Università degli Studi di Ferrara | Dipartimento di Medicina Traslazionale e per la Romagna

LE SINDROMI ASTINENZIALI: DIAGNOSI E TRATTAMENTO

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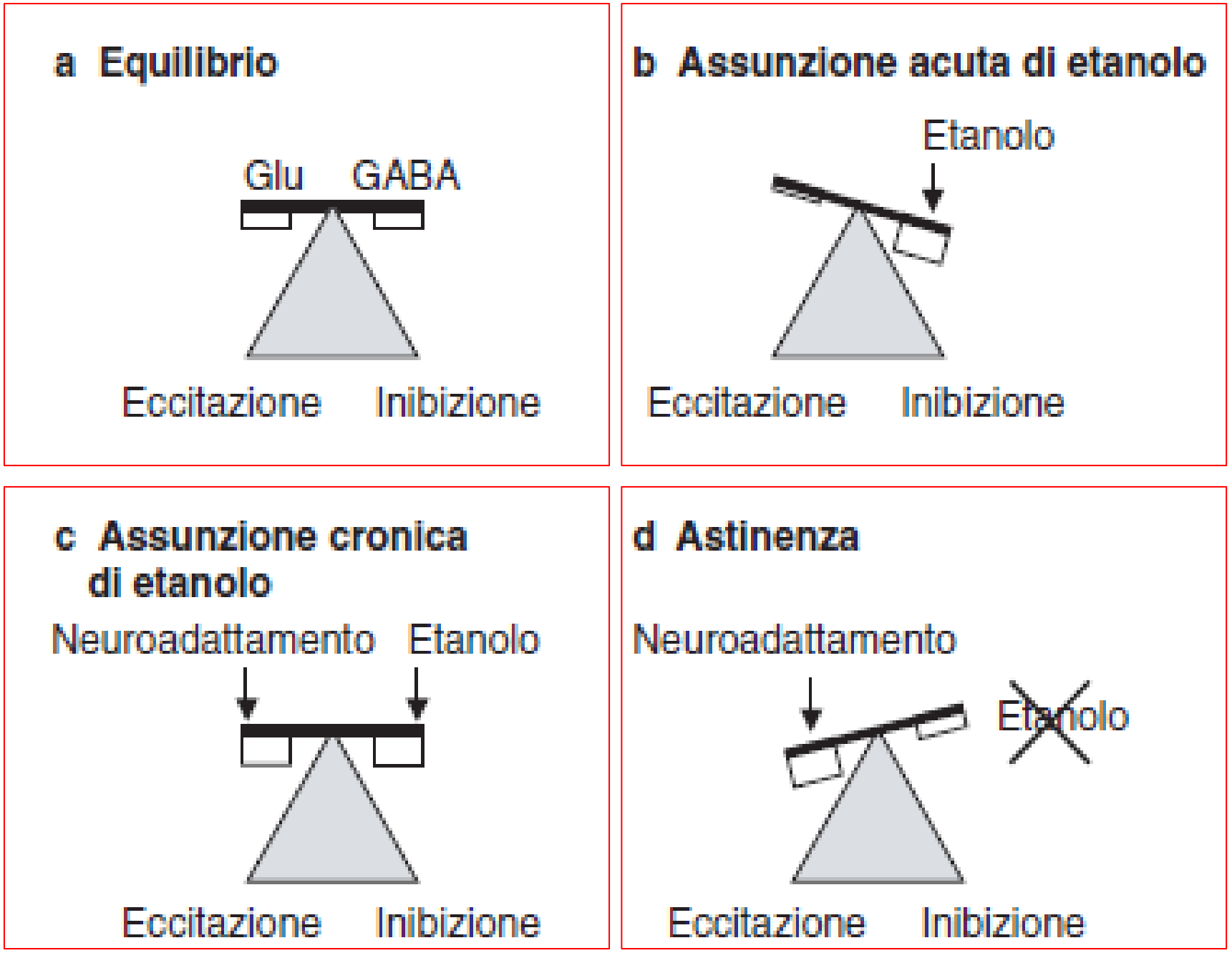
Pharmacological treatment of Alcohol Use Disorder (AUD)

- **-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)**



(Himmelsbach, Ann Int Med, 1941)

