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SITOX
Paracelso nel XXI secolo:
«Dosis sola facit, ut venenum non fit»
BOLOGNA
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Savoia Regency Hotel

CORSO PRE-CONGRESSUALE: GESTIONE OSPEDALIERA DEL DISTURBO DA USO DI SOSTANZE

LA SINDROME ASTINENZIALE DA ALCOL: GESTIONE OSPEDALIERA

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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)

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

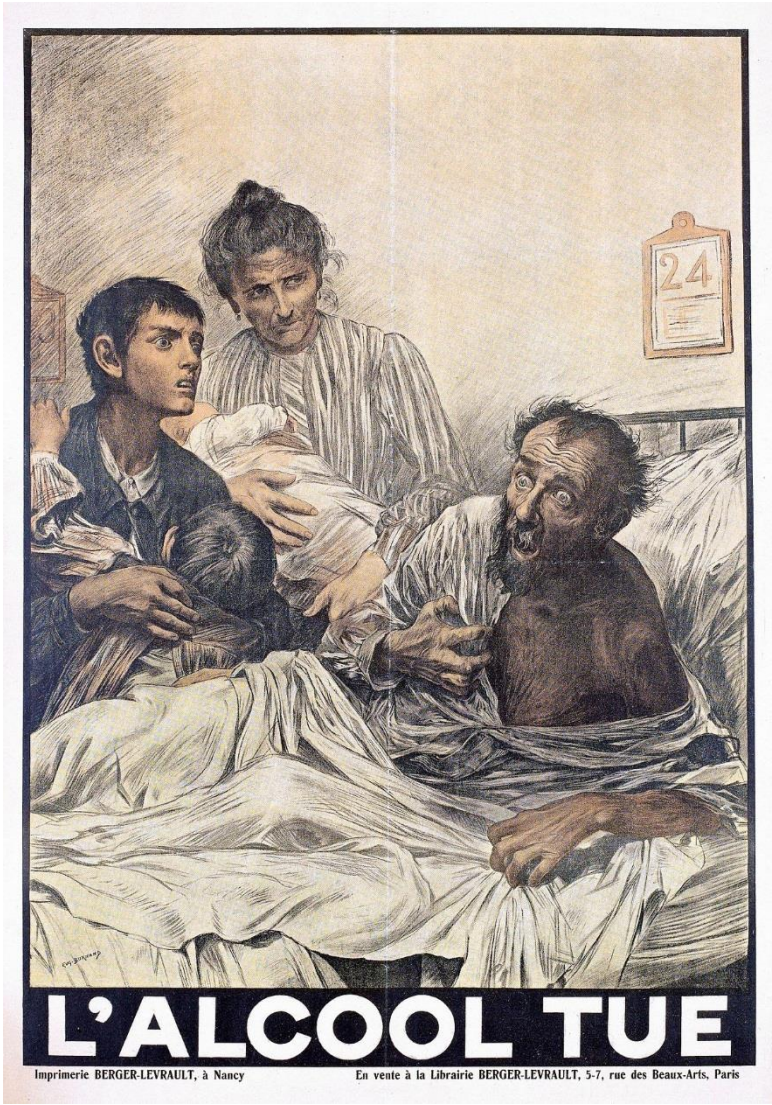
Decreased attention and awareness

Disturbance in attention, awareness, memory, orientation, language, visuospatial 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

