Management of Alcohol Withdrawal Syndrome in Patients with Alcoholic Liver Disease

Prabhat Kumar Chand [*], Udit Panda [†], Jayant Mahadevan [*], Pratima Murthy [‡]

[*]Centre for Addiction Medicine, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India, [†]Kalinga Institute of Medical Sciences, Bhubaneshwar, India and [‡]National Institute of Mental Health and Neurosciences, Bangalore, India

Alcohol withdrawal syndrome (AWS) is a common condition that is seen in treatment-seeking patients with Alcohol use disorder (AUD) and alcoholic liver disease (ALD). AWS, which typically starts within 4–6 h of the last alcohol use, can range from mild symptoms such as insomnia, tremors, and autonomic hyperactivity to more severe symptoms such as seizures and delirium tremens. Clinical Institute Withdrawal Assessment Scale—Alcohol Revised (CIWA-Ar) is the most commonly used scale to assess AWS in clinical practice. The presence of moderate withdrawal as indicated by a score of more than 8 is an indication for pharmacotherapy. Lorazepam and oxazepam are preferred agents for the management of AWS in the setting of ALD. In severe ALD, benzodiazepines should be used cautiously with monitoring due to the risk of excessive sedation or precipitating hepatic encephalopathy. (J Clin Exp Hepatol 2022;12:1527–1534)

Alcohol use disorder (AUD) is estimated to affect approximately 18% of the global population in their lifetime and 5% annually.[1] The terms "chronic alcoholism" and "alcohol withdrawal syndrome" (AWS), namely "tremors of the lip and tongue and sometimes of the whole body," was described by the Swedish physician Magnus Huss (1807–1890).

Alcoholic liver disease (ALD) is one of the leading causes of chronic liver disease worldwide and accounts for up to 48% of cirrhosis-associated deaths in the United States. Individuals with AUD are at risk to develop advanced liver disease including alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma.[2,3]

The prevalence of AWS in the general population has been found to be low (~5%) and has remained stable over time.[4] The unadjusted prevalence of AWS in medical inpatients is also 5%, but this increases to 26.4% among those with past year AUD and 62.5% among those with past year AWS.[5]

Hepatologists may often encounter AWS in patients with ALD, since the presence of underlying medical or surgical conditions increases the likelihood of AWS.[6,7] This may either be in the outpatient department with milder symptoms or emergency and ICU settings with severe withdrawal symptoms. The presence of AWS is known to complicate the course of medical illness including liver disease and, therefore, identification and management of the same is a priority.

This narrative review of AWS focuses on the clinical problem, pathophysiology, clinical presentation, approaches to therapy, with particular emphasis on ALD. It reviewed articles retrieved from Pubmed, Scopus, Web of Science, and Google Scholar using the following terms: alcohol, alcohol abuse, alcohol dependence, alcohol use disorders, problematic drinking, alcoholic liver disease, hepatic cirrhosis, hepatic steatosis, alcoholic hepatitis, alcohol withdrawal syndrome, and liver transplantation.

PATHOPHYSIOLOGY OF ALCOHOL WITHDRAWAL SYNDROME

Gamma-aminobutyric acid (GABA) and glutamate, the main inhibitory and excitatory neurotransmitters in the central nervous system (CNS), respectively, are primarily implicated in the development of symptoms of AWS. Acute alcohol ingestion leads to enhanced GABAergic neurotransmission and reduced glutamatergic activity, thereby producing CNS depression.[8,9] Chronic alcohol use leads to adaptive changes in several neurotransmitter systems, including GABA, glutamate, and norepinephrine pathways. This is associated with downregulation, that is, reduction in number, function, and sensitivity to GABA-A receptor and upregulation, that is, increase in number, sensitivity, and affinity for NMDA-glutamate receptors.[8]

Keywords: alcohol, withdrawal, alcoholic liver disease, assessment, treatment

Received: 11.1.2022; *Accepted:* 13.3.2022; *Available online 18 March 2022*

Address for correspondence. Jayant Mahadevan, Assistant Professor of Psychiatry, Centre for Addiction Medicine, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India.

