Appropriatezza, rischio clinico e buone prassi nel trattamento delle dipendenze patologiche

CONGRESSO REGIONALE SITD SICILIA

SOCIETÀ ITALIANA TOSSICODIPENDENZE

Linee guida e buone prassi sui problemi alcolcorrelati

Michele Parisi

Viagrande (CT), 18 Ottobre 2019 – Hotel Villa Itria

LINEE GUIDA ALCOL

Le caratteristiche proprie della Sindrome Alcolica rendono indispensabile fornire risposte differenziate, adeguate alle caratteristiche proprie di ogni soggetto, tenendo conto non solo dell'ambito personale, ma anche di quello sociale, lavorativo, ecc.

Un corretto intervento deve essere interdisciplinare e longitudinale nel tempo.

Diagnostic and Statistical Manual of Mental Disorder (DSM-V)

Broad Domain	DSM-5 Diagnostic Criteria	DSM-IV
Impaired Control	**1.** Drinking larger amounts or over longer periods than intended.	Dependence
	2. Desire or unsuccessful attempts to cut down or control alcohol use.	Dependence
	3. A great deal of time spent obtaining, using or recovering from alcohol	Dependenc
	4. Craving, or a strong desire or urge to use alcohol	New for DS
Social Dysfunction and Physical Risk	**5.** Failure to fulfil major role obligations as a result of alcohol use	Abuse
	6. Continued drinking despite social or interpersonal problems	Abuse
	7. Diminished social, occupational or recreational activities due to drinking	Dependenc
	8. Recurrent alcohol use in physically hazardous situations	Abuse
	9. Continued drinking despite physical or psychological problems	Dependenc
Physiological Dependence	**10.** Tolerance, as evidenced by a markedly diminished effect	Dependenc
	11. Withdrawal Syndrome, or drinking to prevent withdrawal	Dependenc

Threshold for diagnosis of AUD

At least 2 symptoms

Severity AUD index

Mild = 2/3 symptoms
Moderate = 4/5 symptoms
Severe = 6 or more symptoms

Specifiers

Early remission: 3-12 mo without AUD
Sustained remission: > 12 mo
(*except craving*)

(American Psychiatric Association, 2013)

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)

Management of acute alcohol intoxication in adolescents

–adolescents do not show tolerance to the effects developed by repeated exposure to ethanol and they have immature hepatic alcohol deydrogenase activity: more exposed to the toxic effect of alcohol and rapid onset of coma

–the lethal dose of alcohol varies as widely among children and adolescents as it does among adults: lethal BAC for infants and adolescents is not certain

–hypoglycaemia and hypothermia tend to be more severe in young individuals than in adults: management for all adolescents should be focused on the correction of hypoglycaemia, hypothermia and restlessness (haloperidol)

–the administration of antiemetics is preferred to gastric content aspiration, as well as maintaining airway patency; venous access is necessary to ensure fluid administration

–so far, no studies have been performed on metadoxine use for the improvement of symptoms of AAI in the paediatric population

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

Management of acute alcohol intoxication in adults

–no drugs are generally necessary: monitor vital function, liquids administration, observe patient for the onset of alcohol withdrawal symptoms

–in the case of coma, support ventilation mechanically, correct hypoglycaemia with 5% glucose solution, hydro-electrolyte imbalance and base acid balance, administer vitamin B and vitamin C supplements, perform gastro-lavage and administer activated charcoal only within 2 h of drinking a considerable amount of alcohol

–in the case of the simultaneous use of other sedative drugs, antidotes should be administered: naloxone (0.4 mg i.v. or i.m. repeated, if necessary, every 30 min) for the use of opioids and flumazenil (0.2 mg, repeated, if necessary, every minute up to 3 mg) for the use of benzodiazepines

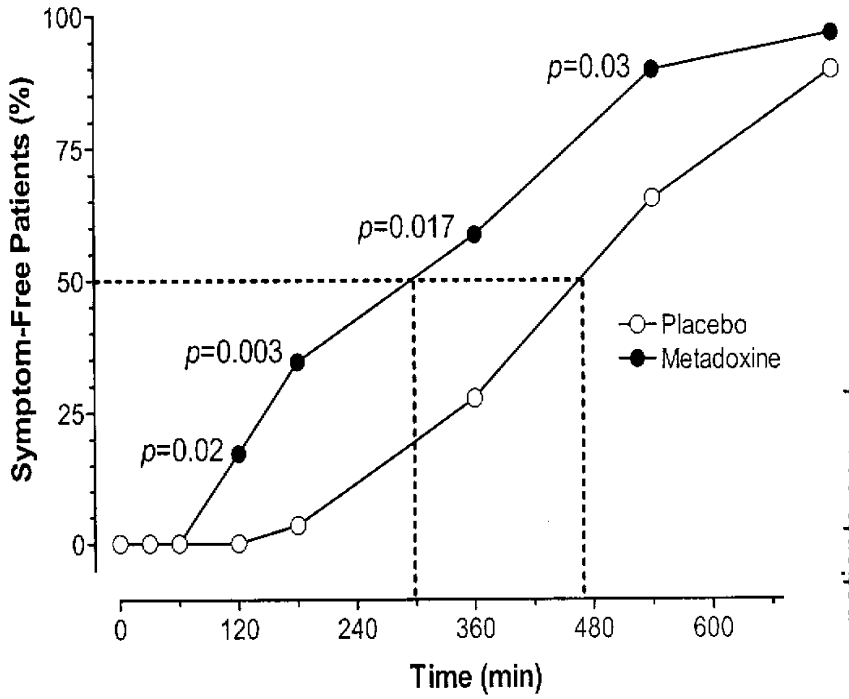
–metadoxine 900 mg i.v. reduces BAC and leads to a more rapid resolution of the symptoms (Grade A2)

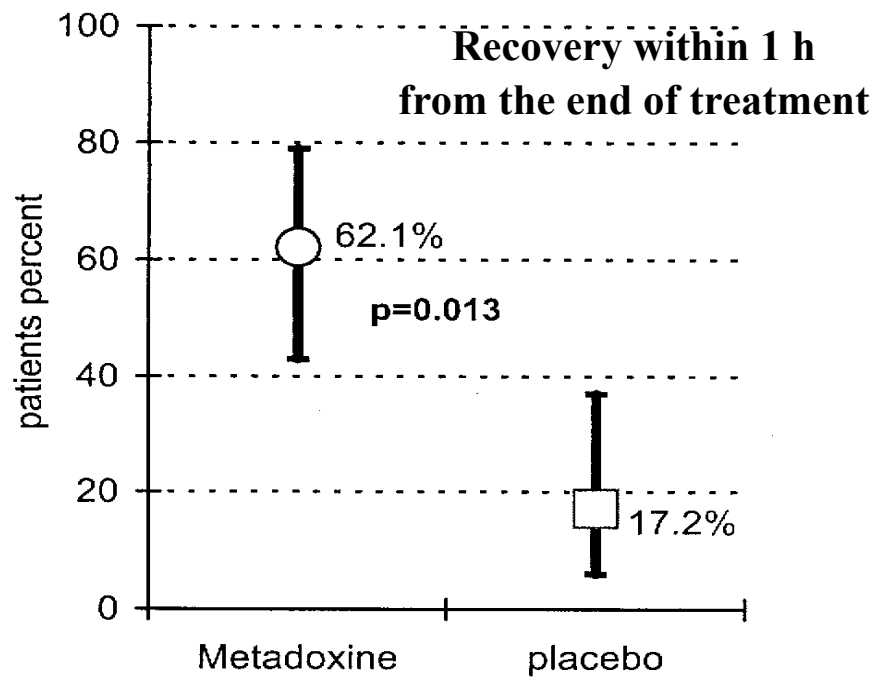
–alcohol hangover: fruit and fruit juice, sleep and physical rest, anti-acid drugs, acetylsalicylic acid, and caffeine may be helpful

