Emergencies in AUD: acute alcohol intoxication and alcohol withdrawal syndrome

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ABSTRACT

Excessive alcohol consumption is linked to several consequences involving health, social, working, relational and economic fields.

Acute alcohol Intoxication is the direct consequence of high alcohol consumption, particularly if consumed in a short time-frame. Traumas (e.g., road accidents, pedestrian injuries, head injuries, falls, crashes), violence (e.g., domestic) and suicide attempts represent the direct consequences. The number of admissions to emergency departments for acute alcohol intoxication is constantly rising.

Alcohol Withdrawal Syndrome is a potentially life-threatening clinical syndrome occurring when individuals with severe alcohol use disorder (AUD) abruptly cease or significantly reduce alcohol consumption.

Despite individual's decision to stop drinking, AWS can develop as a consequence of medical treatments that accelerate ethanol's metabolism and elimination from plasma.

Both acute alcohol intoxication (AAI) and alcohol withdrawal syndrome (AWS) represent two pivotal and interconnected issues resulting from alcohol abuse.

The present review will highlight the primary manifestations of alcohol-related harm, focusing on the acute consequences of alcohol consumption, namely acute alcohol intoxication, and the subsequent challenges presented by alcohol withdrawal syndrome. These two facets underscore the complex and multifaceted nature of alcohol misuse.

INTRODUCTION

Alcohol – *ethanol* – has been widely consumed in our society since the sawn of time. Estimates indicate that the majority of people will consume alcohol during their lives and about a third of them could develop alcohol-related disorders[1,2]. Excessive alcohol consumption has been linked to several consequences involving health, social, working, relational and economic fields[3].

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Alcohol abuse has been recently ranked as the ninth cause of disability-adjusted life years (DALYs), with a significant increase (37%) from 1990 to 2019[4]. In this connection, alcohol misuse and alcohol use disorder (AUD) show an increasing prevalence across all ages, particularly among young people[3]. As a consequence, the hardest hit of alcohol abuse is on subjects aged 25-49 years, being the first preventable cause of disease in this age population[4].

Harmful alcohol consumption spans a wide spectrum across populations and exerts a significant impact on healthcare systems, with increasing medical and social costs[5]. This has been the object of an action plan by the World Health Organization in order to revert this trend[6]. Unfortunately, the burden of alcohol abuse has been amplified by the recent COVID-19 pandemic, that has imposed lockdowns, social isolation, job losses and smart-working, with a consequent increase in alcohol consumption and domestic violence[7,8].

Acute alcohol intoxication (AAI) is the direct consequence of high alcohol consumption, particularly if consumed in a short time-frame. This condition has been associated with traumas (e.g., road accidents, pedestrian injuries, head injuries, falls, crashes), violence (e.g., domestic) and suicide attemps[5], carrying a significant burden of morbidity and mortality[9-13]. In the last decade, even the number of admissions to emergency departments (EDs) for acute alcohol intoxication has been constantly rising[14-16]. The persistence of alcohol abuse, particularly when associated with social, working and familial problems, can lead to the development of alcohol use disorder (AUD)[5].

Alcohol withdrawal syndrome (AWS) is a clinical syndrome occurring when individuals with severe AUD abruptly cease or significantly reduce alcohol consumption[17]. It represents a life-threatening condition, requiring a prompt recognition and an appropriate treatment. Despite individual's decision to stop drinking, AWS can develop as a consequence of medical treatments when ethanol's plasma levels tend to zero, for example, in those patients managed in Emergency Departments (EDs), as well as those admitted to any inpatient setting for complications of AAI[5,17]. Both AAI and AWS represent two pivotal and interconnected issues resulting from alcohol abuse.

The present review will highlight the primary manifestations of alcohol-related harm, focusing on the acute consequences of alcohol consumption, namely Acute Alcohol Intoxication, and the subsequent challenges presented by Alcohol Withdrawal Syndrome. These two facets underscore the complex and multifaceted nature of alcohol misuse.

ACUTE ALCOHOL INTOXICATION

The AAI represents an immediate and discernible consequence of excessive alcohol consumption, being characterized by elevated blood alcohol levels. The pathophysiological and behavioural manifestations of AAI are well-documented, including:

- *Central Nervous System Depression:* alcohol acts as a central nervous system depressant, leading to impaired cognitive and motor function. Impaired coordination, slurred speech, memory deficits, and decreased reflexes are also common[18];
- *Behavioural disturbances:* AAI diminishes inhibitory control and impairs judgment, often resulting in impulsive, aggressive, or hazardous behaviors[19];
- *Medical Complications:* AAI is associated with several complications, including liver disorders, digestive system damage, dehydration, hypoglycemia, and, in severe cases, coma[20]. Cardiovascular implications include an elevated risk of stroke and myocardial infarction[21].

According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), the diagnosis of AAI should include all of the following criteria: the recent consumption of alcohol; the presence of clinically relevant behavioral or psychological changes (e.g., inappropriate sexual or aggressive behaviour, mood lability, impaired judgment) developed during, or shortly after, alcohol use; the presence of one (or more) of the following signs or symptoms (e.g., slurred speech, incoordination, unsteady gait, nystagmus, impairment in attention or memory) developing during, or shortly after, alcohol use; the signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance[22] (Table 1).

Clinical features

Symptoms of AAI rely on the amount of alcohol consumed, the time-frame and the eventual co-ingestion with foods. Symptoms can range from euphoria to coma, respiratory depression and death[5,23].

While clinical history and physical examination are pivotal in diagnosing AAI, the determination of ethanol levels in breath or blood represents the most valuable diagnostic method for quantitatively assessing the severity and potential progression of AAI[5]. Although clinical manifestations of AAI are correlated with Blood Alcohol Concentration (BAC), individual factors, including body weight, gender, age, and alcohol tolerance, can influence alcohol metabolism and the severity of AAI[24]. As a matter of fact, higher BAC levels are associated with more severe and potentially life-threatening manifestations (Table 2).

