TRATTAMENTO FARMACOLOGICO DELLA DIPENDENZA DA ALCOL

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PRESIDIO
UNICO
OSPEDALIERO

Alcohol-use disorders

Marc A Schuckit

Lancet 2009; 373: 492–501
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See Editorial page 433

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Alcohol dependence and alcohol abuse or harmful use cause substantial morbi
disorders are associated with depressive episodes, severe anxiety, insomnia, suic
Continued heavy alcohol use also shortens the onset of heart disease, stroke, cancers
the cardiovascular, gastrointestinal, and immune systems. Heavy drinking can also c
temporary cognitive deficits, sleep problems, and peripheral neuropathy; cause gas
bone density and production of blood cells; and cause fetal alcohol syndrome. A
assessment and treatment of other medical and psychiatric problems. Standard crite
more severe disorder—can be used to reliably identify people for whom drink
consequences and persistent impairment of quality of life and ability to function. Cl
for alcohol disorders, using clinical interviews, questionnaires, blood tests, or a combi
include environmental factors and specific genes that affect the risk of alcohol-us
enzymes that metabolise alcohol, such as alcohol dehydrogenase and aldehyde dehy
disinhibition; and those that confer a low sensitivity to alcohol. Treatment can incl
help people to evaluate their situations, brief interventions to facilitate more heal
address withdrawal symptoms, cognitive-behavioural therapies to avoid relapses,
diminish cravings or discourage relapses.

(Schuckit, Lancet, 2009)

BENZODIAZEPINES
DISULFIRAM
NALTREXONE
ACAMPROSATE

Treatment of alcohol-use disorders

In the treatment of alcohol dependence, Marc Schuckit (Feb 7, p 492)[1] omits baclofen. This is most regrettable for two reasons.

First, Schuckit's proposed treatment excludes patients with liver cirrhosis from receiving any anticraving medication. Alcohol intake in patients with cirrhosis is associated with high mortality.[2] With cirrhosis, naltrexone is contraindicated and the safety of acamprosate, topiramate, and disulfiram has not been tested because these agents undergo extensive liver metabolism. Baclofen is the only anticraving medication shown in a randomised trial[3] to be safe and effective at promoting abstinence in patients with cirrhosis. Depriving cirrhosis patients of baclofen would deprive them of the benefit patients without cirrhosis get from standard anticraving treatment.

Second, a new translational model of treatment based on animal studies has been proposed, in which medication-induced suppression of craving could translate into effortless suppression of dependence in alcohol-dependent patients.[4] In animals, baclofen is the only drug that has been shown to suppress the urge to consume alcohol. All other anticraving medications used in the treatment of alcohol-dependence only reduce this urge.[5] In alcoholic patients, suppression of dependence through suppression of craving has never been reported with naltrexone, acamprosate, or topiramate despite thousands of patients trialled on these drugs.

Baclofen should be offered to patients with cirrhosis, and craving suppression should be tested in randomised trials.

I declare that I have no conflicts of interest.

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23 rue du Départ BP37, 75014 Paris, France

1 Schuckit MA. Alcohol-use disorders. *Lancet* 2009; 373: 492–501.
2 Pessione F, Ramond MJ, Peters L, et al. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis: effect of alcoholic hepatitis, smoking and abstinence. *Liver Int* 2003; 23: 45–53.
3 Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007; 370: 1915–22.
4 Ameisen O. Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: a self-case report of a physician. *Alcohol Alcohol* 2005; 40: 147–50.
5 Ameisen O. Naltrexone for alcohol dependency. *JAMA* 2005; 294: 899–900.

Marc Schuckit[1] clearly highlights the psychosocial and pharmacological aspects of alcohol-use disorders. As regards the topic of medications, however, he cites topiramate—a GABA-ergic drug—despite the fact that it is still not approved for the treatment of alcoholism, but he does not consider γ hydroxybutyric acid (GHB)—a further GABA-ergic medication—which has been approved for more than 10 years and which is currently used in some European countries.

The efficacy of GHB both for the treatment of alcohol withdrawal syndrome and as an anticraving drug has been well documented by several clinical trials in more than 700 patients.[2,3] In particular, when GHB has been used to treat alcohol withdrawal syndrome, an efficacy similar to diazepam and to clomethiazole has been shown;[2,3] additionally, when GHB is used as an anticraving drug, almost 60% of patients remain completely abstinent from alcohol during the treatment period.[3–5]

Although craving for and abuse of GHB remain a crucial point during the clinical administration of this drug, a very limited number of treated patients with alcoholism (less than 10%) are really at risk of this unfavourable effect.[3,5]

Thus, the therapeutic relevance of GHB for the treatment of alcohol addiction has to be mentioned. If physicians are well informed and follow correct guidelines for administration[3–5] (strict medical control with supervision by a family member), GHB is manageable and safe.

We declare that we have no conflicts of interest.

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1 Schuckit MA. Alcohol use disorders. *Lancet* 2009; 373: 492–501.
2 Beghè F, Campanini MT. Safety and tolerability of gamma-hydroxybutyric acid in the treatment of alcohol-dependent patients. *Alcohol* 2000; 20: 223–25.
3 Addolorato G, Castelli E, Stefanini GF, et al, for the GHB Study Group. An open multicentric study evaluating 4-hydroxybutyric acid sodium salt in the medium-term treatment of 179 alcohol dependent subjects. *Alcohol Alcohol* 1996; 31: 341–45.
4 Caputo F, Addolorato G, Lorenzini F, et al. Gamma-hydroxybutyric acid versus naltrexone in maintaining alcohol abstinence: an open randomized comparative study. *Drug Alcohol Depend* 2003; 70: 85–91.
5 Caputo F, Addolorato G, Stoppo M, et al. Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: an open randomised comparative study. *Eur Neuropsychopharmacol* 2007; 17: 781–89.