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

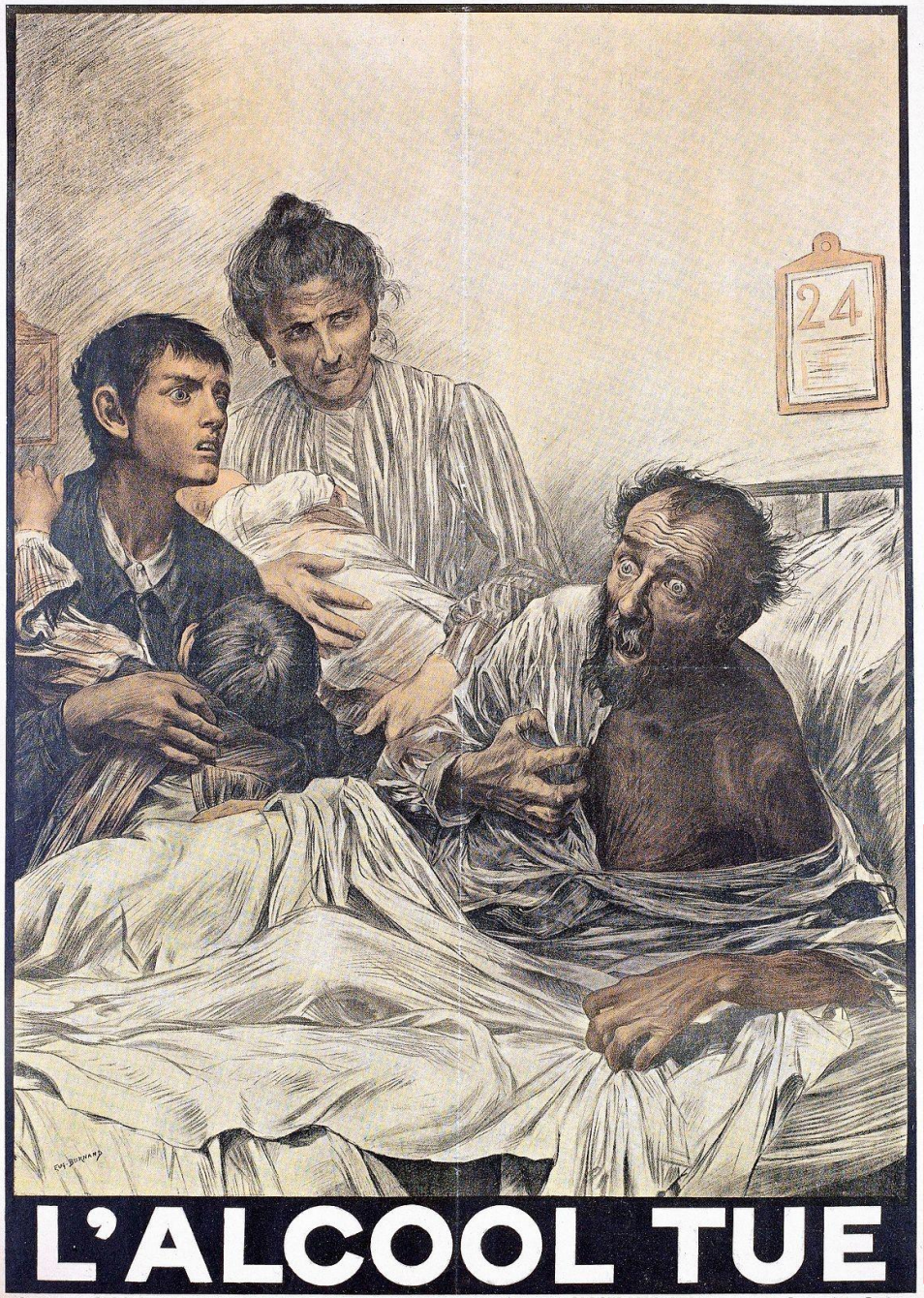
Decreased attention and awareness

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

