Alcohol withdrawal syndrome: diagnostic and therapeutic methods

Sindrome astinenziale da alcol: processi diagnostici e terapeutici

FABIO ATTILIA[1]*, ROBERTA PERCIBALLI[1], CLAUDIA ROTONDO[1], IDA CAPRIGLIONE[1], SILVIA IANNUZZI[1], MARIA LUISA ATTILIA[1], GIOVANNA CORIALE[1], MARIO VITALI[2], FEDERICA CEREATTI[1], MARCO FIORE[3], MAURO CECCANTI[1];
INTERDISCIPLINARY STUDY GROUP CRARL, SITAC, SIPaD, SITD, SIPDip**
*E-mail: fabio_attilia@libero.it

[1]Centro Riferimento Alcologico Regione Lazio (CRARL), Sapienza University of Rome, Italy
[2]ASUR Marche-AV4, Italy
[3]Institute of Cell Biology and Neurobiology (IBCN-CNR), Rome, Italy

SUMMARY. Alcohol withdrawal syndrome (AWS) is a medical emergency, rare in the general population, but very common among alcoholic individuals, which can lead to severe complications when unrecognized or late treated. It represents a clinical condition which can evolve in few hours or days following an abrupt cessation or reduction of alcohol intake and is characterized by hyperactivity of the autonomic nervous system resulting in the development of typical symptoms. According to DSM-5 criteria, the alcohol withdrawal syndrome is defined as such: if patients present at least two of typical signs and symptoms. The Clinical Institute Withdrawal Assessment of Alcohol Scale, revised version (CIWA-Ar), is the tool for assessing the severity of AWS. The support to patient with AWS includes pharmacological intervention as well as general support, restoration of biochemical imbalances and specific therapy. Regarding the pharmacological treatment, benzodiazepines represent the gold standard, in particular long-acting benzodiazepines, administered with a gradual reduction up to cessation.

KEY WORDS: withdrawal, benzodiazepines, GABAergic and glutamatergic systems, CIWA-Ar.

RIASSUNTO. La sindrome astinenziale da alcol (SAA) è una condizione d'emergenza, rara nella popolazione generale, ma altamente rappresentata nel sottogruppo degli alcolisti con possibile comparsa di complicanze anche gravi in caso di mancato riconoscimento o tardivo trattamento farmacologico. Rappresenta una condizione clinica che può svilupparsi nei pazienti alcol-dipendenti entro poche ore o giorni dalla brusca interruzione o riduzione del consumo alcolico, caratterizzata da iperattività del sistema nervoso autonomo con conseguente comparsa di sintomi specifici. Secondo i criteri del DSM-5, la sindrome viene diagnosticata in base alla presenza di almeno due tra i segni e sintomi caratteristici. Lo strumento utilizzato per la valutazione di questi sintomi è il Clinical Institute Withdrawal Assessment for Alcohol, in particolare la forma rivisitata (CIWA-Ar). Il supporto al paziente alcolista con SAA include interventi di natura farmacologica e non. Per quelli terapeutici farmacologici vale il concetto di supporto generale al paziente con la correzione di eventuali squilibri di natura biochimica accanto a terapia specifica. Le benzodiazepine rappresentano il gold standard del trattamento, e si prediligono quelle a lunga emivita, che vanno gradualmente scalate fino alla sospensione con schemi a dosaggio fisso o correlati al sintomo.

PAROLE CHIAVE: astinenza, benzodiazepine, sistema gabaergico e glutammatergico, CIWA-Ar.

INTRODUCTION

Alcohol withdrawal syndrome (AWS) represents a clinical condition that can arise within 6-24 hours following an abrupt cessation or reduction of alcohol intake and is characterized by hyperactivity of the autonomic nervous system resulting in psychomotor agitation, tremors, anxiety, thought disorder, hypertension, tachycardia and fever[1]. AWS symptoms occur in more than 50% of patients with alcoholic problems who require different pharmacological treatments[2,3]. As a syndrome, it can occur in different ways, from mild to severe forms. A well-timed diagnosis and an appropriate treatment are essential, since the AWS represents one of the main predictable causes of mortality and morbidity in people having alcoholic problems[4].

