mild symptoms, such as tremors and malaise, to severe hemodynamic instability or death.

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Healthcare providers constantly encounter patients with alcohol-abuse problems. Physicians and nurses should identify symptoms of alcohol withdrawal, including anxiety, diaphoresis, and seizures, to prevent patients' further deterioration.

The treatment of alcohol withdrawal involves monitoring patients, ruling out other causes, and symptom management with benzodiazepines. Failure to treat alcohol withdrawal can be fatal, whereas overtreatment of symptoms with benzodiazepines can lead to sedation and respiratory depression. Quality-improvement ventures have produced a standardized method of assessing patients with alcohol withdrawal. This protocol, the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar), expedites treatment and minimizes complications.

Withdrawal Symptoms

Alcohol withdrawal usually begins 1 to 3 days after the last drink and can last up to 1 week.[2] Symptoms occur when the central nervous system, previously subjected to prolonged alcohol exposure, abruptly enters a state of decreased alcohol intake. Alcohol elicits central nervous system depression by exciting inhibitory γ-aminobutyric acid (GABAA) A receptors, leading to a reduced level of GABA and GABA-receptor sensitivity. Alcohol also simultaneously inhibits the *N*-methyl-D-aspartate component of the excitatory glutamate receptor.[4] In chronic alcoholism, the CNS increases excitatory tone to

Key Points

- Alcohol withdrawal is a common clinical entity that should be recognized by all physicians. Symptoms range from mild agitation to seizures, autonomic instability, and delirium tremens.
- Long-acting benzodiazepines are a first-line treatment for alcohol withdrawal symptoms. Studies have shown that symptom-triggered dosing of benzodiazepines results in smaller benzodiazepine dosage, shorter treatment duration, fewer adverse reactions, and shorter hospitalizations.
- The Clinical Institute Withdrawal Assessment for Alcohol-Revised is the most validated scale for assessing alcohol withdrawal severity. This scale can be used to determine the proper benzodiazepine dosage for individual patients based on their withdrawal symptoms.

maintain homeostasis. When alcohol cessation occurs abruptly in these individuals, the inhibitory tone is withdrawn, but the compensatory increase in excitatory neurotransmission remains. Furthering this excitatory tone is the role of homocysteine, an excitatory amino acid that also acts as the *N*-methyl-D-aspartate receptor.[5] Its concentration increases during active drinking and remains elevated after the cessation of drinking. The combination of homocysteine with unopposed glutaminergic neurotransmission in withdrawal yields an excitotoxic effect. This causes the common withdrawal symptoms of tremulousness, anxiety, diaphoresis, headache, palpitations, insomnia, and gastrointestinal upset. Folate is a cofactor of homocysteine metabolism and is deficient in most cases of chronic alcoholism. Lack of folate may precipitate further withdrawal symptoms, making supplementation therapeutic.[5]

Withdrawal seizures are a complication occurring within the first 48 hours of cessation. They typically occur as a single generalized tonic-clonic seizure or a brief episode of multiple seizures.[5] Prolongation or recurrence of seizure activity necessitates an infectious disease workup (eg, complete blood count, lumbar puncture, blood cultures). Standard withdrawal therapy of long-acting benzodiazepines is indicated for the treatment of withdrawal seizures.

Delirium tremens (DT), also known as alcohol withdrawal delirium, is the most severe manifestation of alcohol withdrawal, which occurs in approximately 5% to 20% of patients experiencing detoxification.[7] Of the patients whose symptoms have progressed to withdrawal seizures, approximately 33% are expected to progress to DT.[8] The clinical features of DT are disorientation, agitation, hallucinations, tremors, diaphoresis, and abnormalities in vital signs, including tachycardia, hypertension, and low-grade fever. The time of onset is 24 to 72 hours after cessation of drinking, and the condition carries a 5% mortality rate in uncomplicated patients and up to a 25% mortality rate in patients with concomitant complications.[8] A cohort study conducted by Monte et al used a multivariate logistic regression model to conclude that the following findings are independent variables for DT development: number of seizures; 1 or 2 seizures (odds ratio [OR] 2.2), 3 seizures (OR 2.6), systolic blood pressures >150 mm Hg (OR 1.9), and axillary temperature >38°C (OR 1.9).[7]