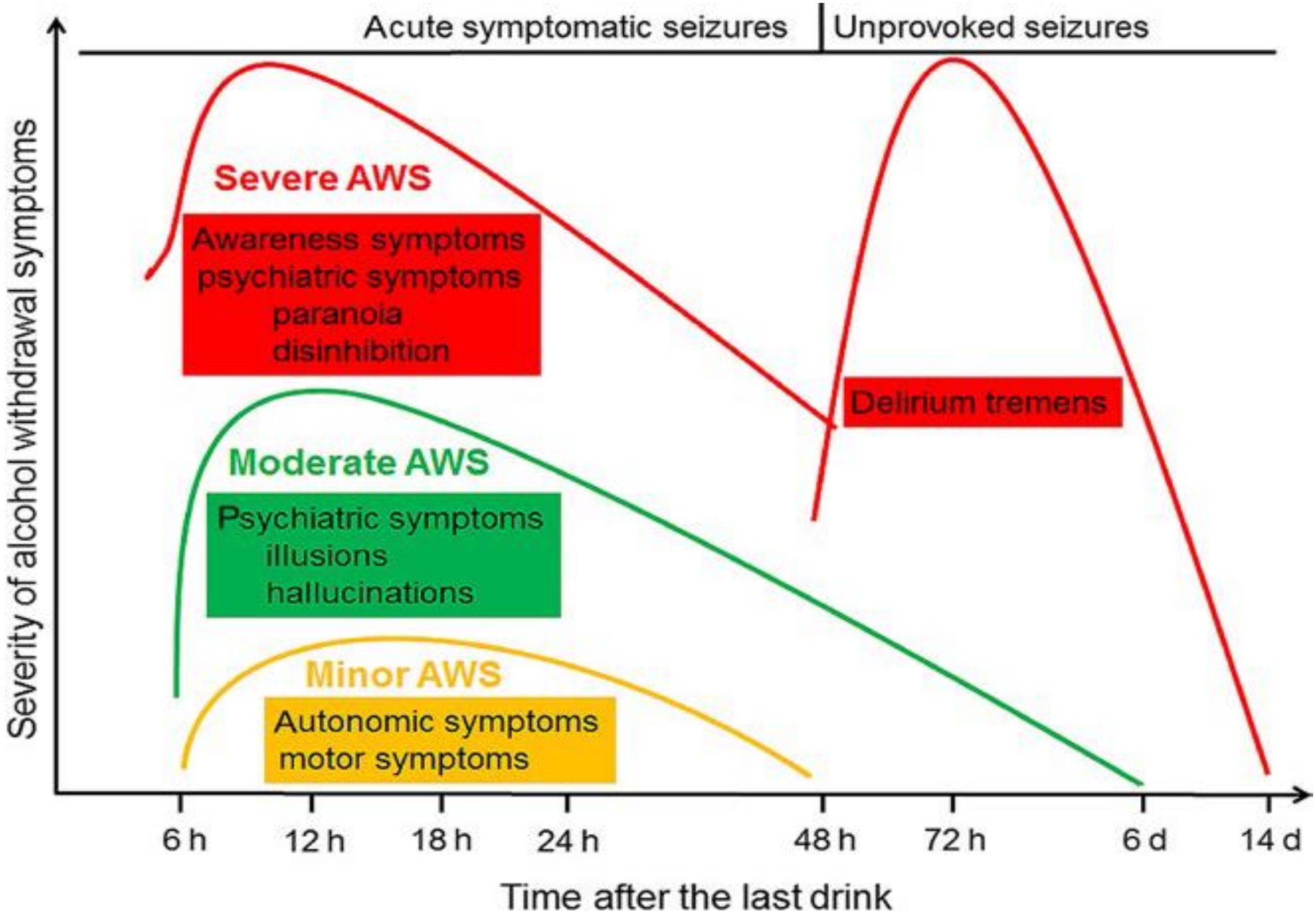
(American Psychiatric Association, 2013)



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)

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)

