IX CONGRESSO NAZIONALE FEDERSERD
Virtual Edition
FeDerSerD
LA CLINICA DELLE DIPENDENZE
Priorità e sostenibilità per un sistema che cambia

Alcol, problematiche legate all'astinenza e intervento farmacologico

SESSIONI CONGRESSUALI ECM
18 | 19 | 20 novembre 2020
live streaming

Fabio Caputo MD, PhD

- *Ricercatore a tempo determinato (RTD-B) - Gastroenterologia – Dipartimento di Medicina Translazionale e per la Romagna, Università di Ferrara*

- *Convenzione presso U.O. Medicina Interna - Ospedale SS Annunziata - Cento (FE) con Alta Specialità in Diagnosi e Trattamento dei Disordini da Uso di Alcol in ambito Internistico e Gastroenterologico*

- *Vice-Presidente della Società Italiana di Alcologia (SIA)*

Università degli Studi di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Ferrara

Società Italiana di Alcologia (SIA)

Alcohol Use Disorder (AUD)

-About 20% of men and 10% of women in most Western societies have an alcohol use disorder (AUD), which is defined as repetitive alcohol-related problems in at least 2 of 11 areas of life (see DSM-V criteria)

-Alcohol-related conditions affect more than 20% of patients in most medical settings

-About 50% of persons with AUD have symptoms of alcohol withdrawal when they reduce or discontinue their alcohol consumption; in 3 to 5% of these persons, grand mal convulsions, severe confusion (a delirium), or both develop

(Schuckit, NEJM, 2014)

Pharmacological treatment of Alcohol Use Disorder (AUD)

- -ACUTE ALCOHOL INTOXICATION

- -ALCOHOL WITHDRAWAL SYNDROME (AWS)

- -RELAPSE PREVENTION

  1. MAINTENANCE OL ALCOHOL ABSTINENCE
  2. REDUCTION OF EPISODES OF HEAVY DRINKING / REDUCTION OF HEAVY DRINKING DAYS (HDDs)

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Criteria for alcohol withdrawal

Cessation of or reduction in heavy and prolonged use of alcohol

At least two of eight possible symptoms after reduced use of alcohol:

- Autonomic hyperactivity
- Hand tremor
- Insomnia
- Nausea or vomiting
- Transient hallucinations or illusions
- Psychomotor agitation
- Anxiety
- Generalized tonic–clonic seizures

Criteria for delirium

Decreased attention and awareness

Disturbance in attention, awareness, memory, orientation, language, visuo-spatial ability, perception, or all of these abilities that is a change from the normal level and fluctuates in severity during the day

Disturbances in memory, orientation, language, visuospatial ability, or perception

No evidence of coma or other evolving neurocognitive disorders

(American Psychiatric Association, 2013)

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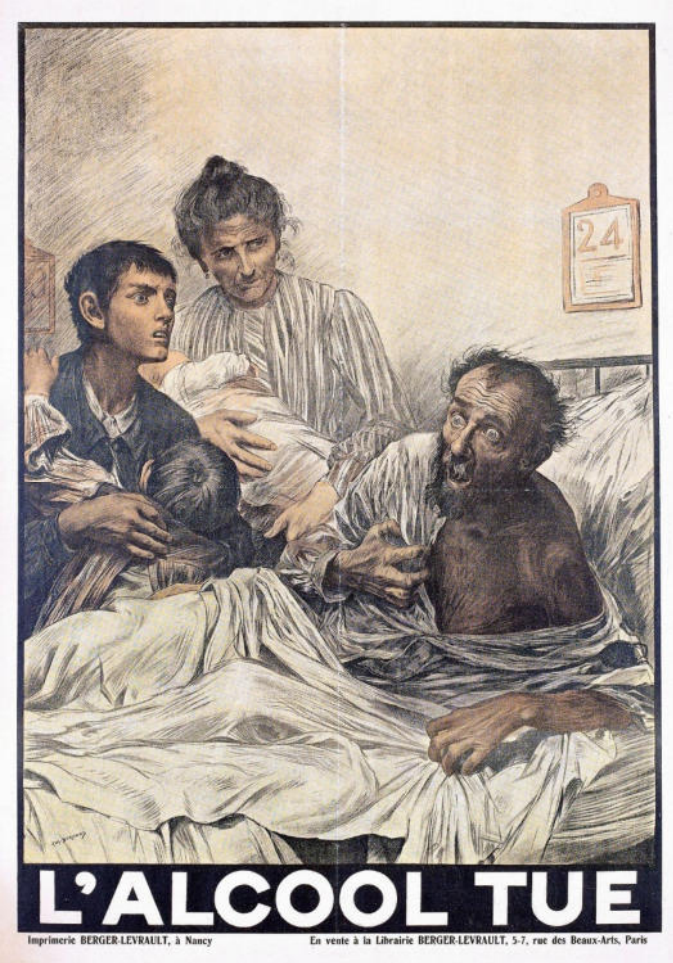

In particolare, il Delirium Tremens (DTs) è una condizione clinica caratterizzata da disturbo cognitivo e dell'attenzione ad insorgenza rapida e fluttuante, talvolta caratterizzata da allucinazioni.