Table 1. Acute Alcohol Intoxication: diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition[22] (adapted from Mirijello et al, Eur J Intern Med, 2023).

Diagnostic criteria for Acute Alcohol Intoxication
1. Recent alcohol consumption
AND
2. Clinically significant behavioral or psychological changes (e.g., inappropriate sexual or aggressive behavior, mood lability, impaired judgment) that developed during, or shortly after, alcohol ingestion
AND
3. One (or more) of the following signs or symptoms developing during, or shortly after, alcohol use
a. slurred speech
b. lack of coordination
c. unsteady gait
d. nystagmus
e. impairment of attention or memory
f. stupor or coma
AND
4.Signs or symptoms not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance

Clinical manifestations of AAI are significantly gender-related, with females more prone to develop more severe symptoms at lower BAC. This difference resides in the reduced tolerance to the effects of alcohol showed by females as compared to males, due to increased bioavailability of ethanol, lower distribution volume, and reduced expression of gastric alcohol dehydrogenase (ADH)[25,26]. Normally, approximately 90% of ethanol is metabolized in the liver through three enzymatic pathways: liver ADH, responsible for about 90% of the metabolism, the microsomal ethanol oxidizing system (MEOS), accounting for around 8-10%, and catalase contributing approximately 0-2%[27]. Individuals with chronic alcohol abuse can exhibit a dramatic overexpression of the MEOS pathway, leading to the production of free radicals and subsequent organ damage[27]. This factor accounts for the metabolic tolerance to the effects of ethanol and affects the variability of clinical manifestations despite BAC levels.

Furthermore, in accordance with the *Mellanby effect*, symptoms of AAI are typically more pronounced during the ascent of alcohol levels as opposed to the descending phase, even at identical BACs[28].

Table 2. Stages of AAI [adapted from Mirijello et al, 2023; Vonghia et al, 2008][5,23].

Stages	BAC	Drinks (approx.)	Signs and symptoms
I – Mild AAI	BAC >50 mg/dl < 100 (10.9 mmol/l)	2-3 drinks	Relaxation Euphoria/dysphoria Increased talkativeness Loss of inhibition
II – Moderate AAI	BAC > 100 mg/dl (21.7 mmol/L)	4-6 drinks	Impaired control mechanisms (e.g., sensitive, motor and psychological) Altered environment perception, incoordination Ataxia, hyperreflexia, Incoordination, nystagmus Prolonged reaction time Slurred speech, behavioral changes Alteration in mood and personality Memory deficits
III – Severe AAI	BAC > 200 mg/dl (43.4 mmol/L) BAC 300-400 mg/dl (65.1-86.8 mmol/L)	13-26 drinks	Global neurological impairment (e.g., amnesia, diplopia, dysarthria) Autonomic dysfunction (i.e., hypothermia, hy potension, nausea, vomiting) Respiratory depression, coma
IV – Life-threatening AAI	BAC >500 mg/dl (108.5 mmol/l)	>30 drinks	Death

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Standard drink and BAC

A single unit of alcohol, often referred to as a *standard drink*, contains approximately the quantity of alcohol found in a 0.33 cl beer, a standard glass of red wine (125 ml), or a 40 ml "shot" of spirits[9]. However, a wide variation in the definition of a standard drink, along with the amount of alcohol it contains, can be observed from country to country. For instance, in the European Union, a standard drink contains 10-12 grams of ethanol, while in the UK, it contains 8 grams, in Australia, 10 grams, and in the USA, 14 grams of ethanol. Consuming one drink leads to an approximate increase in BAC of 20 mg/dl, and it is generally metabolized in 1 hour[22,29].

Severity of AAI

Mild AAI usually occurs with a BAC >50 mg/dl (10.9 mmol/l), equivalent to approximately 2-3 drinks. It is characterized by loss of inhibition, feelings of relaxation, euphoria, dysphoria, and increased talkativeness. However, even tasks requiring fine motor skills may be impaired, contributing to inadequate balance control strategies and an increased risk of falling[5,23,30].

Moderate AAI, typically occurring with a BAC >100 mg/dl (21.7 mmol/L) after approximately 4-6 drinks, involves progressive impairment of sensory, motor, and psychological control mechanisms. Symptoms include altered perception, ataxia, hyperreflexia, incoordination, nystagmus, impaired judgment, prolonged reaction time, slurred speech, behavioral changes, mood alterations, and memory deficits[5,23,30].

Severe AAI appears with a BAC >200 mg/dl (43.4 mmol/L) after around 13-26 drinks. It results in global neurological impairment with symptoms such as amnesia, diplopia, dysarthria, and autonomic dysfunction (e.g., hypothermia, hypotension, nausea, vomiting). BAC levels exceeding 300-400 mg/dl (65.1-86.8 mmol/L) can lead to respiratory depression, coma, and cardiac arrest. Deaths directly attributable to acute alcohol intoxication typically occur with a BAC >500 mg/dl (108.5 mmol/l). However, the lethal dose of alcohol varies significantly depending on an individual's tolerance status, being lower (300 mg/dl; 65.1 mmol/l) in non-tolerant individuals and much higher (>1200 mg/dl; >260.4 mmol/l) in individuals with alcohol use disorder (AUD)[5,23].

