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Review Article

Predictors for Severe Alcohol Withdrawal Syndrome in Clinical Practice

Julliyan Dilleban Arokiadoss[1,*], Narayanan Venkateshan[2], Denilah Pauline[3], Karthika[3], Bhavani Suba Niranjana[3]

[1]Department of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Tamil Nadu, INDIA.
[2]Department of Pharmaceutical Chemistry, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Tamil Nadu, INDIA.
[3]Department of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Tamil Nadu, INDIA

ABSTRACT

Alcohol Withdrawal Syndrome (AWS) presents a significant clinical challenge due to its complex neurochemical underpinnings and varied symptom severity. This review explores the predictors of severe AWS, focusing on the pathophysiology driven by neuroadaptive changes in GABAergic and glutamatergic systems. Key findings indicate that early identification and accurate assessment are critical for managing AWS effectively and preventing severe complications such as delirium tremens and seizures. Tools like the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) and the Total Severity Assessment Scale (TSA) are essential for evaluating withdrawal severity and guiding treatment. Predictive factors, including the history of alcohol use, presence of comorbid conditions and individual patient characteristics, significantly influence treatment outcomes. This article highlights the critical importance of understanding and managing Alcohol Withdrawal Syndrome (AWS) through early identification and intervention to improve patient outcomes.

Keywords: Alcohol Withdrawal Syndrome, Glutamate, Tremors, Seizures, Neurochemical Imbalances.

Correspondence:
Dr. Julliyan Dilleban Arokiadoss
Department of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Tamil Nadu, INDIA.
Email: julliyandilleban@akcp.ac.in

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INTRODUCTION

Alcohol Withdrawal Syndrome (AWS) emerges as a significant clinical challenge when individuals with chronic alcohol use abruptly reduce or cease their alcohol intake. This syndrome is characterized by a range of symptoms that reflect disturbances in neurochemical systems, predominantly involving γ-Aminobutyric acid (GABA) and glutamate. During alcohol intoxication, alcohol acts as a central nervous system depressant by enhancing GABAergic neurotransmission through GABA-A receptors, leading to increased inhibitory effects on neuronal excitability. Simultaneously, alcohol suppresses excitatory neurotransmission mediated by N-Methyl-D-Aspartate (NMDA) receptors. Chronic alcohol exposure induces neuroadaptive changes, including increased NMDA receptor activity and decreased GABA-A receptor function, contributing to the development of tolerance. Upon withdrawal, this balance shifts towards heightened neuronal excitability due to reduced GABAergic inhibition and increased glutamatergic activity. The clinical manifestations of AWS can range from mild symptoms such as tremors and anxiety to severe conditions, including delirium tremens and seizures. The onset and severity of symptoms depend on various factors, including the history of alcohol use, the presence of comorbid conditions and individual patient characteristics. Accurate assessment of AWS is crucial for effective management and the prevention of complications. Established tools such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale and the Total Severity Assessment (TSA) scale provide valuable frameworks for evaluating withdrawal severity and guiding treatment.

PATHOLOGICAL PROCESS IN ALCOHOL WITHDRAWAL

Alcohol withdrawal syndrome is caused by several factors. With the help of inhibitory and excitatory neurotransmitters, the neurochemical balances are regulated by the brain. The γ-aminobutyric acid known as GABA, it is the most important inhibitory neurotransmitter which acts via the GABA-alpha receptor. Glutamate is the excitatory neurotransmitter which acts via the N-methyl-D-aspartate neurotransmitter. The brains excitability was decreased by alcohol, because GABA effect was enhanced by alcohol in GABA-A neuroreceptors.[1] The NMDA receptors are enhanced and the GABA-A receptors are suppressed by the prolonged intake of alcohol, which causes tolerance. During the withdrawal of the alcohol, the condition becomes vice versa