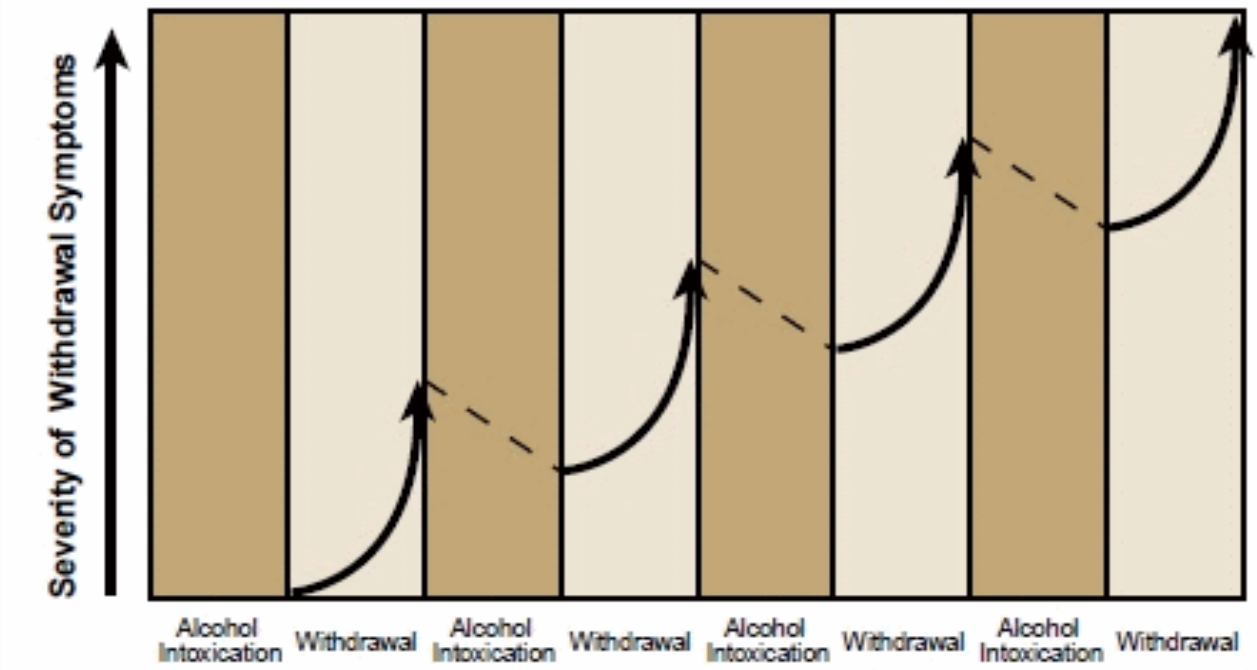
PREDICTORS OF COMPLICATED AWS

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, 2014)

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)

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)

Trattamento non-farmacologico della SAA

-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./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)

