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Diagnosis and treatment of acute alcohol intoxication and alcohol withdrawal syndrome: position paper of the Italian Society on Alcohol

Fabio Caputo[1,2] · Roberta Agabio[3] · Teo Vignoli[4] · Valentino Patussi[5] · Tiziana Fanucchi[5] · Paolo Cimarosti[6] · Cristina Meneguzzi[6] · Giovanni Greco[7] · Raffaella Rossin[8] · Michele Parisi[9] · Davide Mioni[10] · Sarino Arico'[11] · Vincenzo Ostilio Palmieri[12] · Valeria Zavan[13] · Pierluigi Allosio[14] · Patrizia Balbinot[15] · Maria Francesca Amendola[16] · Livia Macciò[17] · Doda Renzetti[18] · Emanuele Scafato[19] · Gianni Testino[15]

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Abstract
The chronic use of alcohol can lead to the onset of an alcohol use disorder (AUD). About 50% of subjects with an AUD may develop alcohol withdrawal syndrome (AWS) when they reduce or discontinue their alcohol consumption and, in 3–5% of them, convulsions and delirium tremens (DTs), representing life-threatening complications, may occur. Unfortunately, few physicians are adequately trained in identifying and treating AWS. The Italian Society on Alcohol has, therefore, implemented a task force of specialists to draw up recommendations for the treatment of AWS with the following main results: (1) while mild AWS may not require treatment, moderate and severe AWS need to be pharmacologically treated; (2) outpatient treatment is appropriate in patients with mild or moderate AWS, while patients with severe AWS need to be treated as in-patients; (3) benzodiazepines, BDZs are the "gold standard" for the treatment of AWS and DTs; (4) alpha-2-agonists, beta-blockers, and neuroleptics may be used in association when BDZs do not completely resolve specific persisting symptoms of AWS; (5) in the case of a refractory form of DTs, the use of anaesthetic drugs (propofol and phenobarbital) in an intensive care unit is appropriate; (6) alternatively to BDZs, sodium oxybate, clomethiazole, and tiapride approved in some European Countries for the treatment of AWS may be employed for the treatment of moderate AWS; (7) anti-convulsants are not sufficient to suppress AWS, and they may be used only in association with BDZs for the treatment of refractory forms of convulsions in the course of AWS.

Keywords Acute alcohol intoxication · Alcohol withdrawal syndrome · Pharmacological treatment

✉ Fabio Caputo
f.caputo@ausl.fe.it

[1] Unit of Internal Medicine, Department of Internal Medicine, SS Annunziata Hospital, Via Vicini 2, 44042 Cento, Ferrara, Italy

[2] "G. Fontana" Centre for the Study and Multidisciplinary Treatment of Alcohol Addiction, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

[3] Section of Neuroscience and Clinical Pharmacology, Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy

[4] Unit of Addiction Treatment, Lugo, Ravenna, Italy

[5] Regional Centre on Alcohol, Careggi Hospital, Florence, Italy

[6] Alcohol Unit, Pordenone, Italy

[7] Alcohol Unit, Ravenna, Italy

[8] Alcohol Unit, Milan, Italy

[9] Alcohol Unit, Nicosia, Enna, Italy

[10] Nursing Home Parco dei Tigli, Teolo, Padova, Italy

[11] Gastroenterology Unit, Mauriziano Hospital, Turin, Italy

[12] "Murri" Clinic of Internal Medicine, Department of Biomedical Science and Human Oncology, University of Bari, Bari, Italy

[13] Alcohol Unit, Alessandria, Italy

[14] Alcohol Unit, Turin, Italy

[15] Regional Centre on Alcohol, Genoa, Italy

[16] Alcohol Unit, Cosenza, Italy

[17] Alcohol Unit, Savona, Italy

[18] Department of Internal Medicine, Mater Dei Hospital, Bari, Italy

[19] National Observatory on Alcohol, National Institute of Health, Rome, Italy

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Introduction

Around 2 billion people worldwide consume alcoholic beverages. Alcohol consumption is responsible for 5.9% of all causes of death and for 5.1% of all causes of disease in the world [1]. The chronic use of alcohol can lead to the onset of an Alcohol Use Disorder (AUD) as defined in the new version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), which, with respect to previous editions, has eliminated the stigmatizing terms of abuse and dependence [2]. The prevalence of AUD ranges from 13 to 30% (about 20% of men and 10% of women) in most Western societies [1, 3]. In addition, up to 42% of patients admitted to general hospitals, one-third of patients admitted to hospital intensive care units [4], and up to 50% of those hospitalized in psychiatric divisions, present an AUD [1, 5].

Within the range of treatments for AUD, some conditions such as acute alcohol intoxication (AAI) and alcohol withdrawal syndrome (AWS) may occur and require a specific approach. In fact, about 50% of persons with an AUD may have symptoms of AWS when they reduce or discontinue their alcohol consumption; in 3–5% of these persons, grand mal convulsions, severe confusion (a delirium), or both develop [6].

Although AUD affects more than 20% of patients in most medical settings, few physicians have been adequately trained in identifying and treating these serious problems [6]. It is, therefore, essential that practitioners, physicians who are experts in AUD working with outpatients, and clinicians working with in-patients in Emergency and Internal Medicine Departments know how to prevent, recognize, and treat AAI and severe withdrawal states so as to minimize costly hospitalizations and avoidable deaths.

Methods

A task force of members of the Italian Society on Alcohol (ISA) consisting of specialists in gastroenterology, hepatology, clinical pharmacology, psychiatry, internal medicine, gerontology, and toxicology experts in the treatment of alcohol addiction was identified by the president, as appropriate. Thereafter, a writing group produced a first draft of the document. To obtain a widespread consensus, the draft was distributed to all the members of the national directive of the ISA. The ensuing final draft was then approved by the ISA.

The following protocols of internal validity such as the National Programme of Guidelines of the Italian Institute of Health [7] and of external validity [8–10], levels of evidence and GRADE of recommendations were assigned (Table 1). Moreover, in the development process of this position paper, we consulted the following guidelines: the American Psychiatric Association [11], the National Institute for Clinical Excellence (NICE) [12], the French Alcohol Society and the European Federation of Addiction Societies [13], and the World Federation of Societies of Biological Psychiatry [14].

Diagnosis and treatment of acute alcohol intoxication

AAI is an intercurrent, potentially transitory condition that is caused by drinking a considerable amount of alcohol. In this condition, the rapid crossing of the blood–brain barrier by large quantities of alcohol is initially responsible for *behavioural alterations* such as euphoria, dysphoria, social disinhibition, sleepiness, belligerence and aggressiveness, and, as the blood alcohol concentration increases, lethargy, stupor and coma can gradually appear [15, 16]. A transitory memory deficit may occur, with

Table 1 Level of evidence and grade of recommendations (adapted from the Italian Programme of Guidelines of the Istituto Superiore di Sanità in accordance with International Programmes)

Level of evidence	
Level 1	Data derived from meta-analyses or systematic reviews or from (multiple) randomized controlled trials with high quality
Level 2	Data derived from a single randomized controlled trial
Level 3	Data derived from multiple non-randomized studies
Level 4	Data derived from retrospective observational studies or case–control studies
Level 5	Data derived from case series studies without control groups
Level 6	Data derived from expert opinions or consensus conference
Grade	
A (strong)	Strong recommendation: factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes and cost
B (weak)	Weaker recommendation: variability in preferences and values, or more uncertainty
C	The existing evidence is conflicting, and does not allow a recommendation to be made for or against the use of the action; however, other factors may influence decision making
D	There is fair evidence to recommend against the action
E	There is good evidence to recommend against the action

the subject not remembering what happened once he or she has sobered up [15, 16]. AAI is able to cause several *metabolic alterations* including hypoglycaemia, lactic acidosis, hypokalaemia, hypomagnesaemia, hypoalbuminaemia, hypocalcaemia, and hypophosphataemia. AAI may occasionally lead to *neurological complications*; these may include *acute myopathy* characterized by pain, muscular flaccidity and rhabdomyolysis with high blood levels of creatinine phosphokinase (CPK) and myoglobinuria: severe cases are potentially lethal due to the onset of hyperkalaemia and acute renal insufficiency due to rhabdomyolysis. *Cardiovascular effects* including tachycardia, peripheral vasodilatation, and volume depletion may appear; these features can contribute to the induction of hypothermia and hypotension. One possible cardiovascular effect is "holiday heart syndrome", characterized by atrial or ventricular tachy-dysrhythmias and new-onset atrial fibrillation after acute alcohol ingestion [16]. *Gastrointestinal effects* include nausea, vomiting, diarrhoea, abdominal pain secondary to gastritis, peptic ulcer, and pancreatitis. AAI can induce *acute alcoholic hepatitis* (AAH), usually in subjects with chronic and heavy alcohol use or in patients affected by alcoholic liver cirrhosis. Most often the diagnosis is suggested by a history of excessive alcohol use in patients with features of hepatic decompensation (see below).