Fino a qualche anno fa, la mortalità per DTs era del 5-15% (ipertermia, aritmie, collasso cardiocircolatorio).
Dopo l'avvento dei farmaci specifici, la mortalità si è ridotta a non più dell'1%.

(Schuckit, NEJM, 2014)

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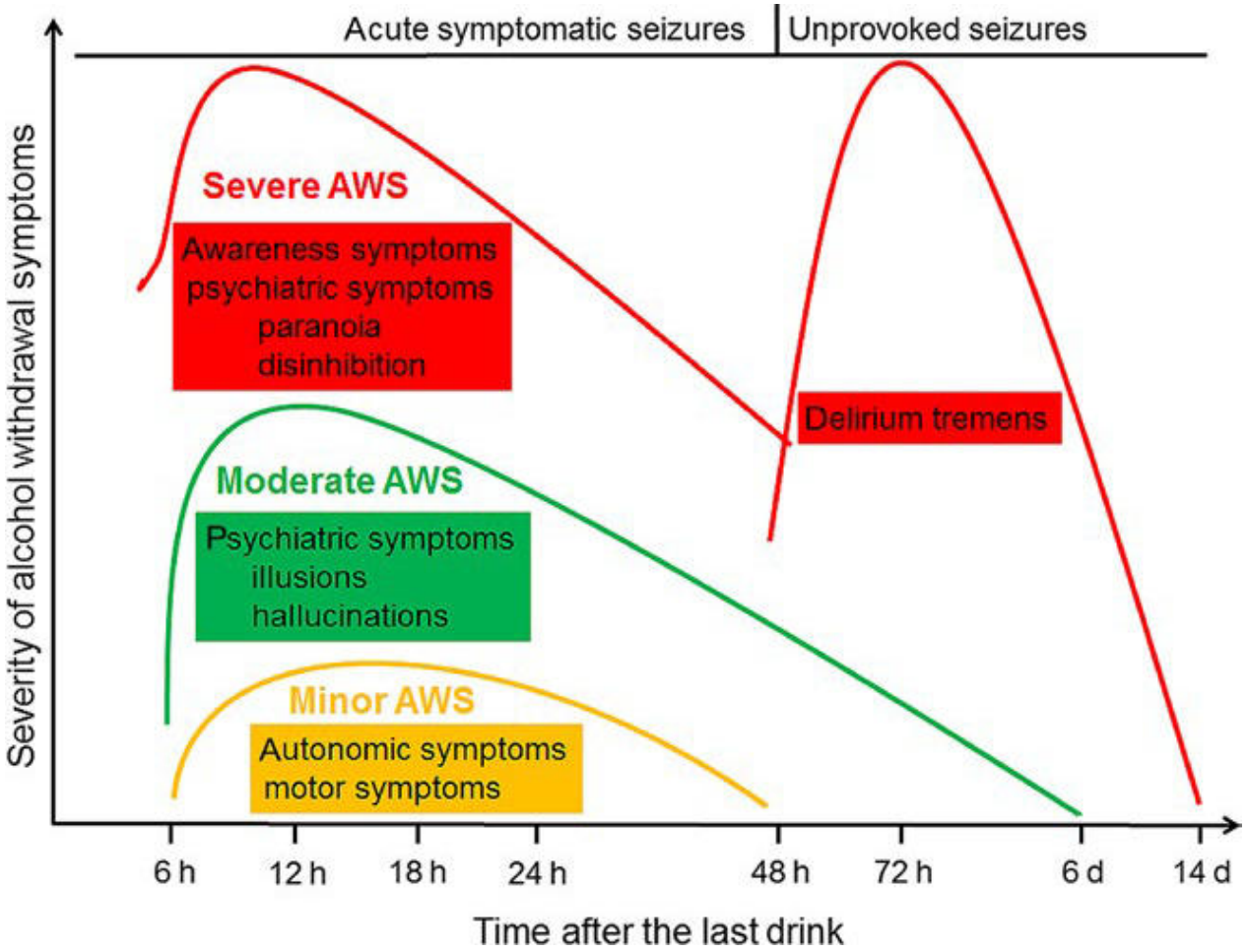
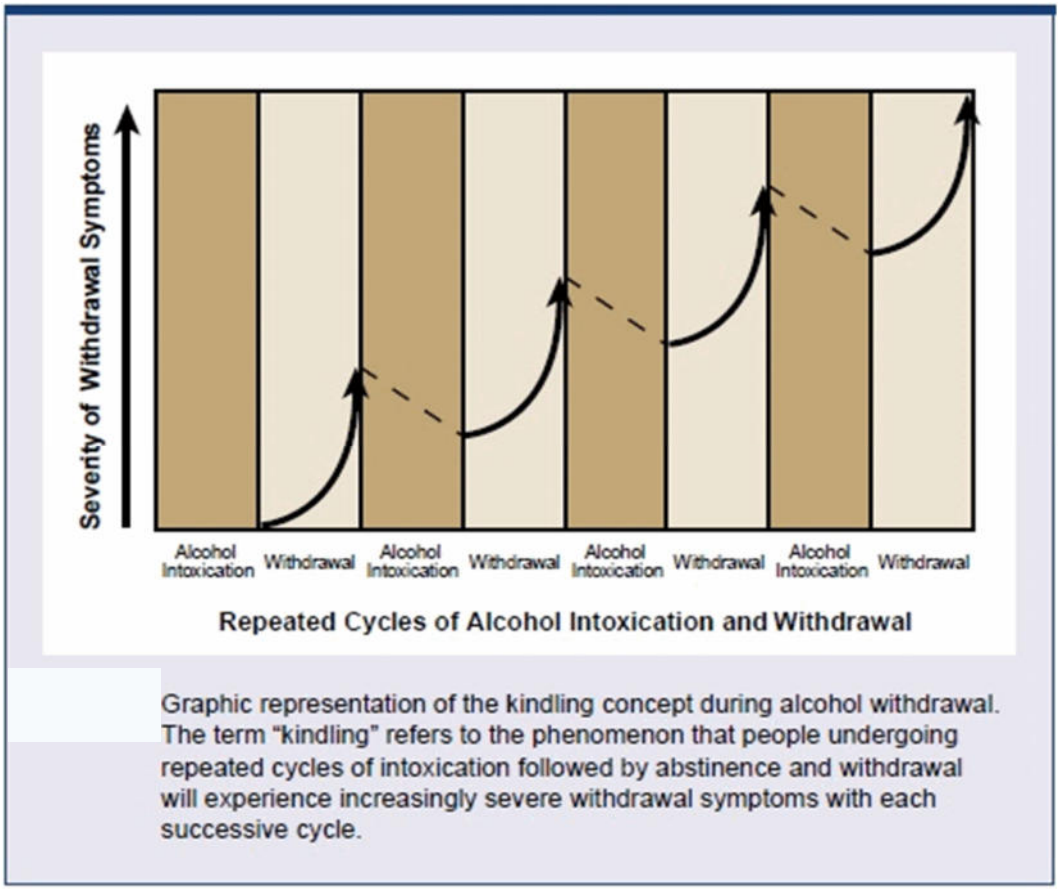