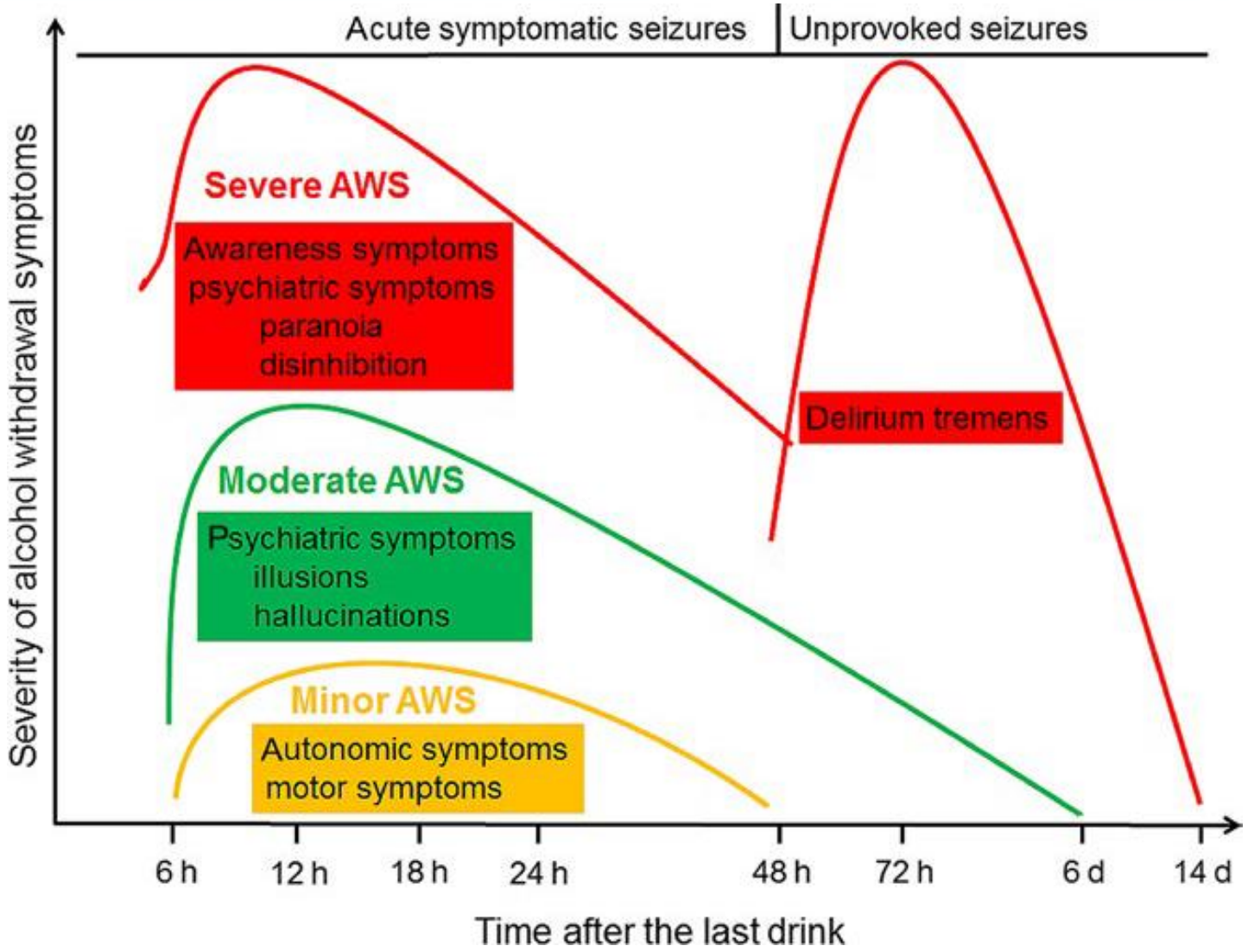
(American Psychiatric Association, 2013)



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.

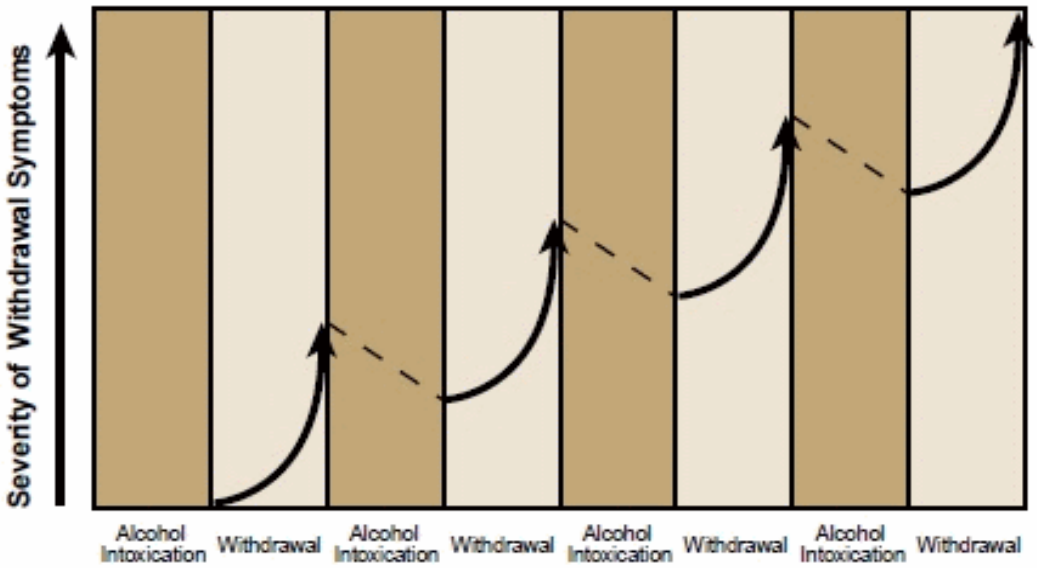
Fino a qualche anno fa, la mortalità per DTs era del 5-15% (ipertermia, aritmie, collasso cardiocircolatorio).
Dopo l'avvento dei farmaci specifici, la mortalità si è ridotta a non più dell'1%.