Symptoms are usually related to blood alcohol concentration (BAC) and, in cases of severe AAI, respiratory depression and arterial hypotension can lead to death. The fatal dose of alcohol is extremely variable due to individual differences in its metabolism. In general, the consumption of a standard drink (an alcoholic beverage containing approximately 12 g of alcohol such as a big glass of beer, a normal glass of wine, or a small glass of gin) induces a BAC of approximately 0.2 g/L. This amount of alcohol is metabolized in approximately 1 h [15, 16]. However, several factors other than the number of drinks influence BAC, such as age, gender, body weight, and consumption during a meal or not. At a BAC higher than 300 mg/dL, there is an increased risk of respiratory depression and arrest. Death attributable to AAI generally occurs at a BAC higher than 500 mg/dL although the lethal dose of alcohol can be variable [15, 16]. However, in AUD patients who develop tolerance to alcohol as a result of repeated exposure to ethanol, these effects may become reduced [15–17]. This phenomenon seems to be related to compensatory changes in excitatory *N*-methyl-D-aspartate (NMDA) and inhibitory gamma-aminobutyric acid (GABA) [15–17]. The risk of fatal AAI further increases when alcohol is assumed in combination with other sedative drugs such as opioids or benzodiazepines (BDZs) [15, 16]. In addition, several different conditions can mimic the clinical features of AAI and should, therefore, be excluded. These conditions include: other substance-related intoxication, metabolic alterations, neurological causes (including seizure and trauma), infectious diseases, hypotension, hypo- or hyperthermia, hypo- or hyperthyroidism, dehydration, hypoxia, and respiratory depression [16].

In the event of AAI, it is necessary to monitor vital functions, perform a careful neurological objective assessment, check for signs of recent trauma and, if possible, measure BAC (< 1 g/L cause euphoria and psychomotor disorders; > 1 g/L trigger the classic symptoms of drunkenness) [15, 16]. In cases of mild/moderate AAI (BAC < 1 g/L), no drugs are necessary, but vital functions should be monitored, liquids administered in the event of dehydration (1500 ml of 5% glucose solutions and saline) and the patient kept under observation for withdrawal symptoms. In cases of severe AAI (comatose/semi-comatose conditions) (BAC > 1 g/L), it is important to support ventilation mechanically, identify any additional causes of coma and, if necessary, correct hypoglycaemia (5% glucose solution), hydro-electrolyte imbalance and acid/base balance, administer vitamin B and vitamin C supplements, perform gastrolavage and administer activated charcoal only within 2 h of drinking a considerable amount of alcohol [15, 16]. If the use of other sedative drugs is suspected, specific antidotes may be administered. Namely, if the use of opioids (e.g. heroin) is suspected, naloxone (an antagonist of mu opioid receptors; 0.4 mg i.v. or i.m.) should be administered every 30 min because of its short half-life, bearing in mind the risk of possible opioid withdrawal syndrome in opioid-dependent subjects. If BDZs are used, flumazenil (an antagonist of benzodiazepines binding sites, 0.2 mg, repeated every min, up to 3 mg) should be i.v. administered until sedation reverses [15]. Because of the short half-life, its administration may need to be repeated after half an hour.

Finally, it is possible to administer drugs that reduce the BAC and acetaldehyde concentrations, such as reduced glutathione 600 mg i.v., *S*-adenosylmethionine 400 mg i.v. or metadoxine 300–900 mg i.v. diluted in 500 cc. of saline or electrolyte solution in a single daily administration for 2–3 days [16]. In particular, 900 mg of metadoxine i.v. can speed up the elimination of alcohol and, therefore, lead to a more rapid resolution of the symptoms of AAI than placebo [18] (see Box 1).

Box 1: Management of acute alcohol intoxication in adults

- In the case of AAI, no drugs are generally necessary, but vital functions should be monitored, liquids administered in the case of dehydration, and the patient kept under observation for the onset of alcohol withdrawal symptoms
- In the case of severe AAI with coma, it is important to support ventilation mechanically, identify any additional causes of coma and, if necessary, correct hypoglycaemia with 5% glucose solution, hydro-electrolyte imbalance and base acid balance, administer vitamin B and vitamin C supplements, perform gastro-lavage and administer activated charcoal only within 2 h of drinking a considerable amount of alcohol.
- In the case of the simultaneous use of other sedative drugs, specific antidotes should be administered naloxone (0.4 mg i.v. or i.m. repeated, if necessary, every 30 min) for the use of opioids and flumazenil (0.2 mg, repeated, if necessary, every minute up to 3 mg) for the use of BDZs.
- The administration of drugs (metadoxine 900 mg i.v.) that reduce the blood alcohol and acetaldehyde concentrations leads to a more rapid resolution of the symptoms (Grade A2).
- Resolve the symptoms of alcohol hangover more rapidly; fruit and fruit juice, sleep and physical rest, anti-acid drugs, acetylsalicylic acid, and caffeine may be helpful.

Acute alcohol intoxication among children and adolescents

Small children tend to present with an AAI when there is an accidental consumption of any product containing ethanol in their composition, such as mouth washes, cosmetics, cleaning products, or beverages left by their parents at home [19]. Making such substances inaccessible to children significantly reduces the likelihood of accidents. BAC depends on the relative amount of total body water. In fact, infants with more body water have a lower BAC than older children after equivalent doses of ethanol; however, immature hepatic alcohol deydrogenase activity limits the ability of children under 5 years of age to metabolize alcohol, so that coma can occur at lower BAC in children than in adults [20]. In addition, younger teenagers may present in coma with a positive pain reaction, on average, at a BAC of 1.5 g/L, and in coma with no pain reaction at a BAC of 1.9 g/L [20]. Data indicate that the lethal dose of alcohol varies as widely among children and adolescents as it does among adults, and it is not possible to draw any definitive conclusions about the lethal BAC for infants and adolescents.

Adolescents also present a higher probability of intentional AAI, especially in a pattern known as "heavy episodic drinking", such as *binge drinking,* which consists in the intake of large amounts of alcohol (5 units or more) in a short period of time (approximately in 2 h). Indeed, approximately 15% of adolescents aged 15 years and older engage in binge drinking [21]. The pattern of repeated binge drinking is frequently correlated to brain disorders that may develop into alcoholism in adulthood. Furthermore, AAI represents the most frequent cause of hospitalization for children under 16 years of age [16, 20, 21]. Namely, 1% of all Emergency Department (ED) visits by 13–15 year olds and 2% of visits by 16–17 year olds are attributable to AAI. Recent data from the Italian Ministry of Health have shown that 8% of ED visits for alcohol problems are subjects < 17 years [22], and 17% of all ED visits for AAI are adolescents < 14 years old [22].

AAI can have several potentially lethal metabolic effects particularly in adolescents. Hypoglycaemia is a rare effect in adults, but children and adolescents are at greater risk of developing it [16, 19, 20]. In particular, hypoglycaemia reported in small children is difficult to detect, and this state is dangerous because a delay in treatment can lead to death or neurologic damage [20]. In normal adults, 44–72 h of fasting is necessary to induce alcohol hypoglycaemia, while in children a smaller period of time is need to deplete reserve of liver glycogen [20]. Other metabolic effects such as acidosis, hypokalaemia, hypomagnesaemia, hypoalbuminaemia, hypocalcaemia, and hypophosphataemia may also occur together with cardiovascular effects (tachycardia, peripheral vasodilation, and volume depletion) that may contribute to the induction of hypothermia and hypotension. Namely, peripheral vasodilatation and depression of the central nervous system lead to hypothermia [20]. In young individuals, the effects of AAI such as hypoglycaemia and hypothermia tend to be more severe than in adults. As adolescents usually do not show tolerance to the effects developed by repeated exposures to ethanol, they may be more exposed to the toxic effects of this substance [20]. Furthermore, the context of drinking and gender differences also plays a relevant role in the occurrence of AAI in adolescents and needs more in-depth investigation. Youth drinking has become more visible over time, because adolescents might have relocated their drinking settings to public places and public facilities and hence are more often admitted to hospital [21]. In a recent study, girls and boys differ significantly in time of admission, drinking situation, drinking occasion and admission context; girls drink more often in public than boys and, in fact, the proportion of patients admitted to hospital from pubs or bars is higher in

girls than in boys [21]. The context of drinking and gender, therefore, needs to be considered in the development and implementation of targeted group-specific prevention and intervention measures.