(Jesse et al., Acta Neurol Scand, 2017)

Mechanism of kindling



Graphic representation of the kindling concept during alcohol withdrawal. The term "kindling" refers to the phenomenon that people undergoing repeated cycles of intoxication followed by abstinence and withdrawal will experience increasingly severe withdrawal symptoms with each successive cycle.

(Gonzales et al., ACER, 2001)

Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

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

<8 mild withdrawal
8-15 moderate withdrawal
> 15 severe withdrawal

If initial score < 8, assess q 4 h x 72 hrs
If score < 8 for 72 hrs, discontinue assessment

(Sullivan et al., Br J Addict, 1989)

PREDICTORS OF COMPLICATED AWS

1. Previous episodes of AWS
2. Previous alcohol withdrawal seizures
3. History of DT
4. History of alcohol rehabilitation treatment
5. Previous episodes of blackouts
6. Concomitant use of CNS-depressant agents, such as benzodiazepine or barbiturates
7. Concomitant use of other illicit substances
8. Recent episode of alcohol intoxication
9. Blood alcohol level (BAL) on admission > 200 mg/dl
10. Evidence of increased autonomic activity (tremor, sweating, agitation, nausea, HR > 120)

≥4 criteria suggest HIGH RISK to develop moderate to severe AWS; prophylaxis and/or treatment may be indicated

(Maldonado et al, Alcohol Alcohol, 2014)

Controindications to outpatient treatment of AWS

Abnormal laboratory results
Absence of a support network
Acute illness
High risk of delirium tremens
History of a withdrawal seizure
Long-term intake of large amounts of alcohol
Poorly controlled chronic medical conditions (e.g., diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure)
Serious psychiatric conditions (e.g., suicidal ideation, psychosis)
Severe alcohol withdrawal symptoms
Urine drug screen positive for other substances

Adapted from Myrick H, Anton RF. Treatment of alcohol withdrawal. Alcohol Health Res World. *1998;22(1):40.*

(Muncie et al., Am Family Physicians, 2013)

Outpatient Management of Alcohol Withdrawal Syndrome

HERBERT L. MUNCIE JR., MD, *Louisiana State University School of Medicine, New Orleans, Louisiana*
YASMIN YASINIAN, MD, *New Orleans, Louisiana*
LINDA OGE', MD, *Louisiana State University School of Medicine, New Orleans, Louisiana*

Approximately 2% to 9% of patients seen in a family physician's office have alcohol dependence. These patients are at risk of developing alcohol withdrawal syndrome if they abruptly abstain from alcohol use. Alcohol withdrawal syndrome begins six to 24 hours after the last intake of alcohol, and the signs and symptoms include tremors, agitation, nausea, sweating, vomiting, hallucinations, insomnia, tachycardia, hypertension, delirium, and seizures. Treatment aims to minimize symptoms, prevent complications, and facilitate continued abstinence from alcohol. Patients with mild or moderate alcohol withdrawal syndrome can be treated as outpatients, which minimizes expense and allows for less interruption of work and family life. Patients with severe symptoms or who are at high risk of complications should receive inpatient treatment. In addition to supportive therapy, benzodiazepines, either in a fixed-dose or symptom-triggered schedule, are recommended. Medication should be given at the onset of symptoms and continued until symptoms subside. Other medications, including carbamazepine, oxcarbazepine, valproic acid, and gabapentin, have less abuse potential but do not prevent seizures. Typically, physicians should see these patients daily until symptoms subside. Although effective treatment is an initial step in recovery, long-term success depends on facilitating the patient's entry into ongoing treatment. (*Am Fam Physician*. 2013;88(9):589-595. Copyright © 2013 American Academy of Family Physicians.)