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

Metadoxine vs placebo

Metadoxine 900 mg i.v.





(Shpilenya et al, Alcohol Clin Exp Res, 2002)

Clinical Practice Guidelines (Alcohol Use Disorder)

Reus VI, Fochtmann LJ, Bukstein O et al (2018) The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *Am J Psych* 175:86–90

Pilling S, Yesufu-Udechuku A, Taylor C, Drummond C, Guideline Development Group (2011) Diagnosis, assessment, and management of harmful drinking and alcohol dependence: summary of NICE guidance. *BMJ* 342:d700

Rolland B, Paille F, Gillet C, Rigaud A, Moirand R, Dano C, Dematteis M, Mann K, Aubin HJ (2016) Pharmacotherapy for alcohol dependence: the 2015 recommendations of the French alcohol society, issued in partnership with the european federation of addiction societies. *CNS Neurosci Ther* 22:25–37

Soyka M, Kranzler HR, Hesselbrock V, Kasper S, Mutschler J, Möller HJ, WFSBP Task Force on Treatment Guidelines for Substance Use Disorders (2017) Guidelines for biological treatment of substance use and related disorders, part 1: alcoholism, first revision. *World J Biol Psychiatry* 18:86–119

Alcohol withdrawal syndrome: diagnostic and therapeutic methods

Sindrome astinenziale da alcol: processi diagnostici e terapeutici

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Pharmacological treatment of alcohol use disorder. Scientific evidence

Trattamento farmacologico del disturbo da uso di alcol. Evidenze scientifiche

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(Attilia et al., Riv Psich, 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

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Abstract

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

Keywords Acute alcohol intoxication · Alcohol withdrawal syndrome · Pharmacological treatment

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

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

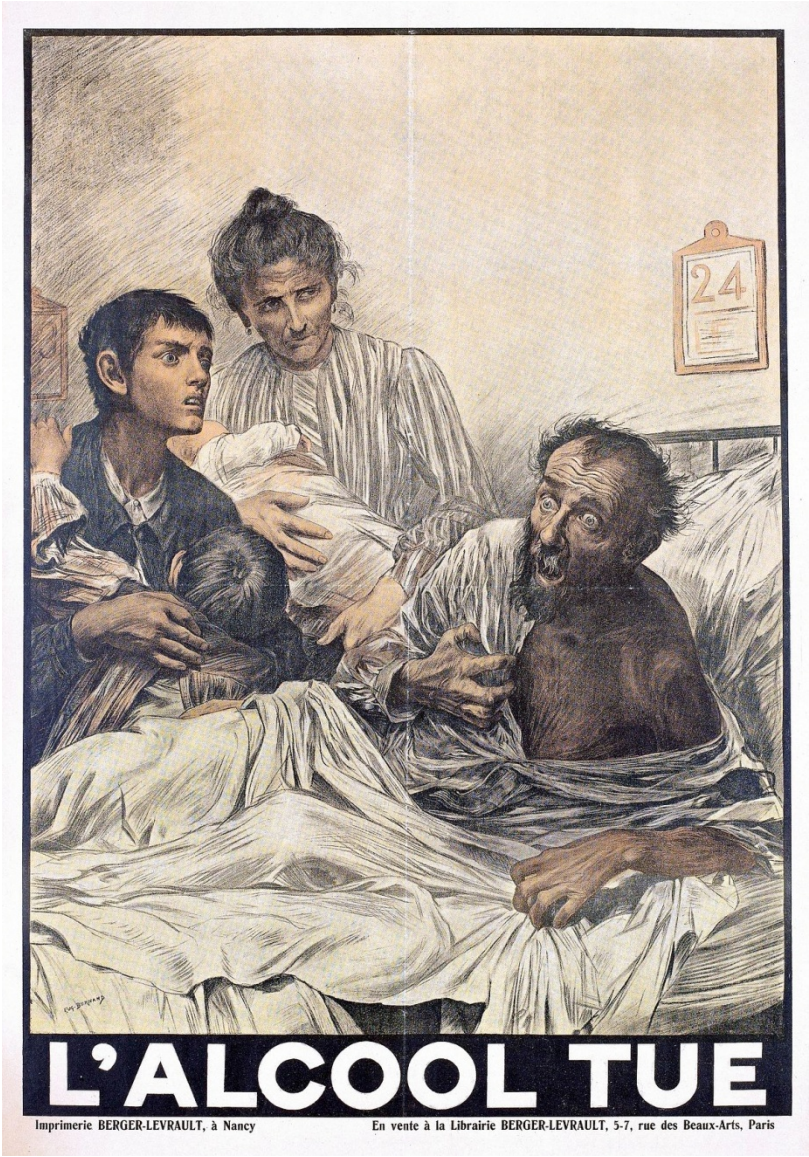
Decreased attention and awareness

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)

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)

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 sindrome da astinenza da alcol in pazienti ricoverati

-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)

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]