(Schuckit, NEJM, 2014)



(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)

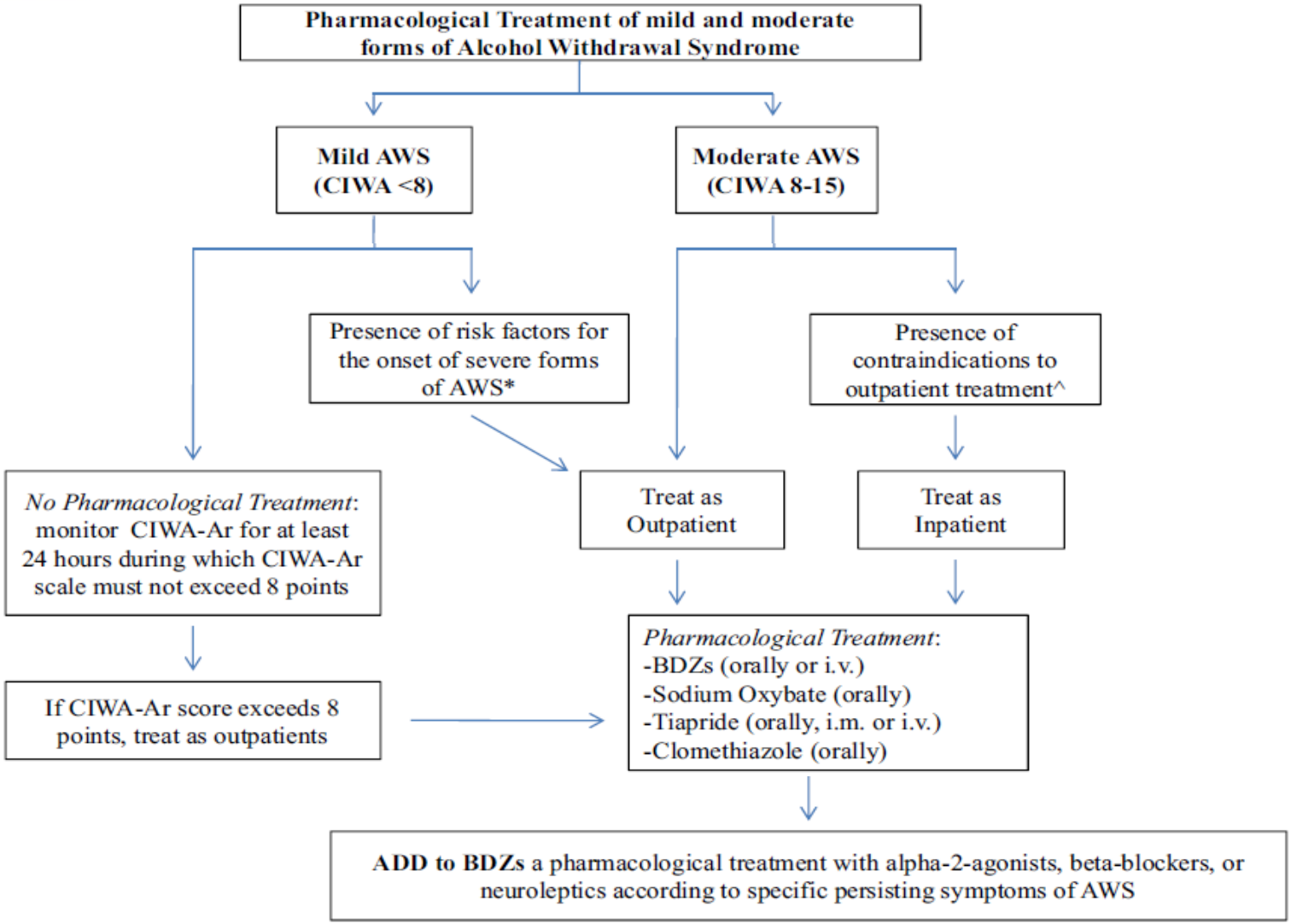
Treatment with a symptom-triggered regimen
Chlordiazepoxide: 50–100 mg orally[a]
Diazepam: 10–20 mg orally or i.v.[a]
Lorazepam: 2–4 mg orally, i.v. or i.m.[a]
Oxazepam: 60–90 mg orally[a]
Treatment with a fixed-schedule regimen
Chlordiazepoxide: 50–100 mg every 6 h (day 1), then 25–50 mg every 6 h (days 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