Before starting treatment of AAI, it is important to estimate the BAC. If BAC is increasing, the adolescent should be closely monitored for depression of the central nervous system. When this objective measure is not available, it can be estimated by the amount consumed and how much time has passed since the last drink. The management of AAI for all adolescents should be focused on the clinical complications present, such as the correction of hypoglycaemia, hypomagnesaemia, or management of restlessness. For severe restlessness, typical antipsychotics, such as haloperidol, should be preferred, because of a lower chance of alcohol interaction. Gastric content aspiration should be prevented with the administration of antiemetics, as well as maintaining airway patency, depending on the degree of patient sedation. Venous access may be necessary, to ensure fluid administration. In children and adolescents, the treatment follows the same guidelines as adults, with special attention to hypoglycaemia and hypothermia. There are no studies on metadoxine use for this purpose in the paediatric population [16, 19, 20].

The challenge in the care of children and adolescents thus starts at problem detection, which is often correlated to the co-assumption of alcohol and other drugs. The delay in the diagnosis or non-diagnosis of a disorder caused by psycho-active substance use in the ED may increase hospitalization time, costs, and the risk of re-hospitalization. In addition, drug testing in adolescents always includes important ethical and confidentiality issues with parents. Generally, the adolescent should always consent to the test. In serious situations, such as accident victims, suicide attempts, seizures, or other risk situations in which the patient's consent cannot be obtained, it is justifiable to perform them without his/her consent. Adolescents may authorize or not authorize their parents' access to the result, although parents are always authorized to see the results of drug and alcohol tests in the case of an acute risk situation, regardless of the patient's wishes. When an adolescent who uses psycho-active substances is identified, a more detailed assessment of this use becomes necessary. In an ED, information on the concomitant use of psycho-active substances, amounts, and time since the last intake is essential for symptom management. Based on these data, it should be estimated whether the intoxication symptoms will increase or decrease in the next few hours [19]. The ED may thus be an appropriate setting in which to intervene at a time directly coupled to the consequences of an alcohol-related event or problem [19]. Because adolescents may not recognize their alcohol consumption as being problematic, know where to seek assistance, or may be embarrassed to ask for help, an ED visit can play an important role in early identification and prevention of heavy alcohol use [23]. However, studies are still controversial on this topic, showing that brief intervention performed in an ED, even if it appears feasible, is not always efficient in terms of prevention of further episodes of heavy alcohol use among adolescents [24]. Further considerations on improving the outcomes for this relevant target group are, therefore, required [21] (see Box 2).

Box 2: Management of acute alcohol intoxication in adolescents

- Adolescents usually do not show tolerance to the effects developed by repeated exposure to ethanol and they have immature hepatic alcohol deydrogenase activity, so they may be more exposed to the toxic effect of alcohol and consequently to the rapid onset of coma.
- The lethal dose of alcohol varies as widely among children and adolescents as it does among adults, and it is not possible to draw any definitive conclusions about the lethal BAC for infants and adolescents.
- Hypoglycaemia and hypothermia induced by AAI tend to be more severe in young individuals than in adults, so that the management of AAI for all adolescents should be focused on the prompt correction of hypoglycaemia, hypothermia and restlessness; for severe restlessness, typical antipsychotics (such as haloperidol) should be administered, because of a lower chance of alcohol interaction.
- The administration of antiemetics is preferred to gastric content aspiration, as well as maintaining airway patency; venous access is necessary to ensure fluid administration.
- So far, no studies have been performed on metadoxine use for the improvement of symptoms of AAI in the paediatric population.

Hangover syndrome (HS)

A few hours after stopping drinking, when the blood alcohol level starts to fall, the symptoms of AAI gradually lead to the onset of symptoms known as hangover syndrome (HS) [25, 26]. HS is characterized by a series of physical symptoms (headache, asthenia, tremors, sweating, red eyes, myalgia, thirst, systolic arterial hypertension and tachycardia) and mental symptoms (dizziness, photophobia, increased sensitivity to noise, cognitive and mood disorders, especially depression-, anxiety and irritability). The symptoms peak when the blood alcohol concentration reaches zero and may continue for the next 24 h. There are factors that exacerbate the intensity of HS, including fasting,

sleep deprivation (in terms of both quality and quantity), and increased physical activity during AAI (due to the accelerated metabolism of alcohol). An important role in the onset of HS is played by the type of alcohol drunk: drinks with few additives (vodka, pure alcohol and gin) are associated with a lower incidence of HS, while alcoholic drinks containing a number of additives (red wine, brandy and whisky) are associated with a higher incidence of this syndrome. HS generally abates within 8–24 h [25, 26]. The general indications for the treatment of this syndrome are: fruit or fruit juice to reduce the intensity of the syndrome, fructose-rich foods and complex carbohydrates to improve hypoglycaemia, antacid drugs to improve nausea and vomiting, acetylsalicylic acid or non-steroidal anti-inflammatory drugs to reduce headache and myalgia, (*caution* in the case of nausea and abdominal pain; these can cause and exacerbate gastritis), caffeine to improve tiredness and general malaise, and sleep and physical rest to improve the tiredness caused by alcohol-induced sleep deprivation. Drinking alcohol to treat HS is contraindicated as it creates a vicious circle that intensifies the symptoms and the toxicity of the alcohol [27].

Diagnosis of alcohol withdrawal syndrome

According to the DSM-V criteria, AWS is defined as: (a) cessation or reduction in alcohol use that has been heavy and prolonged; (b) two (or more) of the following, developing within several hours to a few days after criterion A: autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual/auditory/tactile hallucinations or illusions, psychomotor agitation, anxiety, and generalized tonic–clonic seizures [2].

From the pathophysiologic point of view, chronic exposure to alcohol leads to significant modifications in the receptor systems present in the central nervous system (CNS). In particular, there is a reduction in the number, the functions and the sensitivity of the $GABA_A$ receptor to gamma-aminobutyric acid (GABA) (the main inhibitory neurotransmitter present in the CNS) known as down-regulation, and an increase in the number, the sensitivity and the affinity of glutamate (the main excitatory neurotransmitter present in the CNS) to the *N*-methyl-D-aspartate (NMDA) receptors known as up-regulation [17, 28]. The abrupt reduction or suspension of alcohol intake in a subject with a severe AUD is receptorially characterized by reduced GABA activity and increased glutamatergic activity with hyperexcitability and development of withdrawal symptoms [29, 30]. In addition, the over-regulation of the dopaminergic and noradrenergic system might be responsible for the development of, respectively, hallucinations and autonomic hyperactivity. The mechanism of kindling (triggering, evoking) is represented by an increase in neuronal sensitivity and excitability that occur in the CNS after repeated episodes of AWS; this mechanism has been proposed as a risk factor for the progression from mild AWS to its more severe form. In fact, subjects who over time present repeated episodes of AWS have a greater risk of developing a more severe form of the syndrome with more rapid onset of the symptoms.

The symptoms of AWS generally appear 6–8 h after the last drink and reach a peak in the subsequent 24–72 h [31, 32]. The first symptoms of AWS are tremor, nausea, vomiting, insomnia, agitation, delirium and visual (macro and micro-zoopsias) or auditory hallucinations (voices), or other perception disorders. These may be compounded by symptoms of autonomic hyperactivity: red face, tachycardia, profuse sweating, hypertension and hyperthermia. Six to 48 h after the last drink, convulsions may also appear, which are usually generalized unless there is an underlying neurological disease. Epileptic disease is rare. Subjects with an epileptic seizure during AWS must not be considered as affected by "latent epilepsy", and do not need chronic anticonvulsant treatment. Trauma, stress, intercurrent infections and malnutrition, but also inappropriate pharmacological treatment, can cause AWS to progress towards its most dramatic complication, delirium tremens (DTs) [6, 30, 33]. In particular, DTs is a clinical condition characterized by a cognitive and attention disorder with rapid and fluctuating onset, sometimes also accompanied by hallucinations [6]. In 80% of cases, DTs abates within 72 h if treated pharmacologically, and the patient often does not remember the occurrence. Rarely, one or more relapses in DTs characterized by alternated periods of total or partial lucidity may occur, lasting for period of a few days up to 4–5 weeks.