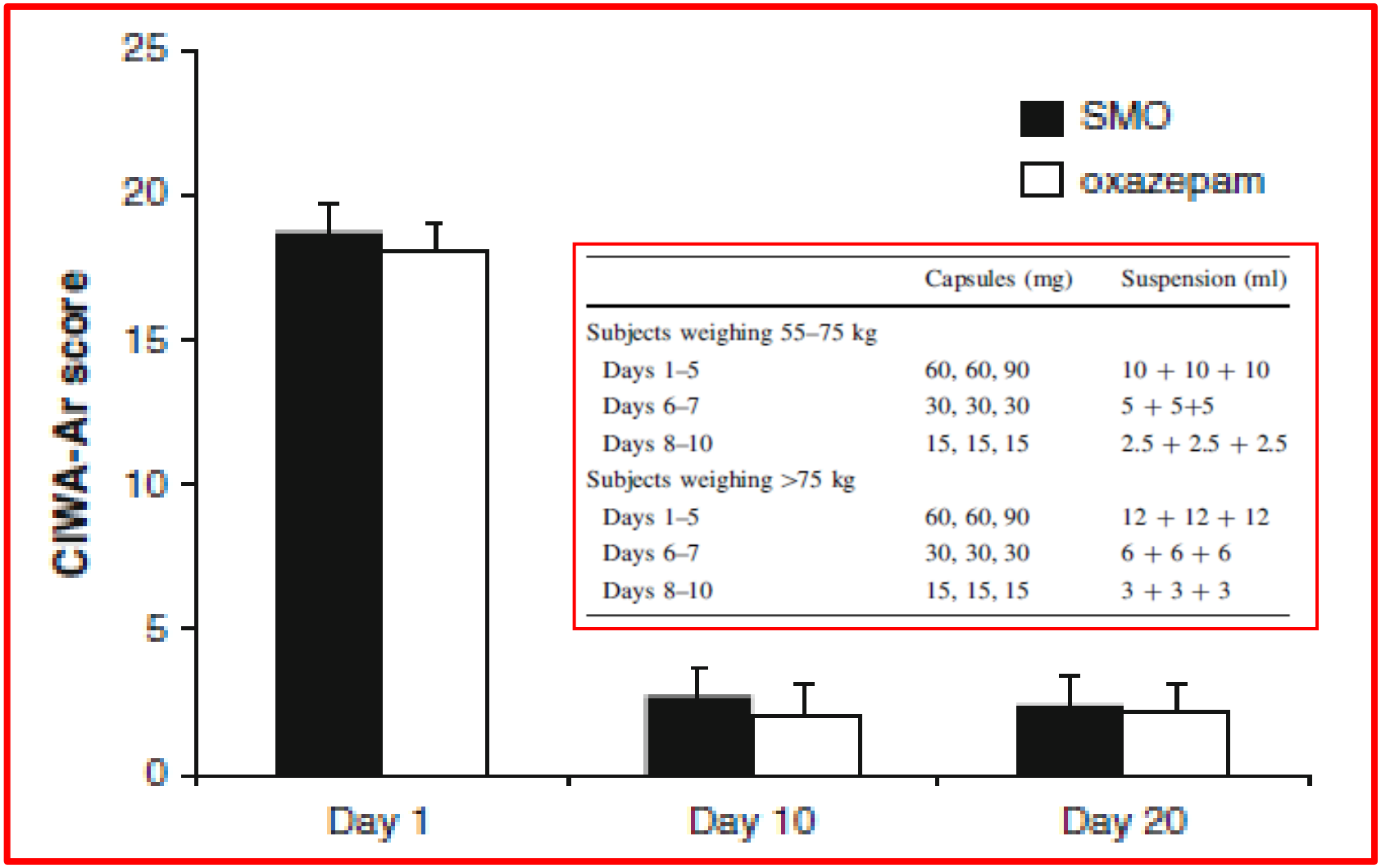
Sodium oxybate: 50–100 mg/kg fractioned into 3 or 6 daily administrations (every 4 or 6 h) from day 1 to day 3[c]

[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

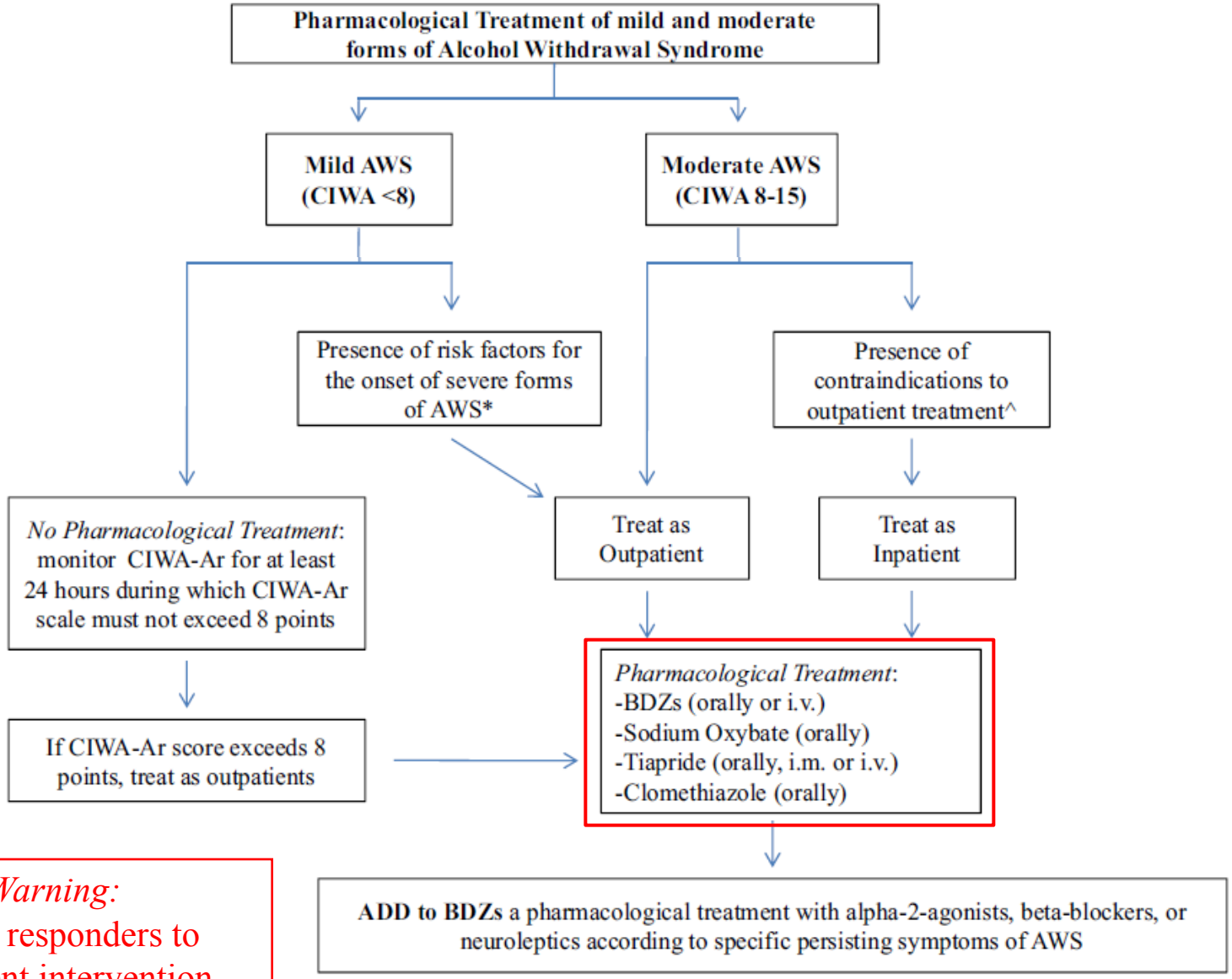
[c]On day 4, follow a tapering procedure according to the attenuation of symptoms: you may then decide to continue the administration of the drugs in the maintenance of alcohol abstinence at the dosages of 50 mg/kg per day for sodium oxybate and 300 mg/day for tiapride