Authors' reply

Olivier Ameisen and Fabio Caputo and colleagues highlight several important issues. A brief Seminar cannot comprehensively cover all clinically interesting topics for a disorder as complex as alcohol dependence, and I had to make decisions about which findings I felt to be most central to the overview. Many additional drugs and psychological approaches have been proposed for the alcohol-use disorders, but they could not be adequately discussed. These letters highlight two drugs that I considered in the original draft of the Seminar, but were deleted because of space constraints.

Regarding baclofen, given at 5–10 mg three times per day, this interesting direct agonist of the $GABA_B$ receptor has some potential

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FARMACOTERAPIA DELL'ALCOLISMO

Approvati

- **BENZODIAZEPINE ($GABA_A$ agonisti)**
- **SODIO OXIBATO ($GABA_B$ e GHB-R -agonista)**
- **DISULFIRAM (blocco ALDH)**
- **NALTREXONE (antagonista recettori μ e κ)**
- **ACAMPROSATO (antagonista recettori NMDA)**

Non approvati

- **NALMEFENE (antagonista recettori μ, κ e δ)**
- **BACLOFENE ($GABA_B$ agonista)**
- **TOPIRAMATO ($GABA_A$ agonista / antagonista NMDA)**
- **GABAPENTIN ed ACIDO VALPROICO ($GABA_A$ agonista)**
- **PREGABALIN (inibisce canali del calcio)**

(Schuckit, Lancet, 2009; Caputo, Curr Pharm Des, 2010)

Treatment of AW

Monitoring (CIWA-Ar < 8-10 pts)	**CIWA-Ar test every 4 to 8 h**
Symptom-triggered regimens (CIWA-Ar > 8-10 pts)	**CIWA-Ar every h** **Chlordiazepoxide (50-100 mg)** **Diazepam (10-20 mg)** **Lorazepam (2-4 mg)**
Fixed-Schedule regimens (CIWA-Ar > 8-10 pts)	**One of the following medication every 6 h:** **Chlordiazepoxide (50 mg every 6 h for 4 doses, then 25 mg every 6 h for 8 doses)** **Diazepam (10 mg every 6 h for 4 doses, then 5 mg every 6 h for 8 doses)** **Lorazepam (2 mg every 6 h for 4 doses, then 1 mg every 6 h for 8 doses)**

Mayo-Smith, JAMA, 1997

Solo in associazione alle benzodiazepine

- **Neurolettici (aloperidolo: 0.5-5 mg per os ogni 4 ore o 0.5-5 mg e.v./i.m. ogni 30-60 minuti)**

∀ **β-bloccanti (atenololo: 100 mg/die per os) o simpaticolitici centrali (clonidina: 0.150-0.300 mg/die per os)**

- **Anticonvulsivanti (carbamazepina: 800 mg/die per os i primi 3 giorni; 600 mg/die dal 4 al 7 giorno; 400 mg/die giorno 8; 200 mg/die, giorno 9)**

Mayo-Smith MF et al., Arch Intern Med, 2004
Schuckit, Lancet, 2009

SODIO OXIBATO / ACIDO GAMMA IDROSSIBUTIRRICO (GHB)

50-100 mg / kg / die per os per 3-6 gg.