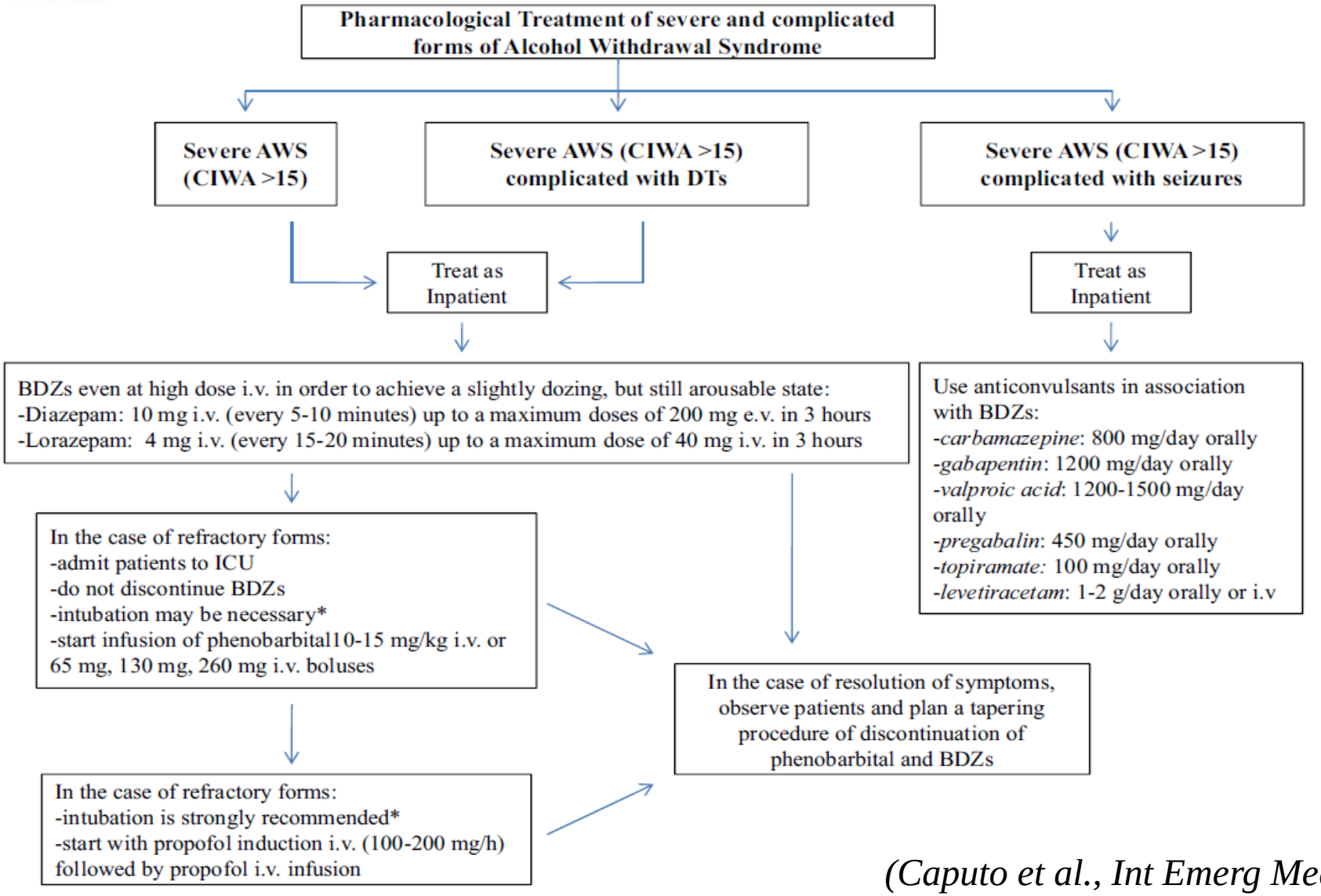
[b]On day 4, start to gradually reduce the dose by 25% every day until day 7, then suspend