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



	Capsules (mg)	Suspension (ml)
Subjects weighing 55–75 kg		
Days 1–5	60, 60, 90	10 + 10 + 10
Days 6–7	30, 30, 30	5 + 5+5
Days 8–10	15, 15, 15	2.5 + 2.5 + 2.5
Subjects weighing >75 kg		
Days 1–5	60, 60, 90	12 + 12 + 12
Days 6–7	30, 30, 30	6 + 6 + 6
Days 8–10	15, 15, 15	3 + 3 + 3

(Caputo et al., CNS Drugs, 2014)



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

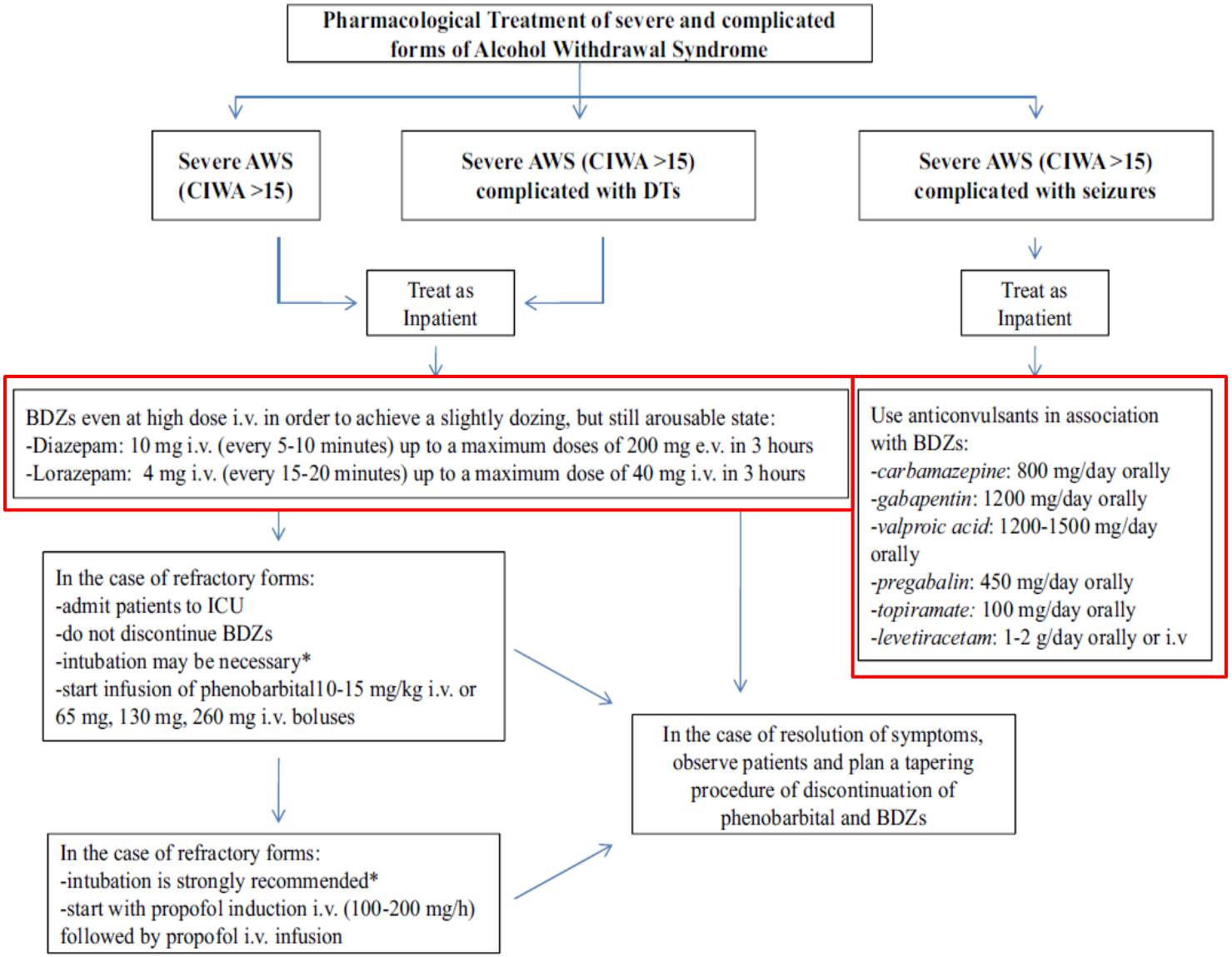
(Caputo et al., Int Emerg Med, 2019)

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, 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)

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

General indications (CIWA-Ar score > 8 points)

- -Benzodiazepines (BDZs) with short half-life: lorazepam (1 or 2 mg once a day [qd] or twice daily [bid]) or oxazepam (15 mg qd or bid), with subsequent titration up to the dose achieving complete symptom remission

***Caution**: A trigger-dose approach (administration only at the onset of symptoms) to avoid the risk of drug accumulation is preferable, starting with the lowest therapeutic doses. Close medical supervision is needed.*

- -Parenteral thiamine (200 mg/day for 3-5 days) to prevent Wernicke encephalopathy
- -Haloperidol (0.5 mg-5 mg every 30-60 minutes intravenously or intramuscularly or 0.5 mg-5 mg every 4 hours orally) to treat hallucinations
- -α_2-agonists or β-blockers to reduce autonomic hyperactivity

(Caputo et al., Hepatology, 2019)

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)

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

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CrossMark

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

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-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

-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

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

Protracted withdrawal, strictly defined, is the presence of substance-specific 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
July 2010
Volume 9
Issue 1
News for the Treatment Field

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)