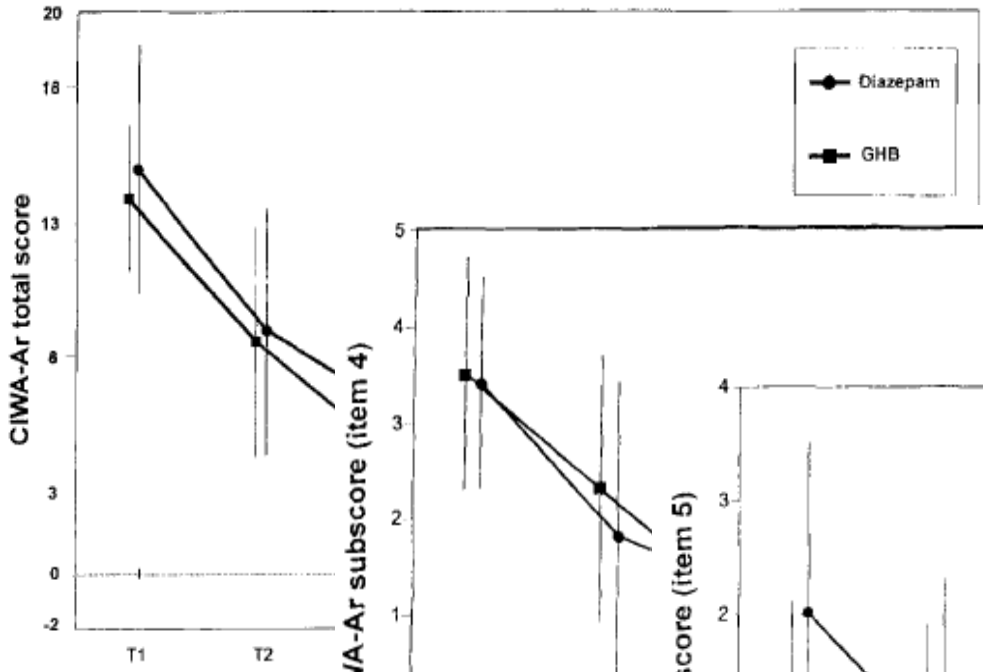
frazionato in 3 o 6 dosi giornaliere

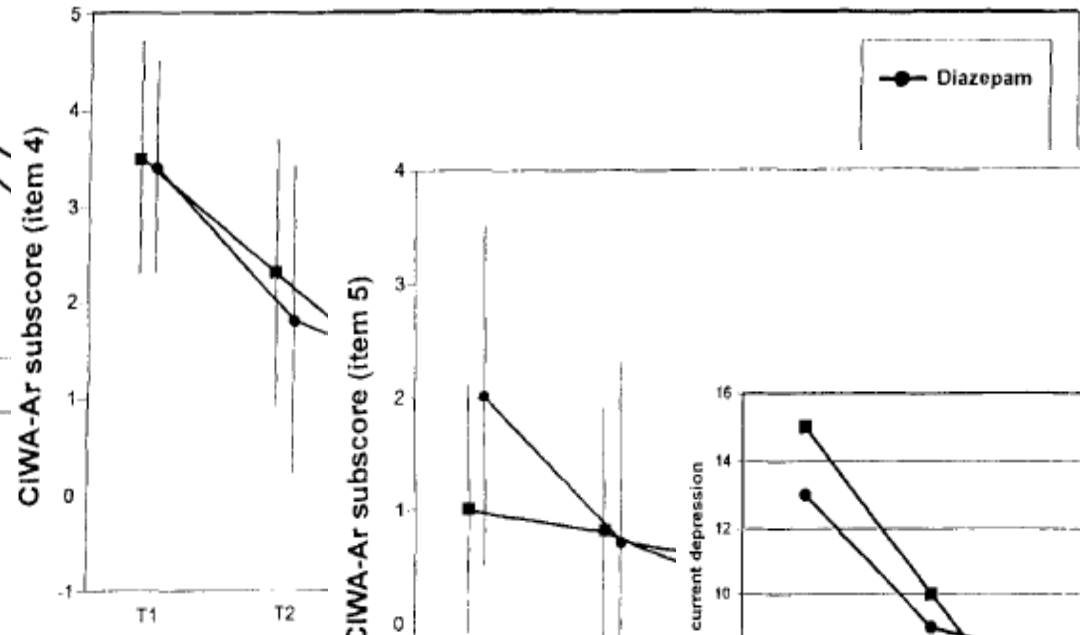
paziente di 70 kg di peso corporeo

3.5-7 g/die = 21-42 ml/die (7-14 ml x 3/die)

Adodolorato et al., *Exp Opin Invest Drugs, 2009*
Caputo et al., Lancet, 2005, 2009
Caputo, Curr Pharm Des, 2010

Sodium Oxybate vs Diazepam





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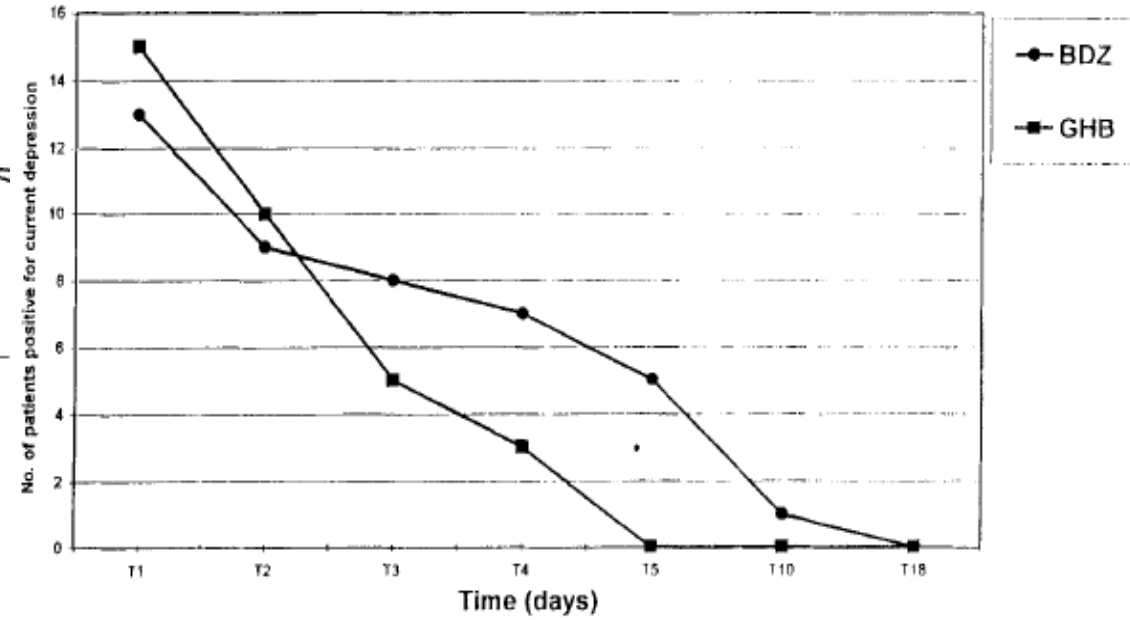

Diazepam 0.5-0.75 mg/kg body weight
Sodium Oxybate 50 mg/kg body weight

Addolorato et al, Alcohol Clin Exp Res, 1999

Baclofen vs Diazepam

The American Journal of Medicine (2006) 119, 276.e13-276.e18

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BRIEF OBSERVATION

Baclofen in the Treatment of Alcohol Withdrawal Syndrome: A Comparative Study vs Diazepam