(Muncie et al., Am Family Physicians, 2013)

Trattamento non-farmacologico in pazienti ospedalizzati

-monitoraggio parametri vitali, continua rassicurazione del paziente e, se disponibile, una stanza tranquilla senza rumore non eccessivamente illuminata o eccessivamente scura
-idratazione fino a 1500-2000 cc (soluzioni glucosata al 5% e salina)
-complessi vitaminici per prevenire l'insorgenza del quadro clinico di encefalopatia di Wernicke (oftalmoplegia del VI nervo cranico, atassia e confusione mentale):

- Vit B_1 (tiamina) (250 mg di Vit B_1 i.m. o e.v./die, per 3-5 gg.)
- Vit B_6 e B_{12}, vitamina C e folati

NB: in caso di encefalopatia di Wernicke il trattamento prevede l'utilizzo di una dose maggiore di tiamina:

- 500 mg i.m. o e.v. tre volte al giorno per almeno 2 giorni insieme a Vit B_6 e B_{12} e Vit C (Agabio, 2005)

-tiamina va somministrata prima di ogni infusione di glucosio per evitare l'insorgenza o la progressione della sindrome di Wernicke
-controllare i valori sierici di magnesio e, se ridotti, integrarli in quanto l'uso cronico di bevande alcoliche e la SAA sono strettamente correlate al prolungamento dell'intervallo QT con rischio di aritmie (Espay, 2014)

(Schuckit, NEJM, 2014)

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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

(Caputo et al., Int Emerg Med, 2019)

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Internal and Emergency Medicine
https://doi.org/10.1007/s11739-018-1933-8

CE - ORIGINAL

CrossMark

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]

-BDZs are the "gold standard" for the treatment of AWS and DTs (Grade A1)

-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 (Grade A1)

-alpha-2 agonists, beta-blockers, neuroleptics, and anticovulsants may be used in association with BDZs when BDZs do not completely resolve specific persisting symptoms of AWS and the refractory forms of convulsions in the course of AWS (Grade A1)

(Caputo et al., Int Emerg Med, 2019)

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Alcohol Use in Patients with Chronic Liver Disease

Drug	Dosage	Use in Patients with Liver Disease
Diazepam	10–20 mg orally every 1–2 hr as needed until symptoms are minimal*	Yes, but avoid use in patients with poor synthetic function, decompensated cirrhosis, or both
Chlordiazepoxide	50 mg orally every 1–2 hr as needed until symptoms are minimal*	Yes, but avoid use in patients with poor synthetic function, decompensated cirrhosis, or both
Lorazepam†	2 mg orally every 1–2 hr as needed until symptoms are minimal*	Yes
Oxazepam†	30 mg orally every 1–2 hr as needed until symptoms are minimal*	Yes

(Fuster & Samet, N Engl J Med, 2018)

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Alcohol Use in Patients with Chronic Liver Disease

TO THE EDITOR: In the review article by Fuster and Samet (Sept. 27 issue)[1] regarding alcohol use in patients with chronic liver disease, the authors rightly consider short-acting benzodiazepines (oxazepam and lorazepam) to be the cornerstone of treatment for the alcohol withdrawal syndrome. In addition, γ-aminobutyric acid (GABA) compounds that have not been approved by the Food and Drug Administration were discussed as potential alternatives.

We think that the GABA type B receptor agonist sodium oxybate, which has been approved for the treatment of the alcohol withdrawal syndrome in Italy and Austria for more than 20 years, merits mention.[2] It proved to be as efficient as oxazepam in suppressing the symptoms of this syndrome.[3] Its use in patients who have the alcohol withdrawal syndrome with cirrhosis and ascites has been documented by a case report.[4] However, because of its very short half-life (30 to 45 minutes),[2] its pharmacokinetic profile was similar in patients with ascites and those without ascites.[5]

Extensive studies of the use of short-acting benzodiazepines in patients with chronic liver disease are limited. It should be noted that their half-life (5 to 25 hours) is far longer than that of sodium oxybate.[3,4] Thus, to reduce the risk of drug accumulation, sodium oxybate may be considered as a safe and efficient pharmacologic option in patients with cirrhosis and the alcohol withdrawal syndrome.

