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Molecular Crosstalk Between The Renin–Angiotensin–Aldosterone System And Neurotransmitter Dysregulation In Alcohol Withdrawal Syndrome

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Abstract
The Renin-Angiotensin-Aldosterone System (RAAS) plays a critical role in the pathophysiology of Alcohol Withdrawal Syndrome (AWS), influencing several physiological processes, including blood pressure regulation, fluid balance, and electrolyte homeostasis. Chronic alcohol consumption can disrupt RAAS, leading to hypertension, electrolyte imbalances, and autonomic dysregulation, which contribute to the severity of AWS symptoms. This interaction between RAAS and the nervous system further complicates the withdrawal process, affecting stress response mechanisms and neurochemical balance. Laboratory findings in AWS often show significant alterations in RAAS components, such as increased levels of renin, angiotensin II, and aldosterone, which are associated with cardiovascular and electrolyte disturbances. To assess the severity of withdrawal, tools like the Clinical Institute Withdrawal Assessment and Prediction of Alcohol Withdrawal Severity Scale help guide therapeutic decisions. Traditional treatment of AWS often focuses on benzodiazepines (BZDs), but the growing understanding of RAAS's role has led to alternative strategies, including the use of RAAS inhibitors, anticonvulsants, and alpha2 agonists. These interventions aim to address RAAS dysregulation and reduce the need for BZDs, potentially minimizing the risk of dependence and adverse effects. Future research should explore the genetic aspects of RAAS in alcohol dependence, investigate RAAS inhibitors for their therapeutic potential in AWS, and assess their long-term impact on relapse prevention. Understanding these mechanisms will pave the way for personalized treatments, improving the management of AWS and reducing the likelihood of recurrence in alcohol-dependent individuals.

Keywords: Alcohol withdrawal syndrome, renin-angiotensin-aldosterone system, renin, angiotensin, aldosterone, electrolyte balance.

Introduction

Alcohol withdrawal syndrome (AWS) is a life-threatening medical condition diagnosed by anxiety, sleep disorder, autonomic unsteadiness, hyper-reactivity and in complex cases delirium tremens (DTs), seizures, and ultimately death. AWS has become a sizeable economic burden and health concern. It is estimated that around one-fifth of total national healthcare expenditure in the United States is utilized to mitigate and manage disorders associated to excessive alcohol consumption, where a substantial percentage of that expenditure employed every year to operate approximately 500,000 events of acute AWS. Numerous studies impart that these episodes transpire during post-operative recovery and distinctively in trauma patients (Antonelli et al., 2023)

Globally health agencies have recognized AWS as substantial clinical condition, where studies and data indicate that nearly half of individuals with alcohol use disorder (AUD) will develop some degree of AWS when they reduce or quit alcohol consumption. In hospitals, particularly among patients with well-characterized alcohol dependence, the incidence of AWS is estimated at 15–20% during their stay. AWS is reported to affect approximately 1–2% of all admissions in the general hospital population, and the incidence in intensive care units (ICUs) can be as high as 15%, with more severe manifestations (e.g., seizures or DTs) (Long et al., 2017)

In terms of severity, around 85–90% of individuals with AWS demonstrate mild to moderate symptoms that include tremors, anxiety, and sweating, while 10–15% experience severe consequences such as seizures and delirium tremens. The mortality rate for mild AWS is low at <1%, while the rate can increase to 5–15% for severe withdrawal if untreated.

The mortality rate can drop to approximately 1–4% for severe AWS with an appropriate medical treatment. According to hospitalization data (inpatient hospital admissions) from the United States, AWS causes more than 250,000 hospital admissions each year, with patients experiencing AWS requiring hospital stays that are two to three times longer than those not suffering from AWS (Day & Daly, 2022)

There are several risk factors for the development and severity of AWS including chronic heavy alcohol intake (greater than eight drinks per day for long periods of time), a history of previous withdrawal episodes, comorbid medical illnesses including liver disease and poor nutritional status with thiamine deficiency. Worldwide, consumption of alcohol in low- and middle-income countries is also on the rise, which is associated with increased risk of AWS. Regions such as North America, Europe, and Australia currently report the highest rates of AWS-related hospitalizations (Wood et al., 2018).

An increase of cases on AWS has been observed between 2022 and 2024 after COVID-19, which was attributed to more alcohol consumption during lockdowns but with immediate discontinuation of alcohol when availability was reduced. Importantly, there has been an increase in AWS-related hospitalizations among younger adults 25–40 years old, a reversal from previous reports where predominantly older populations were affected. These transforming patterns highlight an increased risk of AWS and the implementation of focused clinical awareness and intervention measures to combat AWS effectively (Creswell et al., 2024).

Alcohol penetrates Central nervous system (CNS) by precipitously crossing the blood-brain barrier (BBB) and act as CNS depressant. Alcohol stimulates gamma-amino butyric acid (GABA) and suppress glutamate receptor secretion thus leading to cognitive deficits leading to impaired communication due to neuronal damages. Literature suggests that continued heavy alcohol consumption causes neuroadaptive alterations which is hard to mitigate due to continued presence of ethanol in the brain due to its small molecular size and high solubility. As a preventive mechanism brain tries to moderate these neuroadaptive changes by enhancing glutamatergic and attenuating GABAergic neurotransmission that was disrupted GABA/glutamate imbalance. It is observed that neuronal toxicity is caused by extracellular calcium influx and deployment of supplementary calcium from endoplasmic reticulum due to surge of glutamate signalling and activation of N-methyl-d-aspartate (NMDA) glutamate receptors. Even sudden cessation of alcohol intake eliminates alcohol from the brain, exposing the disordered GABA/glutamate balance that comes in AWS. Numerous studies reflects, only a handful of glutamatergic genetic factors appear to have a role significant role in the withdrawal process (Modzelewski et al., 2024).

Genetic variance is highly related to susceptibility to AWS, in addition to the severity of AWS symptoms experienced during withdrawal. For instance, some genetic differences can impact the extent to which an individual's brain adapts to chronic alcohol exposure and the way it functions when alcohol use is discontinued. Differences in genes related to neurotransmitter systems particularly along the GABA and glutamate pathways have been implicated in withdrawal symptoms. Studies highlights that polymorphisms in the gamma-aminobutyric acid (GABA) type A receptor subunit alpha2 gene (GABRA2), which encodes for a GABA-A receptor subunit, have been associated with increased risk for more severe AWS warning sign like anxiety, seizures, and delirium tremens (Becker, 2008).

Certain genetic factors that influence the metabolism of alcohol, particularly polymorphisms in the alcohol dehydrogenase 1B (ADH1B) and aldehyde dehydrogenase 2 (ALDH2) genes, can indirectly modulate the severity of withdrawal by influencing the pattern and severity of alcohol dependence. The neurobiological mechanisms of addiction vary individuals with given genetic profiles may experience greater cravings, neurochemical dysregulation with withdrawal, or physical symptoms such as increased heart rate and blood pressure. Family and twin studies have also shown that heritability accounts for a substantial portion of the variability in AWS risk. Further, identification these genetic influences could lead to more systematic withdrawal management strategies in the future, allowing for targeted prevention and treatment approaches basis the individual genetic profiles (Verhulst et al., 2015).

Research literature highlights notable efficacy of three anti-glutamatergic approaches in restoring withdrawal severity in the humans. Here, benzodiazepines continue to the gold standard when treating AWS in clinical practice. Benzodiazepines works by antagonizing the GABA receptors simulation thus effectively ameliorate the withdrawal severity and influencing mortality. It is indicated that glutamate levels are not impacted by benzodiazepines and reduced inhibitory GABAergic neurotransmission are observed. Allowing this hyper-glutamatergic state uncorrected has been accompanying with more intense alcohol yearning and higher probability of post-withdrawal relapse, and may possibly have neurotoxic consequences (Baldwin, 2022).