E-mail: jayantmahadevan@gmail.com

Abbreviations: ALD: alcoholic liver disease; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AUD: alcohol use disorder; AUDIT: Alcohol Use Disorder Identification Test; AUDIT – C: Alcohol Use Disorder Identification Test – Consumption; AWS: alcohol withdrawal syndrome; CNS: central nervous system; CIWA – Ar: Clinical Institute Withdrawal Assessment for Alcohol Revised; EtG: ethyl glucuronide; EtS: ethyl sulphate; GABA: gamma-aminobutyric acid; GGT: gamma glutamyl transferase; HE: hepatic encephalopathy; MCV: mean corpuscular volume; NMDA: N-methyl-D-aspartate

https://doi.org/10.1016/j.jceh.2022.03.003

AWS is associated with blunting of GABA inhibition with resultant signs and symptoms of agitation, psychomotor activity, and increased risk for seizures. The upregulation of glutamate at NMDA is also associated with AWS symptoms. These include tachycardia and hypertension, an arousal state that leads to seizures, tremors, delirium tremens (DT), and excitotoxic neuronal death.[10] There are interactions between the NMDA system and the dopaminergic system. Dopaminergic dysfunction is related to depressive symptoms in alcohol withdrawal.[10] Recent studies also point to an upregulation of the glutamate receptors a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainite.[11]

In summary, the symptoms of alcohol withdrawal, either due to complete cessation or substantial reduction, are because of imbalance due to both the acute reduction of GABA activity and the increase of glutamatergic action, leading to hyperexcitability in CNS.

CLINICAL FEATURES OF ALCOHOL WITHDRAWAL SYNDROME

AWS comprises a continuous spectrum of symptoms, ranging from mild and self-limiting to severe and potentially life threatening. The appearance of AWS correlates with reduction in blood alcohol level that typically starts between 4 and 6 h after reduction or cessation of drinking.

AWS is further divided into simple and complicated withdrawal (i.e., seizures and DT).[12] On similar lines, it may also be classified into four stages, namely[13–15];

Stage 1 AWS—These usually begin 4–6 h after the last use of alcohol, are most intense in the first 48 h and then subside over the course of 1 week. They include hand tremors, diaphoresis, nausea/vomiting, insomnia, anxiety, tachycardia (pulse rate>100/min and tachypnea).

Stage 2 AWS—These typically develops within 24–48 h within the emergence of Stage 1 symptoms. They include marked tremulousness, sometimes of the whole-body, increased restlessness, diaphoresis, and tachycardia (pulse rate >100/min) indicating sympathetic hyperactivity. The patient remains lucid and oriented to time, place, and person; however, may complain of perceptual disturbances such as hearing threatening voices, or feeling insects crawling over the body. A typical scenario in patients admitted for a medical condition such as ALD, would be that they may misinterpret the IV line or urinary catheter as a snake. These symptoms can worsen in the evenings.

Stage 3 AWS—This typically occurs 24–48 h after the last drink and is characterized by generalized, tonic-clonic seizures, usually with little or no postictal period. The occurrence of seizures with other semiology (partial or complex partial), after 72 h of the last alcohol intake or in the absence of other withdrawal symptoms should arouse the suspicion of a different etiology. Status epilepticus may occur but is relatively uncommon in AWS. About 10% of all patients with AWS go on to develop seizures.[16] Among patients with seizures, one-third go on to develop DT.

Stage 4 AWS or DT—DT is the most severe form of AWS, occurring among 5% of patients with AWS. DT usually develops 48–72 h after the last drink but can sometimes develop later. It is characterized by a disturbance of consciousness and change in cognition, i.e., disorientation, perceptual disturbances, which are features of delirium, along with severe withdrawal symptoms, that is, autonomic symptoms (sweating, nausea, palpitations, and tremor) and psychological symptoms (i.e., anxiety).[17,18] The occurrence of symptoms within 24 h or after 120 h of last alcohol intake, hypoactive delirium, high fever, or focal neurological signs should prompt investigation for other causes in addition to AWS.

A common diagnostic dilemma in patients with comorbid AUD and ALD, is the differentiation of alcohol withdrawal delirium or DT from hepatic encephalopathy (HE). The major distinguishing factor is that DT is a hyperactive delirium where the patient is aroused and agitated. In contrast, metabolic causes for delirium, including HE, typically present with a mixed or hypoactive subtype of delirium, where the patient is drowsy and retarded. Additionally, tremors in HE is only visible at hands (flapping tremors), as opposed to whole-body tremors seen in DT. Empirical studies have also noted differences in the symptom profile of patients with delirium due to AWS and those due to medical/surgical/multifactorial causes.[19,20]

In the background of medical illness, it is important for the clinician to be aware of the factors influencing progression to complicated withdrawal[21–23] (Table 1). The Prediction of Alcohol Withdrawal Scale can be used in clinical practice to assess the risk of complicated withdrawal among medically ill inpatients.[24]

Table 1 Risk factors for severe and complicated alcohol withdrawal syndrome.