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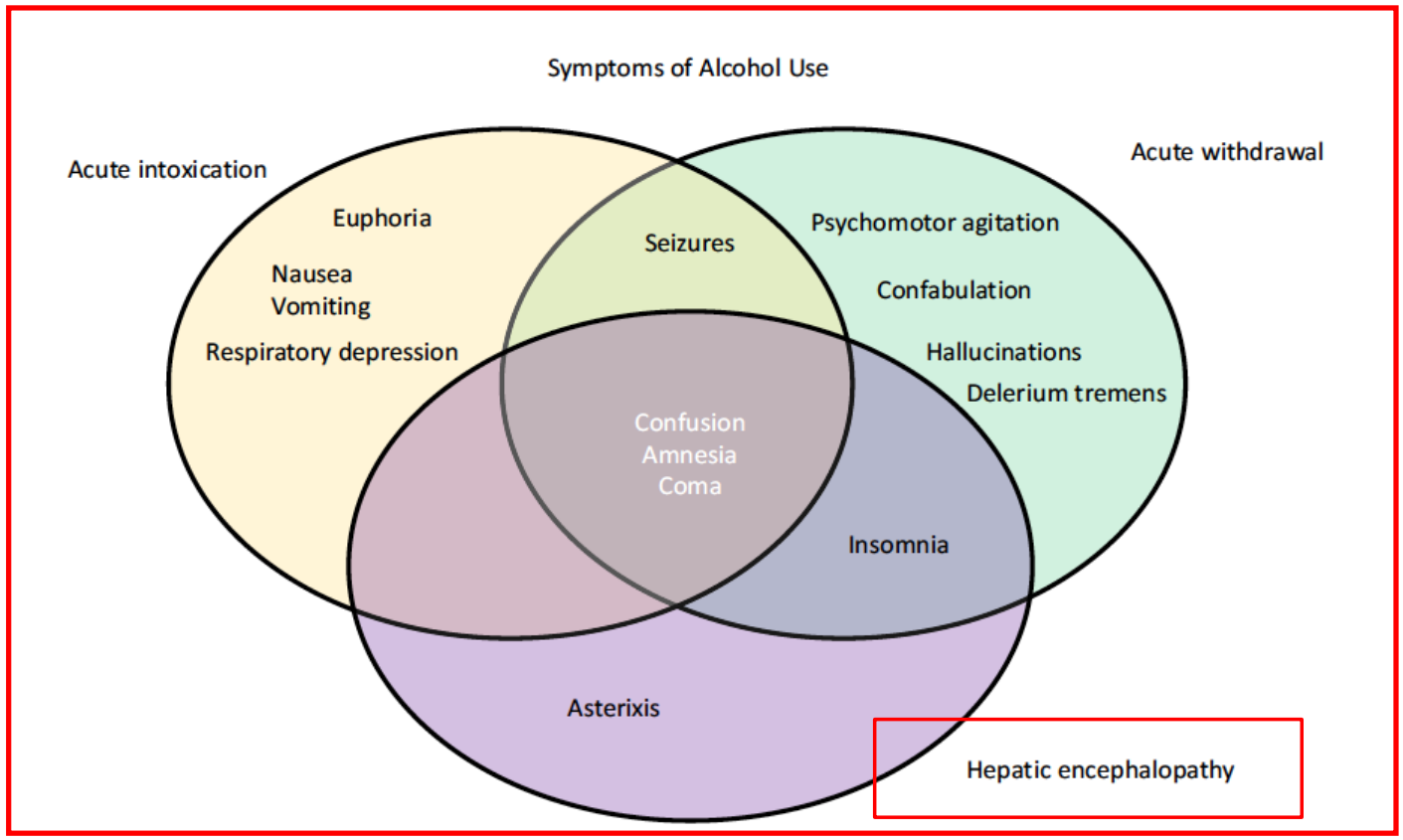
No potential conflict of interest relevant to this letter was reported.

1. Fuster D, Samet JH. Alcohol use in patients with chronic liver disease. N Engl J Med 2018;379:1251-61.
2. Keating GM. Sodium oxybate: a review of its use in alcohol withdrawal syndrome and in the maintenance of abstinence in alcohol dependence. Clin Drug Investig 2014;34:63-80.
3. 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.
4. Caputo F, Bernardi M, Zoli G. Efficacy and safety of

(Caputo et al., N Engl J Med ,2018)

Effects of alcohol on the brain



(Davids and Bajaj, Alcohol Clin Exp Res, 2018)

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HEPATOLOGY
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
CONCISE REVIEW | HEPATOLOGY, VOL. 0, NO. 0, 2019

Diagnosis and Treatment of Alcohol Use Disorder in Patients With End-Stage Alcoholic Liver Disease

Treatment in specific settings

-*HE:* Prompt treatment should be pursued; then treatment of AWS can be initiated.

-*Ascites, hepatorenal syndrome, and variceal hemorrhage:* Ascites *per se* does not contraindicate short-acting BDZs. In patients with hepatorenal syndrome, BDZs should be used with great caution due to the simultaneous impairment of liver and kidney functions. Intravenous short-acting BDZs such as lorazepam (oxazepam is not available in intravenous formulation) can be used in patients with variceal hemorrhage.