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

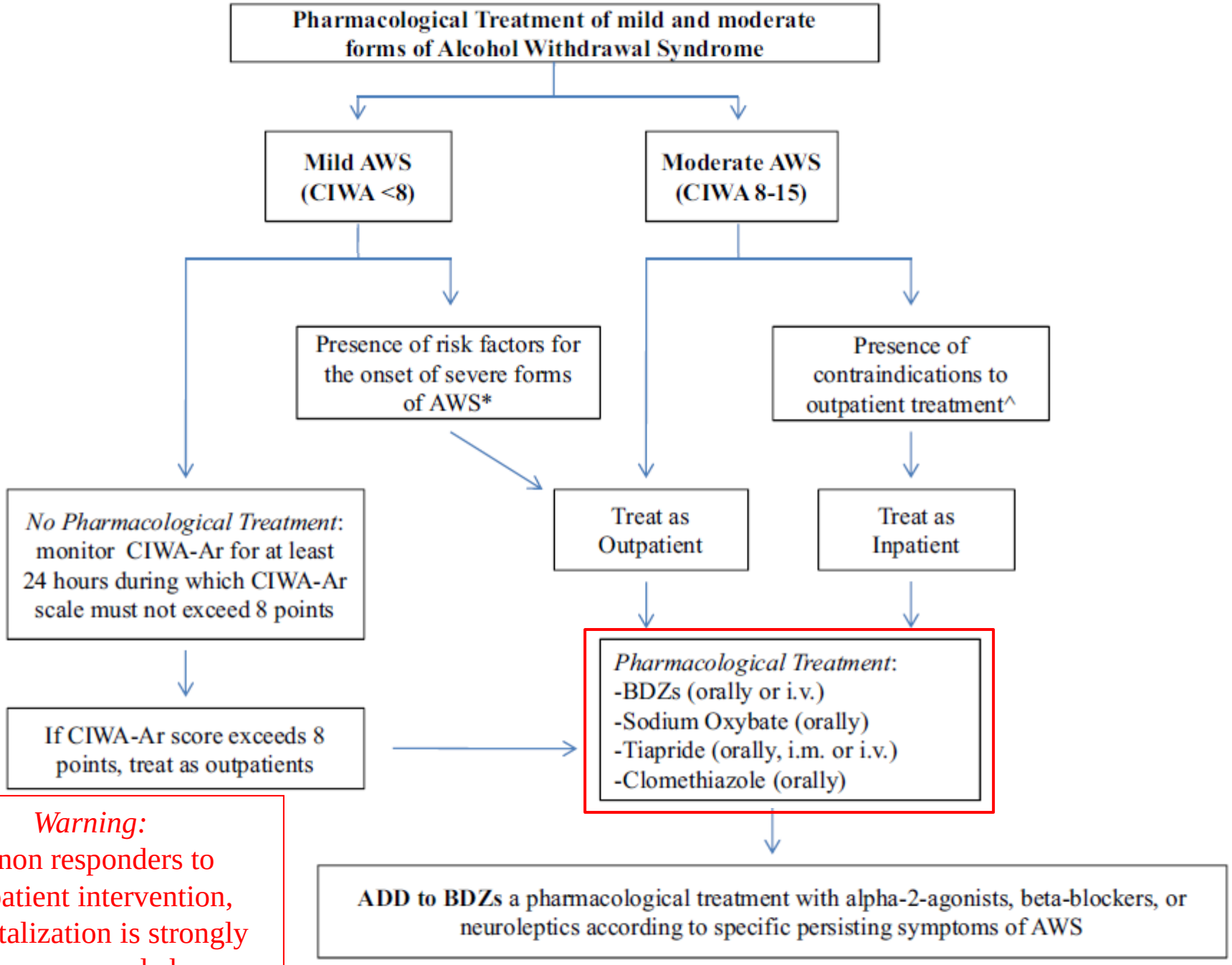
Treatment with a symptom-triggered regimen
Chlordiazepoxide: 50–100 mg orally[a]
Diazepam: 10–20 mg orally or i.v.[a]
Lorazepam: 2–4 mg orally, i.v. or i.m.[a]
Oxazepam: 60–90 mg orally[a]
Treatment with a fixed-schedule regimen
Chlordiazepoxide: 50–100 mg every 6 h (day 1), then 25–50 mg every 6 h (days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

(Caputo et al., Int Emerg Med, 2018)



Warning:
in non responders to outpatient intervention, hospitalization is strongly recommended

(Caputo et al., Int Emerg Med, 2018)