Food and Drug Administration–Approved Medications for Treating AUD

	Medication[a]			
	Disulfiram	Naltrexone	Long-Acting Injectable Naltrexone	Acamprosate
Indication	Management of selected chronic alcohol patients who want to remain in a state of enforced sobriety	Treatment of alcohol dependence	Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting	Maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent
Dosage	FDA-approved dosage: 250-500 mg/d orally Dosage used in clinical trials: 125-500 mg/d	FDA-approved dosage: 50 mg/d orally Dosage used in clinical trials: 50-100 mg/d, with an initial dosage of 25-50 mg/d	FDA-approved dosage: 380 mg/mo intramuscularly Dosage used in clinical trials: 190 mg or 380 mg/mo	FDA-approved dosage: 1998 mg/d orally Dosage used in clinical trials: 1000-3000 mg/d
Effect size(s)	A meta-analysis of 22 studies (N = 2414)[13] showed an association of disulfiram with sustained abstinence from alcohol compared to control conditions only in open-label studies (Hedges g = 0.70, 95% CI, 0.46 to 0.93); there was not a significant association in blinded trials (Hedges g = 0.01, 95% CI, −0.29 to 0.32).[b] Disulfiram was associated with a better response than control conditions when medication adherence was supervised (N = 13 studies; Hedges g = 0.82, 95% CI, 0.59 to 1.05), but not when it was unsupervised (N = 9 studies; Hedges g = 0.26, 95% CI, −0.02 to 0.53).[13]	A meta-analysis (N = 16 studies and 2347 patients) showed a risk decrease (RD) for a return to any drinking associated with naltrexone 50 mg/d (RD = −0.05 (95% CI, −0.10 to −0.002); number needed to treat (NNT) = 20]. Naltrexone was also associated with reduced risk of binge drinking [19 studies; N = 2875; RD = −0.09 (95% CI, −0.13 to −0.04); NNT = 12).[11]	In the only placebo-controlled trial of long-acting naltrexone, the median monthly number of binge drinking days declined by 13.3 in the placebo group (to 6.0/mo), 14.8 in the 190-mg group (to 4.5/mo), and 16.2 in the 380-mg group (to 3.1/mo).[20]	In a meta-analysis of 16 studies (N = 4827),[11] acamprosate treatment was associated with a greater reduction in the risk of drinking among abstinent patients [RD = −0.09 (95% CI, −0.14 to −0.04); NNT = 12], but no reduction in the likelihood of binge drinking.

(Kranzler & Soyka, JAMA, 2018)

Sodium Oxybate in alcohol withdrawal syndrome and for the maintenance of abstinence in alcohol dependence

- Liquid formulation of the sodium salt of gamma-hydroxybutyric acid (GHB)
- At least as effective as diazepam and clomethiazole in alcohol withdrawal syndrome, providing rapid alleviation of symptoms
- At least as effective as naltrexone or disulfiram in the maintenance of abstinence in alcohol dependent patients
- Generally well tolerated
- Low risk of abuse when administered at the recomended dosage under the supervision of the designed family member and the continuous strict medical surveillance

(Keating, Clin Drug Investig, 2014)

ORIGINAL ARTICLE

doi:10.1111/adb.12645

Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level

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and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenbu
Health, Heidelberg University, Mannheim, Germany[20]

	Male ♂	*Female ♀*
Low DRL	1 to 40 g	1 to 20 g
Medium DRL	41 to 60 g	21 to 40 g
High DRL	61 to 100 g	41 to 60 g
Very high DRL	101+ g	61+ g

(van den Brink et al., Addict Biol, 2018)

Incidence of abuse/misuse, central nervous system depression and dependence to sodium oxybate in alcohol-dependent patients (EMA 2017)

Number of events (incidence)	*Clinical trials, N = 3436*	*Pharmacovigilance database, N = 260 000*
Abuse/misuse	100 (2.91%)	6 (0.002%)
CNS depression	19 (0.55%)	14 (0.005%)
Dependence/withdrawal	4 (0.12%)	2 (0.001%)

CNS depression refers to 'depressed level of consciousness' and 'sedation' cases.

Importantly, no deaths attributable to the use of sodium oxybate have ever been reported in the pharmacovigilance database or in the clinical database

(Alcover Assessment Report, EMA/833636/201, 2017)

Non-Food and Drug Administration–Approved Medications for Treating AUD

	Medication			
	Nalmefene	Baclofen	Gabapentin	Topiramate
Indication(s)	United States: Complete or partial reversal of opioid drug effects European Union: Help reduce alcohol consumption in adults with alcohol dependence who consume >60 g (≈4 drinks) per day (men) or >40 g (≈3 drinks/ day) (women).	Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis	Management of postherpetic neuralgia in adults and adjunctive therapy in the treatment of partial seizures in patients age 3 and older.	Monotherapy for partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for partial onset seizures or primary generalized tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome; migraine prophylaxis; weight loss and chronic weight management (in combination with phentermine)
Dosage	Approved dosage for AUD (in the European Union): 18 mg/d (as needed) Dosage in clinical trials for AUD: 5-80 mg/d in 1 dose or 2 divided doses	Dosage in clinical trials for AUD: 30-180 mg/d in up to 4 divided doses	Dosage in clinical trials for AUD: 600-1800 mg/d in 3 divided doses	Dosage in clinical trials for AUD: 75-300 mg/d in 2 divided doses
Effect size(s)	In a meta-analysis of 5 RCTs (N = 2567),[16] nalmefene treatment was associated with a reduction in binge drinking of 1.65 d (95% CI, 0.89 to 2.41) more per month at 6 mo and by 1.60 d more per month (95% CI, 0.35 to 2.85) at 1 y, and with a reduction in total alcohol consumption of 20% (95% CI, 0.10 to 0.30) at 6 mo.	In a meta-analysis of 13 RCTs (N = 1492),[17] baclofen was associated with a significantly greater time to first lapse to drinking [SMD = 0.42 (95% CI, 0.19 to 0.64)] and a greater likelihood of abstinence during treatment [odds ratio = 1.93 (95% CI, 1.17 to 3.17)], with no greater difference at a higher dosage (>60 mg/d). Persons who drank very heavily at study entry had a greater association of abstinence with baclofen.	Of 3 peer-reviewed, placebo-controlled RCTs (total N = 231), the largest (N = 150) showed that gabapentin resulted in a rate of abstinence of 11.1% (95% CI, 5.2 to 22.2) in the 900-mg/d group and 17.0% (95% CI, 8.9 to 30.1) in the 1800-mg/d group, compared with 4.1% (95% CI, 1.1 to 13.7) for placebo. The rate of no binge drinking was 22.5% (95% CI, 13.6 to 37.2) in the placebo group, 29.6% (95% CI, 19.1 to 42.8) in the gabapentin 900 mg/d group, and 44.7% (95% CI, 31.4 to 58.8) in the 1800 mg/d group.[20] Preliminary findings from a multi-center trial of enacarbil ER (N = 346)[52] showed no treatment effect on the primary outcome measure, percent of subjects with no binge drinking (28.3% vs 21.5% for placebo) or any other drinking measures.	In a meta-analysis of 7 RCTs (N = 1125), there were small-to-medium effects of topiramate on abstinent days (Hedges g = 0.468)[a] and binge drinking days (Hedges' g = 0.406).[18]