Table 1. Alcohol Withdrawal Syndrome

Symptoms	**None**	**Mild**	**Moderate**	**Severe**
Sweat	Not occur	Less, rarely visible	Sweat beads	Sweating profusely
Orientation or Confusion	Orientation to time, location, and people	Disoriented to either time (by more than two days, or by the incorrect month or year) or place (by the building's city, name or state), but not both	Lack of awareness of time and location	Person disorientation

Symptoms	None	Mild	Moderate	Severe
Agitation	RASS=0	RASS=+1	RASS=+2	RASS=+3 and +4
Tremor	Not occur	Not apparent, but perceptible	Moderate, with arms outstretched	At rest, without arms outstretched
Hallucinations	Not occur	Intact reality testing, unclear report	More specific hallucinations	Poor reality testing, clearly reacting to internal stimuli

Table **1** illustrates the brief AWS: In the mild stage, symptoms include occasional, barely perceptible sweating, and slight disorientation (limited to either time or place). The agitation is mild as indicated by a Richmond Agitation-Sedation Scale (RASS) score of +1, and tremors are not visible at this time but can be palpated with subtlety. These early hallucinations are subtle, with patients maintaining intact reality testing.
When the symptoms advance to the moderate stage, sweating is intensified with the formation of droplets of sweat. There is disorientation at multiple levels: all times and all places. There is agitation rated RASS + 2. The patients also have tremors when they extend their arms. There is specificity to the hallucinations and some level of reality testing.
At the severe stage, the patients have profuse sweating and disorientation, including the nature of their identity. Severe agitation is also present, rated RASS + 3 to + 4. The patients also have tremors even at rest. The hallucinations are intense. The patients cannot differentiate hallucinations and reality. They tend to respond to internal stimuli (Mirijello et al., 2015).

Physiological Changes During Alcohol Withdrawal

Alcohol withdrawal, as the name suggests, happens when the use of alcohol, which has been used regularly over a period of time, is suddenly stopped or reduced, resulting in a series of physiological changes as the body tries to regain its homeostasis. These physiological changes result mainly from the alterations in the CNS as well as other organs of the body as a result of the prolonged exposure to alcohol (Kumar & Singh, 2021). The physiological changes resulting from alcohol withdrawal, as shown in figure 1, are explained below.

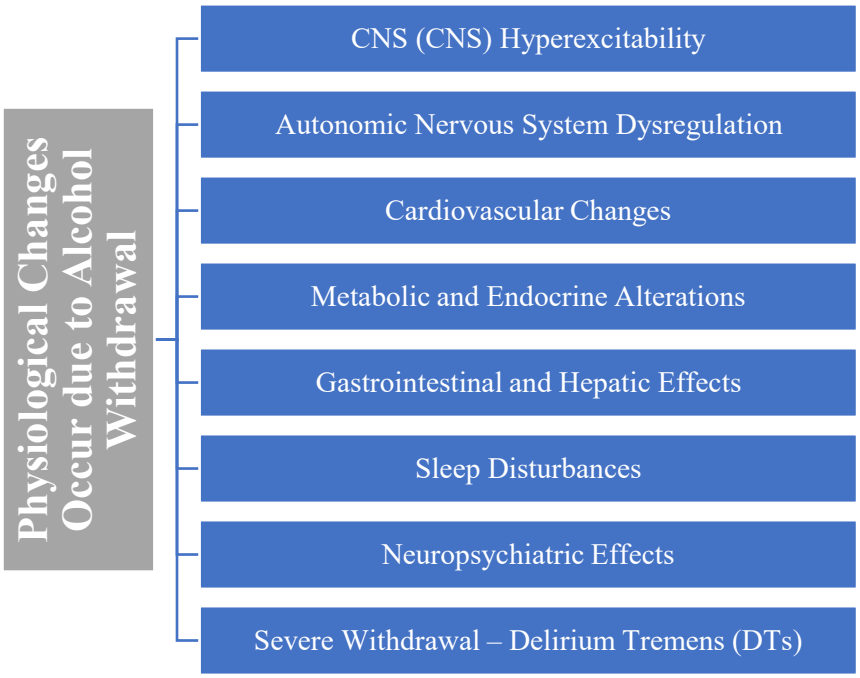

Figure 1. Physiological Changes happens due to Alcohol Withdrawal

CNS Hyper-excitability

Chronic alcohol use results in the development of the repressive activity of the neurotransmitter GABA and suppresses the activity of the excitatory neurotransmitter glutamate. If alcohol is suddenly stopped, the balance shifts to extreme neuronal excitation, causing a hyperactive CNS. Consequently, the individual feels anxious, agitated, has tremors, and seizures. Delirium tremens, a life-threatening health issue, can occur, which includes symptoms such as confusion, agitation, and hallucinations. Hyper-excitability can cause sleep problems and cognitive problems. Medical care is needed to manage the symptoms as well as the health issues that can arise as a consequence of severe alcohol withdrawal symptoms (Ngui et al., 2022).

Autonomic Nervous System Dysregulation

Alcohol withdrawal impacts the autonomic nervous system, showing an imbalance, indicating hyperactivity of the sympathetic nervous system. The effects of alcohol usually reduce the sympathetic nervous system; however, when this substance is absent in the body, too much norepinephrine is released into the system, leading to tachycardia, hypertension, excessive sweating, and hyperthermia. Anxiety and restlessness are also some of the symptoms of nervous system dysfunction. In some cases, the overactive sympathetic nervous system may cause serious health complications, which may be life-threatening. The manipulation of beta-blockers and alpha-2 agonists such as clonidine is used to prevent serious cardiovascular complications during withdrawal (Herring et al., 2025).

Cardiovascular Changes

Alcohol withdrawal leads to major cardiovascular changes due to increased sympathetic activity and abnormal functioning of the autonomic nerve system. Alcohol increases parasympathetic activity and decreases sympathetic activity in the body when consumed. Stopping the intake of alcohol leads to a rebound effect in alcohol withdrawal, causing sympathetic activity to increase in the body. The catecholamine that was in excess and caused tachycardia, vasoconstriction, and finally atrial fibrillation, ventricular tachycardia, and premature ventricular beats in alcohol withdrawal was found to be norepinephrine. (Gao et al., 2021). The most common electrolyte imbalances in alcohol withdrawal syndrome are hypokalemia, hypomagnesemia, and hypophosphatemia. This could lead to extended QT intervals and potentially life-threatening arrhythmias such as torsades de pointes. The risk of ischemia is due to the imbalance between the supply and demand of the heart's oxygen supply, in addition to the increase in cardiac activity. This can substantially increase the risk of ischemia occurring, especially if the individual suffers from cardiovascular disease. The withdrawal period is the dangerous period in which the sympathetic surge and electrolyte imbalance have a critical period to be addressed (Lee, 2010).

Extreme alcohol withdrawal may cause DT, which is characterized by the development of symptoms such as increased blood pressure, hyperthermia, and instability in the autonomic nervous system. Moreover, cardiac failure may occur due to circulatory overload, especially in the case of existing alcohol-induced cardiomyopathy. Cardiovascular instability that occurs during the withdrawal period due to the aforementioned problems needs to be managed (Pizon, 2015).

Anti-seizure medications such as benzodiazepines, which act on the hyperactive sympathetic nervous system, are also required for the prevention of seizures as well as the management of the cardiovascular effects of alcohol withdrawal syndrome. The administration of electrolytes is also required for the correction of imbalances that could otherwise lead to arrhythmias. Cardiac monitoring is an essential tool for the management and prevention of alcohol withdrawal symptoms, especially for high-risk patients. The cardiovascular stress that is caused by withdrawal necessitates monitoring as well as management for the avoidance of the life-threatening effects on the heart. Aside from the fact that it is safe, timely medical replacement therapy can minimize the chance of severe alcohol withdrawal symptoms, which can result in morbidity and death (Faulx & Francis, 2008).

Metabolic and Endocrine Alterations

Alcohol has also been found to affect the liver's gluconeogenesis process. Severe hypoglycemia, hypokalemia, hypomagnesemia, and hyponatremia have also been associated with alcohol withdrawal. These conditions can cause severe neurological and cardiac complications. Anxiety and restlessness of an alcoholic patient may increase as a consequence of the increase in cortisol and catecholamine caused by the withdrawal symptoms. To avoid complications such as seizures, heart failure, and dehydration in an alcohol-dependent patient, the symptoms of alcohol withdrawal should be managed properly (Poe et al., 2024).