Treatment of alcohol withdrawal syndrome

Non-pharmacological treatment

The main aim of the treatment of AWS is to minimize the severity of the symptoms in order to prevent the onset of the more severe complications of this syndrome (convulsions and DTs) and to improve the patient's quality of life.

The non-pharmacological approach is important as, in some cases, it is enough to resolve the AWS. This includes nursing support to monitor vital parameters (blood pressure, heart rate and body temperature) and continuous reassurance of the patient; if available, a quiet room, with not too much light but not too dark, is very useful.

Hydration (if necessary) up to 1500–2000 cc with 5% glucose solutions and saline together with the administration of vitamin supplements, in particular, Vit B_1 (thiamine) (200 mg daily i.m. or preferably i.v. for 3–5 days), Vit B_6

and B_{12}, vitamin C and folates to prevent the onset of Wernicke's encephalopathy is considered the most appropriate approach [34, 35]. Indeed, thiamine is a vital component of carbohydrate metabolism and deficiency leads to decreased glucose utilization [36]. Wernicke's disease is characterized by ophthalmoplegia of the VI cranial nerve, ataxia and mental confusion; however, this full triad is present in only one-third of cases, requiring an aggressive search for its presence [36]. If the diagnosis of Wernicke's encephalopathy is confirmed, the treatment consists of a higher dose of thiamine (500 mg i.m. or i.v. every 8 h for at least 3 days) plus Vit B_6, B_{12} and Vit C [35–37]. Since the i.v. administration of glucose can theoretically trigger or worsen Wernicke's disease, the thiamine should be administered before the glucose infusion. In the event of peripheral neuropathy, it is advisable to continue the oral administration of Vit B_1 at the dose of 300 mg/day until a clinical improvement is achieved [31, 32].

Moreover, during AWS, magnesium acts by inhibiting the neurotransmission of glutamate, thus inducing a reduction in the hyperexcitability of the NMDA system. However, a recent Cochrane review shows that there are not enough reports in the literature to support the use of magnesium to prevent or treat AWS [38]. Nevertheless, in view of the fact that the chronic use of alcohol and AWS is closely correlated with the lengthening of the QT interval, with the risk of dysrhythmia [39], the serum values of magnesium should be checked and supplemented if necessary. Finally, hypokalaemia is frequently encountered and repletion is necessary [36].

Pharmacological treatment: the benzodiazepines (the "gold standard")

The decisional process that guides the pharmacological treatment of AWS is based on an assessment of the real need for treatment, and on the repeated clinical checks that indicate whether or not the treatment should be continued. Monitoring involves using an easy-to-administer, repeatable and sensitive measuring scale. The scale most commonly used is the Clinical Institute of Withdrawal Assessment for Alcohol Scale (CIWA-Ar) (Table 2) [40]. This scale is used to determine the severity of the AWS. The CIWA-Ar scale examines 10 parameters: nausea and vomiting, agitation, anxiety, hearing disorders, visual disorders, sensory alterations, headache, sweating, tactile disorders and tremors. The scale can be administered at the patient's bedside in around 5 min; it is important to administer the scale frequently so that, when necessary, pharmacological treatment can be promptly started. The CIWA-Ar makes it possible to identify three categories of AWS:

- *Mild AWS (CIWA-Ar < 8 points)*: The patient does not need pharmacological treatment, but the withdrawal symptoms should be monitored for at least 24 h during which the CIWA-Ar scale, administered every 8 h, must not exceed 10 points, and, in any case, if risk factors predicting the onset of a severe form of AWS are present, a pharmacological treatment has to be considered as well [6, 31, 41] (Fig. 1);
- *Moderate AWS (CIWA-Ar 8–15 points)*: Pharmacological treatment is appropriate and the CIWA-Ar scale should be administered every hour to evaluate the efficacy of the treatment (Fig. 1);
- *Severe AWS (CIWA-Ar > 15 points)*: Pharmacological treatment is strongly recommended since this condition may be complicated by the onset of convulsions and DTs (Fig. 2); the scale should be administered every hour to evaluate the efficacy of the treatment [6].

Out-patient treatment is appropriate in patients with mild or moderate AWS with a CIWA-Ar < 15, this approach minimizes expense and allows for less interruption of work and family life. However, if contraindications to an outpatient treatment exist, a residential treatment is required [42]. In addition, patients with a severe AWS with a CIWA-Ar > 15 always need to be treated as in-patients.

BDZs are the "gold standard" for the pharmacological treatment of AWS since they have demonstrated a similar efficacy to neuroleptics, clonidine, beta-blockers and anticonvulsants in resolving withdrawal symptoms [30]. BDZs are, moreover, the only class of drugs with confirmed efficacy in preventing the development of AWS complications, with a reduction in the incidence of convulsions (84%), DTs and the associated risk of mortality [29, 33]. No study has shown a clear superiority of one benzodiazepine with respect to another in the treatment of AWS. The efficacy of BDZs in the treatment of AWS appears to be mediated by stimulation of the $GABA_A$ receptors, thus with alcohol-mimicking properties. The clinical effect of BDZs is connected to the drug itself, and to its metabolites produced by hepatic oxidation and subsequently rendered inactive and eliminated. Diazepam is the first-choice BDZ in the treatment of AWS (Table 3). The most important scientific evidence of the efficacy of BDZs was in fact found in those with a long half-life such as chlordiazepoxide and diazepam. However, in view of the increased risk of excessive sedation, memory and motor disturbances and respiratory depression, particular care should be taken with the use of BDZs with a long half-life in elderly patients and in those with hepatic insufficiency, preferring BDZs with a short half-life such as oxazepam (15 mg, 1 or 2 times a day and, if necessary, increasing with caution up to 15 mg in 3 or 4 daily administrations) and lorazepam (1–2 mg, 1 or 2 times a day, then adjusting the dose according to the tolerability and the patient's response);

Table 2 CIWA-Ar scale for measuring the severity of alcohol withdrawal syndrome (score from 0 to 67). Adapted from Sullivan et al. [40]

Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised

Patient: _____ **Date:** _____ **Time:** _____ **(24-hour clock, midnight = 00:00)**

Pulse or heart rate, taken for one minute: _____ **Blood pressure:** _____

NAUSEA AND VOMITING

Ask "Do you feel sick to your stomach? Have you vomited?" Observation.

0 No nausea and no vomiting
1 Mild nausea with no vomiting
2
3
4 Intermittent nausea with dry heaves
5
6
7 Constant nausea, frequent dry heaves and vomiting

TACTILE DISTURBANCES

Ask "Have you had any itching, pins and needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?" Observation.

0 None
1 Very mild itching, pins and needles, burning or numbness
2 Mild itching, pins and needles, burning or numbness
3 Moderate itching, pins and needles, burning or numbness
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

TREMOR

Arms extended and fingers spread apart. Observation.

1 Not visible, but can be felt fingertip to fingertip
2
3
4 Moderate, with patient's arms extended
5
6
7 Severe, even with arms not extended

AUDITORY DISTURBANCES

Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.

0 Not present
1 Very mild harshness or ability to frighten
2 Mild harshness or ability to frighten
3 Moderate harshness or ability to frighten
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

PAROXYSMAL SWEATS

Observation.

0 No sweat visible
1 Barely perceptible sweating, palms moist
2
3
4 Beads of sweat obvious on forehead
5
6
7 Drenching sweats

VISUAL DISTURBANCES

Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.

0 Not present
1 Very mild sensitivity
2 Mild sensitivity
3 Moderate sensitivity
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

ANXIETY

Ask "Do you feel nervous?" Observation.

0 No anxiety, at ease
1 Mildly anxious
2
3
4 Moderately anxious, or guarded, so anxiety is inferred
5
6
7 Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

HEADACHE, FULLNESS IN HEAD

Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.

0 Not present
1 Very mild
2 Mild
3 Moderate
4 Moderately severe
5 Severe
6 Very severe
7 Extremely severe

AGITATION

Observation.

0 Normal activity
1 Somewhat more than normal activity
2
3
4 Moderately fidgety and restless
5
6
7 Paces back and forth during most of the interview, or constantly thrashes about

ORIENTATION AND CLOUDING OF SENSORIUM

Ask "What day is this? Where are you? Who am I?"