(Caputo et al., Hepatology, 2019)

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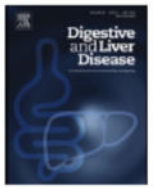
Digestive and Liver Disease 52 (2020) 21–32

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Guidelines

Management of end-stage alcohol-related liver disease and severe acute alcohol-related hepatitis: position paper of the Italian Society on Alcohol (SIA)

Gianni Testino[a], Teo Vignoli[b], Valentino Patussi[c], Emanuele Scafato[d], Fabio Caputo[e,f,*], on behalf of the SIA board (Appendix A) and the external expert supervisors (Appendix B)

-management of complications (i.e. HE: lactulose / lactilol and rifaximin 400 mg t.i.d. or 550 mg b.i.d. in cases of refractary forms of HE)
-management of AWS (short acting benzodiazepines; trigger symptoms regimen)
-vitamin supplementation

(Testino et al., Dig Liv Dis, 2020)

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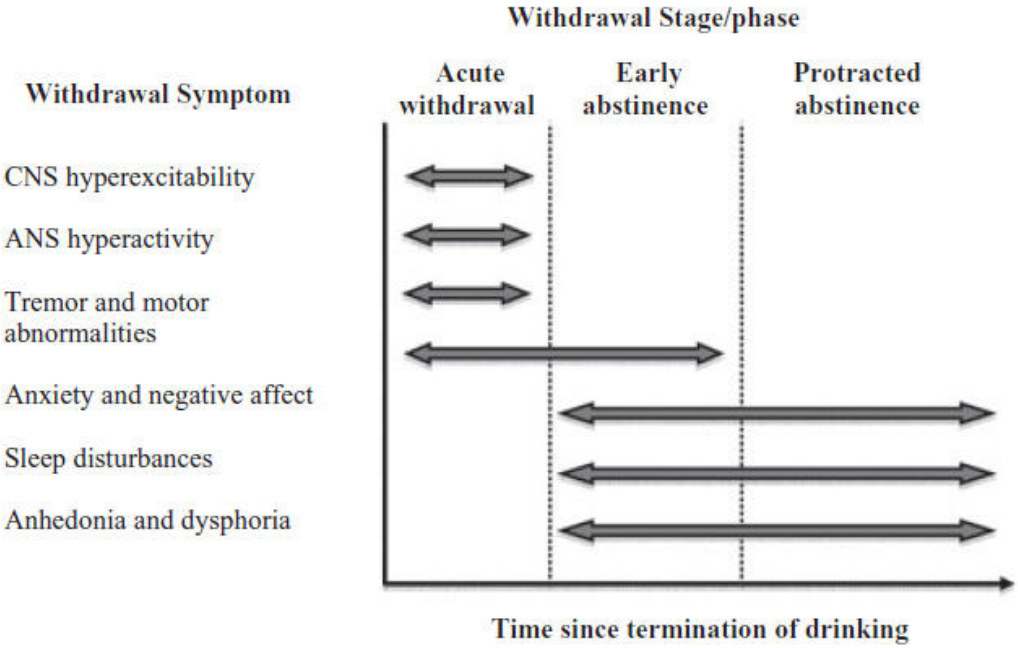

Acute withdrawal phase: humans (48–72 hours); animals (24–48 hours).
Early abstinence phase: humans (3–6 weeks); animals (1–2 weeks).
***Protracted abstinence phase*: humans (> 3 months); animals (> 1 month).**

(Heilig et al., Add Biol, 2010)

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Protracted withdrawal, strictly defned, is the presence of substance-specifc signs and symptoms common to acute withdrawal but *persisting for several months* beyond the generally expected acute withdrawal timeframes *(Schuckit, Lancet, 2009)*

(U.S. Department of Health and Human Service, 2010)

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Substance Abuse Treatment

ADVISORY

News for the Treatment Field

July 2010
Volume 9
Issue 1

PROTRACTED WITHDRAWAL

- Anxiety
- Sleep difficulties
- Problems with short-term memory
- Persistent fatigue
- Difficulty concentrating and making decisions
- Alcohol or drug cravings
- Impaired executive control
- Anhedonia
- Difficulty focusing on tasks
- Dysphoria or depression
- Irritability
- Unexplained physical complaints
- Reduced interest in sex

(U.S. Department of Health and Human Service, 2010)

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Perspectives

The recognition and management of protracted alcohol withdrawal may improve and modulate the pharmacological treatment of alcohol use disorder

Psychopharm

Journal of Psychopharmacology
1–5

DOI: 10.1177/0269881120936483
journals.sagepub.com/home/jop
SAGE

Fabio Caputo[1,2], Mauro Cibin[3], Antonella Loche[4], Roberto De Giorgio[5] and Giorgio Zoli[5]

Stages of alcohol withdrawal syndrome (AWS)	Acute alcohol withdrawal	Early abstinence, protracted alcohol withdrawal
Medications	Bezodiazepines (or sodium oxybate§) plus (if indicated) symptomatic drugs^	NMDA antagonist* plus GABA agonist*
Period of treatment	7–10 days	To be defined*

(Caputo et al., J Psychopharmacol, 2020)