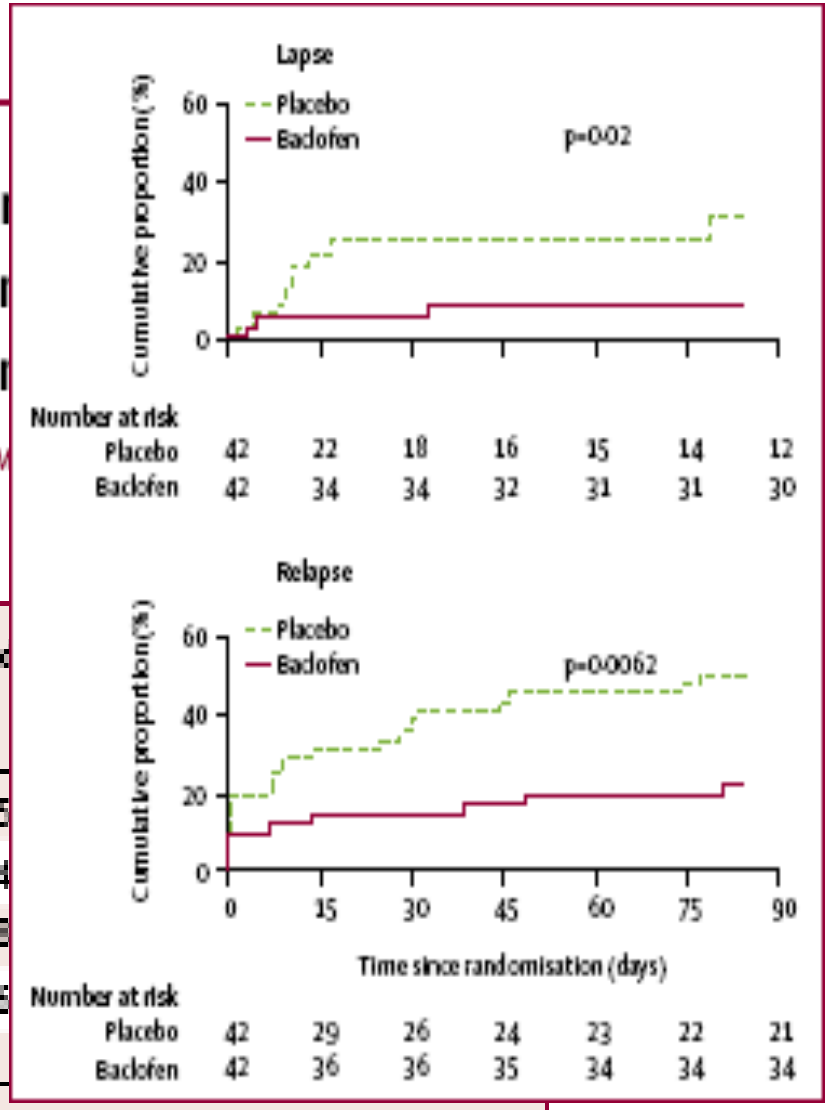
(Kranzler & Soyka, JAMA, 2018)

Effectiveness and safety of baclofen for alcohol abstinence in alcohol-depender cirrhosis: randomised, double-blind co

Giovanni Addolorato, Lorenzo Leggio, Anna Ferrulli, Silvia Cardone, Luisa Vonghia, Antonio M
Fabio Caputo, Antonella Zambon, Paul S Haber, Giovanni Gasbarrini

	Total alcohol abstinence (n [%])		Oc
	Placebo	Baclofen	
Child-Pugh A	1/6 (17)	3/4 (75)	15
Child-Pugh B	5/20 (25)	12/20 (60)	4
Child-Pugh C	6/16 (38)	15/18 (83)	8
Total	12/42 (29)	30/42 (71)	6

Table 4: Total alcohol abstinence by Child-Pugh classification



(Addolorato et al, Lancet, 2007)

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of alcohol-related liver disease☆

European Association for the Study of the Liver*

Recommendations

- The term alcohol use disorder (defined by DSM-V crite-
ria) should be used in prefere
abuse, alcohol dependence or r
- AUDIT or AUDIT-C should be u
AUD and dependence (**Grade A**
- Patients with AUD should be
psychiatric disorders and other
- Benzodiazepines should be used to treat AWS but should not be prescribed beyond 10–14 days because of the potential for abuse and/or encephalopathy (**Grade A1**)
- Gastroenterology/Hepatology centres should have access to services to provide effective psychosocial therapies (**Grade A**)
- Pharmacotherapy should be considered in patients with AUD and ALD (**Grade A1**)

Suggestions for future research

- Further trials of pharmacotherapy in patients with advanced ALD are urgently required
- Studies to demonstrate the efficacy of a multidisciplinary team intervention

(Thursz et al, J Hepatol, 2018)

Baclofen for the treatment of alcohol use disorder: the Cagliari Statement

*Roberta Agabio, Julia MA Sinclair, Giovanni Addolorato, Henri-Jean Aubin, Esther M Beraha, Fabio Caputo, Jonathan D Chick, Patrick de La Selle, Nicolas Franchitto, James C Garbutt, Paul S Haber, Mathis Heydtman, Philippe Jaury, Anne R Lingford-Hughes, Kirsten C Morley, Christian A Müller, Lynn Owens, Adam Pastor, Louise M Paterson, Fanny Pélissier, Benjamin Rolland, Amanda Stafford, Andrew Thompson, Wim van den Brink, Renaud de Beaurepaire, Lorenzo Leggio

Panel: Consensus statement of the Cagliari Expert Consensus Group on the use of baclofen to treat patients with moderate-to-severe alcohol use disorder

Effectiveness of baclofen in the treatment of patients with alcohol use disorder

4 Baclofen is not licensed as an approved treatment of alcohol use disorder, and its use is therefore off-label.

5 Clinical research evidence is not clear about the most effective setting for baclofen treatment, but patients with alcohol use disorder may be treated in a range of treatment settings by clinicians with appropriate experience and training.

6 The majority of clinical trials started baclofen after detoxification and obtaining abstinence. In clinical practice, some physicians prescribe off-label baclofen while the patient is still drinking. These patients should be warned of the risks of side-effects (eg, excessive sedation) due to the pharmacological interaction of baclofen and alcohol.

7 Baclofen should be considered a second-line pharmacotherapy in patients who have not responded to approved pharmacological treatments for alcohol use disorder. However, the off-label use of baclofen may be considered among first-line pharmacological treatments in patients with contraindication to approved medications (eg, patients with advanced liver disease for whom the use of disulfiram or naltrexone may be contraindicated).

8 The daily baclofen dose should be based on safety, tolerability, and patient's response.

9 The daily dose of baclofen required to achieve abstinence, a substantial reduction in alcohol consumption, or a substantial decrease in craving for alcohol can vary widely between patients, over a ten-fold range.

10 Baclofen should be started at a low dose (5 mg three times per day) and slowly titrated upwards (eg, 5–10 mg per day, every three days) to minimise possible side-effects, including sedation and overdose.

11 There is no evidence on the use of baclofen in combination with other medications for alcohol use disorder (eg, disulfiram, naltrexone, acamprosate, or nalmefene).

12 Baclofen should not be used instead of benzodiazepines in the treatment of alcohol withdrawal syndrome, as there is no evidence of its efficacy in preventing the development of potentially life-threatening complications of alcohol withdrawal syndrome, such as seizures and delirium tremens.