Tolerance and other substances co-abuse

Tolerance, an adaptation of the central nervous system (CNS) to chronic alcohol exposure, involves the down-regulation of GABA transmission and the up-regulation of NMDA glutamatergic pathways, resulting in CNS desensitization to ethanol's effects and long-term reduction of its neurotropic effects[17]. Importantly, the co-consumption of other sedative substances (e.g., benzodiazepines, antihistamines, opioids) increases the risk of life-threatening AAI. Therefore, clinicians should investigate the possible co-abuse of other substances in individuals presenting with AAI[30].

Approach to Patients with AAI

The approach to patients with AAI includes: the identification of potentially hazardous medical conditions, creating a safe environment for patient's recovery, and identifying any underlying AUD. It's noteworthy that there is a notable incidence of subclinical medical and traumatic issues in patients presenting with AAI[31]. Thus, all patients should undergo a meticulous assessment to determine the extent of mental status impairment, to detect signs of co-morbidities, and assess for signs of trauma[5,32,33]. This examination should begin with the evaluation of vital signs, hydration status and nutritional deficits[24,25]. Skin observation can reveal signs indicative of prolonged alcohol abuse (e.g., telangiectasias, spider naevi, palmar erythema). Further assessment should encompass chest, cardiac, abdominal, and neurological examinations. While mild tachycardia, hypotension, and hypothermia are frequently observed in AAI, any pronounced or sustained abnormalities should be subject to further investigation[31].

Given the high risk of respiratory depression, individuals with reduced levels of consciousness must undergo multiparametric monitoring. It should be emphasized that the risk of hypoventilation does not linearly correlate with BAC and can be influenced by patient's tolerance to ethanol, the presence of cardiopulmonary comorbidities, concurrent exposure to another sedative agent, and drugs administered in ED for the management of agitation[5,31]. Finally, the presence or co-occurrence of AAI-mimickers (Table 3) should be always evaluated[5,23].

The American Society of Addiction Medicine (ASAM) recommends to perform routine laboratory studies, such as a complete blood count, electrolyte levels, liver and kidney function tests, in those patients who exhibit signs of concurrent medical comorbidities, such as blood loss, persistent vomiting, or abnormal vital signs[31]. Similarly, brain CT scan should be requested in patients with a history of trauma or in those who show a dissociation between neurological status and BAC levels[31].

The effects of AAI extend to several organs and systems:

Neurological complications of AAI can include seizures with associated rhabdomyolysis, acute alcoholic encephalopathy, or Gaye-Wernicke encephalopathy,

Table 3. Acute alcohol intoxication: clinical mimickers [adapted from Mirijello et al, 2023; Vonghia et al, 2008][5,23].

Clinical syndromes	Differential diagnosis
Other substances intoxication	Alcohols (non-ethanol): Methanol, Isopropyl alcohol Drugs of abuse: Cocaine, Opiates, Tetrahydrocannabinol Drugs: Barbiturates, Benzodiazepines, Tricyclic antidepressants, Disulfiram Carbon monoxide
Metabolic causes	Alcoholic ketoacidosis Diabetic ketoacidosis Electrolyte disturbances: Hypo/hyper-natremia, Hypo/hyper-calcemia Hepatic encephalopathy Hyperosmolar coma Hypertensive encephalopathy Hypoglycemia Uremic syndrome
Infectious disease	Encephalitis Meningitis Sepsis
Neurological causes	Cerebrovascular accidents Seizures
Psychiatric causes	Alcohol withdrawal syndrome Wernicke–Korsakoff syndrome
Trauma	Concussion syndromes Intracranial bleeding Subdural hematoma
Respiratory causes	Hypoxia Respiratory depression
Other	Dehydration Hyper-/hypothermia Hyper-/hypothyroidism Hypotension

chronic Korsakoff's syndrome, central pontine myelinolysis, Marchiafava-Bignami Syndrome, and tobacco-alcohol amblyopia[5]. In addition, repeated AAI episodes and chronic alcohol abuse have been linked to CNS alterations (e.g., reduced cortical gyrification, grey matter reduction, memory deficits, and long-term dementia)[34,36].

Metabolic alterations associated with AAI include electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia), hypoglycemia, hypoalbuminemia, lactic acidosis[37]. However, hyponatremia, hypomagnesemia, alcoholic ketoacidosis and thiamine deficiency are the most common complications of AAI[31].

Cardiovascular manifestations of AAI are vasodilation, increased heart rate, hypotension, and heat dispersion. Moreover, ECG modifications and elevated serum troponin concentrations can be observed after heavy drinking episodes[38-40]. These cardiac disturbances can lead to conditions like paroxysmal atrial fibrillation[41,42]. Respiratory depression and an increased risk of lower respiratory tract infections are common in patients with AAI, attributed to aspiration, ciliary mucosal clearance dysfunction, and alcohol-related immune dysfunction[43]. Gastrointestinal symptoms, such as gastritis, peptic ulcer, pancreatitis, nausea, vomiting, diarrhea, and abdominal pain, can arise due to direct inflammation and altered gastrointestinal motility. Prolonged vomiting may contribute to electrolyte imbalances, and hematemesis can result from esophageal mucosal lacerations (Mallory-Weiss syndrome)[44].

The liver is highly susceptible to alcohol-induced damage, making AAI a potential trigger for acute alcoholic hepatitis (AH), infections, drug-induced liver injury, and portal vein thrombosis[45]. Additionally, AAI can lead to the manifestation of Zieve syndrome when jaundice is accompanied by haemolytic anaemia and hypertriglyceridemia[46].

Treatment of AAI

In individuals presenting with AAI, the main objective of treatment is to prevent the risk of respiratory depression and cardiac arrest. Thus, particularly in patients with severe AAI, the assessment and stabilization of airways is pivotal to prevent hypoventilation, loss of airway reflexes, and aspiration[31]. Patients with respiratory failure will need oxygen supplementation up to ventilatory support. Approximately 1-4% of AAI patients will require admission to the Intensive Care Unit (ICU)[32,33,47].