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and causes imbalance of dopaminergic system. These conditions cause numerous signs and symptoms of alcohol withdrawal syndrome. During withdrawal some of the symptoms are caused by increased level of GABA in plasma and Cerebrospinal Fluid. Also, the changes in the mechanisms of GABA-A and GABA-B receptors by the ethanol withdrawal and intoxication can lead to the anxiety and other behavioural changes. The abnormal functions of NMDA and GABA-A receptors are responsible for the seizures during alcohol withdrawal. Hallucination formation is caused by the altered dopaminergic function.[2] In acute alcohol consumption, it enhances the inhibitory neurotransmission by enhancing GABA-A function. In chronic alcohol consumption it causes tolerance and by reducing the function of GABA-A receptor and enhancing NMDA receptors. This causes increased excitability of neurons that decreases the threshold for seizures. Hallucinations are caused by increased function of noradrenergic and dopaminergic receptors in the alcohol withdrawal patients.[3] To maintain stability within the central nervous system, inhibitory signals mediated by the GABAergic system are counterbalanced by excitatory neurotransmitters like glutamate. Alcohol, known for its CNS depressant effects, enhances the activity of the GABAergic system. In acute intoxication, this can lead to various clinical effects such as reduced inhibition, feelings of euphoria and sedation. The impact of alcohol in the acute phase varies with dosage: lower doses tend to stimulate, while higher doses tend to sedate. Chronic alcohol consumption induces neuroadaptive changes that disrupt the GABA-glutamate balance by increasing glutamate levels to compensate for alcohol-induced elevation of GABA, alongside a decrease in endogenous GABA production. Consequently, upon alcohol cessation, there may be a relative deficit of GABA and an excess of glutamate, precipitating the excitatory symptoms characteristic of alcohol withdrawal syndrome.[5]

IMPACT OF PREDICTORS ON TREATMENT OUTCOME

The hospital mortality and duration of stay decides the severity of alcohol withdrawal syndrome. But there is no common consent in the prediction of severity of alcohol withdrawal syndrome.[4] Alcohol Withdrawal Syndrome (AWS) represents number of symptoms that can range in severity, influenced by factors such as the amount, frequency and duration of alcohol consumption, prior withdrawal experiences and individual susceptibility.[1,4] Typically, symptoms manifest within 6 to 24 hr after discontinuation of alcohol consumption.[9] Certain readily measurable parameters upon admission can help forecast the severity of alcohol withdrawal, particularly in predicting the onset of Withdrawal Seizures (WS) or Delirium Tremens (DT). By utilizing specific nomograms, healthcare providers can assess the probability of patients experiencing WS or DT during their withdrawal process. The presence of structural brain lesions in a patient's medical history necessitates thorough monitoring and careful observation[6] PAWSS represents the inaugural validated tool designed to predict severe Alcohol Withdrawal Syndrome (AWS) in medically ill patients. Its application can facilitate early recognition of individuals at risk for complex AWS, enabling proactive measures to prevent severe AWS from developing.[7] The CIWA-Ar protocol is widely employed in our in managing alcohol withdrawal and is frequently utilized by family physicians.[8] Alcohol withdrawal symptoms assessed by CIWA-Ar exhibit multidimensionality.[9] A 10-item scale has been created to clinically assess the severity of alcohol withdrawal syndrome, providing enhanced efficiency without compromising its clinical utility, validity and reliability. This scale is suitable for integration into routine patient care during alcohol withdrawal and in clinical trials evaluating withdrawal treatments[10] The Total severity assessment Scale is the another widely used Scale to measure the severity of Alcohol withdrawal Syndrome. Gross *et al.* (1973) developed the TSA scale to develop the degree of severity in alcohol withdrawal and to simplify the quantification of the withdrawal syndrome. The CIWA, considered the 'gold standard' for comparison, involved a straightforward initial assessment by a physician, rating overall severity. The CIWA has been employed in both research and clinical practice, enhancing clinicians' familiarity with its application. Its ease and rapidity of administration by trained personnel make it appropriate for use by nursing staff in both hospital wards and community settings.[11]

CLINICAL PRESENTATION OF SEVERE ALCOHOL WITHDRAWAL SYNDROME

The clinical symptoms differ from mild to severe, typically appearing a few times after the recent alcohol intake. Common signs include tremor, restlessness, sleeplessness, distress, anxiety, sudden sweats, rapid heartbeat, febrile, vomiting, convulsant, delusion, increased agitation and tremor. In some incident, patients may experience very severe alcohol withdrawal syndrome, such as delirium tremens. This sign arises from disruptions of various neurotransmitter circuits involved in the alcohol pathway and indicate a central nervous system undergoing homeostatic readjustment.[12]