PATHOPHYSIOLOGY

Acute consumption of ethanol causes a depression of the central nervous system (CNS) as result of increased GABAergic activity as well as decreased glutamatergic activity[5-7] while chronic consumption leads to a new adaptive balance of different neurotransmitters such as GABA, glutamate and norepinephrine resulting in the phenomenon of alcohol tolerance[8-10]. Abrupt reduction or cessation of alcohol intake leads to decreased blood ethanol levels resulting in re-

duced GABAergic activity and increased glutamatergic activity. This imbalance causes neuronal over excitability leading to AWS symptoms that include neuropsychiatric complications, such as Delirium tremens (DTs) and seizures, as consequence of autonomic nervous system hyperactivity as well[8,11]. Repeated withdrawal episodes lead to the so-called "kindling" in which neuronal hyperexcitability causes an increased severity of AWS over time[12,13].

SIGNS AND SYMPTOMS

AWS is a complex and dynamic disease, whose aspects change depending on temporality, the general condition of the patient and clinical history (previous complicated episodes of AWS, mode of alcohol intake).

During the early stages, symptoms mainly depend on autonomic hyperactivity (e.g. tremors of limbs or tongue, psychomotor agitation, headache and insomnia), and quickly arise after the last drink. Symptoms may last several hours to 1-2 days. Later, perception disorders such as illusions, hallucinosis and hallucinations that can affect any sensory sphere can occur. In addition, seizures may occur after 6-48 hours following the last ethanol ingestion. In most cases tonic-clonic seizures occur. Usually they are self-limiting, although in 9-25% of cases they may evolve in status epilepticus[14]. The risk of developing seizures increases in the case of repeated AWS episodes or the so-called "kindling"[15]. In addition to previous seizure episodes, concurrent risk factors in developing seizures in more than 50% of cases are organic cerebral injuries and a simultaneous consumption of other psychotropic drugs resulting in an increased mortality risk[16,17].

During the later stages, unrecognized or a not well treated syndrome can be complicated by DTs[11,18,19,20], a consciousness impairment associated with cognitive modifications and early onset hallucinations not related to other pre-existing disorders[21]. Tipically, DTs occurs three days after the onset of symptoms[22] and lasts 1-8 days (generally 2-3 days). Mortality is around 1-8% among hospitalized patients, a rate that can decrease with a well-timed diagnosis and an appropriate treatment. Death follows hyperthermia, heart rhythm disorders, and seizures. Predictive factors are: CIWA-Ar score >15 (see below), arterial hypertension, tachycardia, a recent seizure episode, previous AWS, and simultaneous medical disorders (in particular: hypokalemia, hypomagnesemia, thrombocytopenia; respiratory, cardiovascular and gastrointestinal diseases)[23].

DIAGNOSTIC TOOLS

Since AWS concerns only individuals with alcohol use disorder (AUD), a correct diagnosis and a meticulous lifetime drinking and toxicological history should precede any kind of treatment to exclude causes of different origins.

Measurement of blood ethanol in an individual with suspected AWS should be related to a correct anamnesis, when possible, in order to obtain information about the last ingestion. Repeated measurements of blood ethanol at regular intervals until the substance disappears in the blood, provides an assessment of the individual's ability to metabolize alcohol. Measurement of blood ethanol can be detected by both direct and indirect methods. In addition, assessment of vital signs is important as well (i.e. blood pressure, heart rate, body temperature, blood glucose). Some patients, for example those who are taking beta-blockers, could show normal vital signs. Thus, a meticulous observation of symptoms over time is important. According to DSM-5, AWS diagnosis is established when patients present at least two of the following symptoms: tremors, sweating, tachycardia, insomnia, nausea or vomiting, illusions, transient hallucinations (auditory, visual or tactile), psychomotor agitation, anxiety or seizures[24].

The Clinical Institute Withdrawal Assessment for Alcohol, particularly the revised version (CIWA-Ar), is a tool to assess AWS symptoms and consists of 10 items[25-27]. The CIWA-Ar is easy to implement and allows the assessment of the effectiveness of the administered therapy[25,26]. According to the international scientific literature, a score <8 defines a mild AWS; a score between 8 and 15 defines a moderate AWS; a score >15 defines a severe AWS[28].

Luebeck Alcohol withdrawal Risk Scale (LARS)[19] and Prediction of Alcohol Withdrawal Severity Scale (PAWSS)[17] represent a further tool of assessment but are not commonly used since they need validation. (Recommendation B2 of Table 1)[29].