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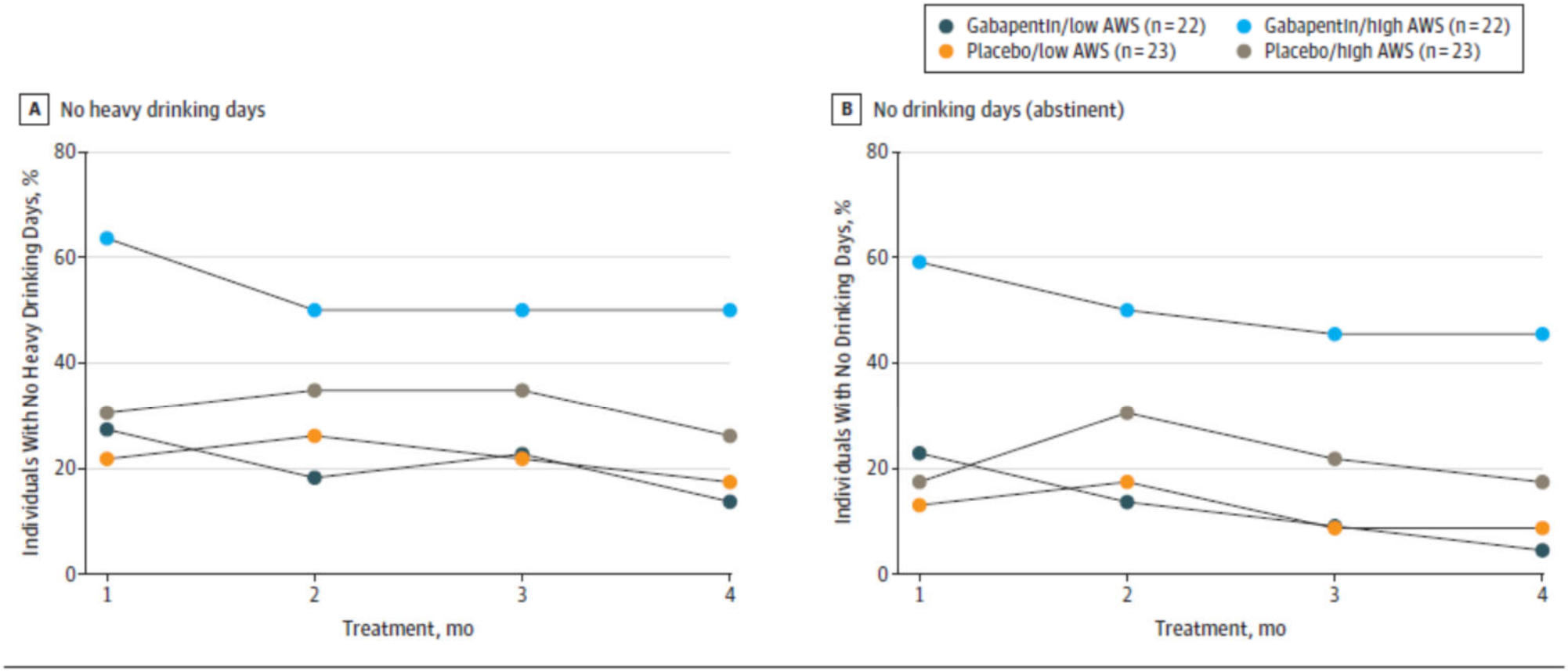
Research



(Anton et al., JAMA Intern Med, 2020)

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Research

JAMA Internal Medicine | Original Investigation

Efficacy of Gabapentin for the Treatme in Patients With Alcohol Withdrawal Sy
A Randomized Clinical Trial

Raymond F. Anton, MD; Patricia Latham, PhD; Konstantin Voronin, MD, PhD; S
Michaela Hoffman, PhD; James Prisciandaro, PhD; Emily Bristol, BA

Conclusions

The weight of the evidence now suggests that gabapentin might be most efficacious after the initiation of abstinence to sustain it and that it might work best in those with a history of more severe alcohol withdrawal symptoms. To further confirm this, future studies should specifically evaluate symptoms related to protracted alcohol withdrawal during gabapentin treatment. Armed with this knowledge, clinicians may have another alternative when choosing a medication to treat AUD and thereby encourage more patient participation in treatment with enhanced expectation of success.

(Anton et al., JAMA Intern Med, 2020)

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SC/PD-MGM/DG

AIFA/SC/P/115854

AGENZIA ITALIANA DEL FARMACO

Ufficio Sperimentazione Clinica

Roma, 20/10/2020

GB PHARMA SERVICES & CONSULTING SRL-
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OGGETTO: **EudraCT number: 2019-001834-33**

TITOLO: Efficacia e sicurezza del Sodio Oxibato nella riduzione del consumo alcolico e nel mantenimento dell' astinenza in pazienti alcool dipendenti a rischio elevato/molto elevato di bere.

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Scala sintomi della Sindrome Astinenziale Protratta

Centro: _____ ID Paziente: _____ Data: _____

Visita n°: _____ giorni/settimane da inizio trattamento: _____

Introduzione: valutare l'intensità di alcuni sintomi che vengono correlati alla "Sindrome Astinenziale Protratta".
Interrogazione: il sintomo sotto riportato è ora ASSENTE o è stato tale nei giorni precedenti? Se invece è presente, con quale intensità si può definire: LIEVE, MODERATA o GRAVE ?
Procedura:

- Barrare, in corrispondenza di ognuno dei 7 sintomi elencati, l'intensità che più si adatta a quanto il Paziente riferisce, in una scala da zero (assente) a 3 (grave)
- Riportare lo score totale dei 7 sintomi (intervallo 0 -21)
- Sulla base della letteratura vigente, la presenza, alla visita iniziale, di almeno 3 di questi sintomi a livello almeno 1, consente di fare diagnosi di SAP
- La scala applicata all'inizio e ogni **nx** (dove **x** esprime l'unità di tempo, giorni / settimane / mesi) consente di valutare l'efficacia del trattamento