Gastrointestinal and Hepatic Effects

Moreover, the gastrointestinal tract also undergoes significant changes during alcohol withdrawal, which can lead to nausea, vomiting, and abdominal pain. Excessive production of stomach acid can cause gastrointestinal bleeding, peptic ulcers, and gastritis, especially in individuals with underlying alcohol-related illnesses. As the liver is the main organ for the metabolism of alcohol and is already affected in individuals with underlying alcohol-related illnesses, this shows the body's inability to eliminate alcohol and its byproducts. Moreover, underlying liver disease such as cirrhosis and alcoholic hepatitis can also worsen during alcohol withdrawal.

PPIs and hydration can be used to treat gastrointestinal symptoms, and liver function can also be used to prevent liver problems such as hepatic encephalopathy during alcohol withdrawal (Nojkov & Cappell, 2016).

Sleep Disturbances

Alcohol interferes with the regular sleep pattern by increasing slow wave sleep and reducing rapid eye movement (REM) sleep. When the person stops the intake of alcohol, there is a rebound effect on the person, which may lead to nightmares and sleeplessness. The person cannot sleep and also wakes up during the night. The sleep pattern that lasts for weeks may lead to tiredness and irritability. Cognitive impairment may also result from the sleep pattern. Moreover, the person may be tempted to take alcohol as self-medication; hence, the sleep pattern may lead to relapse (Thivierge, 2023). During the withdrawal phase, melatonin, trazodone, and sleeping habits may be used to improve sleep.

Neuropsychiatric Effects

Mental health status is also affected in a person who is experiencing alcohol withdrawal. Mood changes such as sadness, etc., follow anxiety. When the sedative effects of alcohol are withdrawn, there is an increase in glutamatergic activity, leading to an increase in stress responses as well as emotional instability. Visual as well as audio hallucinations also take place. In addition, suicide behaviors also increase, especially in individuals who have a history of mental health disorders. To manage symptoms as well as for the safe withdrawal process, psychological interventions may be required along with benzodiazepines, antidepressants, antipsychotics, etc. (Wittmann et al., 2019).

Severe Withdrawal-Delirium Tremens (DTs)

In 5 to 10 percent of cases, DT is the most severe expression of alcohol withdrawal syndrome. Severe disorientation, agitation, hallucinations, fever, autonomic instability, and potentially fatal cardiovascular complications are the hallmarks of DT. Alcohol withdrawal syndrome-induced DTs begin 48 to 72 hours after the withdrawal and persist for several days. If not treated, the mortality rate may rise to 37 percent, although prompt medical care greatly minimizes the mortality rate. Tapering alcohol intake in high-risk individuals is one way to prevent DTs (Mulkey & Olson, 2020).

Importance of studying the interaction between Renin Angiotensin Aldosterone System (RAAS) and AWS

The importance of studying the interaction between the RAAS and AWS is multifaceted, encircling physiological, clinical, and therapeutic perspectives and summarized in table 2.

Table 2: multifaceted, encompassing physiological, clinical, and therapeutic perspectives

Category	Key Aspect	Description
Physiological Insights	**Understanding Mechanisms**	Investigating how chronic alcohol consumption affects RAAS can uncover mechanisms underlying AWS, including changes in blood pressure regulation and electrolyte balance (Kerinciani et al., 2024).
	Neuroendocrine Interactions	The interaction between RAAS and the CNS during withdrawal provides light to stress responses and neurochemical imbalances that leads to AWS symptoms (Gupta et al., 2021).
Clinical Implications	**Risk of Hypertension**	Chronic activation of RAAS during AWS may lead to hypertension, making it necessary for healthcare professional to monitor blood pressure in withdrawing patients (Boarder et al., 2017).
	Electrolyte Imbalances	Understanding RAAS's role in electrolyte homeostasis can help clinicians manage potential imbalances (e.g., hypokalemia) that may complicate AWS treatment (Noor & Rahman, 2025).
	Complications Management	Knowing the impact of RAAS on cardiovascular health during AWS can guide intermediations to prevent complications such as cardiac arrhythmias and heart failure (Inceu et al., 2023).
Therapeutic Strategies	**Targeted Treatments**	Knowledge of RAAS's involvement in AWS may inform the use of medications (e.g., ACE inhibitors or angiotensin receptor blockers) to relieve symptoms and stabilize blood pressure (Mubarok et al., 2021).
	Personalized Care	Understanding individual diversity in RAAS activation may lead to more tailored treatment plans for AWS patients, improving outcomes and reduction in relapse rates (Sapna et al., 2023).
	Preventive Measures	Knowledge gained from this interaction can help develop preventive strategies for patients at risk of severe AWS, possibly reducing the incidence of withdrawal-related complications (Steel et al., 2021).

Laboratory Outcomes in AWS

Laboratory investigations play an important role in the diagnosis of AWS. They not simply support clinical diagnosis but also help rule out alternative conditions and characterize complications associated with chronic alcohol use. Table 3 below presents a summary of the key laboratory findings that are commonly observed in patients with AWS.

Table 3. Summary of key laboratory findings commonly observed in AWS.

Laboratory Test	Expected Findings in AWS	Clinical Significance
Blood Alcohol Level (BAL)	May be low or undetectable at the time of withdrawal	Confirms recent alcohol use but is not always elevated in AWS (Pribek et al., 2021).
Electrolytes (Na^+, K^+, Mg^{2+}, PO_4^{3-}, Cl^-)	**Hyponatremia** (due to SIADH or fluid retention) **Hypokalemia** (from renal losses due to aldosterone activation) **Hypomagnesemia** (common in alcoholics, increases seizure risk) **Hypophosphatemia** (often seen in malnourished patients)	Electrolyte imbalances can contribute to seizures, arrhythmias, and muscle weakness (Espay, 2014).
Blood Glucose	Hypoglycemia or hyperglycemia	Hypoglycemia occurs due to liver dysfunction; hyperglycemia may result from stress response (Papachristoforou et al., 2020).
Liver Function Tests (LFTs)	Elevated AST & ALT (AST:ALT ratio >2:1), elevated GGT, elevated bilirubin	Suggests alcoholic liver disease or hepatic dysfunction (Jain et al., 2023).
Complete Blood Count (CBC)	**Leukocytosis** (stress response) **Anemia (macrocytic)** (due to folate or B12 deficiency) **Thrombocytopenia** (from splenic sequestration or bone marrow suppression)	Indicates possible chronic alcohol-related bone marrow suppression or liver dysfunction (Berad & Chand, 2019).
Coagulation Panel (PT, INR, aPTT)	Prolonged PT/INR	Suggests liver dysfunction or vitamin K deficiency (Violi et al., 2021).
Thiamine (Vitamin B1) Level	Low in chronic alcoholics	Deficiency increases risk of Wernicke's encephalopathy (Praharaj et al., 2021).
Renal Function Tests (BUN, Creatinine)	Elevated BUN and creatinine in dehydration or hepatorenal syndrome	Indicates kidney impairment or dehydration from vomiting and poor fluid intake (Kiran et al., 2014).
Arterial Blood Gas (ABG)	Metabolic acidosis (lactic acidosis) or respiratory alkalosis	Lactic acidosis may be due to sepsis, poor tissue perfusion, or alcohol-related metabolic disturbances (Marenco, 2022).
Creatinine Kinase (CK)	Elevated in cases of seizures or rhabdomyolysis	Seizures during AWS may cause muscle breakdown, increasing CK levels (Reason et al., 2017).

Tools to grade the severity of AWS

To manage AWS effectively it is important to determine severity of it and studies suggest numerous tools and surveys to assist healthcare providers to diagnose AUD and formulate next steps and plan to manage patients thus by predicting the severity of AWS. Tools and surveys are supporting medium which is completely dependent on the individual's condition and their willingness to cooperate to assess their neurological and cognitive behaviour.

Studies suggest that Clinical Institute Withdrawal Assessment for Alcohol Revised scale (CIWA-Ar) is the most frequently used scale to grade the symptoms of AWS such as nausea, tremors, anxiety, agitation, hallucinations, and disorientation. This CIWA-Ar provides a direction to healthcare providers whether pharmacological intervention is required or not basis severity of AWS where score is usually above 15. Alcohol Use Disorders Identification Test (AUDIT) and Severity of Alcohol Dependence Questionnaire (SADQ) are the most commonly used tool after CIWA-Ar facilitating healthcare providers identify alcohol dependence and predict AWS severity.