0 Oriented and can do serial additions
1 Cannot do serial additions or is uncertain about date
2 Disoriented with date by no more than two calendar days
3 Disoriented with date by more than two calendar days
4 Disoriented with place or person

Total CIWA-Ar score: _____

Rater's initials: _____

Maximum possible score is 67

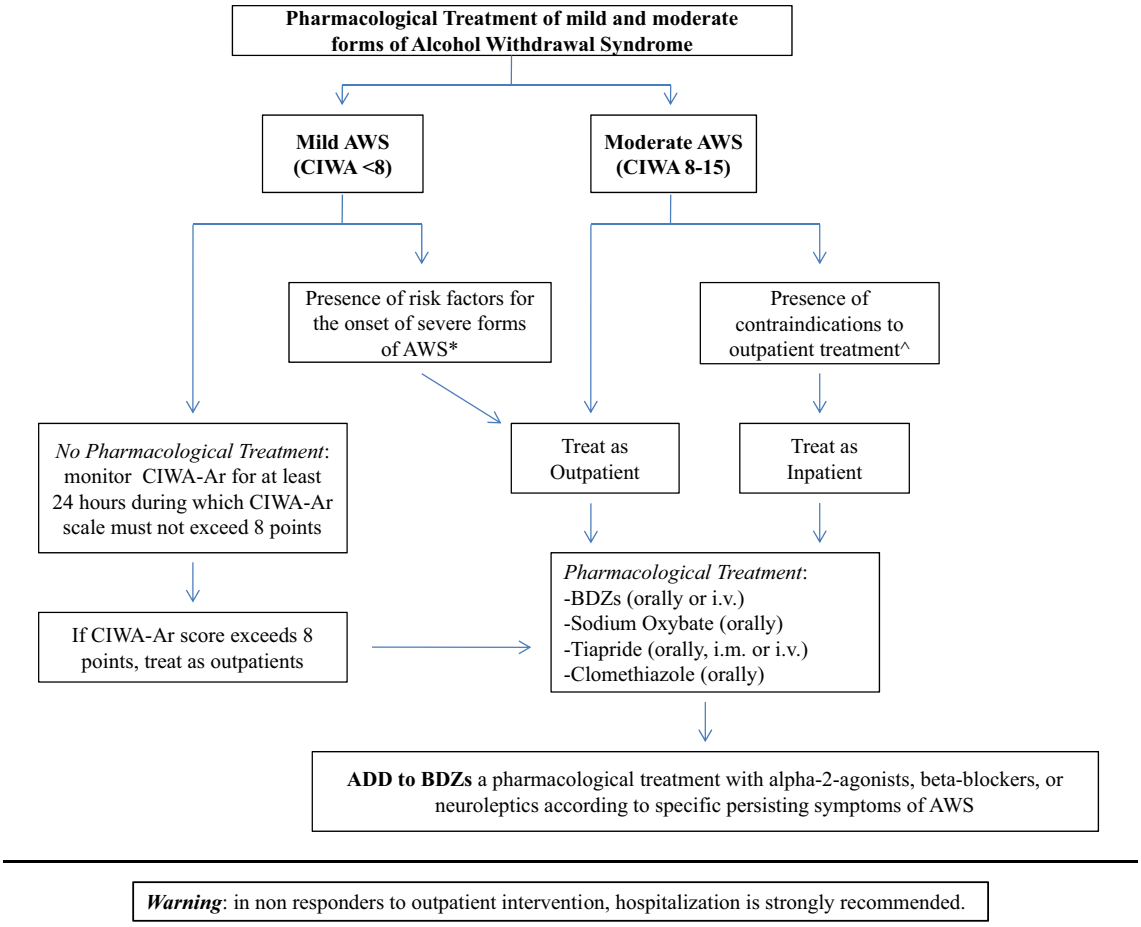

Fig. 1 Algorithm of the pharmacological treatment of the mild and the moderate forms of AWS. *Previous episodes of AWS (detoxification, rehabilitation, convulsions, DTs), concomitant use of CNS sedatives such as benzodiazepines (BDZs) and barbiturates, concomitant use of illegal substances, high blood alcohol levels (> 200 mg/dL), autonomic hyperactivity (systolic arterial pressure > 150 mmHg, body temperature > 38 °C), elderly subjects, concomitant diseases or disorders (infections, liver disease, CNS infections, electrolyte imbalance, hypoglycaemia), trauma and recent surgery and orthopaedic procedures, severe AUD, significant increase of AST, recent episode of AAI, and male gender. ^severe AWS, high risk of DTs and history of withdrawal seizures, poorly controlled chronic medical conditions (diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure), serious psychiatric conditions (suicidal ideation, psychosis), and the absence of a support network

in addition, oxazepam and lorazepam do not undergo hepatic oxidation with subsequent formation of active metabolites [31, 32, 35, 43].

If BDZs do not completely resolve the AWS, other categories of drugs can be used, such as alpha-2-agonists, beta-blockers, neuroleptics and anti-convulsants, but administered only in association with BDZs when the latter are not sufficient to control the symptoms of AWS, in particular, the symptoms of autonomic hyperexcitability, such as arterial hypertension and tachycardia, and those of dopaminergic hyperactivity, such as auditory and visual hallucinations and convulsions [6]. The drugs and their doses are summarized in Table 4.

There are two common methods of administration of BDZs in the pharmacological treatment of AWS; the symptom-triggered regimen and the fixed-schedule regimen (Table 3).

In the fixed-schedule regimen, the BDZs must be administered at regular intervals regardless of the patient's symptoms, reducing the dose by 25% every day from day 4 until day 7, when the treatment is discontinued [30, 33]. Additional doses can be administered if the symptoms are not adequately controlled. This approach is highly effective and its use is preferable in patients at risk of developing a severe form of AWS or in patients with a history of convulsions and DTs. However, patients must be kept under strict surveillance due to the risk of excessive sedation or respiratory depression.

The symptom-triggered regimen is based on the administration of BDZs; the severity of the symptoms is measured every hour, and the dose of the BDZs is adjusted on the basis