In addition, full blood count, liver function tests including total serum bilirubin, renal function tests, pancreatic en-

Table 1. Treatments' efficacy grading of both evidence and recommendations (*adapted from* EASL[29]).

Grading of evidence	**Notes**	**Symbol**
High quality	Further research is very unlikely to change our confidence in the estimate of effect and clinical practice	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate and clinical practice	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate and clinical practice. Any estimate of effect is uncertain	C
Grading of recommendation	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	2

zymes, blood glucose, serum electrolytes, urinalysis and urine toxicological screens are required. *Recommendation A1* (Table 1).

TREATMENT

Treatment includes pharmacological intervention and assistance. Assistance consists of paramedic support, removal of stressful stimuli (e.g. bright lights, noises), conservation of contact with the reality and counseling[30]. Conversely, the pharmacological approach consists of general support to the patient, i.e. the correction of any biochemical imbalance (commonly electrolyte imbalance, dehydration, low blood glucose, and lack of vitamins, in particular the B group and folates) along with specific therapies for any comorbidity. Regarding the pharmacological treatment of AWS symptoms, benzodiazepines represent the gold standard. Benzodiazepines are effective in avoiding complications, resulting in a decreased incidence of seizures, DTs and overall mortality[31-33]. The effectiveness of benzodiazepines stems from their action on the GABA-A receptors whose function is considerably abolished in cases of abrupt alcohol cessation[34]. Current scientific evidence suggests a greater effectiveness of long-acting benzodiazepines, in particular chlordiazepoxide and diazepam[35,36] whose effect derives from themselves as well as from their metabolites (phase I); thereafter hepatic glucuronidation inactivates benzodiazepine metabolites (phase II), and successively kidneys clear them. In liver impairment circumstances, short-acting benzodiazepines should be used in order to prevent excessive sedation and respiratory depression[31]. In this case, oxazepam and lorazepam may be safer since they do not undergo oxidative liver metabolism. Moreover, benzodiazepines have the advantage of multiple administration modalities, excluding intramuscularly as absorption is precluded[37]. Choosing the correct route is related above all to clinical severity. In moderate and severe cases, intravenous administration is recommended, whereas orally is suitable for mild cases not requiring recovery[37]. CIWA-Ar by assessing the symptoms severity allows to choose the most appropriate treatment.

Pharmacological intervention is recommended when CIWA-Ar score is >8 to avoid complications, above all in patients with concurrent risk factors, i.e. previous withdrawal episodes, concomitant use of CNS depressors drugs, hypertensive crisis, fever, male gender, concomitant organic diseases[28,38]. (Recommendation A1 of Table 1).

Benzodiazepines dosage can follow three different schedules:

1. *fixed-dose application*: in cases of high risks in developing severe AWS or previous seizure episodes or DTs. A 24 hour monitoring of clinical conditions is recommended to avoid exaggerated sedation or respiratory depression[39];
2. *diazepam*: 10 mg x 4 for 1 day; 5 mg x 4/die for 2 days thereafter gradual discontinuation;
3. *chlordiazepoxide*: 50-100 mg x 4 for 1 day; 25-50 mg x 4/die for 2 days and following discontinuation (reducing the dose by 25% per day from the fourth to the seventh day). Additional doses are recommended in case of severe symptoms.

Loading dose regimen: administration of high quantities of long-acting benzodiazepines to induce sedation. Diazepam 10-20 mg or chlordiazepoxide 100 mg every 1-2 hours are the most commonly used. The dose of these drugs will be reduced through their metabolism. A very high risk of toxicity may occur, above all during the first phase of treatment. Therefore, it demands a close monitoring through recovery and the availability of intensive care[36].

Symptom triggered treatment: if CIWA-Ar score is >8-10, the physician can choose among diazepam 5-20 mg, chlordiazepoxide 50-100 mg or lorazepam 2-4 mg as well.

Symptoms should be evaluated at least every hour in order to adjust the administered doses[34]. Several studies have investigated which method is more adequate, but no therapeutic regimen seems to be better than others[39-41]. However, the symptom triggered treatment showed a reduction in the quantity of benzodiazepines and in the duration of treatment, above all in patients at low risk of developing AWS with complications. It is a more manageable approach, in particular for outpatients. It requires an accurate history of alcohol use to avoid more epileptic episodes in patients who have had previously AWS related seizures, by adjusting the dose.