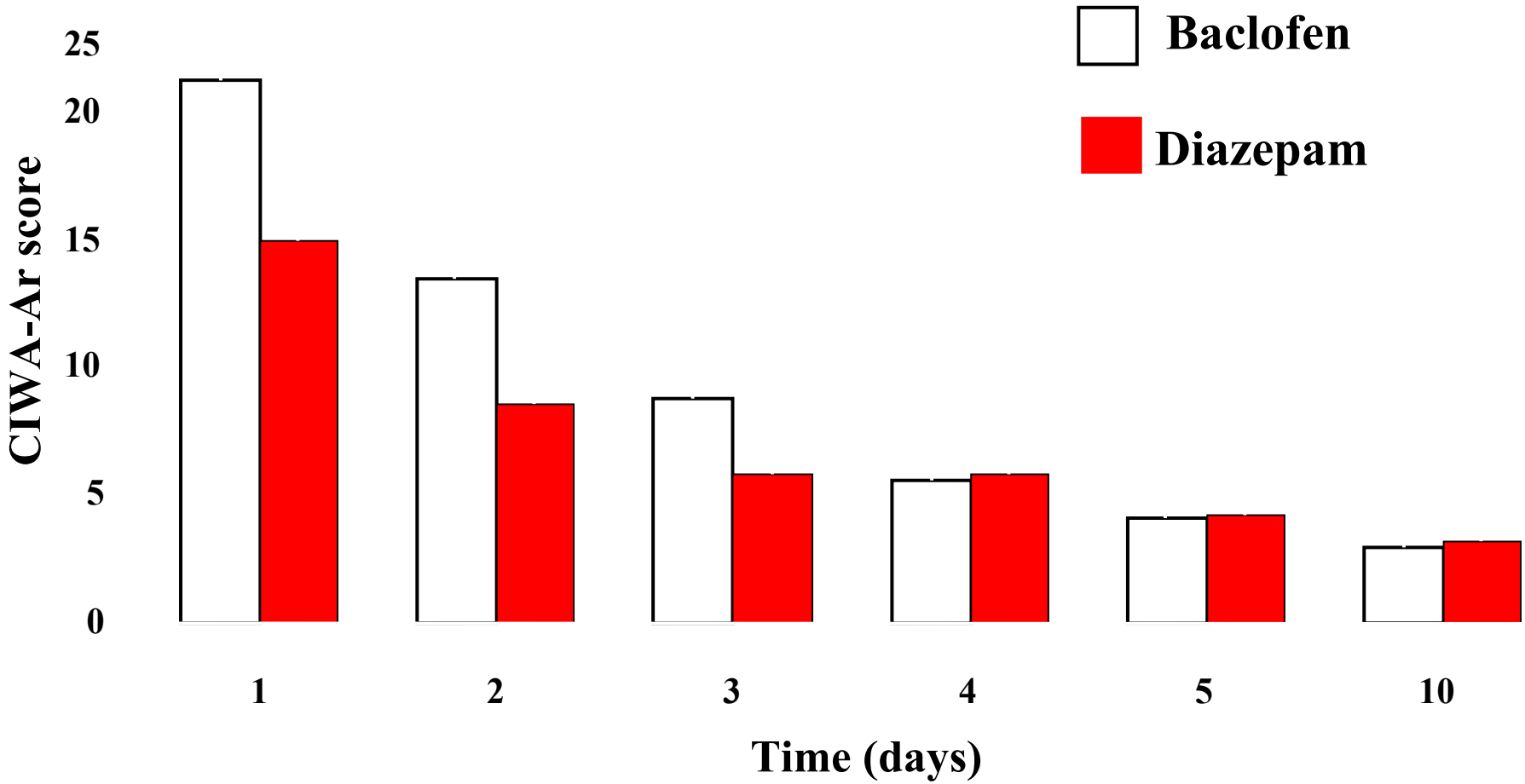
Giovanni Addolorato, MD,[a] Lorenzo Leggio, MD,[a] Ludovico Abenavoli, MD,[a] Roberta Agabio, MD,[b] Fabio Caputo, MD,[c] Esmeralda Capristo, MD,[a] Giancarlo Colombo, PhD,[d] Gian Luigi Gessa, MD,[b,d] Giovanni Gasbarrini, MD[a]

[a]Institute of Internal Medicine, Catholic University of Rome, Rome, Italy; [b]"Bernard B. Brodie" Department of Neuroscience, University of Cagliari, Cagliari, Italy; [c]"G. Fontana" Center for the Study and Treatment of Alcohol Addiction, University of Bologna, Bologna, Italy; [d]C.N.R. Institute of Neuroscience, Section of Cagliari, Cagliari, Italy.