1. Past episodes of alcohol withdrawal (detoxification, rehabilitation, seizures, delirium tremens)
2. Previous history of withdrawal seizures or delirium (kindling)
3. Comorbid medical conditions like ALD (raised AST), malnutrition, infection, and trauma
4. Abnormal liver function (serum aspartate aminotransferase activity >80 U/L)
5. Heavy drinking, old age, male gender
6. Concomitant benzodiazepine use
7. Moderate to severe withdrawal symptoms at the time of presentation (CIWA-Ar Score >10)
8. Medical or surgical illness (i.e., trauma, liver disease, CNS infection, electrolyte disturbances, hypoglycemia, etc.)
9. High blood alcohol level on admission (i.e., > 200 mg/dl)
10. Evidence of increased autonomic activity (i.e., systolic blood pressure [150 mmHg], body temperature > 38 °C)

Table 2 CIWA-Ar Score-based Intervention for Patients with Alcohol Withdrawal Syndrome.

CIWA-Ar score	Setting usually encountered	Intervention	Outline of care
<8: Mild	Outpatient	Pharmacological intervention may not be required unless there is a risk factor	Supportive care Thiamine 100 mg oral supplementation Long-term anti-craving medication Brief intervention counselling
8-15: Moderate	Usually outpatient, inpatient setting if there are many risk factors like cirrhosis	Better to use a pharmacological agent to prevent further progression of the severity of withdrawal	Oral long-acting benzodiazepine-like diazepam (normal or mild elevation of liver enzymes) or oxazepam/lorazepam with ALD Close observation
>15: Severe	Inpatient setting specifically	Pharmacological management strongly indicated	Initial part parental benzodiazepine with supportive care like correction of electrolytes, nutritional -Inj thiamine 500–1500 mg/day for 5–7 days to prevent (Wernicke–Korsakoff syndrome (WKS)

ASSESSMENT AND DIAGNOSIS OF ALCOHOL WITHDRAWAL SYNDROME

AWS usually only occurs in patients with regular heavy alcohol use. Hence, an accurate history of lifetime and current alcohol use from the patient and close family members should precede the diagnosis. This should include details about the quantity/frequency/duration of alcohol use, the amount of alcohol consumed in the last 24 h, presence of withdrawal symptoms in the past, including seizures or altered sensorium, and the time and quantity of the last drink, since these can influence the risk of developing severe alcohol withdrawal.

A detailed physical examination is mandatory with a focus on pallor, icterus, vital signs, hydration status, presence of any external injuries, signs of nutritional deficiencies, and systemic examination.

Laboratory investigations such as complete blood counts, liver (mainly AST, ALT, GGT) and kidney function tests, serum electrolytes, and blood glucose should be considered. ECG also needs to be done due to the risk of cardiac rhythm abnormalities. Chest X-ray should be done in patients with seizures or delirium due to a risk of aspiration and brain imaging studies (CT or MRI—brain) can be done if needed.

In cases where clinical history is not available or unreliable and the symptoms are not clear the testing of biomarkers of recent alcohol consumption such as breath or blood alcohol levels and ethyl glucuronide (EtG) can be useful for corroboration. EtG is a non-volatile, water-soluble, chemically stable, direct metabolite of ethanol that can be detected in body fluids for an extended period (up to 72 h) after the complete elimination of alcohol from the body.[25]

The diagnosis of AWS according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria[26] is based on the observation of signs and symptoms in patients who experienced an abrupt reduction or cessation of alcohol consumption. There should be at least two of the following symptoms: autonomic hyperactivity (sweating or tachycardia); increased hand tremor; insomnia; nausea or vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety; and tonic-clonic seizures.

The Clinical Institute of Withdrawal Assessment for Alcohol (CIWA-Ar) scale is the most commonly used instrument to assess the severity of AWS in both medical and psychiatric settings.[27] Table 2 describes how CIWA-Ar scores can be used to guide interventions in patients with AWS. The CIWA-Ar scale requires the patient to be conscious, cooperative and be able to respond verbally. It is suitable for patients with mild to moderate withdrawal symptoms but may be difficult to administer in patients with delirium.[28–30]

Table 3 Pharmacological Properties of Benzodiazepines Commonly Prescribed in Alcohol Withdrawal Syndrome.[30,41]

Benzodiazepine	Dosage Form	Half-life (Inc active metabolite)	Equivalent dose	Duration of action	Active metabolite
Lorazepam	Oral, IM, IV	10-20 hours	1 mg	Intermediate	No (Preferable in ALD)
Oxazepam	Oral	4-15 hours	30 mg	Short	No (Preferable in ALD)
Diazepam	Oral, IV	30-200 hours	10 mg	Long	Yes
Chlordiazepoxide	Oral	30-200 hours	25 mg	Long	Yes

ALD: Alcoholic liver disease.

TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME

There is a paucity of studies about the management of AWS in patients with ALD, with the literature being mostly limited to case reports and chart reviews. Hence, most guidelines recommend similar treatment approaches as those in patients without ALD, but advise caution and intensive clinical monitoring to prevent adverse effects from medications, particularly in patients with end-stage liver disease.

Treatment Objectives

AWS can cause extreme discomfort and be disabling for patients suffering from AUD. The negative reinforcement of alcohol withdrawal can also dissuade patients from making an attempt at abstaining from alcohol use. The objectives of the treatment of AWS are to minimize severity of withdrawal symptoms, to prevent complicated alcohol withdrawal like seizures or delirium, to facilitate treatment of other comorbid physical or mental illnesses, and to engage patients in treatment and build motivation for long-term abstinence.[31,32]

Treatment Setting

Patients with AWS having mild to moderate withdrawal and without any medical comorbidities can be managed in the outpatient setting. Patients with severe alcohol withdrawal are preferably treated in an inpatient setting, where facilities for regular medical monitoring are available. Apart from severe alcohol withdrawal symptoms, inpatient management of AWS is considered in patients with severe medical illnesses, active behavioral symptoms, suicidality, pregnancy, and extremes of age.[33,34]

Pharmacotherapy

Benzodiazepines

Benzodiazepines are the medication of choice in managing alcohol withdrawal symptoms. They also prevent complicated alcohol withdrawal like seizures or delirium if started early.[35,36] There is no clear evidence of the superiority of one benzodiazepine over the other for the treatment of AWS.[37,38]

In clinical practice, long-acting benzodiazepines like diazepam or chlordiazepoxide are often preferred because they produce a smoother withdrawal course with minimal breakthrough or rebound symptoms.[39] However, diazepam and chlordiazepoxide are metabolized by the liver and produce active metabolites that can lead to a prolonged duration of action, increased risk of sedation and may precipitate HE in patients with advanced liver disease and are best avoided in that context.[40] Lorazepam and Oxazepam, which are intermediate-acting benzodiazepines with renal metabolism are safer and are preferred for the management of AWS in the patients with ALD. Lorazepam is metabolized by conjugation (glucuronidation) rather than by oxidative reaction. It has been shown that glucuronidation is minimally affected in the states of alcoholic liver cirrhosis or liver cirrhosis from other aetiologies.[40] Both, diazepam and lorazepam have a rapid onset of action and can be used when swift symptom control is desired.

In terms of routes of administration, benzodiazepines can be administered through oral, intramuscular or intravenous routes. The oral route is used for mild withdrawal symptoms. The intravenous route is preferred in cases of moderate to severe withdrawal symptoms due to reliable absorption and rapid control of symptoms.[32,35,36] Table 3 outlines the pharmacological properties of benzodiazepines commonly used in the treatment of AWS.

There are two commonly used regimens for dosing benzodiazepines. These are as follows:

a. Fixed-dose regimen: The dose of benzodiazepines as well as the interval of dosing is predetermined by assessing the severity of dependence and withdrawal symptoms. It is often chosen in treating mild to moderate alcohol withdrawal symptoms on an outpatient basis. In a fixed-dose regimen, a longer duration of benzodiazepines is usually given in a tapering dose. There is a risk of under or over-dosing with benzodiazepines if this regimen is chosen.
b. Symptom-triggered regimen: The dose of benzodiazepines is decided based on the severity of withdrawal symptoms, as assessed by clinical examination and an assessment scale like CIWA-Ar. Medications are administered only when withdrawal symptoms are present. It ensures that a more optimal dose and duration of benzodiazepine treatment are delivered. However, it can be practiced only in inpatient or residential settings and require monitoring by trained staff.