Healthcare providers should consider AWS as a potential differential diagnosis for patients exhibiting symptoms, they should analysis about the patient's drinking habits, including the time period, quantity and incidence of liquor intake, as well as the usual onset of signs after a few hr of withdrawal, often in the sunrise upon awakening. Additionally, providers should ask about the patient's history of AWS. The CAGE and Alcohol Use Disorders Identification Test. questionnaires can assist in detecting patients with alcohol use disorder.[13]

After cessation of alcohol use, symptoms of Alcohol Withdrawal Syndrome appear at specific intervals slight withdrawal symptoms manifest within 6-12 hr, alcoholic hallucinosis within half to one day, withdrawal seizures within

24-48 hr and alcohol withdrawal delirium within forty-eight to seventy-two one hr.[12] A positive correlation between a history of prior admissions for alcohol withdrawal and the severity of subsequent withdrawal symptoms. Other studies have also reported similar findings, suggesting that individuals with such a history tend to experience a more prolonged and severe course of alcohol withdrawal, including delirium tremens and higher CIWA scores. Another reason elderly individual may experience less delirium tremens could be due to higher doses of benzodiazepines typically administered in this age group. Due to slower metabolism, increased elimination half-life and higher drug concentration in the elderly caused by factors such as increased body fat, decreased water concentration, slower gastric emptying and reduced intestinal motility benzodiazepines achieve higher blood levels. This elevated concentration likely mitigates the risk of AWS symptoms, thereby decreasing the likelihood of delirium tremens. Additionally, some elderly patients may be prescribed beta-blockers for preexisting hypertension, which, when combined with elevated benzodiazepine levels, could further diminish the intensity of withdrawal symptom.[14]

Presence of co-occurring conditions physical health issues such as significant liver disease epilepsy, cardiac disease, or mobility issues due to brain damage, severe muscle weakness, or neuropathy and gestation. Coexisting mental health conditions including intellectual disability, psychosis, manic depression, personality disorders, or high death risk. Complex social circumstances such as homelessness, domestic violence, or safeguarding concerns. History of frequent unsuccessful community-based Managed alcohol withdrawal attempts, particularly with indication of worsening risk of AWS over time.[16] Alcoholic hallucinosis, which can affect Two-eight percent of individuals with a history of heavy and chronic liquor use, are particularly prevalent among those who initiated drinking at a young age around eighteen or before. These hallucinations usually commence approximately 8-12 hr after the last alcoholic beverage and can present in auditory (hearing sounds), visual (seeing images), tactile (feeling sensations on the skin), gustatory (tasting flavors) and olfactory (smelling odors) forms.[18,20] Alcohol can induce hallucinations through various pathways.[19]

Alcohol status epileptics usually occur one day after the last drink, with risk extending up to 48 hr post-abstinence. They affect 5-10% of those with acute alcohol withdrawal syndrome, typically manifesting as generalized grand mal seizures. If untreated initially, about two-thirds of individuals may experience subsequent seizures closely clustered, while 3% may develop seizure.[17,18] Quitting alcohol delirium tremens, occurs in around 3-5% of hospitalized patients experiencing alcohol withdrawal syndrome.[20] It is marked by confusion, altered consciousness, severe autonomic instability and illusion. It generally initiates after three days of abstinence but can manifest abruptly within 8 hr following a sudden reduction in alcohol intake, especially in persons with a record of complex of quitting episode. 20% of complication in some cases.[7,18] The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines alcohol withdrawal as the onset of more than two distinct signs that appear within some timeline to days after a significant decrease in alcohol intake following a prolonged interval of binge drinking.[18,13]

IMPORTANCE OF EARLY IDENTIFICATION AND PREDICTION

Severe alcohol withdrawal syndrome, characterized by seizures and delirium tremens, poses significant risks of sickness and death. Early identification and pharmacological intervention are crucial in reducing these risks. Predicting complicated alcohol withdrawal remains challenging, with studies exploring associations among clinical, biochemical and sociodemographic factors.[15] Elder age coexisting condition or clinical complaint earlier history of delirium tremens or alcohol quitting seizure Severe abstinence symptoms at early diagnosis, In spite of having significant blood alcohol levels begins with dehydrated event of having had withdrawal seizure during this current withdrawal state before the assessment begin of low blood sodium or low potassium increased Aspartate aminotransferase or Gamma-glutamyl transferase levels Low platelet count The presence of structural brain lesions period of alcohol use and typical regular amount of alcohol consumed are inconsistently predict severe alcohol withdrawal[17] confusion state, mental illness, illusion, heat illness, hypertension crisis, epilepsy and unconsciousness are typical symptoms of acute confusion state. These can lead to patient or staff injury, as well as medical issue such as inhalation pneumonia, arrhythmia, or heart related problem, resulting in death in average one to five percent of patients.