Recent studies elucidate the practical application of these structured assessment tools which can facilitate to improve the clinical outcomes. Study conducted by Maldonado et al. demonstrated that by assessing CIWA-Ar score based on symptom and planning therapy based on the it could significantly reduce the length of stay and benzodiazepines dosage being consumed versus a fixed-dose regimen. Various studies have reported that early implementation of structured & uniform questionnaires in emergency departments increased the early recognition of patients who might develop severe AWS by almost 20%, allowing earlier preparedness for care. However, the reliability of these questionnaires gets affected

when patients are severely intoxicated and cognitively impaired and are unable to cooperate. This gets difficult for one to make a clinical judgement and further use supplementary scale to assess the diagnosis of patients with altered mental status (Maldonado et al., 2014).

Screening tools for AUD

There are numerous questionnaires which are approved to characterize individuals with AUD and are the risk of withdrawal relapse. AUDIT is the most frequently exercised questionnaire to identify excessive drinking behaviours and alcohol dependence. Similarly, the Fast Alcohol Screening Test (FAST) is also employed to quickly identify AUD. Additionally, significant questionnaires include the CAGE test, which consists of four questions regarding the drinking habits of the patient. These include cutting down, annoyed, guilty, and eye-opener due to withdrawal. Likewise, TWEAK test is a noteworthy scale in the identification of alcohol dependence among pregnant females and the conventional population. The TWEAK test includes five questions covering Tolerance, Worried, Eye-opener, Amnesia and K-cut down (Mezzadri, 2024; Paulus et al., 2023).

Prediction of AWS Severity

To establish the probability of severe alcohol withdrawal the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) is the only scientifically recognized and validated tool. PAWSS scale allows clinicians to proactively identify high-risk patients and initiate early interventions to prevent complications.

Assessment Tools for AWS Severity

Once withdrawal symptoms arise these rating scales utilized to manage the treatment decisions through various means and one of the most used and effective rating scales are used known as10-item scale which measures the severity of withdrawal symptoms such as nausea, tremors, anxiety, hallucinations and others via CIWA-Ar scale. It assists in determining whether pharmacological intervention is required or not. AWSc, alternatively, is devised explicitly to assess the severity of alcohol withdrawal symptoms by observing sweating, agitation, mental confusion, and other complications via more structured method of altering medications accordingly. In settings where patients are unconscious and unable to cooperate with alcohol withdrawal scale assessment tools, intensive care units (ICUs) use the RASS scale to assess the level of distress in patients. It helps in managing the delicate balance and preventing complications likely delirium in patients suffering from AWS (Muddapah & Weich, 2023).

Considerations prior to therapeutic intervention in AWS

Before initiating therapeutic intervention for AWS, several key concerns should be acknowledged and focused to manage effective and safe management. The severity of withdrawal symptoms, including the patients' medical past, plus the potential complications should be thoroughly assessed to tailor the treatment approach.

Patient Assessment

A detailed clinical assessment of the patient helps determine the severity of AWS. This entails the history of the patient's alcohol abuse and the time patient had been consuming alcohol and further the patient's withdrawal history is essential to determine whether the patient has comorbid conditions such as liver, cardiovascular or mental health disorders as these conditions affect the withdrawal symptoms and patient treatment management protocol (Korson & Nappe, 2023).

Risk of Severe Withdrawal

Identifying the risk of serious symptoms of withdrawal like a history of DTs, seizures or multiple episodes of alcohol withdrawal in past are important. The PAWSS and other scales like CIWA-Ar maybe beneficial in assessing the complications that may arise. High-risk patients may require more intensive monitoring and pharmacologic management (Davis et al., 2018).

Electrolyte and Nutritional Imbalances

Chronic alcohol use can lead to electrolyte imbalances and nutritional deficiencies, especially thiamine, magnesium, and potassium. These deficiencies need to be treated before withdrawal management is initiated. Thiamine supplementation is critical because of the risk of Wernicke-Korsakoff syndrome, a severe neurological complication (Baj et al., 2020).

Coexisting Conditions

Patients with underlying medical conditions such as cardiovascular disease, psychiatric illness, and liver disease require a patient-centered treatment plan. For instance, cirrhotic patients may require altered doses of drugs due to altered metabolism. Furthermore, psychiatric illnesses such as anxiety, depression, and psychosis should also be taken into consideration during the selection of drugs for symptom control (Soto-Angona et al., 2020).

Setting and Monitoring

The clinical setting may be either an outpatient or an inpatient setting, which may influence the course of action taken by the caretaker. For instance, inpatient care is recommended for individuals who experience moderate or severe withdrawal

symptoms, as well as for those who experience medical comorbidities. The vital signs, hydration, and electrolytes need to be closely monitored during the initial stages of withdrawal.
By taking into consideration the aforementioned factors, the caretaker can regulate the therapeutic interventions, thus minimizing the complications that may arise, for the patient undergoing alcohol withdrawal (Weinstein et al., 2018).

RAAS and their components
RAAS, which is a hormonal system that mainly regulates angiotensin II. Angiotensin 2 is formed by the proteolytic cleavage of angiotensinogen, which further accelerates aldosterone synthesis. Consequently, these two hormones, angiotensin II and aldosterone, are the final endpoints of the hormonal system. Literature review indicates that knowledge obtained from past decades and the newness of the RAAS system in today's world. However, it appears realistic to propose that the major role of RAAS is to regulate arterial blood pressure (Triebel & Castrop, 2024).
Cardiac output is determined by the arterial blood pressure and total vascular resistance. Arterial blood pressure is the measure of the blood volume, which corresponds to the extracellular volume. It is maintained through the intake of appropriate amounts of salt and water and the simultaneous excretion of the salt and water to maintain homoeostasis of the extracellular volume, in which the kidneys are responsible for the elimination of excess amounts of salt and water. Angiotensin 2 stimulates the urge to consume excess amounts of salt and water through the stimulation of the thirst and salt appetite receptors, which results in behavioral changes such as drinking and salt appetite, despite the adequate intake of salt and water. It is difficult to manage in the long term. It may be noted that the simultaneous excretion of salt and water through the direct and indirect effects of angiotensin II results in the body losing salt and water. In the direct impact, changes in the glomerular filtration rate and regulation of salt reabsorption by the renal tubules are perceived, and in the indirect impact, it causes aldosterone production, which unswervingly regulates renal sodium ion preservation. Aldosterone-mediated sodium ion preservation is related to renal potassium ion loss. As such, body sodium and potassium ion homeostasis are related, and it limits the controlling scale of each of the individual processes involved (Pawlonka et al., 2024).
Now we will focus on the second factor that contributes to the management of arterial blood pressure, i.e., vascular resistance via the action of angiotensin II receptors, which is one of the most potent vasoconstrictors in the body that actually maintains blood pressure. The vascular effects of Angiotensin 2 are known and well established. However, the effects of aldosterone on the vasculature should also be reflected. RAAS, as a homeostatic system, misleadingly yet in a simple way, has been recognized as a crucial determining factor in the management of arterial blood pressure along with electrolyte and fluid balance, Figure 2 (Nehme & Zibara, 2017).
Both angiotensin 1-9 and angiotensin 1-7 are significant peptides generated by the action of the enzyme ACE2 and have an important physiological role to play, particularly against the classical action of the RAAS pathway mediated by the action of angiotensin II. Angiotensin 1-7, via the Mas1 receptor, produces vasodilator, anti-inflammatory, anti-fibrotic, and cardioprotective effects against the vasoconstrictive and inflammatory action of the classical RAAS via the action of the AT1 receptor. Angiotensin 1-9 has also been proposed to possess cardioprotective and anti-hypertrophic effects; however, this action is not so well established as the action of angiotensin 1-7.