The symptom-triggered regimen is preferred to the fixed-dose schedule for management of AWS among patients with ALD wherever possible, as it ensures minimal benzodiazepine exposure.[41]

The use of benzodiazepines in the management of AWS in severe ALD is not very clear due to a lack of empirical studies. The natural benzodiazepine hypothesis states that HE may arise in a proportion of patients as a result of accumulation of natural benzodiazepines. These are either derived from the diet or arise from in vivo synthesis in the gut (for example, from bacteria or fungi). In the presence of significant liver disease, these compounds escape hepatic clearance, accumulate in the systemic circulation and contribute to HE by simulating the action of prescription benzodiazepines like diazepam.[42] A number of studies have shown that serum concentrations of endogenous benzodiazepines are raised in cirrhotic patients with HE.[43,44] However, the source of these compounds and its correlation with HE is not clear. In line with this, a study has reported that in cases of severe ALD, there is likely to be a lower requirement for benzodiazepines.[45] A large study also found that benzodiazepines when used for a short duration of 1–2 days did not increase the risk of developing HE.[46]

A number of other (non-benzodiazepine) drugs like carbamazepine, valproate, gabapentin, baclofen, topiramate, propranolol, and clonidine have also been investigated as treatments for AWS. Although sufficient evidence in favor of their use is lacking, topiramate, baclofen, and gabapentin have shown promise for use in AWS.[47] Furthermore, given that they are not extensively metabolized in the liver, they may be considered for use in patients with ALD.

Carbamazepine

Carbamazepine has been demonstrated to be effective in managing at least mild to moderate AWS in few RCTs. The suggested dose range is between 600 and 800 mg per day, which is tapered and stopped over the next week. However, the unfavorable side effect profile (nausea and vomiting, agranulocytosis, Steven–Johnson syndrome, drug interactions, etc.) has limited its extensive use, and it is not routinely prescribed in managing AWS.[48,49]

Valproate

Valproate in the dose range of 1000–1500 mg per day has been shown to produce improvement in AWS and possibly reduce the occurrence of complicated alcohol withdrawal. However, the risk of hepatotoxicity limits its use in alcohol withdrawal management.[49]

Gabapentin

High-dose gabapentin (1200 mg) has been demonstrated to be similar in efficacy to lorazepam in treating mild to moderate alcohol withdrawal symptoms.[50] It has also been shown to reduce benzodiazepine requirement and was overall well-tolerated.[51] A recent RCT reported that gabapentin-treated patients with AUD and a history of AWS demonstrated more abstinent days and a greater reduction in heavy drinking days as compared to placebo.[52] Furthermore, gabapentin does not have hepatic metabolism and is excreted unchanged in the urine.[53] Hence, its use in patients with ALD may be considered and should be explored further.

Baclofen

A GABA-B receptor agonist and centrally acting muscle relaxant, use of Baclofen has been evaluated in both the management of AWS as well as an anti-craving agent. Although there is encouraging evidence that it may be effective in reducing the severity of alcohol withdrawal and reducing craving, definitive evidence is still lacking due to few RCTs.[54,55] Given its safety, in patients with ALD, it may be considered as an option for AWS treatment.

Beta-blockers

Propranolol can cause a reduction in autonomic hyperarousal symptoms of AWS. This may lead to a reduced prescribed dose of benzodiazepines, which risks the development of complicated alcohol withdrawal. The use of beta-blockers like propranolol is not routinely recommended in the management of alcohol withdrawal.[56]

Alpha-2 Agonists

Although routine use is not recommended, clonidine can be used in conjunction with benzodiazepines to reduce symptoms of autonomous hyperexcitation, especially in cases where a high dose of benzodiazepine is contraindicated such as ALD.[57]

Thiamine, Folic Acid, and Multivitamin Supplementation

The supplementation of thiamine, other B-complex vitamins and folate are important in patients with AWS due to the frequent co-occurrence of nutritional deficiencies and the to prevent Wernicke's encephalopathy. Thiamine supplementation should always be done before administering glucose infusions, to prevent the precipitation or aggravation Wernicke's encephalopathy.

Thiamine should be administered at a dose of 1500 mg in three divided doses intravenously for the first 3 days, following which 250 mg of IV thiamine per day should be continued for 1 week.[58] If possible, multivitamin (B-complex) supplementation may be considered.

Magnesium Supplementation

The use of magnesium supplementation in severe AWS comes from an observation of hypomagnesemia in these patients.[59] However, a meta-analysis investigating the use of magnesium found insufficient evidence for either

benefit or harm, suggesting that it not recommended for routine use.[60]

Managing Complicated Alcohol Withdrawal Syndrome (Seizures and Delirium Tremens)

Complicated AWS should be managed in the inpatient setting. The treatment includes measures such as correcting fluid and electrolyte imbalance, preventing and treating concurrent infections, preventing aspiration, high dose thiamine and multivitamin supplementation.