Only in association with BDZs

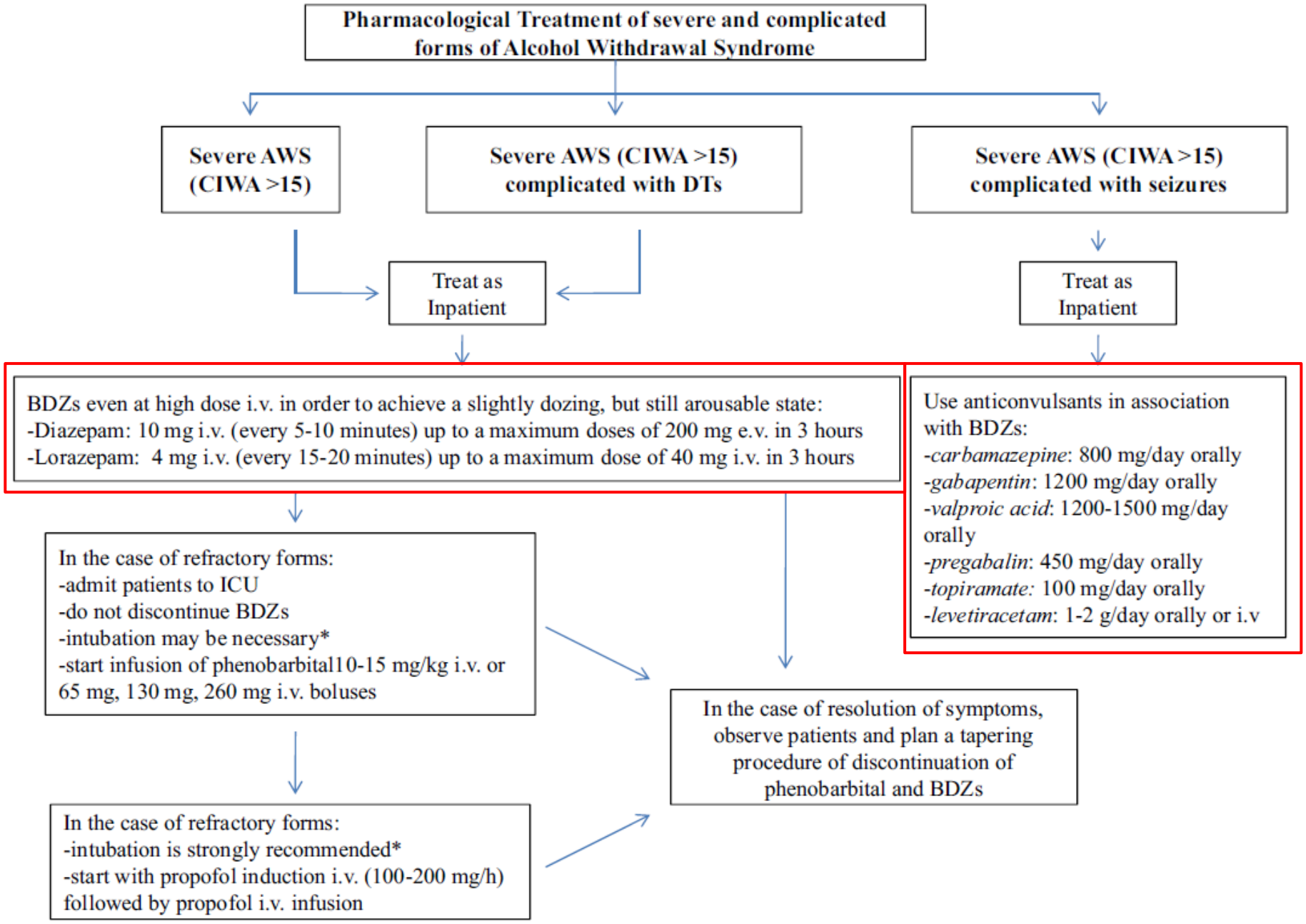
(when high dosages of BDZs are inadequate to control AWS)

- **Neuroleptic agents** (haloperidol: 0.5-5 mg orally every 4 hs or 0.5-5 mg i.v./i.m. every 30-60 minutes)

- **beta-blockers** (atenolol: 100 mg/day orally) or **central sympatholytics** (clonidine: 0.150-0.300 mg/day orally)

- **Anticonvulsants** (carbamazepine: 800 mg/day orally the first 3 days, than 600 mg/day from 4 to 7 day, than 400 mg/day on day 8, than 200 mg/day on day 9)

(Mayo-Smith MF et al., Arch Intern Med, 2004)



(Caputo et al., Int Emerg Med, 2018)

Internal and Emergency Medicine
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CE - ORIGINAL