[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)



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



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

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)

Drugs (2015) 75:353–365
DOI 10.1007/s40265-015-0358-1

THERAPY IN PRACTICE

Identification and Management of Alcohol Withdrawal Syndrome

Antonio Mirijello · Cristina D'Angelo · Anna Ferrulli · Gabriele Vassallo · Mariangela Antonelli · Fabio Caputo · Lorenzo Leggio · Antonio Gasbarrini · Giovanni Addolorato

Drug	Half-life	Active metabolites	Metabolism	Excretion
Diazepam	20–80 h (metabolites 30–100 h)	Yes	Hepatic	Hepatic: urinary (metabolites)
Chlordiazepoxide	5–30 h (metabolites 30–200 h)	Yes	Hepatic	Hepatic: urinary (metabolites)
Lorazepam	10–20	No	Hepatic	Urinary, fecal
Oxazepam	10–20	No	Hepatic	Urinary
Midazolam	2–6	Yes	Hepatic, gut	Urinary

(Mirijello et al., Drugs, 2015)

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)

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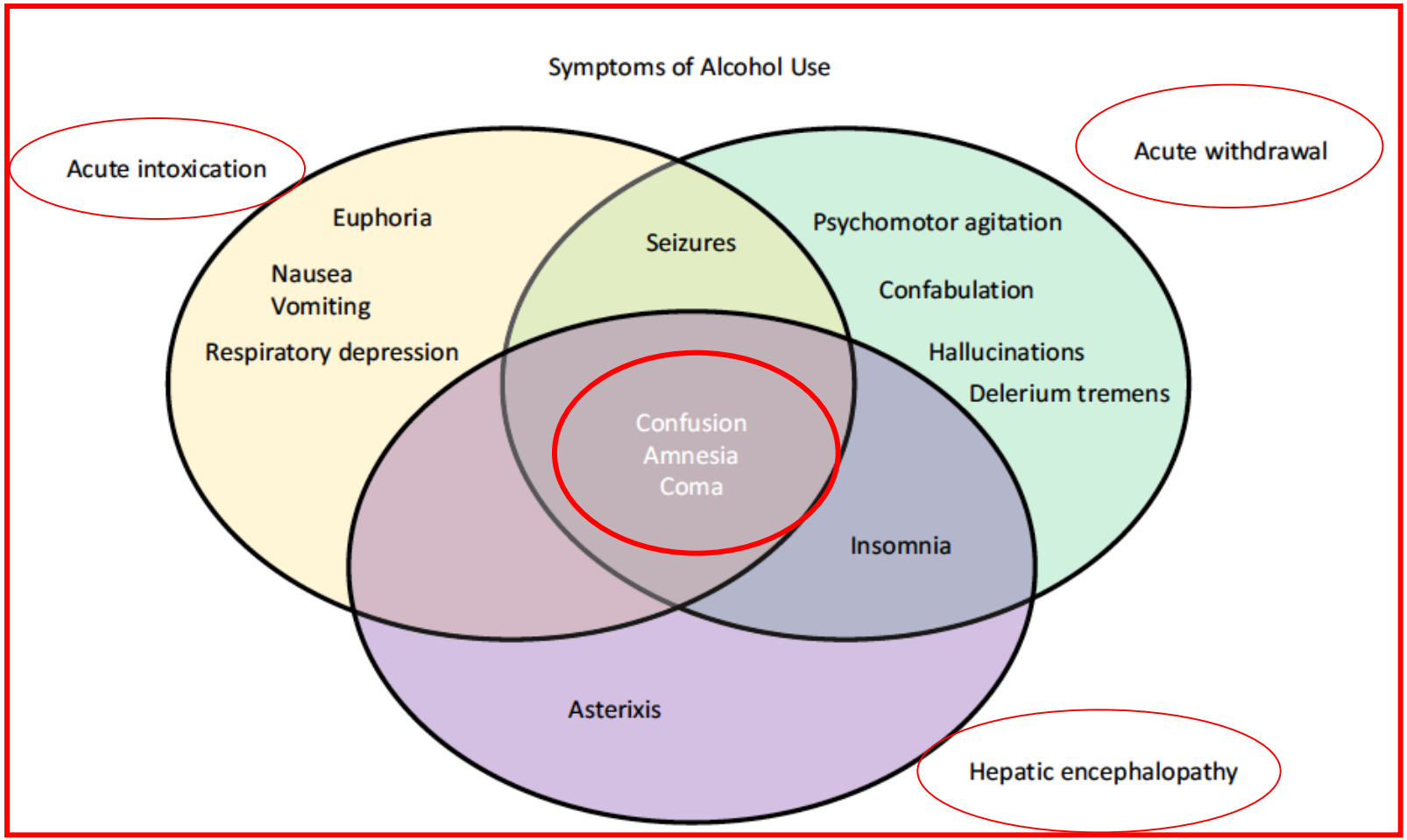
No potential conflict of interest relevant to this letter was reported.