Benzodiazepines represent the core of the treatment of any clinical manifestation of AWS, including seizures and DTs. In particular lorazepam and diazepam are recommended to avoid clinical complications. One could consider administering other drugs in combination with benzodiazepines if required. (Recommendation A1 of Table 1).

Recently other drugs have been taken into consideration in the AWS treatment:

- *Alpha 2-agonists, beta-blockers and neuroleptics drugs*: in association with benzodiazepines. Since they may hide AWS symptoms, it is important to not administer them as monotherapy. Neuroleptics are used for hallucinations and delirium but they may reduce seizure threshold, underlying the importance of using them in combination with benzodiazepines[42,43].
- *Carbamazepine* is an anticonvulsant drug with GABAergic action, able to block NMDA receptors. Several studies have proven its effectiveness in the treatment of mild and moderate AWS[44]. The recommended dose is 600-800 mg the first day and reduced gradually to 200 mg within the fifth day. Because of its side effects (e.g. nausea, vomit, dermatitis, Steven-Johnson syndrome and agranulocytosis) it is not commonly used.
- *Valproate*: it helps improving AWS symptoms via preventing the occurrence of seizures. Moreover, it acts as an anti-kindling. Its action is dose-dependent and needs time to reach a therapeutic effect[45,46]. For this reason, it is not recommended during the acute phase.
- *Sodium oxybate*: also called gamma hydroxybutyric acid, is a carboxylic acid with four carbons and occurs naturally in the brain, particularly in the thalamus, hypothalamus and basal ganglia. Sodium oxybate binds to the GHB and GABA receptors with high affinity to the former and low affinity to the latter[47]. Its effects are mediated by the GABA-B receptors stimulation in a competitive manner with alcohol. Its alcohol-like GABAergic activity represents a basis upon which to conduct studies on alcohol addiction treatments. Concerning the treatment of AWS symptoms, the effectiveness of sodium oxybate has been studied by administering 50 mg/kg spread into three equal doses per day. Re-

sults were compared to the benzodiazepines' effectiveness[48-50]. In these studies, the goal was to reduce AWS symptoms, therefore the CIWA-Ar score. In 2010 a Cochrane Collaboration meta-analysis has shown that GHB (50 mg/kg/die) is more effective than placebo in reducing AWS symptoms but has a comparable efficacy when compared to benzodiazepines. More recently, the GATE 1 study showed sodium oxybate efficacy comparable to benzodiazepines' efficacy in treating AWS symptoms[51]. It should be stressed that in patients with previous, complicated withdrawal seizures, GHB should be administered in combination with benzodiazepines since the former does not act on seizures. (Recommendation A1 of Table 1).

- *Baclofen*: is a GABA-B receptor agonist, normally used in the control of spasticity, with the ability to decrease AWS symptoms by acting on GABA-B receptors and NMDA receptors. The administration of baclofen at a dosage of 10 mg x 3/die for ten days does not show significant differences in decreasing CIWA-Ar score when compared to benzodiazepines[52]. A more recent study on baclofen vs placebo found that administrating the former reduces the probability of using lorazepam as needed[53]. However, more studies are required to assess baclofen efficacy in the AWS treatment.
- *Gabapentin*: is a GABA-like drug, that enhances the synthesis of GABA in the brain. It is used as an additional treatment for partial seizures. Currently, studies on the effectiveness of this drug on AWS symptoms are controversial.
- *Topiramate*: is an anticonvulsant drug whose actions are carried out through several mechanisms: increasing GABA-A inhibitory activity, antagonizing the glutamatergic activity, modulating ion channels. Thus, topiramate reduces CNS hyperexcitability[54].

In addition to benzodiazepines, thiamine should be administered. This is also known as vitamin B1, a water-soluble molecule provided through food. Its lack causes a nerve-conduction impairment in the periphery and central nervous system, resulting in peripheral neuropathy and encephalopathy[55].

It should be stressed that glucose causes the depletion of thiamine increasing the risk of encephalopathy[56].

Since chronic alcohol consumption causes a lack of thiamine, it is necessary to administer this vitamin at a dose of 100 mg/die for 3-4 days to avoid neurological complications, especially encephalopathy[55-61]. (Recommendation A1 of Table 1).