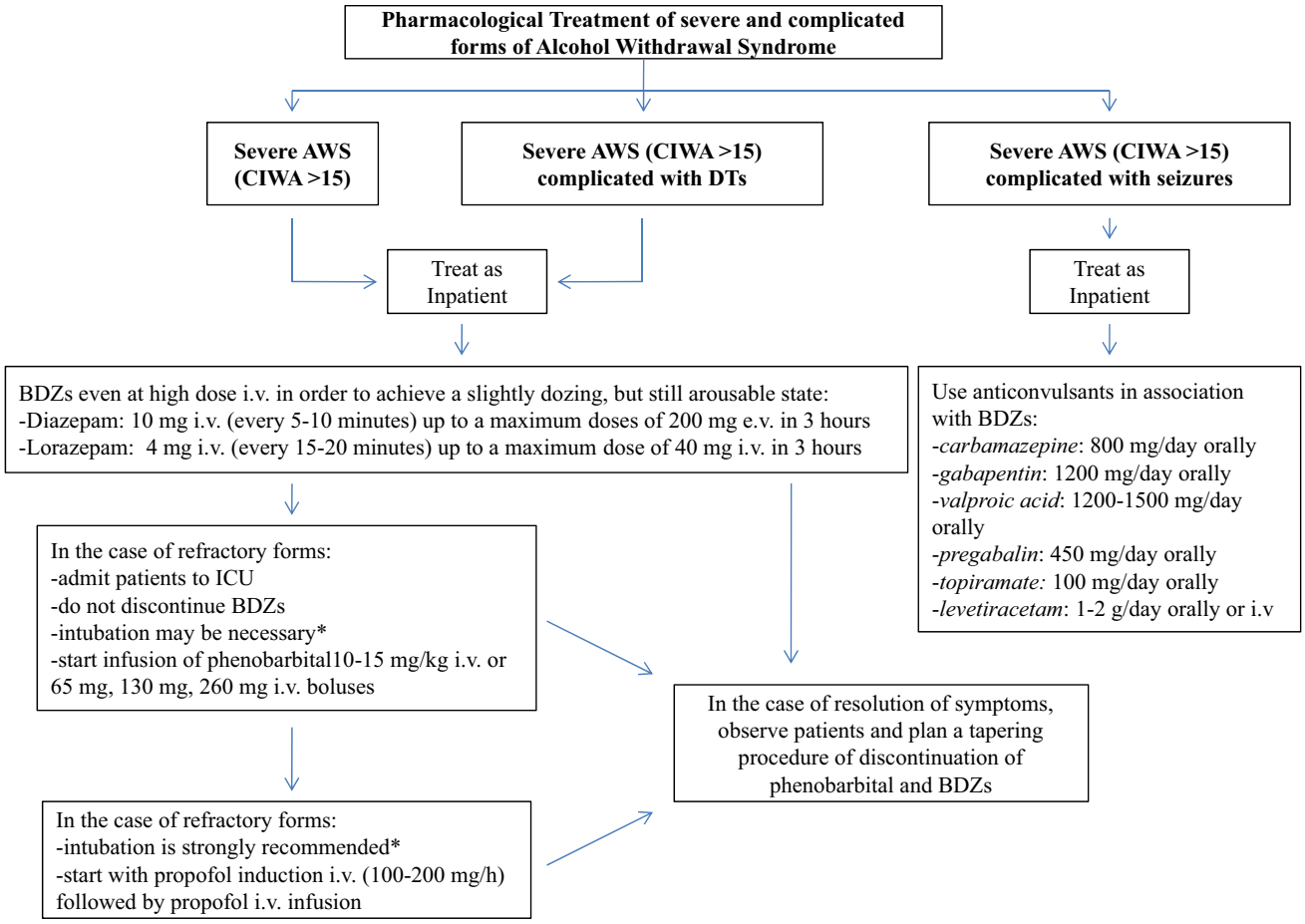

Fig. 2 Algorithm of the pharmacological treatment of the severe and complicated forms of AWS. *Propofol and barbiturates increase the likelihood of respiratory insufficiency and coma so that before beginning a treatment with these two drugs intubation and mechanical ventilation is often necessary and the need for ICU is, thus, warranted

Table 3 The two methods of treatment for alcohol withdrawal syndrome (treat only if CIWA-Ar > 8 points)

Treatment with a symptom-triggered regimen
Chlordiazepoxide: 50–100 mg orally[a]
Diazepam: 10–20 mg orally or i.v.[a]
Lorazepam: 2–4 mg orally, i.v. or i.m.[a]
Oxazepam: 60–90 mg orally[a]
Treatment with a fixed-schedule regimen
Chlordiazepoxide: 50–100 mg every 6 h (day 1), then 25–50 mg every 6 h (days 2 and 3)[b]
Diazepam: 10 mg orally or i.v. every 6 h (day 1), then 5 mg every 6 h (days 2 and 3)[b]
Lorazepam: 2 mg orally or i.v. every 6 h (day 1), then 1 mg every 6 h (days 2 and 3)[b]
Oxazepam: 60–90 mg orally or i.v. every 6 h (day 1), then 30–60 mg every 6 h (days 2 and 3)[b]
Tiapride: 400–1200 mg orally i.m. or i.v. every 4–6 h from day 1 to day 3[c]
Sodium oxybate: 50–100 mg/kg fractioned into 3 or 6 daily administrations (every 4 or 6 h) from day 1 to day 3[c]

[a]Administer CIWA-Ar every hour, and if score persists > 8 points, repeat the administration of the drug

[b]On day 4, start to gradually reduce the dose by 25% every day until day 7, then suspend

[c]On day 4, follow a tapering procedure according to the attenuation of symptoms: you may then decide to continue the administration of the drugs in the maintenance of alcohol abstinence at the dosages of 50 mg/kg per day for sodium oxybate and 300 mg/day for tiapride

Table 4 The drugs listed below should only be used in addition to BDZs if some specific symptoms of AWS are present

In the case of persistent agitation, perception disorders or thought disorders (visual and/or auditory hallucinations or illusions) use neuroleptics
Haloperidol: 0.5–5 mg every 30–60 min i.v. or i.m. or 0.5–5 mg every 4 h orally
In the case of arterial hypertension use α-adrenergics
Clonidine: 0.150–0.300 mg/day i.m. or orally
In the case of persistent tachycardia use β-blockers
Atenolol: 100 mg/day orally

of the severity of the symptoms and can be repeated every hour until the CIWA-Ar score is < 8.

Even if published studies have not shown any significant differences between the two methods of treatment of AWS, the symptom-triggered regimen reduces the total consumption of BDZs and the duration of the treatment compared to the fixed-schedule regimen in patients with a low risk of developing a severe form of AWS. From a practical point of view, in a hospitalized patient where close monitoring of clinical conditions is possible, the symptom-triggered regimen could be preferable in order to achieve the clinical effect with minimal administration of BDZs.

There is another treatment method that can be adopted only in hospitalized patients, and if an intensive care unit is available. This is the loading-dose treatment strategy. This method requires the administration of moderate doses of a BDZ with a long half-life (e.g. diazepam 10–20 mg or chlordiazepoxide 100 mg every 1–2 h) in order to induce sedation; the doses of the drug self-reduce through the drug's metabolism. The risk of toxicity is high during the initial stages of the treatment, and patients must be kept under close observation, but this approach seems to be the quickest method of treatment and able to reduce the risk of developing a more severe form of AWS by favouring resolution of the syndrome [44] (see Box 3).

Box 3: Management of alcohol withdrawal syndrome

- The most appropriate non-pharmacological approach in the treatment of AWS is hydration (if necessary) and the administration of vitamin supplements (thiamine) to prevent the onset of Wernicke's encephalopathy
- In the case of mild AWS (CIWA-Ar < 8 points), monitoring patients for at least 24 h is necessary; however, in the case of mild AWS with the presence of risk factors for the development of severe forms of AWS, pharmacological outpatient treatment has to be started.
- In the case of CIWA-Ar > 8 points, pharmacological treatment is warranted (Grade A1).
- BDZs are the gold standard for the pharmacological treatment of AWS since they are the only drugs that have been shown to prevent the onset of its serious complications (DTts and seizures) (Grade A1).
- A fixed-schedule regimen is highly effective and its use is preferable in patients at risk of developing a severe form of AWS or in patients with a history of convulsions and DTs; however, patients must be kept under strict surveillance due to the risk of excessive sedation or respiratory depression
- A symptom-triggered regimen with BDZs with a shorter half-life (lorazepam and oxazepam) could be preferable for the treatment of AWS in elderly patients (Grade B3) and in those with acute alcoholic hepatitis and advanced liver cirrhosis (Grade B3) in order to achieve the clinical effect with a minimal administration of drugs, avoiding an accumulation of the same drugs too.
- Outpatient treatment is appropriate in patients with mild or moderate AWS (CIWA-Ar < 15 points) without contraindications.
- Inpatient treatment is appropriate in severe forms of AWS (CIWA-Ar > 15 points) with or without complications (DTs and seizures).
- Alfa-2-agonists, beta-blockers, and neuroleptics should only be administered in association with BDZs when the latter are not effective in controlling specific persisting symptoms of AWS.
- GABA-ergic medications such as sodium oxybate (Grade A1) and clomethiazole (Grade A1), and dopaminergic antagonist drugs such as tiapride (Grade A1) are approved in some European Countries for the treatment of AWS and may be a further pharmacological option for the treatment of moderate forms of AWS.
- Anti-convulsants have not shown sufficient scientific evidence of efficacy for the treatment of AWS (Grade C1).

The treatment of life-threatening condition: the delirium tremens

DTs requires a specific pharmacological treatment with high doses of BDZs repeated at brief intervals of time in

order to induce a slightly dozing but still arousable state [6], using diazepam or lorazepam according to the following protocols:

1. diazepam (method I): 10–20 mg i.v. or orally every 1–4 h, if necessary; diazepam (method II): 5 mg i.v. (2.5 mg/min), then, if necessary, repeat the dose 10 min later and, if still necessary, administer 10 mg i.v. every 10 min (maximum 50 mg) until the symptoms are under control; if they persist, continue administering 5–20 mg every hour;
2. lorazepam (method I): 8 mg i.v., i.m. or orally every 15 min if necessary and, if 16 mg have been administered without regression of the DTs, administer 8 mg in i.v. bolus; lorazepam (method II): administer from 1 to 4 mg i.v. every 5–15 min until the symptoms are under control.

In addition, in the case of refractory forms of DTs, the intensive care unit (ICU) is the most appropriate setting [32, 36, 45] (Fig. 2) and the use of anaesthetic drugs may be necessary also in association with BDZs. Among the anaesthetics, barbiturates and propofol have also proved to be effective in the treatment of severe AWS or refractory DTs: however, before beginning a treatment with these two drugs, intubation and mechanical ventilation are often necessary due to the increased likelihood of respiratory depression and coma [32, 36, 45].