For mild and moderate forms, preventing toxic damage to organs and systems and accelerating alcohol elimination are the main goals[16,23]. Thus, any patient should have placed a stable intravenous access[37].

Although data do not support the routine administration of intravenous fluids since it does not enhance the clearance rate of ethanol and can prolong the length of stay in the ED[48,49], the correction of glucose (hypoglycemia) and electrolyte (hypokalemia) disorders should be prioritized[37]. Administering thiamine before glucose is advisable to avoid hastening the onset of Wernicke's encephalopathy[50]. However, in cases of severe hypoglycemia, the administration of glucose should not be delayed to prepare and infuse thiamine.

Patients with AAI can often present with recurrent vomiting, which can lead to potentially life-threatening medical complications (e.g., variceal bleeding, esophageal laceration/rupture)[5,51]. Anti-emetic drugs (e.g., metoclopramide) have a significant role in reducing the vomiting reflex and to limit the development of hyponatremia and its complications (central pontine myelinolysis)[5].

In those patients manifesting agitation, guidelines recommend verbal de-escalation to reduce patient's aggressivity and improve orientation[31]. The use of restraint measures may, paradoxically, exacerbate the situation[24]. In case of violent behavior or psychomotor agitation, or when verbal de-escalation is not sufficient, the use of sedative drugs (e.g., benzodiazepines, haloperidol and droperidol) can be considered[5,31]. However, caution is necessary, as potential co-intoxication with other drugs, or concurrent multiple therapies due to comorbidities, could lead to adverse effects, such as dystonic reactions and QTc prolongation when using D2 blockers (haloperidol). The use of mood stabilizers (e.g., pregabalin) may serve as an adjunctive treatment[52]. However, patients must be strictly monitored due to the risk of hypotension and respiratory depression[37]. Ketamine has also been proposed as a treatment option for extremely agitated patients[31].

Metadoxine, a pyrrolidone carboxylate of pyridoxine, is currently the only drug indicated for the treatment of AAI[5]. It is approved in some European Union countries but not in the United States. Its effectiveness lies in its ability to accelerate the clearance of ethanol, which results in a reduction in BAC and an improvement in intoxication symptoms. These effects are achieved by maintaining and restoring ATP levels in the brain and liver, enhancing the synthesis of glutathione, promoting ethanol degradation, and increasing the urinary elimination of ketones[53]. One notable advantage of metadoxine is its excellent safety profile, making it a suitable option for managing severe intoxication cases, even in adolescents[16]. When administered intravenously as a single dose, it leads to a more rapid decrease in BAC and faster symptom improvement compared to placebo[53].

It should be underlined that, at present, there is no specific antidote available for the treatment of AAI. Moreover, metadoxine is not classified as an antidote[54]. However, when faced with an intoxicated patient, in addition to providing supportive care, physicians should consider the option of administering a drug that can specifically act by reducing BAC. Metadoxine is presently the only drug demonstrated to significantly reduce BAC more rapidly than a placebo[53].

Furthermore, metadoxine seems to have a role in the treatment of Alcohol Use Disorder (AUD) by increasing abstinence from alcoholic beverages in patients with AUD, especially in those with alcohol-associated liver disease[55]. Its antioxidant properties also make it a safe choice for improving pre-existing alcohol-associated liver disease[55].

ACUTE ALCOHOL INTOXICATION AND ALCOHOL WITHDRAWAL SYNDROME

Although seemingly opposite in etiology, AAI and AWS should be considered as points along a disease continuum[5]. In fact, the pathophysiology is antithetical at first glance: AAI is the result of the consumption of large quantities of ethanol[23], while AWS occurs when individuals with severe AUD abruptly discontinue or reduce alcohol intake[5]. However, alterations in neural circuits involving gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors could exhibit similarities in both conditions, especially in individuals predisposed to repeated episodes of AAI, such as binge drinkers[5].

Both AAI and AWS can manifest with seizures, and the underlying pathophysiology involves an acute disruption of the delicate balance between inhibitory (GABA) and excitatory (glutamate) neurotransmission. This imbalance is particularly pronounced in individuals who have been chronically exposed to significant quantities of ethanol, leading to the development of tolerance. It should be underlined that some patients, especially

those involved in accidents, may initially present with AAI upon hospital admission and subsequently develop AWS during hospitalization if not properly identified and treated[17]. It's crucial to emphasize that a BAC exceeding 200 mg/dl upon hospital admission should be considered a risk factor for the subsequent development of severe AWS[17]. Additionally, the treatment of AAI can potentially trigger AWS symptoms in individuals with severe AUD who experience a rapid reduction in ethanol levels. On the other hand, individuals without AUD have a lower tolerance to the effects of ethanol, which can lead to more severe symptoms and consequences of AAI, such as respiratory depression and coma. This continuum of effects, ranging from AAI to AWS, underscores the intricate relationship between alcohol consumption, tolerance, and withdrawal in individuals with varying degrees of alcohol dependence. The dual vulnerability of individuals with AUD to both conditions, depending on factors like their current BAC and the context of treatment, underscores the complex challenges faced by clinicians when managing these patients.

ALCOHOL WITHDRAWAL SYNDROME

Alcohol Withdrawal Syndrome (AWS) is a clinical syndrome that occurs when individuals with a severe Alcohol Use Disorder (AUD) suddenly stop or markedly reduce their alcohol consumption[17]. AWS can manifest with a high variable symptoms and unpredictable progression[31]. The prevention of AWS in at-risk patients, its identification and prompt treatment are crucial to reduce the progression to severe forms of disease and the associated morbidity and mortality[17,56].