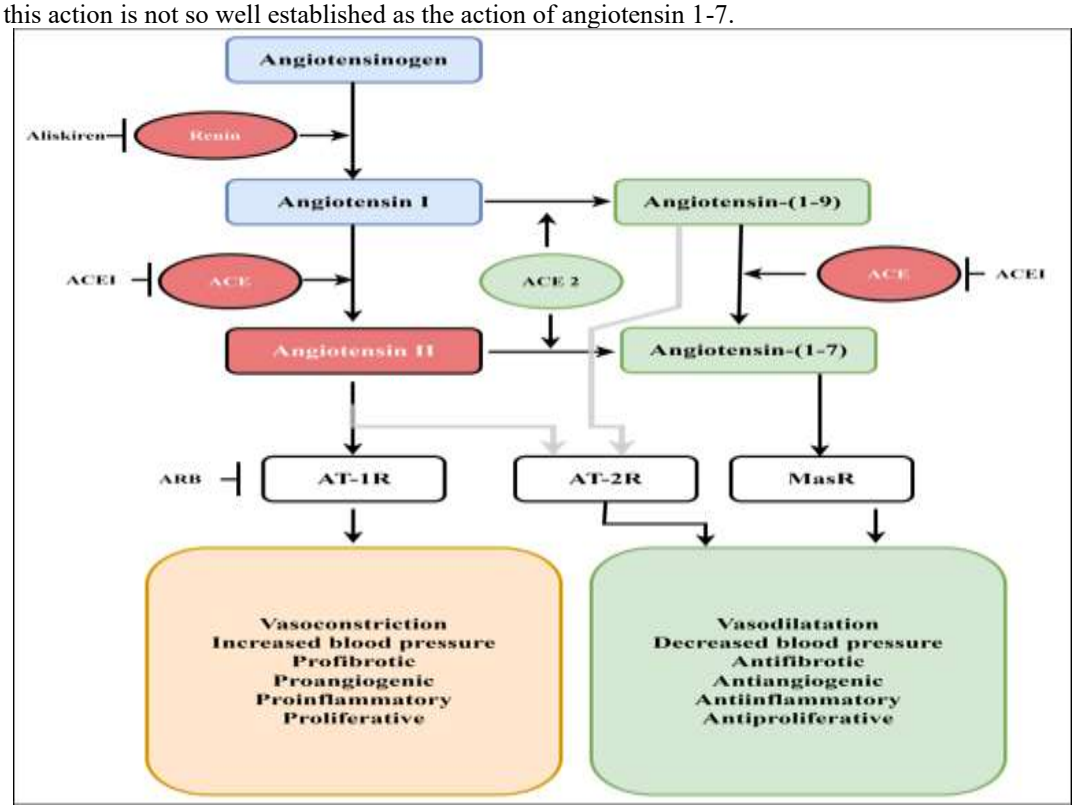

Figure 2. Graphic presentation of RAAS – renin–angiotensin–aldosterone system and its plausible impacts mediated by angiotensin receptors. ACE- angiotensin-converting enzyme, ACE2 – angiotensin-converting enzyme type 2, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin II receptor blocker, AT-1R – angiotensin receptor type 1, AT-2R angiotensin receptor type 2, Mas1R- G-protein-coupled receptor Mas.

RAAS and its interaction with the nervous system

The RAAS interacts considerably with the nervous system, particularly in regulation blood pressure and maintain fluid balance. This interaction primarily involves the sympathetic nervous system (SNS) and has consequences for numerous physiological and pathophysiological processes. The interaction between RAAS and the nervous system are discussed below.

Sympathetic Nervous System Activation

One of the components of RAAS, Angiotensin II (Angiotensin II), is known to increase sympathetic nerve activity. It binds to specific receptors in the brain, particularly in regions such as the rostral ventrolateral medulla and the hypothalamic paraventricular nucleus, which are involved in sympathetic regulation. This increases norepinephrine release and subsequently causes vasoconstriction and increased blood pressure (Shanks & Ramchandra, 2021).

Neuroplastic Changes

This can lead to neuroplastic changes in the central neural networks and to factors like hypertension. For example, early life stress can sensitize these neural networks to lead to an exaggerated sympathetic response in adulthood. This can be attributed to changes in brain regions that control blood pressure (Xue et al., 2020).

Humoral-Neural Coupling

There is a humoral-neural link connecting the system RAAS and CNS. The renin-angiotensin system of the brain communicates with the rest of the system in order for blood pressure and fluid volume status to be controlled adequately. This is crucial for maintaining homeostasis in various physiological states (Tsuda, 2012).

Inflammation and Sympathetic Overactivity

This interaction between the RAAS and the inflammatory pathways may result in an increase of sympathetic activity, thus heightening hypertension. The RAAS may work synergistically with the inflammatory pathways, thus inventing a feedback loop that results in hypertension (Saxena, 1992).

Parasympathetic Modulation

Although Angiotensin II is considered to be related to sympathetic activity, it is also known to have an impact on parasympathetic activity through the mechanism involving angiotensin type 1 receptors (AT1R). This is another example of the complex nature of the interaction between the RAAS and the two branches of the nervous system (Takahashi et al., 2011).

The interaction between the nervous system and the RAAS is vital in the comprehension of acclimatization to hypertension or heart failure and, in some cases, other cardiovascular diseases. Management strategies involving the mechanisms of the RAAS, such as ACE inhibitors and receptor blockers, may help in the moderation of excessive sympathetic activity and may be helpful in the prognosis of such conditions in humans. This interaction not only promotes the management of existing conditions but also provides insights into the prevention of cardiovascular diseases (Balakumar & Jagadeesh, 2015).

Pathophysiology of Alcohol Withdrawal

Mechanisms of Alcohol Dependence

Studies highlight that alcoholism leads to neurochemical changes within the brain, mainly modulating neurotransmitters such as glutamate and GABA. These chemical changes and mechanistic pathways are described below

GABA and Glutamate Neurotransmitter Imbalance

GABA

GABA is the major inhibitory neurotransmitter in the brain and alcohol acts as an excitatory catalyst in the case of GABA leading to intensified inhibitory responses in the firing of the neurons. Hence, after drinking people usually feel calm and relaxed. Studies describe that GABA-A receptors are less sensitive to GABA in people with long term history of consuming alcohol. Here, individual who regularly consumes alcohol becomes less responsive to normal GABA activity when compared to a person who does not regularly drink alcohol or stops drinking abruptly and this leads to excitatory neurotransmission, that is why these individuals' experiences withdrawal symptoms like anxiety and convulsions. Even reduced GABA activity fails to suppress excessive brain excitation, leading to hyperexcitability and seizures (Olsen & Liang, 2017).

Glutamate

Glutamate is a key excitatory neurotransmitter that plays role in learning and memory. Alcohol acts on NMDA receptor in the brain and disrupts its mechanism, NMDA gets suppressed and results in declined brain normal excitatory activity due to intoxication. When alcohol is consumed over prolonged periods, NMDA becomes more active to compensate for GABA inactivity, eventually increasing sensitivity in the brain and this stimulation further leads to increased risk of seizures during alcohol withdrawal. Brain tries to recover from overload compensates again to withdrawal symptoms like agitation and seizure and this phenomenon arises as NMDA receptors become overactive during alcohol withdrawal, and brain strives to restore equilibrium after extensive alcohol exposure exposure (Domi et al., 2021). Evidence suggests that the RAAS is not limited to cardiovascular regulation but also interacts with primary neurotransmitter systems involved in AWS. Hence, RAAS-based therapies have started gaining importance in the experimental studies, where angiotensin II has been recognized as one of the central components of RAAS, which can modulate both GABAergic and glutamatergic signalling pathways in the brainstem and the limbic regions. More explicitly, angiotensin II has been shown to have an influence on NMDA receptor-mediated glutamate transmission and further regulate the release of GABA and moderate the expression of GABA A and GABA B receptors in regions such as the nucleus tractus solitarius, central amygdala, and specific hypothalamic nuclei, and are mainly mediated through stimulation of the AT1 receptor. Further, NMDA receptor hyperactivity is due to alcohol withdrawal while weakening the release of GABAergic inhibition and neuroadaptive changes vary corresponding to brain region and receptor subtype, together they shift neural signaling toward excitation. In this situation, angiotensin II may further disrupt the balance within the inhibitory and excitatory pathways, thus increasing neuronal excitability and contributing to autonomic instability during alcohol withdrawal (Singh et al., 2021).