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., NEJM, 2018)

Effects of alcohol on the brain



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

HEPATOLOGY
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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)

Digestive and Liver Disease 52 (2020) 21–32

Contents lists available at ScienceDirect

Digestive and Liver Disease

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

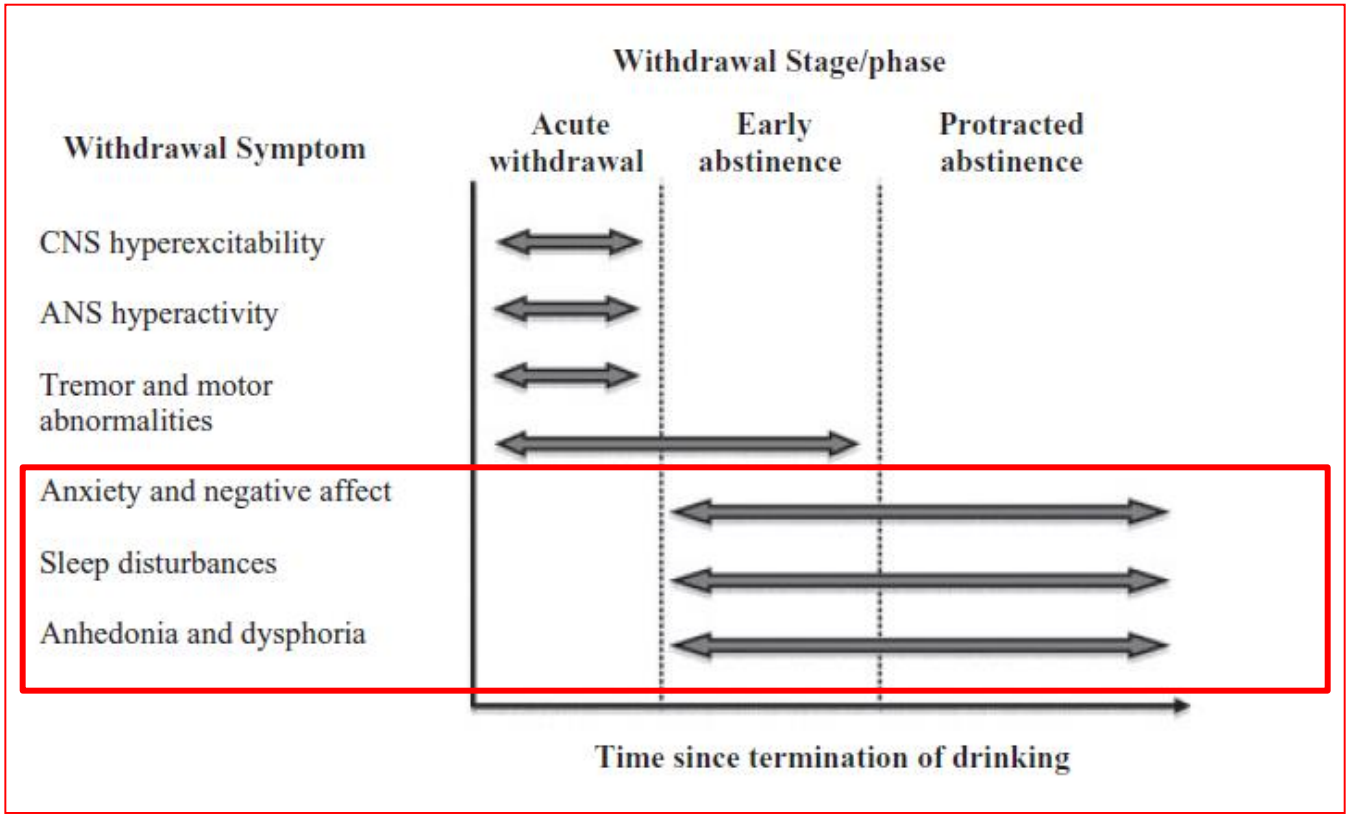
Guidelines

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)