For acute control of withdrawal seizures, lorazepam 2–4 mg or diazepam 5–10 mg intravenously should be administered. If needed, the same dose can be repeated after 10–15 min.[61] The use of anti-epileptics such as phenytoin is not routinely recommended.[62] Patients with alcohol withdrawal seizures are more likely to develop DT and should be closely monitored.

DT should preferably be managed in an intensive care unit (ICU). Lorazepam IV in doses of 2–4 mg or diazepam IV in doses of 5–10 mg should be repeated every 10–15 min till patient achieves mild sedation. IV diazepam or lorazepam should then be repeated every 4–6 h with serial CIWA-Ar scoring and monitoring cardio-respiratory functions.[17,18,63] Cases of refractory DT, who do not improve with high doses of benzodiazepines (50 mg of diazepam or 10 mg of lorazepam within the first hour OR 200 mg of diazepam or 40 mg of lorazepam in 3 h) may benefit from use of dexmedetomidine, barbiturates, or propofol with continuous vital monitoring.[61,64] Dexmedetomidine has limited hepatic metabolism and can be considered in patients with ALD because it reduces benzodiazepine dose requirement in the ICU setting.[65] Haloperidol can also be used to manage symptoms of delirium in patients with ALD in the ICU setting. However, a risk of decreased seizure threshold and cardiac arrhythmias must be considered.[66]

As mentioned previously, the usual diagnostic dilemma in treating DT in the presence of ALD is to distinguish HE from DT. It is important to remember that high-dose benzodiazepines always carry the risk of excessive sedation, respiratory depression, and cognitive impairment, which may be more pronounced in cases with pre-existing hepatic dysfunction. Hence, it is recommended to use low doses of benzodiazepines such as lorazepam based on a symptom-triggered regimen for management of DT.[67] The specific considerations to be kept in mind while managing AWS with ALD are summarized in Table 4.[68,69]

Hepatologists are likely to encounter AWS in their patients with AUD. AWS can range from mild symptoms such as insomnia, tremors, autonomic hyperactivity to more severe symptoms such as seizures and DT. The symptoms usually start within 4–6 h of the last drink and peak between 24 and 72 h. Benzodiazepines (Oxazepam and Lorazepam) are the preferred treatment of AWS in patients with ALD. In patients with severe ALD, benzodiazepines should be used cautiously and with monitoring in an inpatient setting. The use of non-benzodiazepine agents such as baclofen and gabapentin may also be considered especially in patients with moderate to severe ALD. Supportive care should include fluid and electrolyte balance, treatment of concurrent infections and thiamine supplementation. Thiamine supplementation is critical to prevent the development of Wernicke's encephalopathy and must be instituted in all patients. The clinician should also use this time to engage patients in treatment and work on building patient's motivation for long-term abstinence.

Table 4 Considerations for managing alcohol withdrawal syndrome in patients with alcoholic liver disease.

• It is critical to distinguish cases of alcohol withdrawal delirium from hepatic encephalopathy, since the use of benzodiazepines may be counterproductive in the latter.
• Benzodiazepines should preferably be prescribed as symptom triggered regimen with close monitoring for the patient with simple AWS and milder ALD.
• Intermediate-acting benzodiazepines with renal metabolism (i.e., lorazepam, oxazepam) are safer and should be preferred.
• Benzodiazepines should be discontinued after the acute withdrawal period is over. Monitor for changes in alertness, orientation & respiratory depression periodically while the patient is receiving benzodiazepines.
• Benzodiazepines may be cautiously used when symptoms of end stage liver disease like ascites, variceal bleeding, hepatic encephalopathy are present. The presence of hepatorenal syndrome requires greater vigilance while dosing benzodiazepines.
• Baclofen and gabapentin can also be considered as alternative agents to manage mild to moderate AWS.
• Supportive care should include fluid and electrolyte balance, treatment of concurrent infections and prevention of aspiration.
• High-dose thiamine supplementation is critical to prevent the development of Wernicke's encephalopathy and must be instituted in all patients with severe AWS.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

PM, PKC, and JM—Conceptualization; UP and PKC—Writing—Original draft preparation; PM and PKC—Supervision; PM, PKC, and JM—Writing—Reviewing and Editing.

CONFLICTS OF INTEREST

There are no conflicts of interest to be declared by any of the authors.

FUNDING

The research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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