Wernicke syndrome, a potential complication of thiamin deficiency, is characterized by cognitive impairment, delirium, paralysis of eye muscles, and an abnormal gait. Incidences of Wernicke encephalopathy can be as high as 12.5% in patients with chronic alcoholism.[9] Korsakoff syndrome, also known as amnestic-confabulation syndrome, is caused by thiamin deficiency.[2] Thiamin, folic acid, and multivitamins are added to standard benzodiazepine therapy to prevent progression to Wernicke encephalopathy. These measures, in addition to intravenous fluids, nutritional supplementation, and the repletion of potassium, magnesium, and phosphate, represent the full spectrum of management of the patient withdrawing from alcohol.

Pharmacological Treatment of Withdrawal

In the United States, the accepted practice for pharmacological treatment of alcohol withdrawal begins with the administration of benzodiazepines (US Preventive Services Task Force grade A recommendation: consistent, high-quality evidence).[10] The most commonly administered benzodiazepines are chlordiazepoxide and diazepam. Other benzodiazepines may be administered based on desired duration of action, rapidity of onset, and cost. In a meta-analysis of the pharmacological management of alcohol withdrawal, benzodiazepines significantly reduced seizures ($P = 0.003$) and reduced the incidence of delirium ($P = 0.04$).[10] In a Cochrane review of 57 randomized controlled trials on the efficacy of benzodiazepines in alcohol withdrawal, benzodiazepines were found to be significantly superior to placebo in preventing alcohol-withdrawal seizures ($P = 0.04–0.69$).[11] Longer-acting benzodiazepines (eg, chlordiazepoxide, oxazepam) may be more effective in seizure prevention (US Preventive Services Task Force level II: randomized trials with high false-positive and/or high false-negative errors) and may result in a more uneventful withdrawal course with less breakthrough of symptoms (level I: randomized trials with low false-positive and low false-negative errors).[10] Longer-acting benzodiazepines also carry a greater risk of oversedation (level III: nonrandomized, concurrent cohort comparisons), especially in elderly adults and those with liver disease.[10] Short-acting benzodiazepines (eg, diazepam, alprazolam, lorazepam) are shown to have more addictive potential as compared with long-acting benzodiazepines (level I).[10]

Continuous infusions of short-acting benzodiazepines (eg, lorazepam, midazolam) have been tried. Studies have found that costs were >10 times higher with continuous infusions versus intravenous or bolus therapy without significant changes in outcomes or adverse effects.[10]

In comparing different benzodiazepines to prevent withdrawal seizures, chlordiazepoxide outperformed lorazepam, diazepam, and alprazolam, but results were not statistically significant.[11] To prevent withdrawal delirium, diazepam was more effective than alprazolam, chlordiazepoxide, abecamil, and lorazepam, but results were not statistically significant.[11]

In addition, other medications, including anticonvulsants, antipsychotics, beta-blockers, and antihypertensives, are used to treat alcohol withdrawal. A meta-analysis of the pharmacological management of alcohol withdrawal by Mayo-Smith found that benzodiazepines are more effective than phenothiazines in reducing delirium ($P = 0.002$) and seizures ($P < 0.001$).[10] In a 2010 Cochrane review, Amato et al found that benzodiazepines are not significantly superior to other drugs (anticonvulsants, including chlormethiazole, sodium valproate, phenobarbital, carbamazepine; antipsychotics, including chlorpromazine, haloperidol, thioridazine; or clonidine, bromocriptine, thiamin, hydroxyzine, baclofen, propranolol, and nitrous oxide) in preventing withdrawal seizures (relative risk 0.21–1.31) or delirium (RR 0.21–1.98).[11] Antipsychotics are not recommended in alcohol

withdrawal syndrome because of their proconvulsant properties.[11] In a similar study, chlormethiazole, barbital, and tetrabamate were found to be equal to benzodiazepines in the reduction of signs and symptoms of withdrawal.[10] There was no significant difference in adverse events when comparing different benzodiazepines to one another or with other drugs.[11]