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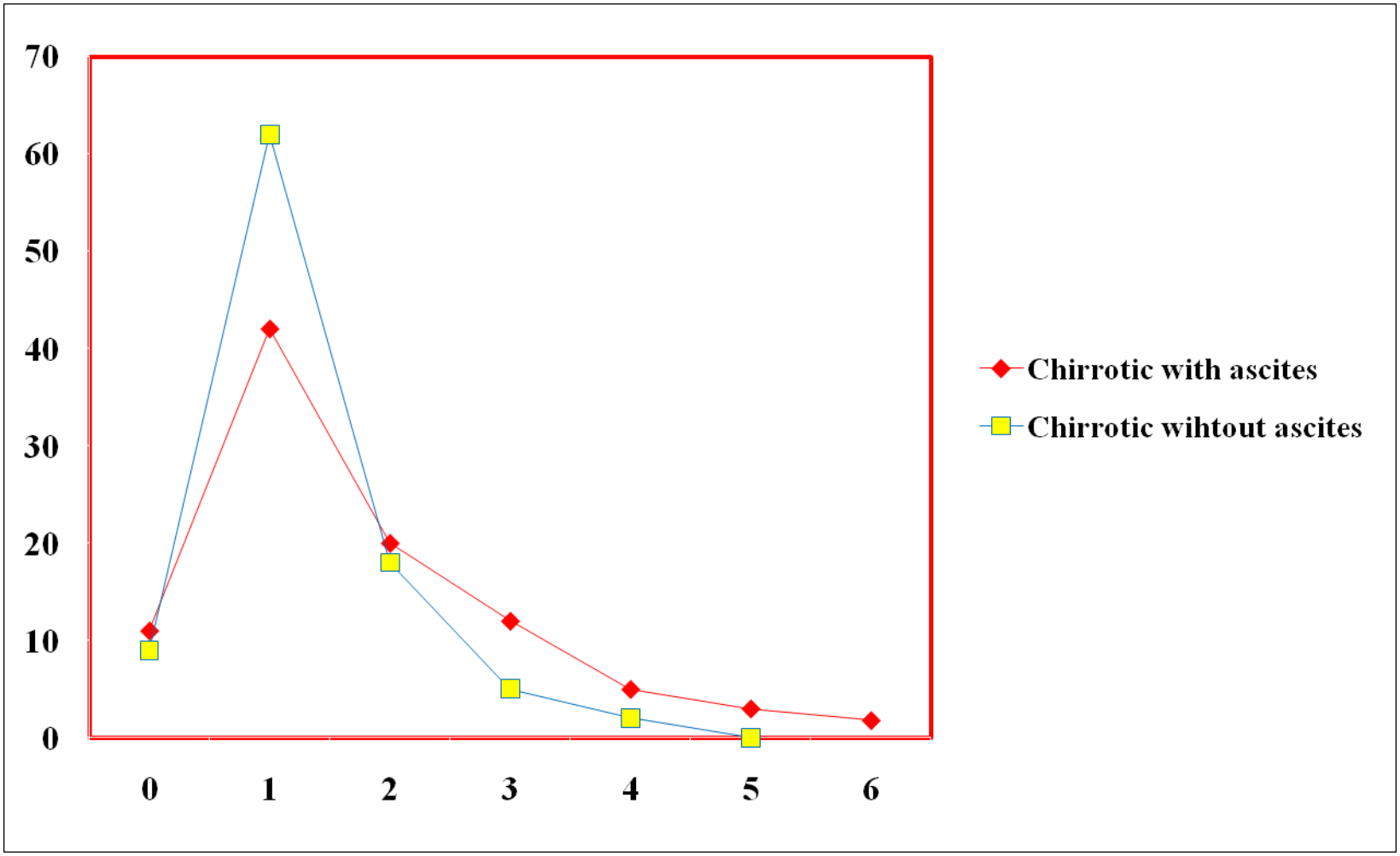
No potential conflict of interest relevant to this letter was reported.

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)

Effect of moderate or severa liver dysfunction on the pharmacokinetic of gamma hydroxybutiric acid



(Ferrara et al., Eur J Clin Pharmacol, 1996)

Encefalopatia Epatica (EE)

Sindrome neuropsichiatrica che si può manifestare in pazienti affetti da cirrosi epatica

La sua prevalenza in questa popolazione varia tra 20 e 80% (5-25% nei primi 5 anni dalla diagnosi di cirrosi)

Tale ampia oscillazione riflette le differenze dei vari studi in termini di definizione, metodiche diagnostiche e coorti di pazienti inclusi

(AASLD-EASL. J Hepatol 2014)

Encefalopatia Epatica

20% dei pazienti affetti da cirrosi epatica ospedalizzati in Italia presentano EE

Quasi il **40%** dei pazienti ospedalizzati per EE saranno nuovamente ospedalizzati entro 1 anno per cause correlate all'encefalopatia

Necessità di gestione a breve e a lungo termine.