Diazepam 0.5-0.75 mg/kg body weight
Baclofen 30 mg/day

Addolorato et al, Am J Med, 2006

Baclofene vs Diazepam

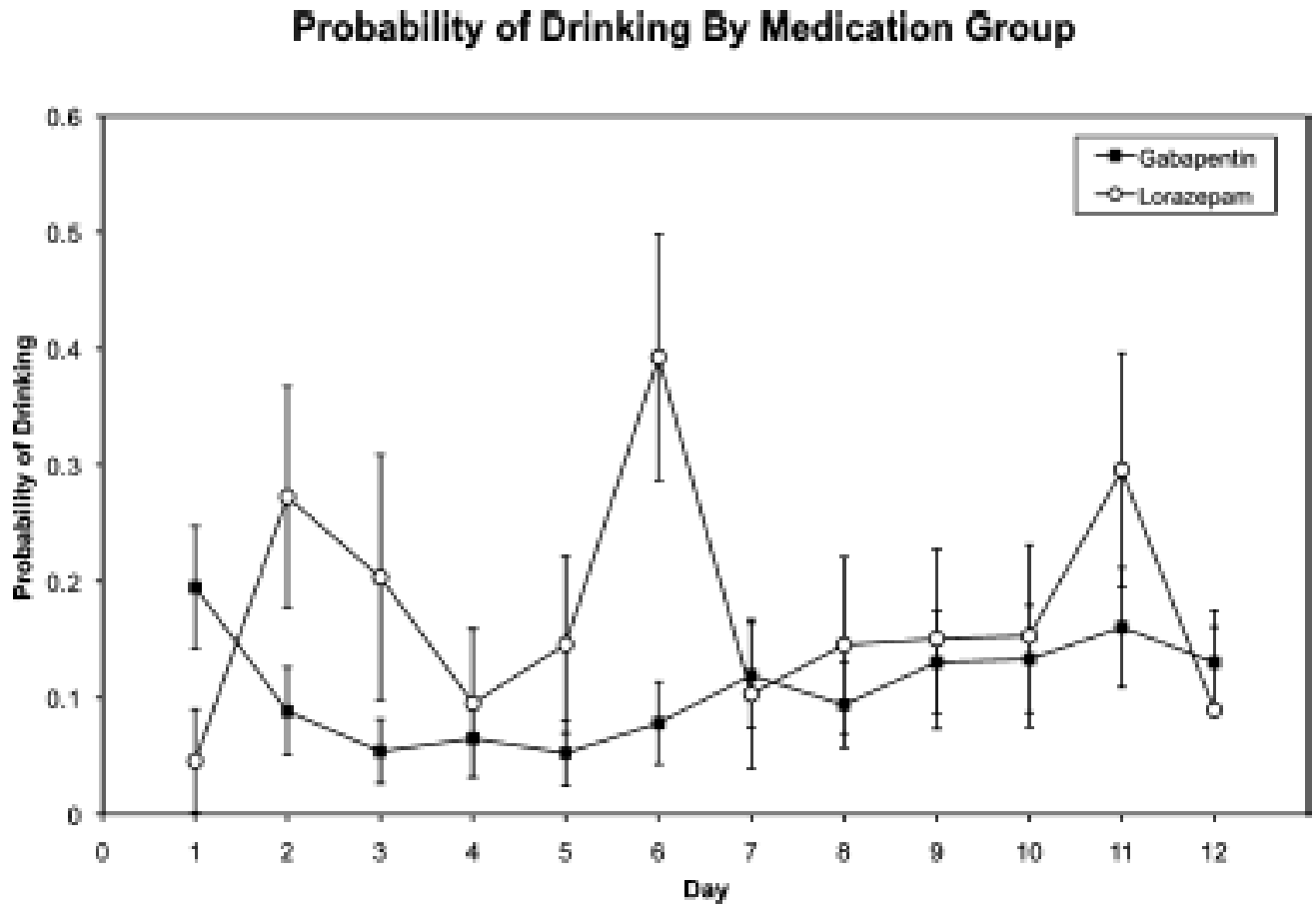


one-way ANOVA for baclofen: p<0.001
one-way ANOVA for diazepam: p<0.001
2-way ANCOVA baclofen vs diazepam: p:ns

Addolorato et al, Am J Med, 2006

Vol. 33, No. 9
September 2009

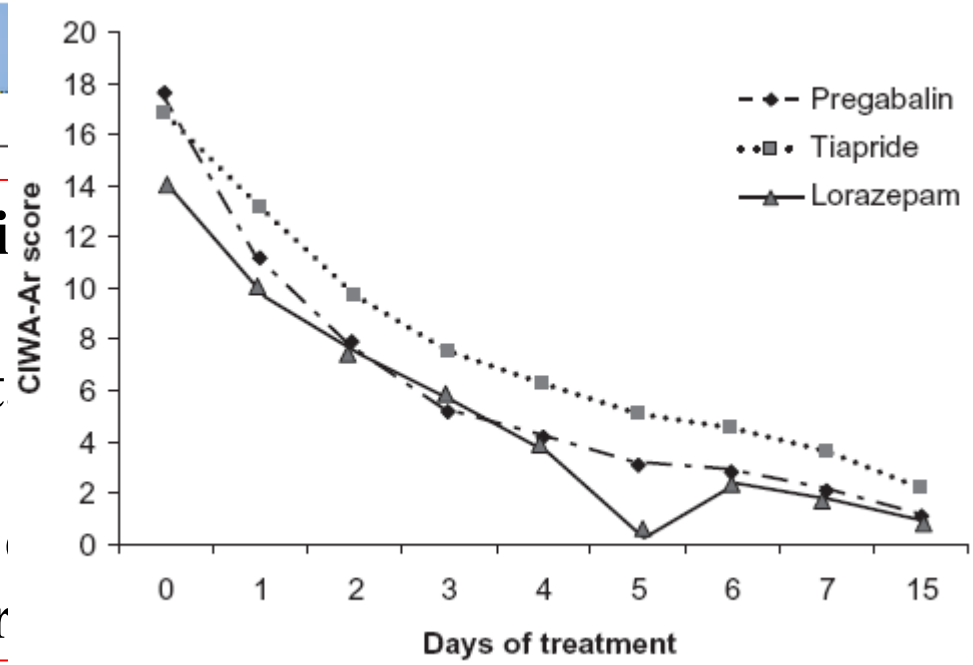
A Double-Blind Trial of Gabapentin Versus Lorazepam in the Treatment of Alcohol Withdrawal