Barbiturates (i.e. phenobarbital) are drugs that increase the effect of the GABA system, acting synergistically with BDZs thanks to a different receptor mechanism. They can be administered orally (60–200 mg orally per day), i.m. or i.v. (10–15 mg/kg of body weight: mostly 20–260 mg every 6 h) [32, 36, 45]. Unfortunately, barbiturates have a low therapeutic index with a long half-life which makes them difficult to manage. Since there are no antidotes for barbiturates, they are rarely used in the treatment of AWS in ICU [46, 47].

Propofol increases the inhibitory effect of the $GABA_A$ receptor and reduces the excitatory circuits of the NMDA system. Due to its important lipophilic properties, it acts rapidly and thanks to its short half-life it is easy to adjust the dosage increase without the risk of accumulation [32, 36, 45]. It should be noted, however, that the induction dose requirements of propofol are increased in alcoholic patients anaesthetized with this drug [48]. Its use should, therefore, be limited to a small number of cases and, in any case, to those refractory forms of AWS to BDZs [49, 50], in hospitalized patients or in ICU settings, starting intravenously with a loading dose of 100–200 mg/h [51] (see Box 4).

Box 4: Management of severe forms of AWS complicated with seizures and delirium tremens

- Inpatient treatment is always warranted.
- BDZs are the drug of first choice for the treatment of AWS complicated with seizures (Grade A1); in the refractory forms, the association with anti-convulsants is recommended (Grade A1).
- DTs requires a specific pharmacological treatment with high doses of BDZs (diazepam or lorazepam) (Grade A1) repeated at brief intervals of time in order to induce and to achieve a slightly dozing but still arousable state.
- In the case of forms of DTs refractory to the treatment of BDZs, the use of anaesthetic drugs such as phenobarbital or propofol in association with BDZs is the most appropriate pharmacological approach (Grade A1) and the ICU is the most appropriate setting where intubation and mechanical ventilation may be necessary and in some cases strongly recommended.

Alternative and approved drugs

As an alternative to BDZs, some studies have experimented the use of other compounds such as GABA-ergic drugs (sodium oxybate, baclofen, clomethiazole, and anti-convulsants), and dopamine antagonists (tiapride) for the treatment of AWS. Sodium oxybate is approved in Italy and in Austria for the treatment of AWS, for the prevention of relapse and to maintain alcohol abstinence. Baclofen is authorized in France as a "temporary recommendation for use" [52]. Clomethiazole is approved for the treatment of AWS in Germany and Austria. Tiapride is approved in some European Countries for the treatment of AWS.

GABA-ergic drugs

Sodium oxybate, also called gamma-hydroxybutyric acid, is a short-chain fatty acid physiologically present in the CNS, particularly in the thalamus, the hypothalamus and the basal ganglia [53]. Sodium oxybate is structurally similar to the GABA neurotransmitter and binds to the $GABA_B$ receptor [54–57]. Due to its alcohol-mimicking effect in the CNS [58], it has been tested in pre-clinical and clinical settings for the treatment of AWS, with satisfactory results [56]. A Cochrane meta-analysis shows that sodium oxybate at a dose of 50 mg/kg divided into 3-6 daily administrations is more effective than placebo and as effective as BDZs (diazepam) and clomethiazole in reducing symptoms of alcohol withdrawal [55]. In particular, it acts more quickly than diazepam in suppressing some symptoms of alcohol withdrawal such

as anxiety, agitation and depression [59]. Moreover, a recent phase IV, multicentre, randomized, controlled, double-blind study with parallel groups (GATE 1) shows that the efficacy of sodium oxybate is comparable to oxazepam in the treatment of AWS [60]. Baclofen is a compound acting on the $GABA_B$ system and it is indicated for control of spasticity [61]. Baclofen can reduce the symptoms of AWS [62, 63]. In fact, a randomized single-blind study comparing baclofen (10 mg t.i.d. for 10 days) with diazepam (0.5–0.75 mg/kg/day for 6 days, then reduced by 25% a day from day 7 to day 10) for the treatment of AWS does not show any difference between the drugs in reducing the CIWA-Ar score and, thus, in suppressing symptoms of alcohol withdrawal [64]. Baclofen is manageable and well tolerated, without risk of abuse [62, 63]. Although the data are encouraging, further clinical confirmation is necessary to establish the role of baclofen in the treatment of AWS. However, a recent Cochrane analysis has shown that no conclusions can be drawn about the efficacy and safety of baclofen for the management of AWS since little and very low quality evidence has been published so far [65].

Clomethiazole has a mechanism of action characterized by reinforcement of GABA system activity with a specific action on the $GABA_A$ receptors. Clomethiazole also inhibits the activity of the alcohol-dehydrogenase enzyme responsible for the transformation of alcohol into acetaldehyde, with a consequent lowering in the onset of AWS. In a double-blind study with two different formulations (tablets and oral solution), this drug administered at a daily dose of 1 g proves to be as effective as sodium oxybate in improving symptoms of alcohol withdrawal [66] and, in a further study carried out on hospitalized patients undergoing treatment for alcohol withdrawal, clomethiazole shows a reduction in the risk of premature discharge with respect to carbamazepine [67].

Dopamine antagonists

Tiapride, a D2 and a D3 receptor antagonist [68], is frequently used for the treatment of hyperkinetic disorders, agitation and aggressiveness [69]. It has been suggested and approved for treatment of AWS for its effect in reducing dopamine hyperactivity at the dosage of 400–1200 mg/day (up to 1800 mg/day if required) [70]. Tiapride seems to be effective in reducing psycho-vegetative symptoms, such as hyperhidrosis and tremor (not seizures and hallucinations) that may occur during AWS [71]. This may be of relevance for patients with less severe forms of AWS, including outpatients. In addition, it does not cause dependence or respiratory depression and it does not reduce vigilance during treatment. Several studies have proposed the association of tiapride and carbamazepine with positive results [72, 73]. A more recent study has shown that up to a maximum of 800 mg per day of tiapride for 15 days is as effective as lorazepam in the treatment of AWS; the application of the rescue protocol for a patient of the tiapride group for DTs suggests that the use of tiapride should be limited to non-severe and non-complicated types of AWS [74].

Alternative and not approved drugs

Several anti-convulsants (valproic acid, carbamazepine, gabapentin, levetiracetam, pregabalin and topiramate) have been tested for the treatment of AWS. However, a Cochrane review that includes the analysis of 56 studies with a total of 4076 subjects does not show sufficient scientific evidence in favour of anti-epileptics for the treatment of AWS [75]. The current indication for the use of anti-convulsants is, therefore, the association with BDZs when these latter are unable to control convulsions in the course of AWS (Fig. 2).

Treatment of alcohol withdrawal syndrome in course of acute alcoholic hepatitis

Acute Alcoholic hepatitis (AAH) is a distinct clinical syndrome characterized by the recent onset of jaundice often associated with fever (even in the absence of infection), malaise, weight loss and malnutrition with or without other signs of liver decompensation [i.e. ascites or encephalopathy (HE)] in patients with ongoing alcohol abuse [76]. The laboratory profile of AH reveals neutrophilia, hyperbilirubinemia, and serum levels of AST greater than twice the upper limit of normal range, with an AST/ALT ratio typically greater than 1.5–2.0. In severe forms, prolonged prothrombin time, hypoalbuminaemia, and decreased platelet count are frequently observed. Liver biopsy (performed by transjugular route to reduce the risk of bleeding) can be useful to confirm the diagnosis, rule out other diagnoses found in 10–20% of cases, and for prognostication [76].

Treatment of AWS can be tackled by administering short-acting BDZs like lorazepam and oxazepam, which should be preferred to diazepam or chlordiazepoxide, because of their short half-life (10–20 h) and the lack of active metabolites [77]; administration at the onset of symptoms ("trigger" approach) is preferable to a fixed dose to avoid drug accumulation due to reduced hepatic clearance [77]. Particular caution has to be adopted in AAH complicated by HE, ascites, hepatorenal syndrome, and variceal haemorrhage. In the case of HE, treatment with lactulose and rifaximin should be primarily established; once a favourable effect on HE is achieved, AWS treatment should be guided by the severity of the CIWA-Ar score (> 8 points) [77, 78] and started with short-acting BDZ. Hallucinations would benefit from haloperidol, and $alpha_2$-agonists or β-blockers should be considered to control autonomic hyperactivity [77, 78]. Moreover, ascites "per se" does not contraindicate the use of short-acting BDZs. The only study to evaluate sodium oxybate,

a GABA-ergic medication, in a patient with end-stage ALD, ascites and AWS without HE shows that this drug is safe and effective [79]. Intravenous short-acting BDZs can also be used in patients with variceal haemorrhage, unless severe HE is present [77, 78]. No data on the use of BDZs in patients with hepatorenal syndrome are available, but the simultaneous impairment of liver and kidney functions dictate the greatest caution.