In the event of complications (seizures, DTs), treatment consists of benzodiazepines in association with thiamine[62]. In no responder patients, for example those intubated in intensive care unit (ICU), propofol can be administered[63]. Where there are persistent agitation or hallucinations, the recommendation is to administer antipsychotic drugs (haloperidol 0.5-5 mg every 30-60 minutes intramuscularly or intravenously at the maximum dose of 20 mg). Finally, the evaluation of medical conditions and the monitoring of vital signs should be executed in a noise-free and stimuli-free environment that facilitates sedation and raises seizure threshold.

CONCLUSIONS

AWS is definitely a health-emergency condition, since even mild forms may get complicated and could result in disabling, or even deadly, complications. Thus, the focus must be completed each time a patient is suspected of suffering from AUD in order to promptly operate and avoid health deteriorations.

Conflict of interests: the authors have no conflict of interests to declare.

***Interdisciplinary Study Group - Centro Riferimento Alcologico Regione Lazio (CRARL), Società Italiana per Il Trattamento dell'Alcolismo e delle sue Complicanze (SITAC), Società Italiana Patologie da Dipendenza (SIPaD), Società Italiana delle Tossicodipendenze (SITD), Società Italiana di Psichiatria e della Dipendenza (SIPDip)*: Giovanni Addolorato, Vincenzo Aliotta, Giovanni Alessandrini, Giuseppe Barletta, Egidio Battaglia, Gemma Battagliese, Valentina Carito, Onofrio Casciani, Pietro Casella, Fernando Cesarini, Mauro Cibin, Rosaria Ciccarelli, Paola Ciolli, Angela Di Prinzio, Roberto Fagetti, Emanuela Falconi, Michele Federico, Giampiero Ferraguti, Daniela Fiorentino, Simona Gencarelli, Angelo Giuliani, Antonio Greco, Guido Intaschi, Luigi Janiri, Giuseppe La Torre, Angela Lagrutta, Giovanni Laviola, Roberta Ledda, Lorenzo Leggio, Claudio Leonardi, Anna Loffreda, Fabio Lugoboni, Simone Macrì, Rosanna Mancinelli, Massimo Marconi, Icro Maremmani, Marcello Maviglia, Marisa Patrizia Messina, Martino Mistretta, Franco Montesano, Esterina Pascale, Michele Parisi, Fabiola Pisciotta, Giampaolo Spinnato, Alessandro Valchera, Valeria Zavan.

REFERENCES

1. McKeon A, Frye MA, Delanty N. The alcohol withdrawal syndrome. J Neurol Neurosurg Psychiatry 2008; 79: 854-62.
2. Saitz R. Clinical practice. Unhealthy alcohol use. N Engl J Med 2005; 352: 596-607.
3. Hall W, Zador D. The alcohol withdrawal syndrome. Lancet 1997; 349: 1897-900.
4. Mokdad AH, Marks JS, Stroup DF, et al. Actual causes of death in the United States, 2000. JAMA 2004; 291: 1238-45.
5. Malcolm RJ. GABA systems, benzodiazepines, and substance dependence. J Clin Psychiatry 2003; 64 (suppl 3): 36-40.
6. Davis KM, Wu J-Y. Role of glutamatergic and GABAergic systems in alcoholism. J Biomed Sci 2001; 8: 7-19.
7. Chastain G. Alcohol, neurotransmitter systems, and behavior J Gen Psychol 2006; 133: 329-35.
8. Littleton J. Neurochemical mechanisms underlying alcohol withdrawal. Alcohol Health Res World 1998; 22: 13-24.
9. Gold J, Nelson LS. Ethanol withdrawal. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE (eds). Goldfrank's toxicologic emergencies. 9th ed. New York: McGraw-Hill, 2011.
10. Fadda F, Rossetti ZL. Chronic ethanol consumption: from neuroadaptation to neurodegeneration (review). Progr Neurobiol 1998; 56: 385-431.
11. Kattimani S, Bharadwaj B. Clinical management of alcohol withdrawal: a systematic review. Ind Psychiatry J 2013; 22: 100-8.
12. Lejoyeux M, Solomon J, Adès J. Benzodiazepine treatment for alcohol-dependent patients. Alcohol Alcohol 1998; 33: 563-75.
13. Reoux JP, Saxon AJ, Malte CA, et al. Divalproex sodium in alcohol withdrawal: a randomized double-blind placebo-controlled clinical trial. Alcohol Clin Exp Res 2001; 25: 1324-9.
14. Hillbom M, Pieninkeroinen I, Leone M. Seizures in alcohol-dependent patients: epidemiology, pathophysiology and management. CNS Drugs 2003; 17: 1013-30.
15. Becker HC. Kindling in alcohol withdrawal. Alcohol Health Res World 1998; 22: 25-33.
16. Rathlev NK, Ulrich AS, Delanty N, D'Onofrio G. Alcohol-related seizures. J Emerg Med 2006; 31: 157-63.
17. Brathen G, Brodtkorb E, Helde G, Sand T, Bovim G. The diversity of seizures related to alcohol use. A study of consecutive patients. Eur J Neurol 1999; 6: 697-703.