(Agabio et al., Lancet Psychiatry, 2018)

Baclofen for the treatment of alcohol use disorder: the Cagliari Statement

*Roberta Agabio, Julia MA Sinclair, Giovanni Addolorato, Henri-Jean Aubin, Esther M Beraha, Fabio Caputo, Jonathan D Chick, Patrick de La Selle, Nicolas Franchitto, James C Garbutt, Paul S Haber, Mathis Heydtman, Philippe Jaury, Anne R Lingford-Hughes, Kirsten C Morley, Christian A Müller, Lynn Owens, Adam Pastor, Louise M Paterson, Fanny Pélissier, Benjamin Rolland, Amanda Stafford, Andrew Thompson, Wim van den Brink, Renaud de Beaurepaire, Lorenzo Leggio

Panel: Consensus statement of the Cagliari Expert Consensus Group on the use of baclofen to treat patients with moderate-to-severe alcohol use disorder

Safety of baclofen in the treatment of patients with alcohol use disorder

13 History of renal impairment needs to be considered before starting baclofen, because the drug is mainly excreted by the kidneys. If prescribed, the management of baclofen in patients with renal impairment requires close supervision because of the higher risk of baclofen toxicity.

14 The most frequent side-effects observed among patients with alcohol use disorder include: sedation, fatigue, drowsiness, tiredness, somnolence, sleep disorders or insomnia, dizziness, headache, dry mouth, paresthesia, fasciculations, nausea, myalgia, and arthralgia. Most side-effects occur at the beginning of baclofen treatment, or if the dose is increased too rapidly.

15 Many side-effects tend to be dose-related, although the contribution of other factors to the onset or severity of side-effects cannot be ruled out.

16 Particular caution is needed for the combination of baclofen with other sedative medications (including alcohol) since there are additive side-effects (eg, sedation, drowsiness, and somnolence).

17 Particular caution is needed among patients with alcohol use disorder and other comorbidities, such as patients with a history of epilepsy, because baclofen can lower the seizure threshold, patients with mood disorders, because baclofen can increase the risk of hypomanic and manic episodes, and patients with suicidal ideation or a history of suicide attempts, because of the risk of intentional overdose.

18 Treatment with baclofen should not be abruptly interrupted to avoid the risk of withdrawal symptoms. The daily dose should be slowly reduced (eg, 5–10 mg per week).

(Agabio et al., Lancet Psychiatry, 2018)

CNS Drugs
https://doi.org/10.1007/s40263-017-0484-2

CrossMark

SYSTEMATIC REVIEW

Systematic Review of Combined Pharmacotherapy for the Treatment of Alcohol Use Disorder in Patients Without Comorbid Conditions

Andrew C. Naglich[1] · Austin Lin[2] · Sidarth Wakhlu[2] · Bryon H. Adinoff[1,2]

Key Points

Naltrexone was the drug most frequently combined with other agents to reduce alcohol consumption.

No combination of drugs has demonstrated a significantly larger treatment effect when compared with the individual components of the combination.

Targeting combined pharmacological interventions to address specific symptoms of alcohol use disorder known to be influenced by combination components may prove more successful than initiating treatment for alcohol consumption only.

(Naglich et al., CNS Drugs, 2017)

Toward Personalized Medicine in the Pharmacotherapy of Alcohol Use Disorder: Targeting Patient Genes and Patient Goals

Medication	Genetic Variant	Outcome Moderated	Notable Studies
Topiramate	*GRIK1* (rs2832407)	Heavy drinking days (%); side effects	Kranzler et al., 2014 (2); Ray et al., 2009 (4)
Naltrexone	*OPRM1* (Asn40Asp), (rs1799971), DRD4 VNTR	Heavy drinking days (%); abstinence rates; relapse to heavy drinking	Anton et al., 2008 (12); Kim et al., 2009 (13); Oslin et al., 2003 (14); Tidey et al., 2008 (15)
Ondansetron	LL/LS/SS (5-HTTLPR) (rs1042173), *SLC6A4* (5-HTTLPR)	Drinks per drinking day; days abstinent (%)	Johnson et al., 2011 (9)
Sertraline	5-HTTLPR triallelic *SLC6A4*	Heavy drinking days (%); drinking days (%)	Kranzler et al., 2011 (8)
Acamprosate	*GATA4* (rs1327367)	Relapse	Kiefer et al., 2011 (10)
Disulfiram	*DBH* (rs161115)	Adverse events	Mutschler et al., 2012 (11)

(Batki & Pennington, Am J Psychiatry, 2014)

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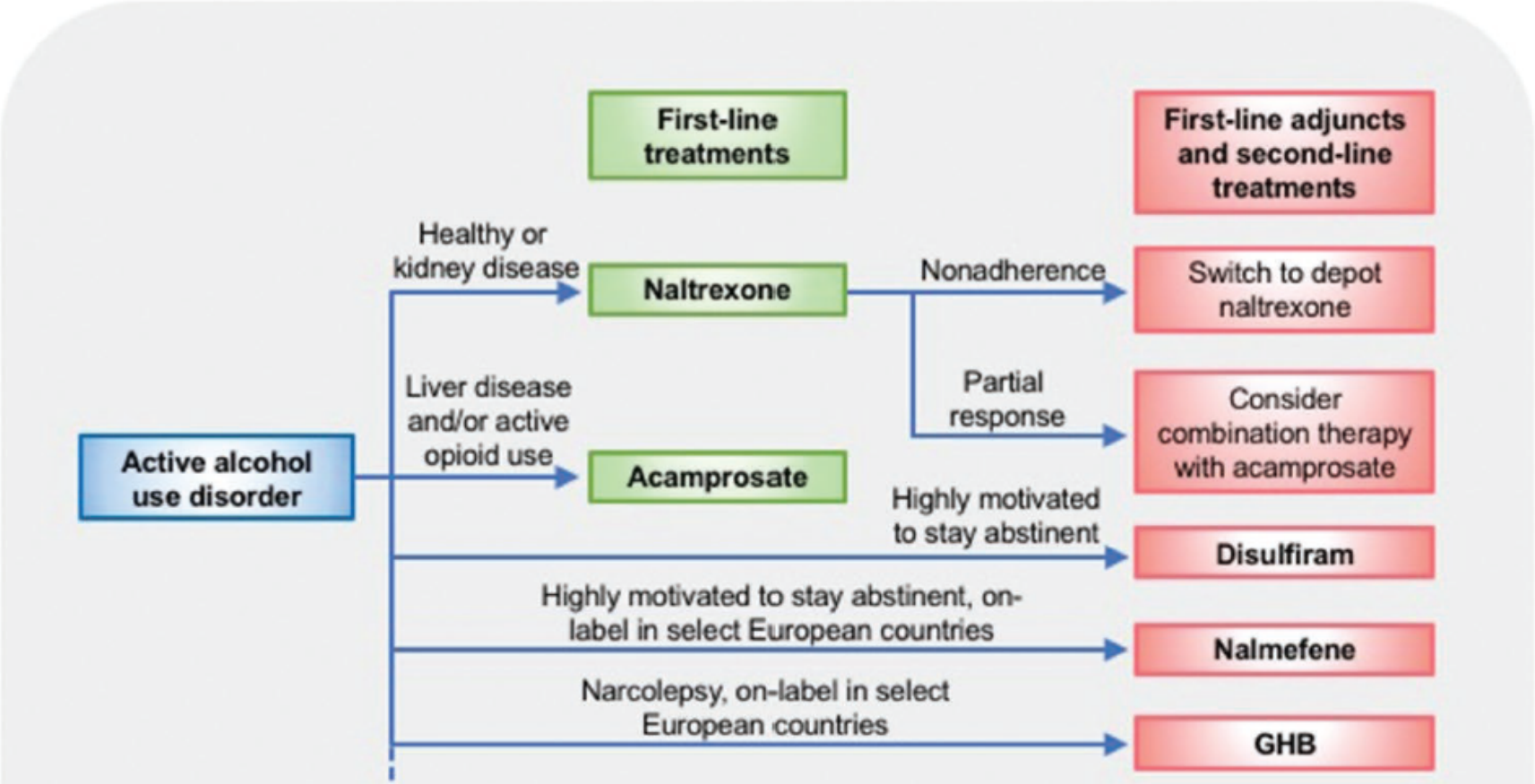