It has been estimated that about half of patients with AUD will experience symptoms of withdrawal during their lifetime[57,58]; however, the majority of them will experience self-resolution of AWS after several days of autonomic hyperactivity[31]. AWS is a potentially life-threatening condition with a spectrum of severity, ranging from mild to moderate forms, characterized by symptoms like tremors, nausea, anxiety, and depression, to severe forms marked by hallucinations, seizures, delirium tremens, and even coma[59].

As mentioned above, mild to moderate forms of AWS are often managed by patients themselves and may resolve within 2 to 7 days from their last drink[58,60]. However, more severe cases of AWS require medical treatment[57,58].

Pathophysiology and Clinical features of AWS – severity

Acute alcohol consumption leads to central nervous system (CNS) depression primarily due to enhanced GABAergic neurotransmission (stimulation of GABA$_A$ receptors) and reduced glutamatergic activity (inhibition of N-methyl-D-aspartate (NMDA) receptors)[61,62].

Chronic alcohol consumption leads to adaptation of GABA, glutamate and norepinephrine systems to restore neurochemical balance[63]. This adaptive process results in reduced responsiveness to the effects of alcohol in the CNS over time, a phenomenon known as tolerance[61,64,65]. Specifically, these changes include a down-regulation of GABA$_A$ receptors and an up-regulation of glutamate NMDA[64,66], alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors[67,68]. These neurochemical adaptations play a crucial role in the development of tolerance and the manifestation of withdrawal symptoms during AWS.

The sudden reduction or cessation of alcohol consumption results in a decrease in GABA activity with consequent increase in glutamatergic activity. This acute imbalance in the CNS produces hyper-excitability, leading to the development of AWS symptoms, which can begin within a few hours after the last alcoholic drink[17]. The up-regulation of dopaminergic and noradrenergic pathways may contribute to the development of hallucinations and autonomic hyperactivity, respectively, during AWS[59].

Table 4 summarizes signs and symptoms of AWS, divided per stage. The AWS encompasses a spectrum of symptoms, ranging from mild withdrawal to the severe condition known as delirium tremens (DT). AWS can manifest in different ways: it can begin with mild symptoms and progress to more severe forms, or it may start with DT, particularly in patients with a history of previous DT episodes or repeated AWS episodes, a phenomenon known as 'kindling'[17].

Typically, first-stage AWS symptoms – *colloquially called "The Shakes"* – include tremors, sweating, nausea/vomiting, high blood pressure, rapid heart rate, elevated body temperature, and rapid breathing emerge 6-12 hours after the last alcohol intake and persist until the next drink[31,69]. It should be noted that, in patients with co-existing medical conditions or taking medications like beta-blockers, changes in vital signs (blood pressure and heart rate) may be masked and appear normal.

Second-stage AWS symptoms, which include visual and tactile disturbances, usually begin around 24 hours after

Table 4. Signs and symptoms of alcohol withdrawal syndrome, divided per stage. From Mirijello et al, Drugs 2015[17], permission n. 5644301465823.

Stage	Time of onset after last drink	Signs and symptoms
I – Minor Withdrawal Symptoms	6-12 h	Tremors, diaphoresis, nausea/vomiting, hypertension, tachycardia, hyperthermia, tachypnea
II – Alcoholic Hallucinosis	12-24 h	Dysperceptions: Visual (zoopsy), auditory (voices) and tactile (paresthesia)
III – Alcohol Withdrawal seizures	24-48 h	Generalized tonic-clonic seizures (with short or no postictal period)
IV – Delirium Tremens	48-72 h	delirium, psychosis, hallucinations, hyperthermia, malignant hypertension, seizures and coma

the last drink. Approximately 25% of AWS patients may experience transient alterations in perception, such as auditory (hearing voices) or less commonly, visual (seeing things) or tactile disturbances. These disturbances can be persecutory and lead to paranoia, causing increased patient agitation. If these symptoms become persistent, the patient has progressed to alcoholic hallucinosis – *"The Horrors"* –. However, patients experiencing alcoholic hallucinosis recognize these hallucinations as unreal and maintain clear sensorium[17,31].

About 10% of patients with withdrawal symptoms progress to alcohol withdrawal seizures – the *"Rum fits"* – (third-stage AWS), typically starting 24-48 hours after the last drink. These seizures are characterized by widespread tonic-clonic movements and often have minimal or no postictal recovery period. While most cases of alcohol withdrawal seizures are self-limiting, they can be challenging to manage, and in nearly one-third of patients, DT may represent a worsening of alcohol withdrawal seizures.

DT represents the most severe manifestation (fourth stage) of AWS and occurs when AWS is left untreated or under-treated[59]. It affects approximately 5% of AWS patients and typically appears 48-72 hours after the last drink, although it can occur up to 10 days later. DT is marked by rapid fluctuations in consciousness and cognition over a short time, accompanied by severe autonomic symptoms (sweating, nausea, palpitations, and tremors) and psychological symptoms like anxiety. Typical DT patients exhibit agitation, hallucinations, and disorientation. The presence of disorientation distinguishes delirium from alcoholic hallucinosis. Delirium is characterized by psychosis, hallucinations, hyperthermia, malignant hypertension, seizures, and coma. DT can lead to patient or staff injury, medical complications (e.g., aspiration pneumonia, arrhythmia, or myocardial infarction), and may result in death in 1-5% of patients[70,71].

Following the acute treatment of AWS, some symptoms may persist for weeks to months after the 5-7 days of acute detoxification, a condition referred to as 'protracted AWS'[59].