18. Mainerova B, Prasko J, Latalova K, et al. Alcohol withdrawal delirium-diagnosis, course and treatment. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015; 159: 44-52.
19. LaRoche SM, Shivdat-Nanhoe R. Subacute encephalopathy and seizures in alcoholics (SESA) presenting with non-convulsive status epilepticus. Seizure 2011; 20: 505-8.
20. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med 2014; 371: 2109-13.
21. Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of alcohol withdrawal delirium: an evidence-based practice guideline. Arch Intern Med 2004; 164: 1405-12.
22. Eyer F, Schuster T, Felgenhauer N, et al. Risk assessment of moderate to severe alcohol withdrawal predictors for seizures and delirium tremens in the course of withdrawal. Alcohol Alcohol 2011; 46: 427-33.
23. Khan A, Levy P, DeHorn S, Miller W, Compton S. Predictors of mortality in patients with delirium tremens. Acad Emerg Med 2008; 15: 788-90.
24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association Press, 2013.
25. Shaw JM, Kolesar GS, Sellers EM, et al. Development of optimal treatment tactics for alcohol withdrawal. I. Assessment and effectiveness of supportive care. J Clin Psychopharmacol 1981; 1: 382-9.
26. Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict 1989; 84: 1353-7.
27. Sullivan JT, Swift RM, Lewis DC. Benzodiazepine requirements during alcohol withdrawal syndrome: clinical implications of using a standardized withdrawal scale. J Clin Psychopharmacol 1991; 11: 291-5.
28. Perry EC. Inpatient management of acute alcohol withdrawal syndrome. CNS Drugs. 2014; 28: 401-10.
29. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol 2012; 57: 399-420.
30. Blondell RD. Ambulatory detoxification of patients with alcohol dependence. Am Fam Physician 2005; 71: 495-502.
31. Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome. Cochrane Database Syst Rev 2011; (6): CD008537.
32. Holbrook AM, Crowther R, Lotter A, et al. Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. CMAJ 1999; 160: 649-55.
33. Adinoff B. Double-blind study of alprazolam, diazepam, clonidine, and the placebo in the alcohol withdrawal syndrome. Alcohol Clin Exp Res 1994; 18: 873-8.
34. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. N Engl J Med 2003; 348: 1786-95.
35. Ntais C, Pakos E, Kyzas P, et al. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev 2005; (3): CD005063.
36. Muzyk AJ, Leung JG, Nelson S, et al. The role of diazepam loading for the treatment of alcohol withdrawal syndrome in hospitalized patients. Am J Addict 2013; 22: 113-8.
37. Perry EC. Inpatient management of acute alcohol withdrawal syndrome. CNS Drugs 2014; 28: 401-10.
38. Maldonado JR, Sher Y, Ashouri JF, et al. The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. Alcohol 2014; 48: 375-90.
39. Daeppen J-B, Gache P, Landry U, et al. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal. Arch Intern Med 2002; 162: 1117-21.
40. Maldonado JR, Nguyen LH, Schader EM, et al. Benzodiazepine loading versus symptom-triggered treatment of alcohol withdrawal: a prospective, randomized clinical trial. Gen Hosp Psychiatry 2012; 34: 611-7.
41. Spies CD, Otter HE, Huske B, et al. Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. Intensive Care Med 2003; 29: 2230-8.
42. Muzyk AJ, Fowler JA, Norwood DK, et al. Role of a 2-agonists in the treatment of acute alcohol withdrawal. Ann Pharmacother 2011; 45: 649-57.
43. Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 2004; 164: 1405-12.
44. Barrons R, Roberts N. The role of carbamazepine and oxcarbazepine in alcohol withdrawal syndrome. J Clin Pharm Ther 2010; 35: 153-67.
45. Reoux JP, Saxon AJ, Shen D. Pharmacokinetic profile of an oral loading dose of divalproex sodium during acute alcohol withdrawal. J Clin Psychopharmacol 2006; 26: 105-7.
46. Muncie HL Jr, Yasinian Y, Oge' L. Outpatient management of alcohol withdrawal syndrome. Am Fam Physician 2013; 88: 589-95.
47. Snead OC, Gibson KM. Gamma-hydroxybutyric acid. N Engl J Med 2005; 352: 2721-32.
48. Skala K, Caputo F, Mirijello A, et al. Sodium oxybate in the treatment of alcohol dependence: from the alcohol withdrawal syndrome to the alcohol relapse prevention. Expert Opin Pharmacother 2014; 15: 245-57.
49. Addolorato G, Balducci G, Capristo E, et al. Gamma-hydroxybutyric acid (GHB) in the treatment of alcohol withdrawal syndrome: a randomized comparative study versus benzodiazepine. Alcohol Clin Exp Res 1999; 23: 1596-604.
50. Nava F, Premi S, Manzato E, et al. Gamma-hydroxybutyrate reduces both withdrawal syndrome and hypercortisolism in severe abstinent alcoholics: an open study vs. diazepam. Am J Drug Alcohol Abuse 2007; 33: 379-92.
51. Caputo F, Skala K, Mirijello A, et al. Sodium oxybate in the treatment of alcohol withdrawal syndrome: a randomized double- blind comparative study versus oxazepam. The GATE 1 Trial. CNS Drugs 2014; 28: 743-52.
52. Addolorato G, Leggio L, Abenavoli L, et al. Baclofen in the treatment of alcohol withdrawal syndrome: a comparative study vs diazepam. Am J Med 2006; 119: e13-8.
53. Lyon JE, Khan RA, Gessert CE, et al. Treating alcohol withdrawal with oral baclofen: a randomized, double-blind, placebo controlled trial. J Hosp Med 2011; 6: 469-74.
54. Krupitsky EM, Rudenko AA, Burakov AM, et al. Antiglutamatergic strategies for ethanol detoxification: comparison with placebo and diazepam. Alcohol Clin Exp Res 2007; 31: 604-11.
55. Mancinelli R, Ceccanti M. Biomarkers in alcohol misuse: their role in the prevention and detection of thiamine deficiency. Alcohol Alcohol 2009; 44: 177-82.
56. Ceccanti M, Carito V, Vitali M, et al. Serum BDNF and NGF modulation by olive polyphenols in alcoholics during withdrawal. J Alcohol Drug Depend 2015; 3: 214-9.
57. Ceccanti M, Hamilton D, Coriale G, et al. Spatial learning in men undergoing alcohol detoxification. Physiol Behav 2015; 149: 324-30.
58. Ceccanti M, Coriale G, Hamilton DA, et al. Virtual Morris Task Responses in individuals in an abstinence phase from alcohol. Can J Physiol Pharmacol 2018; 96: 128-36.
59. Ciafrè S, Fiore M, Ceccanti M, et al. Role of Neuropeptide Tyrosine (NPY) in Ethanol Addiction. Biomed Reviews 2016; 27: 27-39.
60. Ciafrè S, Carito V, Tirassa P, et al. Ethanol consumption and innate neuroimmunity. Biomed Reviews 2018; 28: 49-61.
61. Ceccanti M, Inghilleri M, Attilia ML, et al. Deep TMS on alcoholics: effects on cortisolemia and dopamine pathway modulation. A pilot study. Can J Physiol Pharmacol 2015; 93: 283-90.
62. Hack JB, Hoffman RS. Thiamine before glucose to prevent Wernike encephalopathy: examing the conventional wisdom. JAMA 1998; 279: 583.
63. DeCarolis DD, Rice KL, Ho L, Willenbring ML, Cassaro S. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. Pharmacotherapy 2007; 27: 510-8.