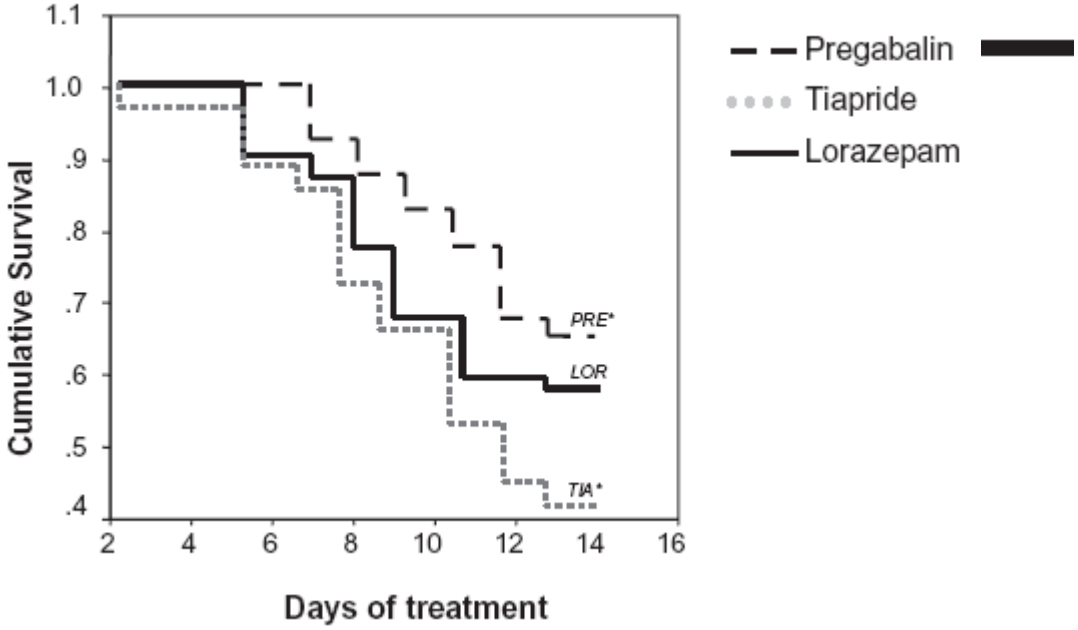


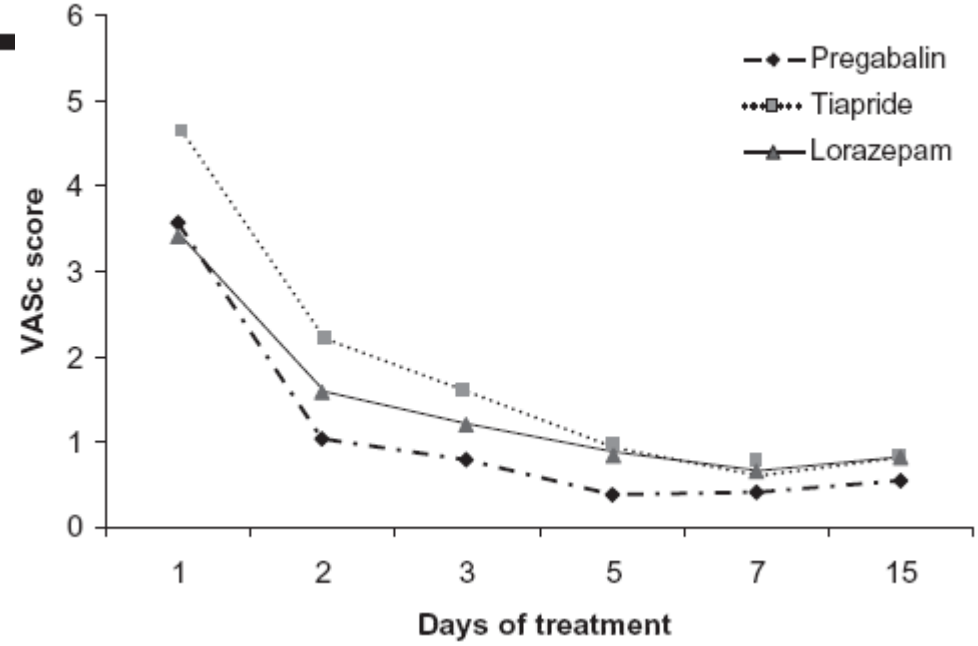
Addiction

RESEARCH REPORT

1. Pregabalin acts as a presynapti
excessive release, in hyperexcited
neurotransmitters, including glut
2. Pregabalin rapidly reduces the
3. It is not protein-bound, has an
and is primarily (92%) excreted r







Benzodiazepines for alcohol withdrawal (Review)

Amato L, Minozzi S, Vecchi S, Davoli M

Benzodiazepines showed a protective benefit against alcohol withdrawal symptoms, in particular seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with other drugs. Nevertheless, no definite conclusions about the effectiveness and safety of benzodiazepines was possible, because of the heterogeneity of the trials both in interventions and the assessment of outcomes.

Vol 463|11 February 2010|doi:10.1038/nature08758 nature

Neural bases for addictive benzodiazepines

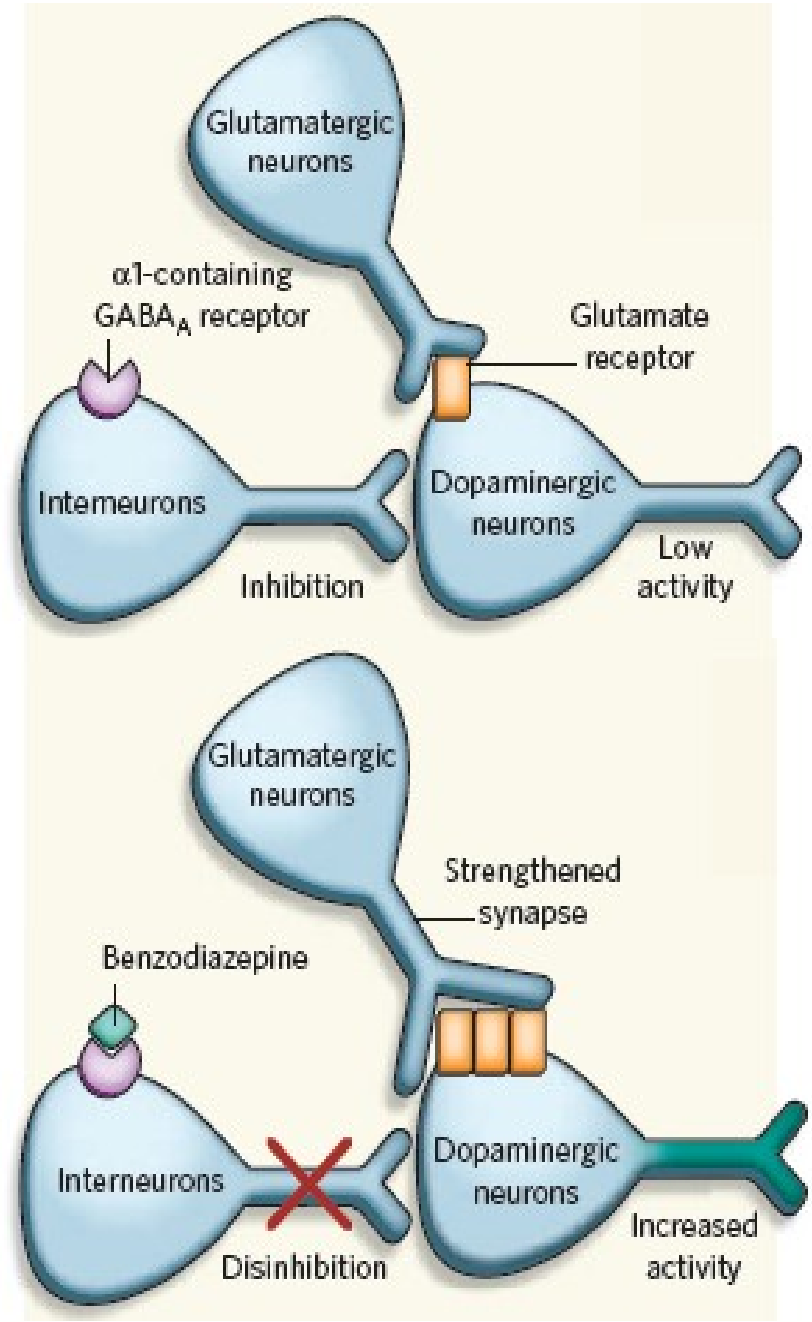
Kelly R. Tan[1], Matthew Brown[1]*, Gwenaël Labouèbe[1]*, Cédric Yvon[1]*
Uwe Rudolph[3] & Christian Lüscher[1,4,5]