When to suspect AWS
Patients who are known to have recently, regularly, and heavily consumed alcohol or have a history of complicated AWS should be carefully evaluated for the presence or likelihood of developing AWS[72]. This evaluation is particularly important for patients exhibiting signs and symptoms consistent with hyperadrenergic state. Patients suspected of AWS should be inquired about their daily alcohol consumption, the timing of their last alcoholic drink, any past experiences of difficulty when attempting to stop drinking, the reasons motivating their decision to discontinue alcohol consumption[17,31]. The assessments of the risk of AWS can be effectively conducted using screening tools designed for identifying unhealthy alcohol use, such as AUDIT-C (Alcohol Use Disorders Identification Test) or CAGE[31,73].

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, the diagnosis of AWS is established by observing signs and symptoms of withdrawal in individuals who have undergone an abrupt reduction or cessation of alcohol consumption[22]. At least two of the following symptoms must be present: autonomic hyperactivity (such as sweating or tachycardia), increased hand tremor, insomnia, nausea or vomiting, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, anxiety, and tonic-clonic seizures[22]. It is also crucial to distinguish symptoms linked to acute or chronic alcohol abuse or withdrawal from those associated with other psychiatric disorders[74].

From a practical point of view, the application of a structured interview may be challenging, and it is conceptually unnecessary because individuals experiencing AWS typically exhibit agitation and confusion. The Clinical Institute Withdrawal Assessment for Alcohol

(CIWA-A) scale, particularly in its ten-item revised form (CIWA-Ar)[59,75,76], represents a consolidated tool for assessing the severity of AWS. Table 5 summarizes the items and the score range, with scores <8 indicating mild withdrawal, scores ranging between 8 and 15 indicating moderate withdrawal, and scores above 15 indicating severe withdrawal. Higher scores also predict the risk of seizures and delirium[77,78]. When the CIWA-Ar score is below 8, pharmacological treatment is typically unnecessary, but it may be considered for patients with scores between 8 and 15 to prevent the progression to more severe forms of AWS (please refer to Table 4 for details). Pharmacological treatment is strongly recommended for patients with CIWA-Ar scores exceeding 15. The CIWA-Ar score should be reassessed at least every 8 hours. For patients with scores higher than 8-10 or those requiring treatment, CIWA assessments should be conducted hourly to monitor the response to treatments. Besides CIWA-Ar, there are other scales validated for the assessment of AWS severity, such as the Brief Alcohol Withdrawal Scale (BAWS), the Alcohol Withdrawal Scale (AWS), the Short Alcohol Withdrawal Scale (SAWS), and the Severity of Ethanol Withdrawal Scale (SEWS)[17,31].

How to prevent

In clinical practice, physicians often need to anticipate the likelihood of a patient developing AWS, particularly its severe form. This is especially important in cases where a comprehensive medical history is not readily accessible, such as in ED, trauma unit, or ICU settings. In such situations, a high risk of complicated AWS may lead medical professionals to opt for a more aggressive treatment approach, even in the absence of severe initial symptoms. Some tools are available for clinicians to predict the risk of AWS, such as, the Luebeck Alcohol Withdrawal Risk Scale (LARS)[79] or the Prediction of Alcohol Withdrawal Severity Scale (PAWSS)[80].

Table 6 summarizes the risk factors for developing severe AWS. In particular, the most significant predictor of severe AWS is a history of complicated AWS (e.g., convulsions, delirium tremens), or prior admission to the ICU[81]. Other known risk factors are the age >65 years, the presence of medical comorbidities, history of severe AUD, concomitant use of benzodiazepines or barbiturates, elevated BAC and/or moderate AWS symptoms at the time of presentation.

The use of pharmacological prophylaxis for preventing AWS is still under-prescribed[17,31]. Although prophylaxis in patients with severe AUD at high risk for AWS is strongly recommended by the Substance Abuse and Mental Health Services Administration (SAMHSA), its use is still poorly diffused[82]. Drugs commonly used for prophylaxis include chlordiazepoxide 25-100 mg every six hours for one day followed by 25-50 mg every six hours for an additional two days. Similar regimens with oxazepam 10-30 mg, diazepam 2.5-10 mg or lorazepam 0.5-2 mg can be used[83]. These patients should be closely monitored for the possible development of excess sedation or, from the other hand, clinically relevant AWS.

Table 5. Clinical Institute Withdrawal Assessment for Alcohol – revised (CIWA-Ar) scale[75]. From Mirijello et al, Drugs 2015[17], permission n. 5644301465823.

Clinical Institute Withdrawal Assessment for Alcohol revised	
Symptoms	**Range of scores**
Nausea or vomiting	0 (no nausea, no vomiting) -7 (constant nausea and/or vomiting)
Tremor	0 (no tremor) – 7 (severe tremors, even with arms not extended)
Paroxysmal sweats	0 (no sweat visible) – 7 (drenching sweats)
Anxiety	0 (no anxiety, at ease) – 7 (acute panic states)
Agitation	0 (normal activity) – 7 (constantly trashes about)
Tactile disturbances	0 (none) – 7 (continuous hallucinations)
Auditory disturbances	0 (not present) – 7 (continuous hallucinations)
Visual disturbances	0 (not present) – 7 (continuous hallucinations)
Headache	0 (not present) – 7 (extremely severe)
Orientation/clouding of sensorium	0 (orientated, can do serial additions) – 4 (Disorientated for place and/or person)

Modified from: Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar). Br J Addict 1989;84:1353-1357.

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Table 6. Risk factors for severe alcohol withdrawal syndrome (CNS: central nervous system; BAL: breathe/blood alcohol concentration; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcoholism, revised; AST: aspartate aminotransferase). From Mirijello et al, Drugs 2015[17], permission n. 5644301465823.