Neurochemical changes due to chronic alcohol use

Dopaminergic System

The mesolimbic dopaminergic pathway mediates reward and reinforcement process and chronic alcohol use increases dopamine signaling, contributing to its agreeable effects. During withdrawal these dopamine levels drops thus advancing cravings and alcohol relapse (Engel & Jerlhag, 2014).

Stress Response

Prolonged alcohol consumption disturbs HPA axis and modifying stress hormone regulation. These transformations aggravate withdrawal severity and intensify relapse risk, as alcohol may be used as coping mechanism to manage stress (Rachdaoui & Sarkar, 2017).

Neuroadaptation

Long-term alcohol consumption triggers neuroadaptations that make individuals more tolerant to alcohol. These neuroadaptations are triggered by withdrawal symptoms and further by compulsive alcohol intake, which further fortifies dependence. Chronic alcohol abuse leads to neurochemical alterations in the brain, particularly affecting excitatory and inhibitory neurotransmitters. Specifically, glutamate and GABA become altered due to prolonged exposure to alcohol. Therefore, for professionals to effectively create and implement management strategies to manage alcohol dependence and AWS, it is essential to understand the underlying mechanisms of alcohol dependence (Yang et al., 2022).

Alcohol and RAAS Dysregulation

Excessive alcohol consumption potential leads to dysregulation of RAAS, thereby resulting in neurological imbalance indicating increased hypertension and synthesis of a potent vasoconstrictor, i.e., angiotensin II which results in narrowing of blood vessels thus causing body to retain fluids and RAAS overactivation is observed.

Alcohol and RAAS Dysregulation Key Insights

RAAS regulates blood pressure and circulatory volume which is clinically affected by alcohol consumption and even withdrawal. Studies suggest that renin, which is an enzyme that triggers RAAS system and is directly stimulated by alcohol consumption. RAAS is mediated via numerous mechanisms that result in the progression of hypertension and eventually vascular damage. This alcohol mediated RAAS stimulates NADPH to NADPH oxidase and overproduction of ROS is observed in contrast to decrease baroreflex sensitivity and stimulates renin release through the overproduction of catecholamines. Alcohol-induced liver damage can alter the metabolism of RAAS peptides and amplify the production of systemic angiotensinogen at the humoral level, thus alter the set point of the system. In addition, alcohol affects salt handling mechanism in the kidney, which further encourages the secretion of renin. Alcohol additionally exerts pro-inflammatory effects by amplifying the production of TNF-α and IL-6. These inflammatory mediators promote the production of Angiotensin II in the kidney as well as brain via activation of the tissue RAAS system. Increases in renin, Angiotensin II and aldosterone during chronic heavy drinking and early withdrawal can consequently be illuminated physiologically by these effects on the peripheral and intrarenal systems (Saravi et al., 2021). The RAAS associated with central neuroendocrine system in the brain exhibits bidirectional interactions. Angiotensin II receptors in the brainstem and hypothalamic nuclei, regulate sympathetic tone and release CRF/ACTH. Consecutively, catecholamines and CRF also influence the systemic RAAS. This interaction enhances autonomic hyperactivity and activation of the stress axis, both characteristic features of AWS, within RAAS activation. Angiotensinogen is converted into angiotensin I by renin and further to angiotensin II using Angiotensin Converting Enzyme (ACE). Angiotensin II, which is a potent

vasoconstrictor, narrows blood vessels and increases blood pressure. It stimulates adrenal glands to release aldosterone, promoting sodium and water retention and potassium excretion out of the body. The resulting increase in blood volume contributes to elevated blood pressure (Poulsen & Fenton, 2019).
Alcohol addiction led to high blood pressure due to long-term consequence of the RAAS system further triggering vascular constriction and fluid retention. In addition, the baroreceptor reflex, which plays a critical role in the regulation of blood pressure, can be impaired in alcohol abusers. Decreased sensitivity to blood pressure fluctuations as a consequence of baroreceptor reflex impairment can cause blood pressure instability.
Other than the activation of the RAAS, alcohol also influences other mechanisms in the control of blood pressure. These include the sympathetic nervous system and the production of nitric oxide to aid in vasodilation. It is clear that the impact of alcohol consumption makes it a significant risk factor in the complications associated with hypertension (Kućmierz et al., 2021).

Potential Consequences of RAAS Dysregulation due to Alcohol
This has a significant impact on the RAAS system and can lead to cardiovascular diseases to a great extent. The continuous increase in the level of angiotensin II and aldosterone due to the activation of the RAAS system by the continuous use of alcohol can lead to high blood pressure, also known as hypertension. Hypertension is a cardiovascular risk factor that can lead to cardiovascular complications such as heart disease, stroke, and so on. Hypertension can cause the heart to beat harder, leading to hypertrophy of the heart. As a result, the heart becomes weak and can lead to heart failure. Apart from this, the continuous use of alcohol can lead to arrhythmia, which can cause atrial fibrillation and lead to stroke, as mentioned in the literature by (Ray et al. 2023).
Aside from the cardiovascular effects, alcohol abuse can cause severe damage to the liver, which will further exacerbate the imbalance of the RAAS system. The liver has a very important role to play in the regulation of blood pressure, as it produces the precursor of angiotensin I, which is the precursor of the RAAS system, namely, the production of angiotensinogen. Severe damage to the liver, as a result of alcohol abuse, can cause liver fibrosis, liver cirrhosis, and dysfunction, which can affect the regulation of the RAAS system, causing water retention, ascites, hypertension, and portal hypertension. Damage to the liver, as a result of liver cirrhosis, can cause hepatorenal syndrome, which can impair the functioning of the kidney. In conclusion, the disruption of the RAAS system, as a result of the intake of alcohol, has set a vicious cycle of health complications, which can cause cardiovascular complications, highlighting the importance of alcohol intake to the cardiovascular health of an individual (Jagdish et al., 2023).

Effects On Blood Pressure
The impact of alcohol on blood pressure is significant and wide-ranging, and the main reason for this is the activation of the renin-angiotensin-aldosterone system, as well as the sympathetic nervous system.

Increased Vascular Resistance due to Angiotensin II
It has also been established that the use of alcohol over a long period result in an increase in the level of angiotensin II, which is a vasoconstrictor and results in an increase in the level of systemic vascular resistance. Vasoconstriction resulting from the use of angiotensin II occurs due to the activation of the AT1 receptor, resulting in the narrowing of the blood vessels and thus the level of blood pressure. The increase in the level of angiotensin II resulting from the use of alcohol thus results in hypertension. Research has shown that the use of large quantities of alcohol results in an increase in the level of blood pressure, which decreases upon withdrawal and thus relates to the level of systemic vascular resistance (Su et al., 2021).

Fluid Retention Leading to Hypertension
Alcohol also increases the level of aldosterone, which is responsible for increasing the retention of sodium and water in the kidneys. This leads to an increase in blood volume and hypertension. The retention of sodium and water also affects the level of other ions such as potassium. The effects of sodium and water retention on blood pressure are also considerable. The increase in aldosterone level during chronic use of alcohol leads to an increase in blood pressure as a result of sodium and water retention in the body (Urso et al., 2015).

Interaction with the Sympathetic Nervous System
This would increase the effect of hypertension through the role of angiotensin II. Alcohol has an effect on the secretion of stress hormones, which include cortisol and catecholamines. An increase in the level of cortisol would lead to the retention of fluids, hence increasing the effect of hypertension. Long-term use of alcohol would affect the sensitivity of baroreceptors, which would have an effect on blood pressure regulation. If the baroreceptors do not respond to changes in blood pressure, it would result in hypertension (Bigalke et al., 2024).

Electrolyte Imbalances

Sodium Retention and Hypernatremia
Alcohol may act as a diuretic, which increases the amount of urine produced through the suppression of the simulation of antidiuretic hormone (ADH). Nevertheless, prolonged intake of alcohol results in the elevation of ADH levels, which

increases the retention of fluid and sodium in the kidneys. This may lead to the elevation of sodium levels, particularly when the amount of consumed fluids is low, leading to a state of hypernatremia. This state may lead to confusion, muscle twitching, and seizures through the disruption of osmotic balance in the body. Some research indicates that people suffering from alcohol dependence may experience hyponatremia, which is a state of low sodium levels, through the influences of beer potomania and excessive intake of water (Adewale & Ifudu, 2014).