Certain types of drugs mentioned above provide specific benefits for patients experiencing alcohol withdrawal. Beta-blockers, such as propranolol, decrease autonomic symptoms.[10] Clonidine, a centrally acting α-adrenergic agonist, is shown to relieve withdrawal symptoms. These drugs, however, are not effective for reducing delirium or seizures and may obscure the adrenergic symptoms of alcohol withdrawal.[10] Carbamazepine is frequently used in Europe to prevent withdrawal seizures and, when compared with benzodiazepines, does not bear the same risks of sedation and respiratory depression.[10]

A 2006 case series described a patient cohort with benzodiazepine-resistant alcohol withdrawal. These patients required ≥50 mg of diazepam in their first hour of admission and large doses of benzodiazepines throughout their hospital course. These patients also received supplemental intravenous barbiturates, experienced vital sign abnormalities at 24 hours despite benzodiazepine treatment, and underwent a more complicated hospital course.[19]

Some medication supplementation is not shown to improve outcomes. Hypomagnesemia is common in alcohol withdrawal. Neuromuscular excitability, refractory hypokalemia, and electrocardiographic abnormalities such as a widened QRS complex are seen in hypomagnesemia and require supplementation. A double-blind, placebo-controlled randomized trial of magnesium supplementation to benzodiazepines showed no difference in incidence of seizures, delirium, and other symptoms of withdrawal.[10] Thiamin administration does not change the incidence of withdrawal delirium or seizures. Clinicians should administer thiamine before carbohydrate infusion to prevent Wernicke-Korsakoff syndrome.[10]

Methods of Treatment: Symptom Triggered Versus Fixed Schedule

Two treatment modalities have been shown to have evidence-based efficacy: symptomatic treatment of alcohol withdrawal with benzodiazepines and fixed-schedule dosing of long-acting benzodiazepines with additional symptomatic treatment. The advantage of symptom-triggered therapy is that significantly smaller benzodiazepine doses are administered yielding less sedation, shorter treatment, fewer adverse reactions, and a decreased risk of respiratory depression. In addition, patients receiving symptomatic treatment were found to require shorter hospitalizations.[10,12–16] Saitz et al showed that the median total administered dose of chlordiazepoxide was 100 mg in a symptom-triggered group versus a median of 425 mg of chlordiazepoxide in a fixed-schedule dosing group.[16] In addition, the mean duration of treatment was significantly shorter in the symptom-triggered group (9 vs 68 hours) when compared with fixed-schedule dosing.[16]

The second treatment modality is fixed-schedule dosing of benzodiazepines regardless of the presence of symptoms. The advantage of a fixed schedule is that frequent reassessment of symptoms is not necessary. This is helpful in a setting with a high patient-to-clinician ratio. In addition, fewer protocol errors are seen in comparison with symptom-triggered therapy. A meta-analysis of 64 studies performed by Amato et al found little difference between the two therapies in terms of final outcomes.[11] Fixed-schedule dosing is often the only way to treat patients withdrawing from alcohol with comorbid medical illnesses or a postoperative status because of inability to assess withdrawal symptoms.[12,17]

Assessing for Withdrawal: CIWA-Ar

The most popular and validated clinical assessment scale is the CIWA-Ar. Its predecessor, the CIWA-A, had been in use since 1978 and has 15 items to consider.[18] The CIWA-Ar is a 10-item survey that assesses a patient's symptoms and scores a patient's severity of symptoms (Table 1).[2] Scores on the CIWA-Ar range from 0 to 67 points. The CIWA-Ar evaluates the following signs and symptoms: sweating; anxiety; tremors; agitation; disturbances of tactile, auditory, or visual nature; headache; and disorientation or clouding of sensorium.[19]