Previous episodes of alcohol withdrawal (detoxification, rehabilitation, seizures, delirium tremens
Concomitant use of CNS-depressant agents, such as benzodiazepine or barbiturates
Concomitant use of other illicit substances
High blood alcohol level (BAL) on admission (i.e., >200 mg/dl)
Evidence of increased autonomic activity (i.e., systolic blood pressure > 150 mmHg, body temperature > 38°C)
Older age
Moderate to severe alcohol withdrawal at diagnosis (CIWA-Ar > 10)
Medical or surgical illness (i.e., trauma, infection, liver disease, CNS infection, electrolyte disturbances, hypoglycaemia, etc.)
Severe alcohol dependence
Abnormal liver function (elevated AST)
Recent alcohol intoxication
Male sex

Treatment of AWS: general and supportive care

Patients with severe AUD are often afraid to stop drinking due to the fear of withdrawal symptoms, causing severe discomfort and sufferance. Thus, making withdrawal as smoother as possible represents the first aim of the treatment to improve patients' quality of life. In addition, preventing more severe forms is always pivotal[59,84]. During the treatment phase, patients should be supported to boost motivation to start long-term alcohol abstinence, also encouraging participation in relapse prevention programs[59,84].

Outpatient management is appropriate for mild AWS, while moderate-to-severe forms require hospitalization[85]. Similarly, for patients with AAI, the creation of a comfortable environment is fundamental (e.g., quiet room without dark shadows, excessive noise, or other stimuli, such as bright lights)[17].

A laboratory workup including BAC, complete blood counts, renal function, electrolytes, glucose, liver panel, urinalysis, and urine toxicology screening should be part of routine practice. Fluid imbalances, hypoglycemia, and electrolyte disturbances should be corrected, with a special emphasis on vitamin supplementation, specifically, thiamine and B-complex vitamins (including folates) for preventing Wernicke's encephalopathy (WE)[86,87]. Thiamine can be administered routinely due to the absence of significant adverse effects or contraindications.

Treatment of AWS: the cornerstone

Currently, benzodiazepines (BZDs) are considered the "gold-standard" for the treatment of AWS[88,89], and the only class of medications able to prevent the progression to severe forms of AWS, including a reduction in the incidence of seizures (84%), delirium tremens (DT), and related mortality[88,90]. The efficacy of BZDs in AWS treatment appears to be linked to the stimulation of $GABA_A$ receptors, which results in effects similar to those of alcohol[91]. While in the United States, BZDs are the primary choice of treatment for AWS, in Europe, clomethiazole is also largely utilized[89].

Diazepam and chlordiazepoxide are the most used drugs due to their long half-lives, even if there is no clear superiority among different BZDs[92]. Moreover, BZDs offer the advantage of multiple administration routes (e.g., oral, intramuscular, intravenous). The IV route is preferable for moderate to severe AWS due to its rapid onset of action, while the oral route can be employed in milder cases. However, it's important to underline to avoid the IM route with chlordiazepoxide and diazepam due to their erratic absorption. On the contrary, lorazepam can be administered through all three routes[56].

Among the three administration regimens available in clinical practice, the *loading-dose strategy* (specifically, giving a moderate-to-high dose of a long-acting BZD – such as diazepam (10-20 mg) or chlordiazepoxide (100 mg) – every 1-2 hours, to induce sedation) is not commonly used given the risk of excessive sedation and respiratory depression.

Thus, the two most used strategies are the *symptom-triggered* and the *fixed-dose*.

With the *symptom-triggered* approach, the drug (e.g., diazepam 5-20 mg, chlordiazepoxide 50-100 mg, or lorazepam 1-4 mg) is administered if the CIWA-Ar score is >8-10 points. Obviously, the severity of symptoms should necessarily be assessed at least every hour, adjusting the dose based on the severity

of the symptoms, until the CIWA-Ar reaches a point-score <8[17]. Advantages of this scheme reside in a lower BZDs requirement[88], a reduction of unneeded doses and of overtreating symptoms. This approach is suggested for the management of AWS in ED[72].

Finally, the *fixed-dose* strategy involves administering a predetermined dose of the chosen drug (for example, diazepam) 10 mg four times a day for 1 day, then 5 mg four times a day for 2 days, regardless of the patient's symptoms. The dose is then tapered off by 25% per day from day 4 to day 7, with the possibility to give extra doses in case symptoms not adequately controlled. The strength of this approach is its high efficacy, making it preferable in patients with severe AWS or with a history of DT. The main limitations are the potential risks of excessive sedation and respiratory depression, requiring a clinical monitoring and suggesting its use for inpatient settings[17,31]. It should be underlined that patients with a history of severe AUD admitted to inpatients setting, for acute medical or surgical illness, or to ICU, should be considered at high risk for AWS. Thus, they should receive pharmacological prophylaxis to prevent the development of AWS. In case withdrawal symptoms will appear, they should receive an adequate treatment with a fixed-dose approach[17].

Treatment of AWS: special circumstances (settings)

Given that most of BZDs have active metabolites generated through phase I liver oxidation[93,94], patients with impaired liver metabolism, such as those with advanced liver disease and the elderly, should receive short-acting agents without active metabolites (e.g., lorazepam and oxazepam)[90,95].

Those patients presenting with severe AWS or requiring high-doses BZDs can be managed in the setting of ICU with the use of barbiturates, even in co-administration with BZDs (e.g., midazolam continued infusion). In cases of severe DT that necessitate mechanical ventilation, combining BZDs and barbiturates can reduce the need for mechanical ventilation and may lead to a shorter ICU stay[96]. Similarly, propofol represents a favourable choice for intensivists given its antagonistic effect on the NMDA receptor, stimulation of the GABAA receptor, and a short duration of effect, allowing for a rapid assessment of a patient's mental status after discontinuation[17,97].