(Kim et al., Drugs Context, 2018)

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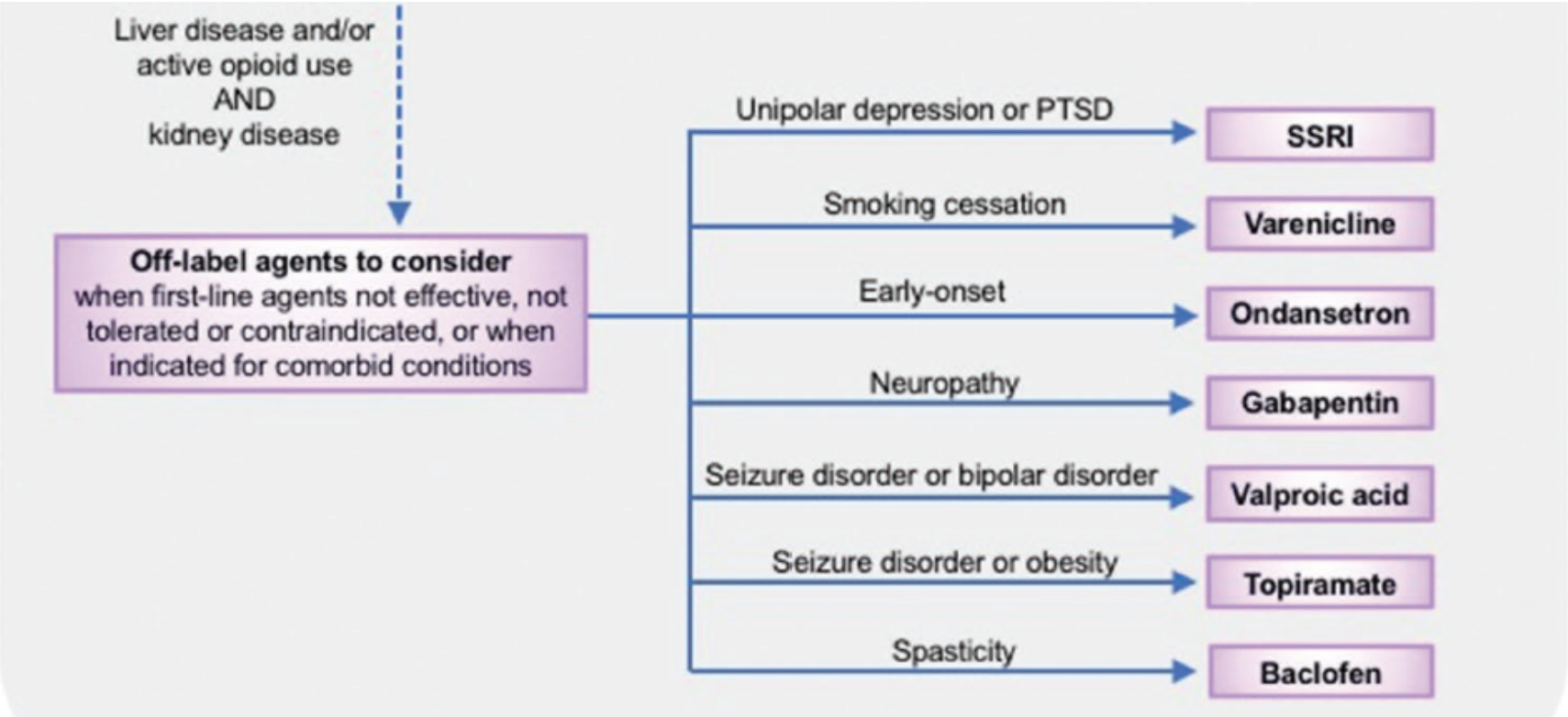

(Kim et al., Drugs Context, 2018)

Alcohol and Alcoholism, 2018, 53(1) 78–88
doi: 10.1093/alcalc/agx078
Advance Access Publication Date: 26 October 2017
Article

OXFORD

Article

Inclusion of Alcoholic Associations Into a Public Treatment Programme for Alcoholism Improves Outcomes During the Treatment and Continuing Care Period: A 6-Year Experience

Variables	Group A Usual treatment (T2) (*N* = 95)	Group B Additional treatment at centres from the CAPA network (T2) (*N* = 112)	Group A Usual treatment (T4) (*N* = 95)	Group B Additional treatment at centres from the CAPA network (T4) (*N* = 112)	Group A Usual treatment (T6) (*N* = 95)	Group B Additional treatment at centres from the CAPA network (T6) (*N* = 112)
Gender (males), *n* (%)	–	–	–	–	62 (65.20)	68 (60.71)
Relapses during the follow-up, mean (SD)	–	–	–	–	2.72 (1.68)	1.27 (1.80)
Months of abstinence during the continuum of care period, mean (SD)	–	–	–	–	29.41 (12.85)	41.58 (9.80)

*(p = 0.002)

°(p = 0.00)

(Rubio et al., Alcohol Alcohol, 2018)

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

REVIEW

doi:10.1111/add.14268

AA attendance and abstinence for dually diagnosed patients: a meta-analytic review

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Clinical referral of dual diagnosis (DD) patients to Alcoholics Anonymous (AA) is common and, in many cases, DD patients who attend AA will report higher rates of alcohol abstinence relative to DD patients who do not attend AA

(Tonigan et al., Addiction, 2018)