After treating of acute Alcohol withdrawal syndrome, certain symptoms can persist for days to month beyond the initial five to seven days of detoxification, indicating onset of the "protracted AWS" phase.[13] These include age, sex and markers of socioeconomic status. These factors are often considered in studies to understand their association with health outcomes, including alcoholism and related medical condition and Socioeconomic status was assessed using health insurance records, distinguishing between individuals covered by Medicaid or those who paid for healthcare themselves (self-pay), compared to those with other types of health insurance. Depression, psychosis, drug abuse and tobacco abuse were identified using specific criteria: depression, psychosis and drug abuse were determined from AHRQ comorbidity indices available in the NRD dataset, while tobacco abuse was identified based on ICD-9 codes and also indicating alcohol-related organ damage or medical conditions directly attributable to alcohol abuse.[21]

Some other predictive factors are patient started consuming alcohol excessively, which could influence the severity of

withdrawal symptoms and complications. Person with a background of multiple withdrawal attempts might be more susceptible for complications due to potential neuroadaptations and physiological changes. Previous episodes of delirium or convulsion indicate a more severe history of drink abstinence, which is predictive of future complications. The severity of abstinence symptoms was not found to be relating with the alcohol intake in the one day before hospitalization. This suggests that acute alcohol intake just before hospitalization may not predict the severity of withdrawal symptoms. The Cushman score is an instrument used to calculate the intensity of reduces the alcohol intake. A nearly significant correlation with higher scores suggests that factors other than recent alcohol intake may influence the severity of withdrawal symptoms and complication.[22]

MEDICAL HISTORY AND COMORBIDITIES AS PREDICTORS

The medication history and objective evidence determine the diagnosis and severity of alcohol withdrawal syndrome. Some of the most crucial data include the duration of alcohol use, past alcohol withdrawals, quantity of alcoholic intake, time of alcohol use, presence of concurrent medical or psychiatric conditions and abuse of other agents. Despite, identifying alcohol withdrawal symptoms, the physical examination should analyze probable complicating medical conditions which include hepatic disease, arrhythmias, coronary heart disease, gastrointestinal bleeding, congestive heart failure, pancreatitis and nervous system impairment. However, common laboratory profiles contain a urine drug screen, determination of alcohol in blood, a complete blood count, electrolyte levels and hepatic function tests.[1]

20% Alcohol dependent Individuals who present in the inner-city hospitals suffer from delirium tremens. It is predicted that one or more concurrent physical illnesses may result in delirium tremens and also due to the cessation of alcohol for 2 or more days during the time of admission.[23] The prevalence of occurrence of seizures in alcohol-dependent patients is about 3 to 10% and 70% of these are correlated with withdrawal.[24]

The alcohol withdrawal patients who are undergoing the withdrawal process are at a higher risk of progressing serious medical complications, such as Wernicke's encephalopathy, electrolyte imbalances and dehydration.[25]

CLINICAL ASSESSMENT SCORING AND TOOL

The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale is a validated 10-item revised form to quantify AWS severity and to monitor and medicate patients going through withdrawal.[13] The CIWA-Ar scale requires minimal patient cooperation to evaluate its ten symptoms. Scores of <8 suggest mild withdrawal, 8-15 suggest moderate withdrawal and greater than 15 suggest severe withdrawal and this scale also forecasts the progress of seizures and delirium.[26] The pharmacological treatment is not needed for those patients with CIWA-Ar scores of<8-10, while the treatment is necessary for those patients with a score between 8 and 15 for the progression into a more advanced form of AWS. CIWA-Ar score >15 patients need a strongly recommended pharmacological treatment. For every 8 hr, the evaluation of CIWA-Ar score should be repeated. For effective treatment, CIWA should be repeated every hour in patients with scores of 8 to 10.[12]