Clinicians used the CIWA-Ar in several clinical studies to assess alcohol withdrawal and determine which patients required benzodiazepines. To study symptom-triggered therapy, Riddle et al created a "standing order set" to administer withdrawal medications based on a patient's CIWA-Ar score.[2] A CIWA-Ar score <8 is indicative of mild withdrawal symptoms. No therapy is indicated at this score and the patient should be reassessed in 4 hours. A CIWA-Ar score of 9 to 15 represents moderate withdrawal and 25 to 50 mg of chlordiazepoxide is given orally as needed every 4 hours for symptoms (maximum 300 mg/24 hours). Patients should have their score reassessed after 2 hours. Severe withdrawal is represented by a score >15. In this case, chlordiazepoxide 50 to 100 mg is given hourly as needed for a maximum of 300 mg/24 hours, with lorazepam 2 to 4 mg given intravenously every 2 hours as needed for a maximum of 24 mg/24 hours. This study found that the overall patients' length of stay, days requiring medication, and quantity of medication administered were less in the symptom-triggered group as compared with the fixed-schedule group.

Prospective and retrospective trials have shown that in cooperative patients experiencing alcohol withdrawal, the CIWA-Ar and its derivatives are associated with reductions in quantity of benzodiazepines administered and in length of treatment.[17]

Discussion (Quality Improvement)

Hospitals and healthcare institutions strive for optimum medical management of patients. Given the current data,

benzodiazepines are recommended for first-line treatment of alcohol withdrawal. Benzodiazepines are shown to be significantly better than placebo for treating withdrawal. Large randomized controlled trials demonstrating benzodiazepine superiority to other medications in alcohol withdrawal are lacking.

Based on the few studies available, using symptom-triggered medication administration for patients with alcohol withdrawal appears to be superior in patients with uncomplicated medical histories. Daeppen et al found that the total dose of oxazepam was less in the symptom-triggered group compared with the fixed-schedule group. The study also found that the

Table 1. Clinical Institute Withdrawal Assessment for Alcohol Scale

Patient: _____ **Date:** _____ **Time:** _____
Pulse: _____ **BP:** _____/_____

Nausea/vomiting. Ask "Do you feel sick to your stomach? Have you vomited?"
0- No nausea and vomiting
1-
2-
3-
4- Intermittent nausea with dry heaves
5-
6-
7- Constant nausea, frequent dry heaves, vomiting

Tremor. Ask patient to extend arms and spread fingers apart.
0- No tremor
1- Tremor not visible but can be felt, fingertip to fingertip
2-
3-
4- Moderate tremor with arms extended
5-
6-
7- Severe tremor, even with arms not extended

Paroxysmal sweats
0- No sweat visible
1- Barely perceptible sweating; palms moist
2-
3-
4- Beads of sweat obvious on forehead
5-
6-
7- Patient drenched in sweat

Anxiety. Ask "Do you feel nervous?"
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 occur in severe delirium or acute schizophrenic reactions

Tactile disturbances. Ask "Do you have any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?"
0- None
1- Very mild itching, pins-and-needles sensation, burning, or numbness
2- Mild itching, pins-and-needles sensation, burning, or numbness
3- Moderate itching, pins-and-needles sensation, 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 to 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 hallucination
7- Continuous hallucinations

Visual disturbances. Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"
0- Not present
1- Very mild sensitivity
2- Mild sensitivity
3- Moderate sensitivity
4- Moderately severe hallucinations
5- Severe hallucinations
6- Extremely severe hallucinations
7- Continuous hallucinations

Headache, fullness in head. Ask "Does your head feel different? Do you feel like there is a band around your head?"
0- Not present
1- Very mild
2- Mild
3- Moderate
4- Moderately severe
5- Severe
6- Very severe
7- Extremely severe

(continued on next page)

Table 1. *(Continued)*

Agitation
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 interview or constantly thrashes about

Total score: _____

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- Date disorientation by no more than 2 calendar days
3- Date disorientation by >2 calendar days
4- Disoriented to place and/or person

symptom-triggered group had a shorter duration of treatment.[15] Similarly, two studies demonstrated that symptom-triggered dosing reduces the duration of mechanical ventilation in the intensive care unit with fewer nosocomial infections.[20,21] A limitation of this method is that absolute staff numbers and inadequate staff training constrain hospitals and other healthcare institutions. Another drawback is a higher proportion of protocol errors.[12] To decrease these errors, additional training to recognize signs and symptoms of withdrawal and efficient, simple hospital protocols should be added to employee curricula. Fixed-schedule medication dosing for alcohol withdrawal avoids protocol errors but bears the risk of oversedation and longer hospital stays.