Potassium Elimination Leading to Hypokalemia

Chronic use of alcohol is also associated with an increase in potassium loss as a result of an increase in aldosterone. Aldosterone promotes sodium retention but also potassium overload in the kidneys. Hypokalemia is a common occurrence among people who are dependent on alcohol. This condition affects about 67% of people who are dependent on alcohol. Hypokalemia can cause weak muscles, muscle cramps, heart arrhythmias, thus affecting cardiovascular health (Moses Elisaf & Rigas Kalaitzidis, 2015).

Consequences for Cardiac Function and Overall Health

This electrolyte imbalance, such as the presence of low potassium levels, which is known as hypokalemia, and high levels of sodium, which is known as hypernatremia, has the ability to affect the heart in a negative manner. This can result in the ability to alter the heart rhythms, which can be life-threatening. Other health complications that can arise as a result of electrolyte imbalance, apart from heart complications, include muscle dysfunction, neurological complications such as confusion, as well as kidney dysfunction. The use of alcohol, therefore, has the ability to exacerbate health complications such as hypertension, which can result from the presence of excessive fluids as well as increased vascular resistance as a result of the RAAS system. The use of the methodology, therefore, to determine the electrolyte levels of an individual with a history of alcohol dependence is crucial in the prevention of complications that arise as a result of withdrawal as well as the use of alcohol (Morelock, 2015).

Stress Response Modulation

The interaction involving RAAS and hypothalamic-pituitary-adrenal (HPA) axis performs a substantial role in the stress management response and predominantly in the context of AWS.

RAAS Involvement in the HPA Axis

Chronic alcohol drinking elicits HPA axis and impels unwarranted release of corticotropin-releasing factor (CRF) from hypothalamus. CRF excites the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which triggers adrenal glands to release cortisol. The RAAS system acts together with the HPA axis as angiotensin II potentially influence this pathway and unequivocally worsen withdrawal outcomes. Both prolonged alcohol use and withdrawal can disturb HPA axis regulation, stemming in abnormal CRF and cortisol release. This dysregulation impairs stress response and intensifies withdrawal symptoms thus complicating the recovery process (Quadros et al., 2016).

Effects of Stress Hormones on AWS Symptoms

Withdrawal symptoms observed such as anxiety, irritability, and dysphoria can be worsened by elevated stress hormones due to cortisol. Individuals with alcohol dependence often face increased level of stress, which has ability to trigger cravings and increase the potential risk of alcohol relapse. Further, activation of HPA axis in the stressful environment can also trigger physiological changes which are not limited to elevated blood pressure and heart rate. These triggers may further intensify AWS and additional stress potentially worsening the severity of withdrawal symptoms (Al-Owaimer et al., 2024).

Role in Relapse Vulnerability and Emotional Dysregulation

Stress is a well-known factor influencing cravings for alcohol leading to dependency and relapse. Compulsive alcohol-seeking behavior in individuals often represents a form of self-medication contemplating increased sensitivity to stress. Elevated levels of CRF are further associated with stress stimulating alcohol cravings, thus emphasizing on the vulnerability of alcohol-dependent individuals. Chronic alcohol drinking impacts one's brain emotional centers, leading to extended negative feelings facilitated by HPA axis dysregulation, which promote relapse risk under psychological as well as environmental stress. Understanding the interplay between the RAAS system, HPA axis, and stress response is therefore important when developing treatments and management for AWS, as targeting these interactions may reduce relapse rates from both functional and psychological perspectives (Al-Owaimer et al., 2024).

Clinical Implications

Importance of Monitoring RAAS Activity in AWS Treatment

RAAS activity is essential to monitor patients undergoing treatment for AWS, as it contributes to tracking blood pressure and fluid balance. Even elevated angiotensin II levels can increase blood pressure and alter vascular resistance and thus making management of withdrawal symptoms more complicated. RAAS activity also directly influences electrolyte levels, comprising sodium and potassium making it important to monitor these parameters to prevent further complications such as hypokalemia and hypernatremia, which may arise from long-term alcohol abuse (Senatore et al., 2021).

Pharmacological Interventions Targeting RAAS

ACE inhibitors may possibly help manage hypertension by inhibiting conversion of angiotensin I to angiotensin II therefore lowering the blood pressure and lessening the withdrawal symptoms associated with unwarranted sympathetic activity. Furthermore, consuming spironolactone antagonizes aldosterone simultaneously promotes sodium excretion and potassium retention thus making it practical for maintaining fluid and electrolyte balance during AWS management. In relation to AWS, it might be of use in the treatment of persons who are suffering from severe cases of fluid overload. Benzodiazepines are used by healthcare professionals as first choice in managing the alcohol withdrawal symptoms, despite being used as indirect inhibitors of the RAAS. This is because they can be used in combination with drugs from the RAAS system in order to offer all-encompassing treatment and help stabilize the neurochemical imbalances that are characteristic of alcohol withdrawal (Bergen, 2022).

Nutritional Support and Managing Electrolyte Imbalances

Abnormalities in electrolytes are a common occurrence in patients suffering from AWS and are related to fluid retention as well as renal impairment. Thus, in the process of providing nutritional assistance to such patients, the body is supplied with the essential electrolytes that it requires, such as salt, potassium, magnesium, and phosphorus. Due to the high probability of thiamine deficiency among alcohol-dependent persons, the supplementation of the same will be required to prevent Wernicke's encephalopathy, which should be administered as part of the nutritional support to a patient with AWS as a form of treatment. Nutritional support to a patient with AWS, therefore, entails the provision of a well-balanced diet to improve the health of the patient, thereby promoting the rate of recovery during the treatment of AWS, which entails the addressing of the calorie requirements of the patient as well as the hydration of the patient to improve the functioning of the kidneys (McNaull & Suchar, 2020).

Practical monitoring and safety considering RAAS inhibitors in AWS:

- Patients with AWS have complex medical conditions (dehydration, altered levels of electrolytes, liver disease, altered mental status), and the use of RAAS inhibitors must be monitored with structured assessment and monitoring, especially when using these drugs outside of their labeled indications or using them in a trial fashion. Some practical suggestions that have been proposed include the following:
- Baseline assessment: Creatinine levels, eGFR, levels of electrolytes, vital signs, orthostatic vital signs, and drug reconciliation of potassium-sparing medications
- Evaluation of laboratory results: Creatinine levels and levels of potassium must be assessed 3-7 days after the initiation of ACE inhibitors or ARBs; however, this must be done sooner (within 24-48 hours) if there is evidence of volume depletion, vomiting, or hypotension
- Evaluation of vital signs: Patients with moderate to severe AWS must be monitored continuously with vitals.
- For the hydration strategy, it is essential to correct hypovolemia before starting RAAS inhibitors to minimize the occurrence of AKI and symptomatic hypotension.
- Avoid or stop criteria for individuals with existing severe hyperkalemia if $K+$ is ≥ 5.5 mmol/L, increasing creatinine levels, severe hypotension, or inability to monitor labs.
- Team approach for co-management with nephrology and cardiology for individuals with CKD, advanced heart disease, or electrolyte disorders (Leon & Tangri, 2022)

Electrolyte considerations when targeting RAAS in AWS:

- RAAS system plays an important role in the occurrence of hypokalemia among chronic alcohol users, but the initiation of RAAS inhibitors may lead to the occurrence of hyperkalemia due to the suppression of the RAAS system, which inhibits the excretion of $K+$ from the body. Hence, the following strategies must be taken into account to address the problem of RAAS system-induced hypokalemia or the risk of developing hyperkalemia upon the initiation of RAAS inhibitors:
- If hypokalemia is the major problem ($K+$ levels less than 3.5 mmol/L), the deficit of $K+$ and $Mg2+$ must be addressed before the initiation of RAAS inhibitors. Replacement of $Mg2+$ is also indicated, especially if the levels of $Mg2+$ are low, which interferes with the replacement of $K+$ levels. Mineralocorticosteroid antagonists must be used with caution only after normalization of $K+$ levels.
- If the levels of $K+$ are ≥ 4.5 or if there is renal impairment, the routine initiation of RAAS inhibitors must be avoided in the acute alcohol withdrawal phase, unless there is a compelling reason to initiate the drug and the patient must be monitored closely. RAAS
- Sodium imbalance in chronic alcohol-related hyponatremia or hypernatremia should be corrected prior to adjustments in RAAS therapy. Inhibitors of RAAS have little effect on serum levels but affect volume status.
- Strategies for minimizing new complications include staged therapy, early monitoring of electrolytes, avoiding combination therapy with potassium-sparing drugs, and consultation with a nephrologist if eGFR is less than 60 mL/min/1.73 m^2.