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)

Substance Abuse Treatment

ADVISORY

News for the Treatment Field

July 2010
Volume 9
Issue 1

PROTRACTED WITHDRAWAL

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)

Substance Abuse Treatment

ADVISORY

News for the Treatment Field

July 2010
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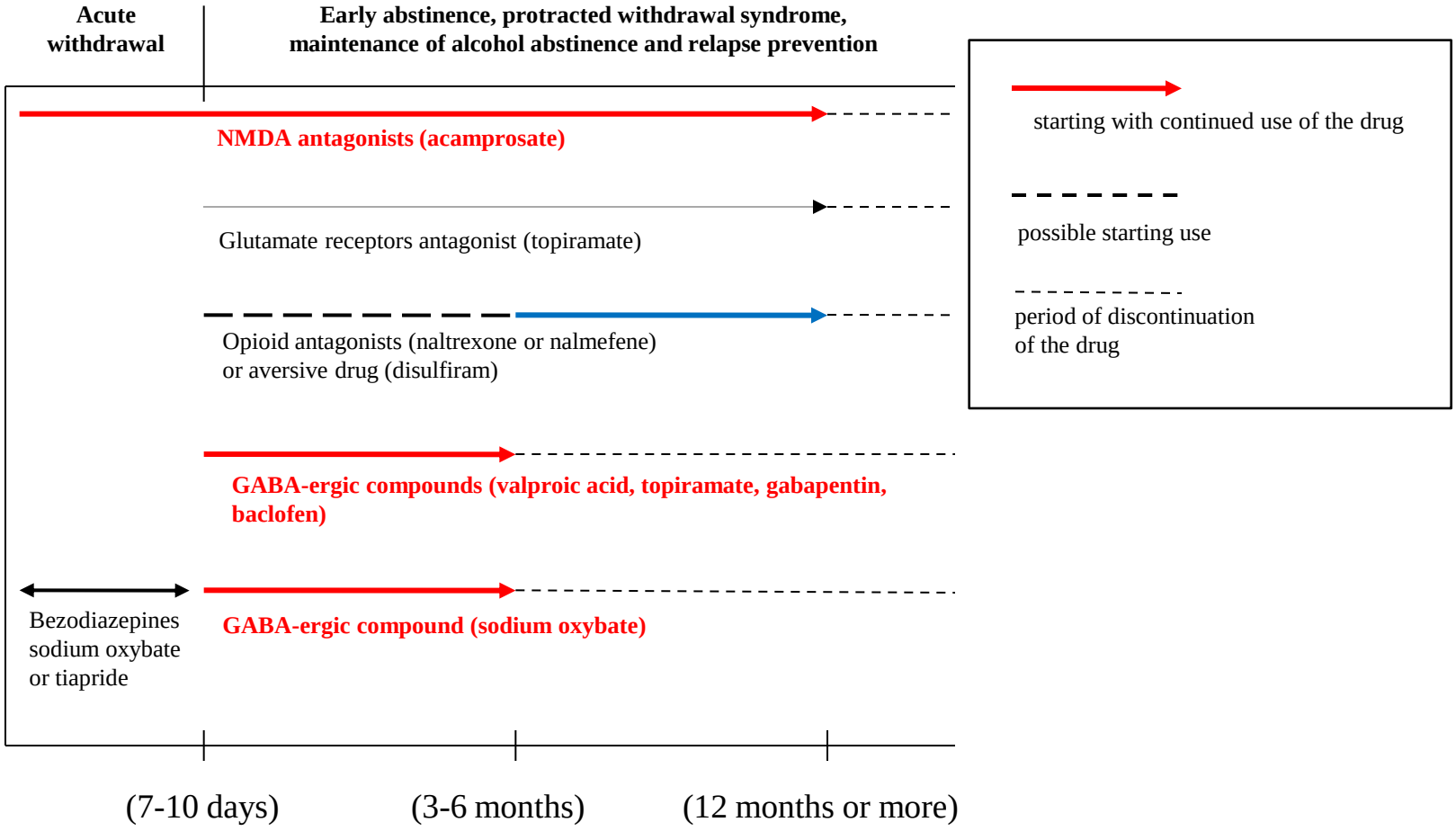
PROTRACTED WITHDRAWAL