(Bass et al. N Engl J Med 2010)

Encefalopatia Epatica

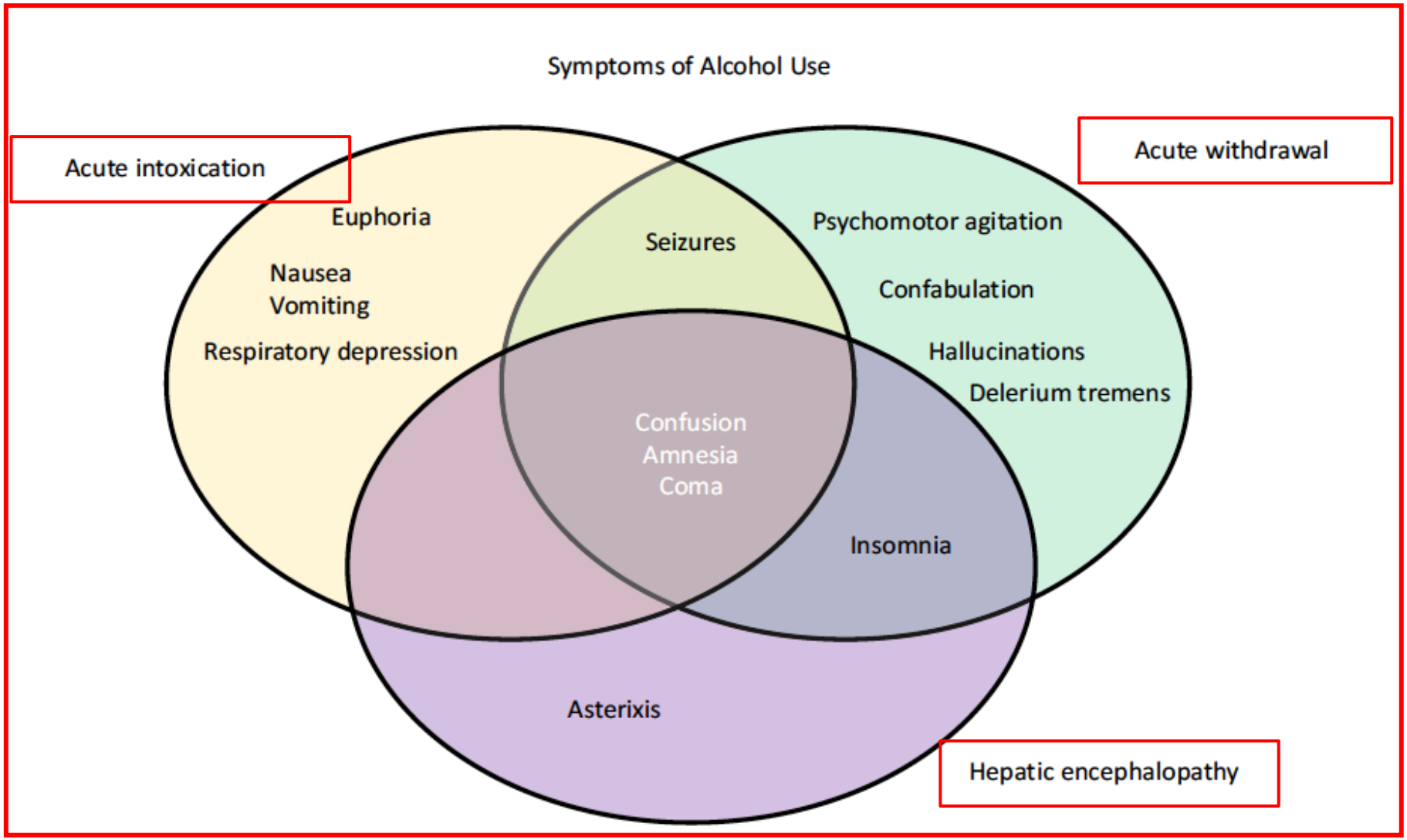
Grado

West Haven Criteria

- **Grado 1.** Disattenzione, incapacità di applicazione, euforia, ansietà, incapacità ad eseguire operazioni aritmetiche semplici
- **Grado 2.** Sonnolenza o apatia, disorientamento nel tempo o nello spazio, modificazione del carattere, comportamento anomalo
- **Grado 3.** Semi-incoscienza, comportamento fortemente confuso e dissociato, conservata risposta agli stimoli
- **Grado 4.** Coma, mancata risposta agli stimoli

(Conn et al. Gastoenterology 1977)

Effects of alcohol on the brain



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

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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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)

Grazie per l’attenzione!!