Difference Between Novel and Traditional AWS Treatment

The treatment of AWS has advanced over the years, with existing established methods primarily relying on benzodiazepines, while novel approaches are developing and providing alternative opinions. A comparison of traditional and novel treatments for AWS are summarized in table **4.**

Table 4. Comparison of Traditional and Novel Treatments for AWS.

Aspect	Traditional Treatment	Novel Treatment
Primary Agents	Benzodiazepines (e.g., diazepam, lorazepam)	Gabapentin, Carbamazepine, Valproic Acid (Fluyau et al., 2018)
Mechanism of Action	Enhances GABA activity	Modulates GABA activity; affects other neurotransmitters (Nava-Mesa et al., 2014)
Administration	Inpatient/outpatient; fixed/symptom-triggered	Outpatient-friendly options available (Sriram et al., 2012)
Nutritional Support	Thiamine and electrolyte management	Similar nutritional considerations apply (Nava-Mesa et al., 2014)
Risk of Dependence	Potential for benzodiazepine dependence	Lower risk with some novel agents (Edinoff et al., 2021)
Efficacy	Effective but may not fully address all symptoms	Emerging evidence suggests benefits beyond traditional methods (Stein et al., 2022)

Alternative Approaches to Benzodiazepines in AWS

In the treatment of AWS, non-benzodiazepines (non-BZD) medications like antipsychotics, anticonvulsants, anesthetics, alpha-2 agonists, and others such as clomethiazole, gamma-hydroxybutyric acid (GHB), sodium oxybate, and baclofen can be used. Each drug has its own benefits and risks depending upon the symptoms and health condition.

Antipsychotics

While antipsychotics such as butyrophenones and phenothiazines may be effective in the management of severe agitation, hallucinations, and delirium in the monitoring of AWS, their use is limited due to the increased risk of lowering the seizure threshold and prolonging the QT interval, which may increase the risk of cardiac arrhythmias. However, their use is cautious and reserved in situations where the use of BZDs does not alleviate the symptoms. It is crucial to continuously monitor vital signs in patients on these drugs (Jesse & Ludolph, 2019).

Anticonvulsants

Agents such as valproate, carbamazepine, and levetiracetam are commonly employed for the management of AWS, especially for the prevention and management of seizures. However, the Cochrane review has not found any significant difference between anticonvulsants and BZDs for the management of AWS, reserving them for the management of individuals with seizures (Rojo-Mira et al., 2022).

Alpha-2 Agonists

Drugs like clonidine work as adjunctive treatments in order to manage the autonomic dysregulation. These drugs lack GABAergic activity like the BZDs but help in reducing the symptoms like hypertension and manages the heart rate, which in turn allows the dosage of the BZD to be reduced (Gold et al., 2024).

Anesthetics

Other anesthetic medications like propofol and barbiturates, which have the effect of potentiating the GABA system, may be used synergistically with BZDs to treat severe AWS but have significant side effects, which include respiratory depression, coma, and the need to put the patient on a ventilator under intensive care facilities. Moreover, the symptoms may recur when the medications are stopped (Jesse et al., 2017).

Clomethiazole, GHB, and Sodium Oxybate

However, the efficacy of clomethiazole has been established in the treatment of AWS. However, there are limitations to the use of this drug, such as the first-pass effect in the liver, which is inhibited by ethanol. The drug can be dangerous if

used with alcohol and has the potential to cause addiction. GHB and sodium oxybate are also GABA-mimic compounds used to treat AWS. However, the euphoric action of these drugs poses the risk of addiction and can be used for short-term treatment only (Elsing et al., 2009).

Baclofen
Baclofen has also been reported to aid in reducing withdrawal symptoms and cravings through GABA potentiation. However, due to insufficient data, it is not highly recommended for AWS treatment (Finnell & McMicken, 2010).

Adjunctive Agents
Magnesium and thiamine supplements are also vital in the management of AWS. Magnesium is very crucial in the regulation of the release of neurotransmitters and the functioning of enzymes. It is also vital in the management of AWS, especially because its deficiency may lead to the worsening of symptoms like arrhythmias. Thiamine supplements should also be used to prevent the occurrence of Wernicke's encephalopathy, which may mimic AWS symptoms. Wernicke's disease has a very high mortality and morbidity; hence, thiamine supplements should be used to treat all AWS cases, especially those who are malnourished or have a history of chronic alcohol intake.
Even though BZDs remain the mainstay of AWS management, other drugs like anticonvulsants, antipsychotics, and adjunctive treatments like magnesium and thiamine have also been used to manage AWS, especially in cases where BZDs have failed or where there is a contraindication to BZD use (Dixit et al., 2016).

Future research direction:
There are quite a few research directions for the future to investigate the role of RAAS in the management and understanding of AWS. An important area to research would be the investigation of RAAS inhibitors in the management of AWS. Considering the significant role RAAS plays in the management and regulation of blood pressure and electrolyte balance with fluid balance during AWS, RAAS inhibitors could provide an important clue to manage hypertension and autonomic imbalance during AWS. RAAS inhibitors could potentially provide an effective tool to manage AWS with the help of RAAS modulation and could also provide an alternative to the use of benzodiazepines in the management of AWS in patients who are at risk of developing dependency and adverse effects with the use of benzodiazepines (Bansal et al., 2025).
Another area of focus in the future would be the identification of the genetic components of the RAAS's such as renin, angiotensinogen, and aldosterone receptors, would help identify the individual components of the difference in the progression of AWS which would further help in the development of targeted interventions to help the patient.
Finally, the long-term effect of RAAS modulation on the prevention of relapse must be studied. Though RAAS inhibitors may be beneficial in the management of the symptoms of acute alcohol withdrawal, their role in the prevention of relapse and the maintenance of recovery from alcohol dependence is not fully understood. Studies on the long-term effect of RAAS modulation on brain chemistry, stress response, and addictive behaviors may lead to the discovery of ways to prevent the relapse of alcohol-dependent persons into alcohol use disorders. These mechanisms would be very useful in the discovery of more targeted and effective therapeutic approaches to the management of alcohol use disorders and AWS (Hopper et al., 2014).

Conclusion
RAAS has a crucial role to play in the pathophysiology of AWS, as it influences blood pressure and electrolyte balance by regulating fluids in the bloodstream. Research has shown that the effect of alcohol-induced RAAS dysregulation has the potential to cause hypertension, electrolyte disturbances, and autonomic dysfunction, which worsens the symptoms of AWS. Prolonged use of alcohol has the effect of maintaining abnormal RAAS, which has the potential to cause cardiovascular complications, thus complicating the treatment of AWS. The significance of the research lies in the fact that RAAS has the potential to improve the treatment of AWS. This assumption is based on the fact that RAAS inhibitors or other medications might reduce the severity of AWS symptoms, especially when the use of benzodiazepines is ineffective or when the use of the drug is a potential side effect. Additionally, the control of RAAS dysregulation would improve the management of associated disorders such as hypertension and electrolyte disorders, which would improve the result of the patient. The role of RAAS in the management of AWS has to be further investigated. The development of RAAS inhibitors as an adjunctive treatment, the assessment of the genetic components of the activity of the RAAS in relation to alcohol dependence, and the long-term effects on the prevention of relapse in alcohol dependence are areas that need further study. This would result in more targeted treatment strategies that would help the outcome of not only AWS patients but also the general population.

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