The severe medical illnesses such as anemia, alcoholic liver disease, coronary heart disease and pneumonia have been reported to induce AWS and tend to enhance the risk of severe AWS.[27]

BIOMARKERS

In several studies, possible predictors for the development of a severe AWS have been investigated. Medical history and laboratory biomarkers are the two most important methods for the identification of patients at high risk.[28] It appears that the most robust predictor for an incident occurrence of DT or seizures is a history of a similar event[10] Clinical findings such as elevated heart rate, systolic blood pressure and temperature are all easily verifiable in the initial patient assessment, although their predictive value to identify patients with AWS who are more likely to develop DT is not high.[29] In a patient with impaired consciousness, laboratory markers represent helpful tools to confirm the suspected clinical diagnosis of an AUD.

MARKERS USEFUL IN THE EMERGENCY SETTING

For the successful treatment of AUD, the quantitative, measurable detection of drinking is important. Therefore, the importance of direct and indirect alcohol markers to determine consumption in the acute clinical setting is increasingly recognized. The detection of ethanol in various specimens itself is still a popular diagnostic tool to prove alcohol consumption. Alcohol ingestion can be measured using a simple breath test. Although ethanol is rapidly eliminated from the circulation, the actual time for detection by breath analysis is relies on the amount of intake as ethanol depletes according to a linear reduction at approximately v 0,15%/1 hr. Alcohol use can otherwise be detected by direct measurement of ethanol in blood or urine[30] The duration of the ethanol concentration in the blood after the ingestion of an alcoholic beverage is controlled by its pharmacokinetics. This represents interplay between the kinetics of absorption, distribution and elimination. Therefore, it is crucial in determining the pharmacodynamic responses to alcohol. As a result of both genetic and environmental factors, there is a large degree of variability in alcohol metabolism. Apart from ethanol itself, indirect markers of AUD are largely available and mostly part of usual laboratory testing. Severe AWS involves variation in electrolytes, especially potassium that is due to peak catecholamine activity

with activation of the sodium-potassium ATPase pump and peak vasopressin. Hypokalemia is not definite for alcohol consumption but is frequently reported to be associated with DT or seizures. Similarly thrombocytopenia (with high negative predictive value) that additionally is predictive of an incident occurrence of DT and seizures[4] More indirect markers, such as AST, ALT, γGT and MCV, are widely available and relatively inexpensive, but their predictive value is restricted because of low specificity. The interpretation of increased values has to take into consideration of other influencing factors including sex, age, comorbidities and medication that also may elevate this marker.[31,32]

CONCLUSION

Alcohol Withdrawal Syndrome (AWS) remains a critical clinical challenge due to its complex neurochemical basis and the range of severity it presents. The pathophysiology of AWS, marked by disturbances in GABAergic and glutamatergic neurotransmission, underscores the necessity for a nuanced understanding and timely intervention. Predicting the severity of AWS is essential to effectively managing and mitigating potential complications, such as delirium tremens and seizures, which pose significant risks to patient health and safety.

This review highlights several key predictors that can inform clinical practice, including the history of alcohol use, presence of comorbid conditions and individual patient characteristics. Tools such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) and the Total Severity Assessment Scale (TSA) are invaluable in assessing withdrawal severity and guiding treatment. These tools enable healthcare providers to identify patients at high risk of severe AWS, allowing for early and targeted interventions.

The findings emphasize the urgent need for personalized management strategies tailored to individual risk profiles. Early identification and accurate assessment are paramount to improving patient outcomes and reducing the incidence of severe withdrawal complications. Enhanced clinical practices, incorporating predictive factors and standardized assessment tools, are crucial for advancing the management of AWS and optimizing patient care. Continued research and refinement of predictive models will further enhance the ability to prevent and manage severe AWS, ultimately improving overall treatment efficacy and patient well-being.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AWS: Alcohol withdrawal syndrome; **GABA:** Gamma-aminobutyric acid; **NMD:** N-methyl-D-aspartate; **CIWA-Ar:** Clinical Institute Withdrawal Assessment Alcohol Scale Revised; **TSA:** Total severity assessment.

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