NEUROSCIENCE

Lack of inhibition leads to ab

Arthur C. Riegel and Peter W. Kalivas

Chronic drug use can lead to addiction, which is initiated by specif circuits. The mystery of how one class of drugs, the benzodiazepi affects activity in this circuitry has finally been solved.



Anticonvulsants for alcohol withdrawal (Review)

Minozzi S, Amato L, Vecchi S, Davoli M

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 3

http://www.thecochranelibrary.com

Results of this review do not provide sufficient evidence in favour of anticonvulsants for the treatment of AWS. Anticonvulsants seem to have limited side effects, although adverse effects are not rigorously reported in the analysed trials.

Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses (Review)

Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F

1. GHB 50 mg is effective compared to placebo in the treatment of AWS, and in preventing relapses in previously detoxified alcoholics at 3 months follow-up, but the results of this review do not provide sufficient evidence in favour of GHB compared to benzodiazepines and Chlormethiazole for AWS prevention;
2. GHB is better than NTX and Disulfiram in maintaining abstinence and it has a better effect on craving than placebo and Disulfiram;
3. Side effects of GHB are not statistically different from those with BZD, NTX or Disulfiram;
4. However, concern has been raised regarding the risk of developing addiction, misuse or abuse, especially in polydrug abusers.

SINDROME
DI WERNICKE-KORSAKOFF

ENCEFALOPATIA DI WERNICKE

- **OFTALMOPLEGIA**
  (VI nervo cranico)
- **ATASSIA**
- **CONFUSIONE MENTALE**

DEFICIT DI TIAMINA (Vit B1)

PSICOSI DI KORSAKOFF

- **AMNESIA ANTEROGRADA**
- **DISORIENTAMENTO SPAZIO-TEMPORALE**
- **CONFABULAZIONE**

Alcohol & Alcoholism Vol. 45, No. 3, pp. 271–277, 2010
Advance Access Publication 26 March 2010

TREATME

Why is Disulfiram Superior to Acamprosate in the Routi
Study in 353 Alcohol-De

Alexander Diehl[1,*], Lisa Ulmer[2], Jochen Mutschler[2], Hans
Karl Mann[2] and Fal

[1]Depa
Behavi

*Cc

1. deterrence;
2. (auto)suggestion;
3. therapeutic ritual around;
4. a frequently renewed active de process;
5. continuous reinforcement of a lifestyle and development of new skills

(Krampe, Curr Pharm Des, 2010)