The use of BZDs, as well as barbiturates and propofol, has several limitations represented by the risk of excessive sedation and respiratory failure, memory deficits and the potential risk for abuse and dependence, mainly in patients with a pre-existing AUD[89]. For this reasons, several non-BZD agents acting on GABAergic circuitry but owing fewer sedation and absence of addictive properties

have been investigated for AWS treatment, with promising results in monotherapy or in adjunction to BZDs[31,72,98]. Among these, the agents with a proven efficacy and safety are carbamazepine (sodium channel blocker, tricyclic anticonvulsivant, enhancing GABAergic neurotransmission and blocking NMDA receptors)[31,99], valproic acid (GABA modulator, mood stabilizer with ability to reduce irritability, anticraving properties)[89], and gabapentin (calcium channel modulator, anticonvulsivant, anxiolytic, and sedative, with anti-craving properties)[100]. Among drugs acting on the GABAergic system, sodium oxybate and baclofen deserve a focused highlight given their action on $GABA_B$ receptors.

Sodium Oxybate (SMO), also known as gamma-hydroxybutyric acid, is a natural short-chain fatty acid found in the mammalian brain (e.g., thalamus, hypothalamus, and basal ganglia). Owing a structure similar to GABA, SMO binds to SMO and $GABA_B$ receptors with different affinity[101]. Due to its alcohol-mimicking effects on the CNS, SMO (50 mg/kg/day in three divided doses) has shown its efficacy in reducing AWS symptoms, with outcomes similar to benzodiazepines (BZDs) and clomethiazole[105,103]. Moreover, its effect was non-inferior even to oxazepam[104]. SMO is also considered safe for the long-term treatment of alcohol dependence and relapse prevention[105] and it is approved for AWS treatment and alcohol relapse prevention in some European countries[106]. Given the possible risk of addiction, this drug has not been approved in other Countries[106]. However, at doses generally used for treating alcohol-dependent patients, SMO abuse appears to be relatively limited[106].

Baclofen is a $GABA_B$ receptor agonist typically used to manage spasticity[17]. In preclinical models, it has shown promises in reducing AWS symptoms by activating GABAB receptors to counteract the enhanced function of NMDA receptors[107]. In a study comparing baclofen (10 mg t.i.d. for 10 days) to diazepam (0.5-0.75 mg/kg/day for 6 consecutive days, tapering the dose by 25% daily from day 7 to day 10), the two drugs showed similar results in reducing CIWA-Ar scores[108]. Moreover, double-blind, placebo-controlled trials revealed that the use of baclofen in association with BZDs was linked to a reduction in the administration of "as-needed" lorazepam and diazepam during AWS[109,110]. Similarly, retrospective data show that the combination of baclofen plus gabapentin is comparable to BZDs in terms of efficacy for the management of inpatients with AWS[111]. Although the level of evidence is still low, baclofen confirms its promising results in treating AWS both as monotherapy, and as BZD-sparing drug[112,113].

In addition, there is growing evidence suggesting a role of baclofen may in the prophylaxis of AWS in hospital-

ized patients at risk for AWS[114]. Baclofen is generally well-tolerated, lacks significant side effects at prescribed doses, and does not cause euphoria or pleasant effects. However, further confirmatory studies are needed to establish its role in AWS treatment definitively. Given that baclofen has a demonstrated efficacy in alcohol relapse prevention, it could represent an interesting treatment for both AWS and post-withdrawal treatment. Importantly, its limited side effects and lack of liver toxicity make it a viable option for treating patients with alcohol use disorder (AUD) who have liver disease[115-118].

The administration of alpha-2-agonists, beta-blockers, and neuroleptics is currently reserved as adjunctive treatments for AWS. Indeed, these drugs are not recommended as monotherapy due to their limited efficacy in preventing severe AWS and the potential risk to mask AWS symptoms[17].

Beta-blockers like atenolol can be used to manage neuro-autonomic symptoms in patients with coronary artery disease[119]. Alpha-2 agonists, such as clonidine, produce sedation after parenteral administration, while oral or transdermal administration, at lower doses, can help control AWS symptoms by reducing autonomic hyperactivity (hypertension and tachycardia)[120]. Similarly, the more recent dexmedetomidine, a more selective alpha-2 receptor agonist, has shown promising results in the control of sympathetic symptoms when adjunct to lorazepam for severe AWS[121]. However, because both beta-blockers and alpha-2-agonists affect tremors, tachycardia, and hypertension, they have the potential to mask AWS symptoms and should be reserved for patients with persistent hypertension or tachycardia despite BZDs[122].

Finally, neuroleptics, such as haloperidol, are typically employed in the management of hallucinosis and delirium. However, they do not effectively prevent the worsening of AWS and may even increase the risk of seizures and prolong the QT interval. Therefore, the use of neuroleptic agents as monotherapy is contraindicated. Moreover, they are associated with longer durations of delirium, higher complication rates, and increased mortality rates[122]. Even neuroleptics should be reserved as adjunctive treatment in cases of agitation, perceptual disturbances, or disturbed thinking that are not adequately controlled by BZDs[122].

CONCLUSIONS

AAI is the direct consequence of excessive alcohol consumption. It can result in a variety of complications, including neurological, metabolic, cardiovascular, respiratory, and gastrointestinal issues. These complications can be particularly severe when AAI is accompanied by other substances' co-abuse. An effective management of AAI involves ensuring patient safety, addressing underlying alcohol use disorder, and treating any medical complications that may arise. Metadoxine represents the only drug able to accelerate alcohol clearance.

Patients presenting with AAI may subsequently develop AWS during hospitalization. AWS is a complex and potentially life-threatening condition. Treatment strategies for AWS, especially in severe cases, predominantly involve the use of benzodiazepines to manage symptoms and prevent progression to DT. However, newer pharmacological agents like baclofen and gabapentin show promise in AWS treatment, providing alternative options.

Conflict of Interest
The authors declare that they have no conflict of interest.

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