Interactions with other drugs: an important issue during the treatment of AWS

Drug–drug interactions are one of the most frequent causes of adverse events during polypharmacy, defined as the chronic co-prescription of several drugs [80]. Since subjects with AUD may be affected by other organic illness or psychiatric diseases, and thus need chronic pharmacological treatment, these events can occur during the treatment of AWS [81].

- *Benzodiazepines*: Once absorbed by the gastrointestinal tract, BDZs and their metabolites generally have a high protein bond and are widely distributed in the body, accumulating in lipid-rich areas, such as the CNS and the adipose tissue. Most BDZs are metabolized by the P450 cytochrome enzymes [23]. Several drugs, metabolized by the same liver cytochromes, alter their blood concentrations or those of BDZs, when they are co-administered: some drugs (i.e. ketoconazole, the macrolide antibiotics clarithromycin and erythromycin, verapamil, diltiazem, and HIV protease inhibitors) slow down the metabolism of BDZs, dangerously increasing their plasma concentrations, while some others (i.e. carbamazepine, phenytoin, phenobarbital) can lower plasma concentrations of BDZs to sub-therapeutic doses [81]. Diazepam is also conditioned by the co-taking of grapefruit juice, which increases its plasma concentrations [82]. Concerning the protein bound drug, the interaction of diazepam with digoxin is of clinical interest. The binding on albumins of both molecules induces a cooperative effect on digoxin binding, reducing its urinary excretion [81], and producing a moderate increase of digoxin half-life in plasma. Lorazepam and oxazepam are not metabolized by liver cytochromes: thus, they might represent ideal treatments in the case of impaired liver function or liver cirrhosis (see above). In any case, other pharmacological interactions may occur: the most clinically relevant is valproate, which decreases lorazepam concentrations by up to 50%, slowing down the clearance of lorazepam glucuronides [81]. Considering the pharmacodynamic action, attention should be paid to the concomitant intake of BDZs with medicines having additive, depressive and sedative effects on the GABA-A receptors and on the CNS (i.e. opioids, antidepressants, anti-convulsants, antihistamines H1-sedative, and neuroleptics) [81]. The association between alcohol and BDZs is also critical: the depressant effect of both drugs may become synergistic rather than a merely additive effect, due to the competitive inhibition on hepatic metabolism of BDZs, following alcohol intake [83].
- *Sodium oxybate*: This is largely absorbed after oral administration; it acts rapidly reaching the plasma concentration peak in 30–120 min, and the terminal half-life is around 30–60 min. It is mainly metabolized in the liver; only a small part (around 2–5%) being excreted unchanged in the urine. Despite the drug being metabolized in the liver, the literature contains no reports of pharmacokinetic interactions between sodium oxybate and other medications. Moreover, being a CNS depressant, when it is co-administered with medications impairing the central nervous system, it shows synergistic effects with only a few of them. Namely, when it is co-administered with lorazepam, increased sleepiness is observed, whereas it is safely administered with tramadol (100 mg), methadone, protriptyline (10 mg) and duloxetine (60 mg) [81, 84]. The co-administration of modest doses of sodium oxybate (50 mg/kg) and ethanol results in increased episodes of vomiting, hypotension, and a greater decrease in O_2 saturation, but only minimal pharmacokinetic interactions [85] and no reciprocal reinforcement effect between the two substances [86] are observed.
- *Clomethiazole*: Like BDZs, this can cause respiratory depression, increasing the risk of pneumonia due to the bronchial accumulation of mucus, and dependence; it should not, therefore, be administered for more than 10 days [87]. Moreover, clomethiazole is metabolized by the isoenzyme CYP2E1 that becomes part of the metabolism of alcohol; its combined administration with alcohol must, therefore, be avoided due to the risk of metabolic interaction and consequent accumulation of the drug.
- *Tiapride*: This may accentuate the effect on CNS depressants, requiring caution and or dosage titration; in addition, co-administration with levodopa may result in reciprocal antagonism of the effects of each drug and this combination is contraindicated. Moreover, an increased risk of extrapyramidal symptoms in co-administration with neuroleptic or metoclopramide has been documented [70]. Tiapride is mainly eliminated by renal excretion principally in unchanged form; the elimination half-life is approximately 3–4 h and may increase with age in impaired renal function [70]. Thus, there is a potential for tiapride to interact with drugs that undergo significant renal clearance.

Conclusions

AAI is an intercurrent, potentially transitory condition that occurs as a result of excessive alcohol intake. In the event of a mild/moderate form of AAI, no drugs are necessary; vital functions should be monitored, keeping the patient under observation for any onset of the signs of AWS and liquids should be administered if the patient is dehydrated. In the event of a severe form of AAI with serious respiratory insufficiency and coma, it is important to implement mechanical ventilation, and, if necessary, to identify any additional causes of coma. In the case of the simultaneous use of other sedative drugs, specific antidotes should be administered (naloxone for the use of opioids; flumazenil for the BDZs). In addition, since adolescents do usually not show tolerance to the effects developed by repeated exposure to ethanol, and they have immature hepatic alcohol dehydrogenase activity, they may be more exposed to the toxic effect of alcohol and consequently to the rapid onset of coma, meaning that careful attention is needed. In particular, considering that hypoglycaemia and hypothermia induced by AAI tend to be more severe in young individuals than in adults, the management of AAI for all adolescents should be promptly started. Finally, it is possible to administer drugs (such as metadoxine) that can reduce the blood alcohol and acetaldehyde concentrations, leading to a more rapid resolution of the symptoms of AAI. When these symptoms disappear, the onset of HS occurs, principally resolved by rest and hydration.

When a subject is affected by a severe AUD, AWS may develop. AWS is a potentially life-threatening medical condition that occurs in subjects affected by AUD who suspend their alcohol intake too quickly or abruptly. The initial phase of AWS is characterized by agitation and a lack of cooperation on the part of the patient; this phase must, therefore, be treated very decisively in order to reduce the risk of complications (seizures and DTs). The use of the CIWA-Ar scale is important in diagnosing AWS and implementing the appropriate treatment. BDZs, together with non-pharmacological support (hydration, correction of hypoglycaemia and electrolyte balance, vitamin B group supplements), are the "gold standard" in the treatment of AWS since they are not only effective in resolving the symptoms of AWS, but they are also the only drugs to have a demonstrated ability to prevent convulsions and DTs. However, the risk of abuse of BDZs limits their medium- and long-term use [88]. In addition, sodium oxybate, tiapride, and clomethiazole represent a further opportunity to treat AWS specifically in its moderate form of presentation, while anti-convulsants have not shown sufficient scientific evidence for the treatment of AWS. Alfa-2-agonists, beta-blockers, and neuroleptics should be administered only in association with BDZs when the latter are not effective in controlling specific persisting symptoms of AWS. A fixed-schedule regimen is highly effective, and its use is preferable in patients at risk of developing a severe form of AWS or in patients with a history of convulsions and DTs; a symptom-triggered regimen with BDZs with a shorter half-life (lorazepam and oxazepam) may be preferable for the treatment of AWS in elderly patients and in those with AAH and advanced liver cirrhosis. Out-patient treatment is appropriate in patients with mild or moderate AWS without contraindications; in-patient treatment is appropriate in severe form of AWS with or without complications (DTs and seizures). BDZs are the drug of first choice for the treatment of AWS complicated with seizures; in the refractory forms, the association with anti-convulsants is recommended. DTs requires a specific pharmacological treatment with high doses of BDZs. In the case of forms of DTs refractory to the treatment of BDZs, the use of anaesthetic drugs such as phenobarbital or propofol in association with BDZs, often in an ICU setting, is the most appropriate pharmacological approach.

In conclusion, the importance of the appropriate and timely treatment of AAI and patients with AUD affected by AWS is crucial both for those working with out-patients and those working with in-patients; this reduces the risk of complications of AWS and the financial costs of hospitalization.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

Statement of human and animal rights The Italian Society on Alcohol has followed the Ethical Statements required for a review paper.

Informed consent For this type of study formal consent is not required.

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