Table 2. Alcohol withdrawal scoring methods

Test	Total points possible	Point allocations
Clinical Institute Withdrawal Assessment for Alcohol - revised[12]	67	Nausea/vomiting (0–7)
		Tremor (0–7)
		Paroxysmal sweats (0–7)
		Anxiety (0–7)
		Agitation (0–7)
		Tactile disturbances (0–7)
		Auditory disturbances (0–7)
		Visual disturbances (0–7)
		Headache, fullness in head (0–7)
		Orientation and clouding of sensorium (0–4)
Modified Severity Assessment Scale[16]	23	Nausea/vomiting (0–3)
		Tremor (0–3)
		Tachycardia (0–3)
		Diaphoresis (0–3)
		Fever (0–3)
		Agitation (0–3)
		Confusion, orientation, contact with reality (0–3)
		Hallucinations (0–2)
Minnesota Detoxification Scale[7]	46	Pulse (0–2)
		Diastolic blood pressure (0–2)
		Tremor (0–6)
		Sweat (0–6)
		Hallucinations (0–3)
		Agitation (0–9)
		Orientation (0–6)
		Delusions (0–6)
		Seizures (0–6)

Interestingly, a randomized controlled trial of outpatients with alcohol withdrawal showed no difference in symptom-triggered versus fixed-schedule dosing of benzodiazepines.[22] Direct extrapolation of these findings to the inpatient population is unclear. The results of this study illustrate the continued debate between the two methods.

If hospitals are to move toward symptom-triggered medication administration, clinicians need an objective way to measure the severity of alcohol withdrawal. CIWA-Ar (Table 1) has been used and reformulated into different scales, including the Severity Assessment Scale and the Minnesota Detoxification Scale (Table 2).[1,13] Prospective and retrospective trials have shown that in cooperative patients experiencing alcohol withdrawal, the CIWA-Ar and its derivatives are associated with reductions in quantity of benzodiazepines administered and length of treatment.[17]

One problem with these scales is that the patient must respond to questions and follow commands, limiting their use in certain patient populations. Withdrawal symptoms may be misinterpreted as infection, pain, or other causes of delirium, and the diagnosis of alcohol withdrawal could be missed entirely. Conversely, a patient without a known history of alcohol abuse admitted for an unrelated condition could have withdrawal symptoms that are misattributed to his primary diagnosis. A high level of clinical suspicion and accurate history taking is required, even with the use of alcohol-withdrawal scales. In addition, continued vital sign and patient monitoring is critical when alcohol withdrawal is suspected.

Conclusions

Several studies validate the use of symptom-triggered benzodiazepine therapy in inpatient and intensive care unit settings for alcohol withdrawal.[11,15,16,20] Benefits include a decrease in benzodiazepine dosage and associated adverse effects, duration of treatment, and the use of a standardized method to assess patients undergoing withdrawal.

Limitations to the CIWA-Ar include protocol errors, ineffectiveness in certain patient populations, and a considerable time investment. Estimates of the length of time needed to conduct the CIWA-Ar range from 5 to 15 minutes.[4,13] Although practical in inpatient detoxification units, the requirements of the CIWA-Ar could overburden nurses and ancillary staff in busy inpatient general hospitals.

Alcohol withdrawal is a common problem facing all clinicians and must be treated appropriately. A staple in management is to use symptom-triggered medication administration rather than fixed-dosed scheduling to tailor each patient's treatment method to the actual condition. This innovation shows promise in terms of quality improvement and deserves focused research.

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