Item	0 = assente	1 = lieve	2 = moderato	3 = grave
Ansia				
Disforia				
Stanchezza				
Disturbi del sonno				
Difficoltà di concentrazione				
Anedonia				
Craving				
Score Totale:				

Note:

- Con DISFORIA si includono sintomi legati a Depressione, Irritabilità, Nervosismo
- Con DISTURBI DEL SONNO si includono sia difficoltà ad addormentarsi che risvegli notturni
- Con ANEDONIA qualsiasi incapacità a provare piacere nelle comuni attività quotidiane
- Con CRAVING il desiderio irrefrenabile per l'alcol (valutare solo in base a quanto riferisce il paziente in questo contesto senza somministrare una scala specifica tipo VAS o altro.).

Symptoms of protracted alcohol withdrawal in patients with alcohol use disorder: a systematic review.

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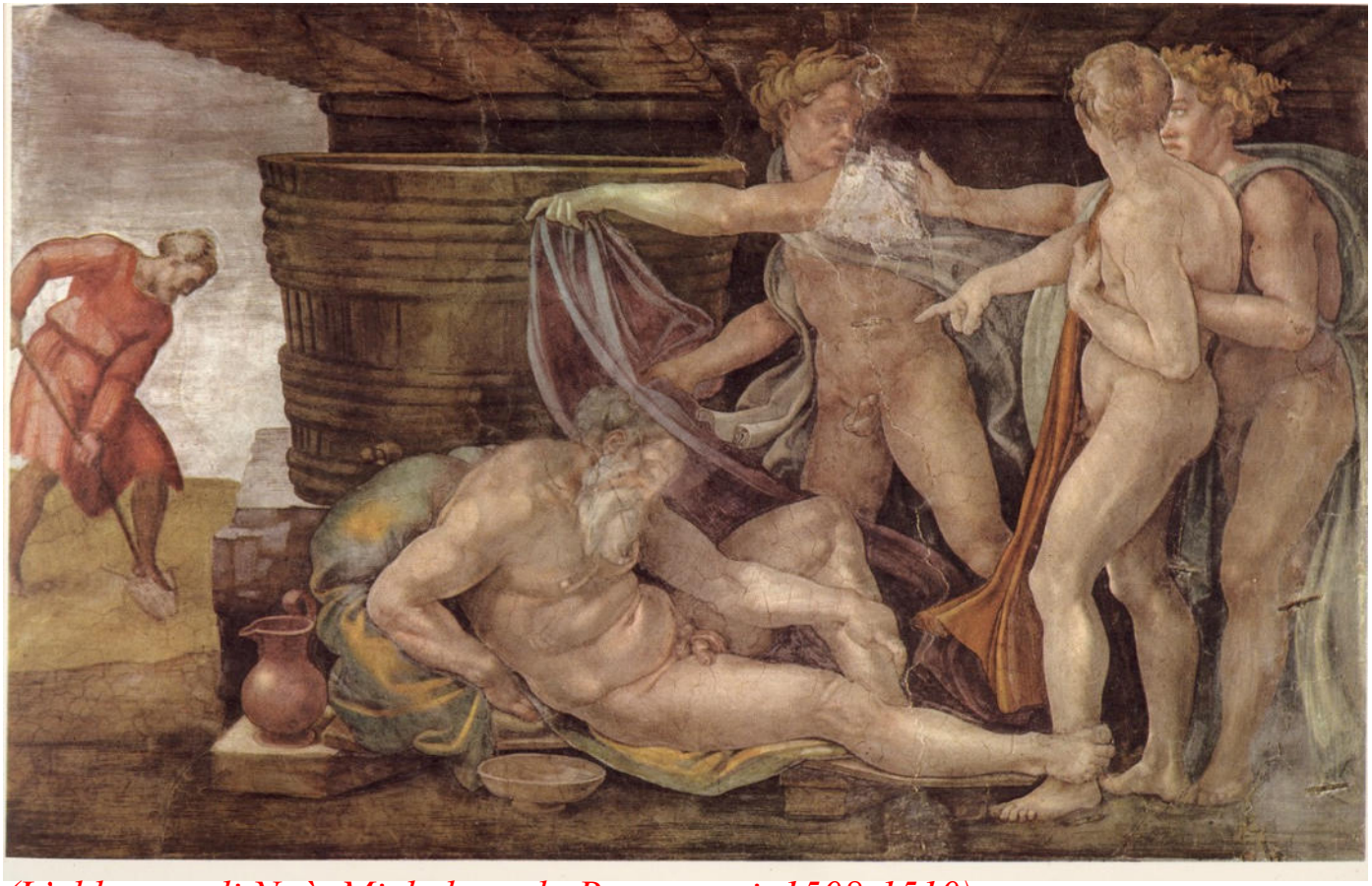

(L'ebbrezza di Noè, Michelangelo Buonarroti, 1508-1510)

Grazie per l'attenzione!