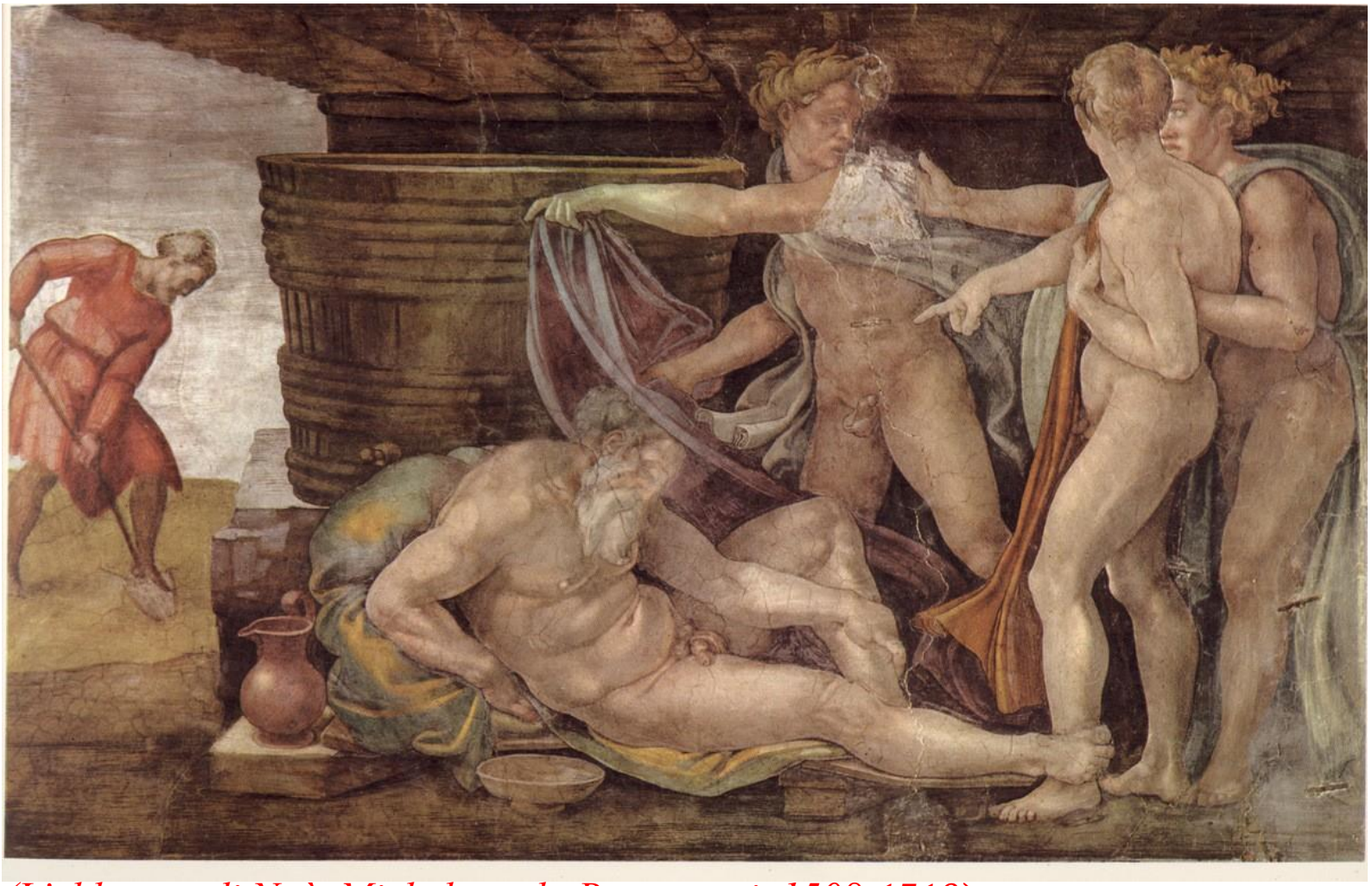
- Anxiety
- Sleep difficulties
- Problems with short-term memory
- Persistent fatigue
- Difficulty concentrating and making decisions
- Alcohol or drug cravings
- Impaired executive control
- Anhedonia
- Difficulty focusing on tasks
- Dysphoria or depression
- Irritability
- Unexplained physical complaints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

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

Hypothesis of starting time of the pharmacological treatment for alcohol use disorder after the first 7-10 days of the detoxification period



(Caputo et al., J Psychopharmacol, submitted)



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

Grazie per l'attenzione!