accumulated time of abs

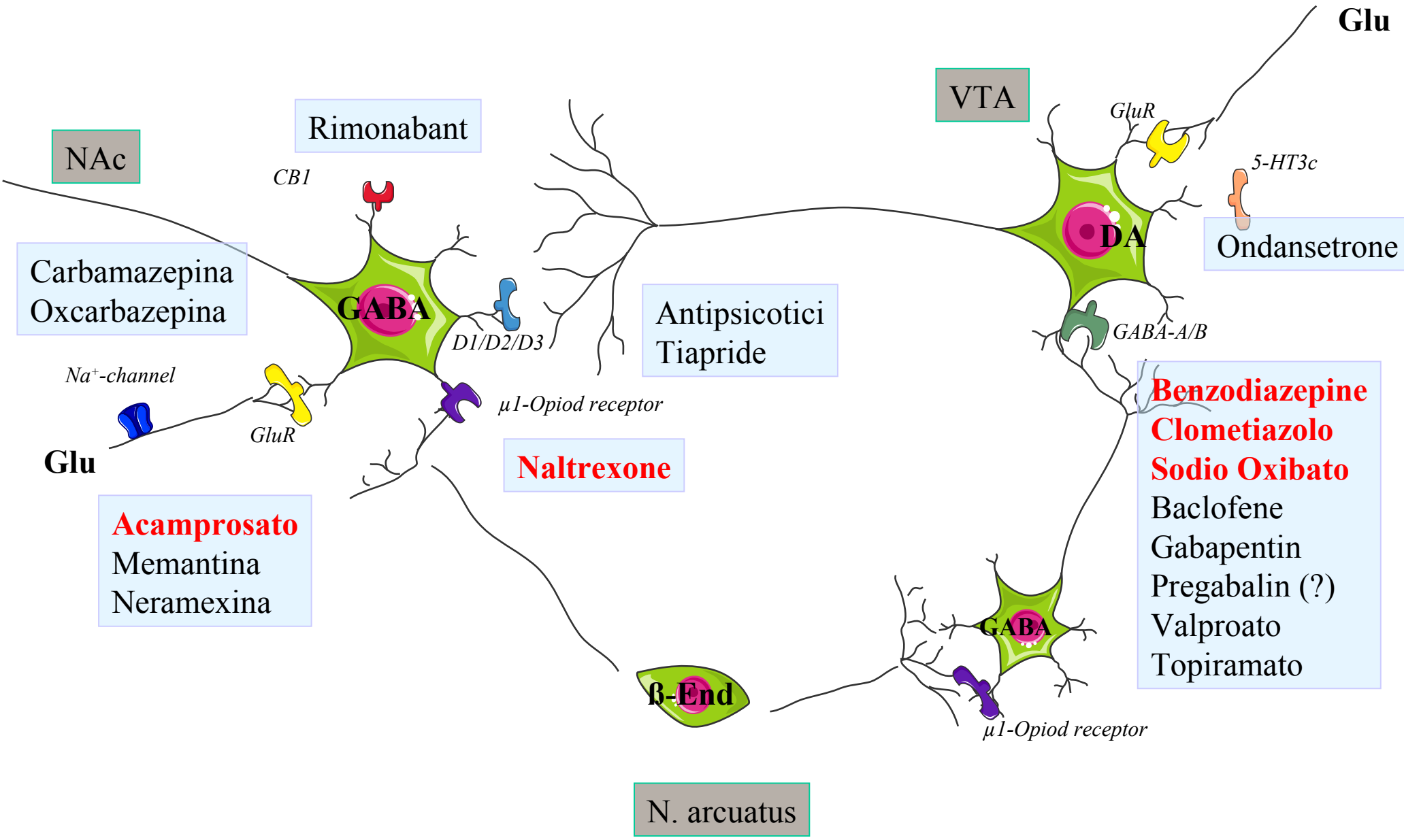
Contraindications of Disulfiram	End-stage liver disease (e.g. liver cirrhosis) Severe cardiovascular disease (e.g. coronary heart disease) History of stroke Acute psychotic disorders Epileptic seizures Florid ulcers Rubber allergy Pregnancy Severe cognitive impairment precluding understanding the disulfiram effect Alcohol consumption within the last 12 hours
Adverse Effects of Disulfiram	**Harmless side effects without alcohol consumption** □ Initial tiredness, sleepiness, headache □ Garlic-like taste and smell □ Unclear: sexual dysfunction → ***Disulfiram intake can be continued*** **Serious side effects without alcohol consumption** □ Rare: **Allergic skin reactions**, e.g. rashes, pruritus, and exfoliative dermatitis; most frequent in the first 2 weeks of treatment □ Rare: **Hepatotoxicity (Disulfiram-induced hepatitis):** most frequent two months after beginning of treatment; important: regular control of liver enzymes □ Rare: Neurological effects (e.g. polyneuropathy): slight increase in frequency with duration of high-dose treatment (>250mg/d) → ***Immediate stop of disulfiram and symptomatic treatment necessary***

Alcohol & Alcoholism Vol. 45, No. 2, pp. 146–150, 2010
Advance Access Publication 27 January 2010
doi: 10.1093/alcalc/agq001

TREATMENT

Supervised Disulfiram in Relapse Prevention in Alcohol-Dependent Patients Suffering From Comorbid Borderline Personality Disorder—A Case Series

Patient	Alcohol induced somatic sequelae	Psychiatric comorbidity (axis I)	Psychiatric comorbidity (axis II)	Dialectic behavioural therapy in the past	Psychiatric medication
A	Peptic ulcer Fatty liver	Depression (F33) Cannabis abuse (F12.1) Benzodiazepine abuse (F13.1) TD (F17.2)	BPD (borderline type) (F60.31)	Yes, as an outpatient	Oxcarbazepine 450 mg/day
B	Insulin-dependent diabetes mellitus by chronic pancreatitis	Bulimia (F50.2) Depression (F33) Benzodiazepine dependence (F13.2)	BPD (borderline type) (F60.31)	Multiple as an outpatient and inpatient	Citalopram 40 mg/day Lamotrigine 125 mg/day
C	Polyneuropathy	Depression (F33) Sedative or benzodiazepine dependence (F13.2) TD (F17.2)	BPD (borderline type) (F60.31)	Yes, as an outpatient and inpatient	Olanzapine 5 mg/day
D	Pancreatitis Dupuytren's contracture Gastritis	Benzodiazepine dependence (F13.2)	BPD (borderline type) (F60.31)	No	Quetiapine 150 mg/day
E	Fatty liver	Depression (F33) TD (F17.2)	BPD (impulsive type) (F60.30)	No	Quetiapine 50 mg/day Citalopram 20 mg/day Trimipramine 50 mg/day Valproate 800 mg/day
F	None	Depression (F33) TD (F17.2)	BPD (borderline type) (F60.31)	No	Citalopram 20 mg/day
G	Fatty liver Polyneuropathy	TD (F17.2) Abuse of cannabis, cocaine, mescaline and benzodiazepines (F19.1)	BPD (borderline type) (F60.31)	No	Mirtazapine 45mg/day Quetiapine 300 mg/day Escitalopram 10 mg/day
H	Fatty liver Peptic ulcer	Depression (F33) Posttraumatic stress disorder (F42.1)	BPD (borderline type) (F60.31)	No	Mirtazapine 45 mg/day Pregabalin 300 mg/day Quetiapine 300 mg/day Escitalopram 20 mg/day


Glu
VTA
GluR
5-HT3c
Rimonabant
NAc
CB1
DA
Ondansetrone
Carbamazepina
Oxcarbazepina
GABA
D1/D2/D3
Antipsicotici
Tiapride
GABA-A/B
Na+-channel
µ1-Opiod receptor
Benzodiazepine
Clometiazolo
Sodio Oxibato
Baclofene
Gabapentin
Pregabalin (?)
Valproato
Topiramato
Glu
GluR
Naltrexone
Acamprosato
Memantina
Neramexina
GABA
ß-End
µ1-Opiod receptor
N. arcuatus

SODIO OXIBATO / ACIDO GAMMA IDROSSIBUTIRRICO (GHB)

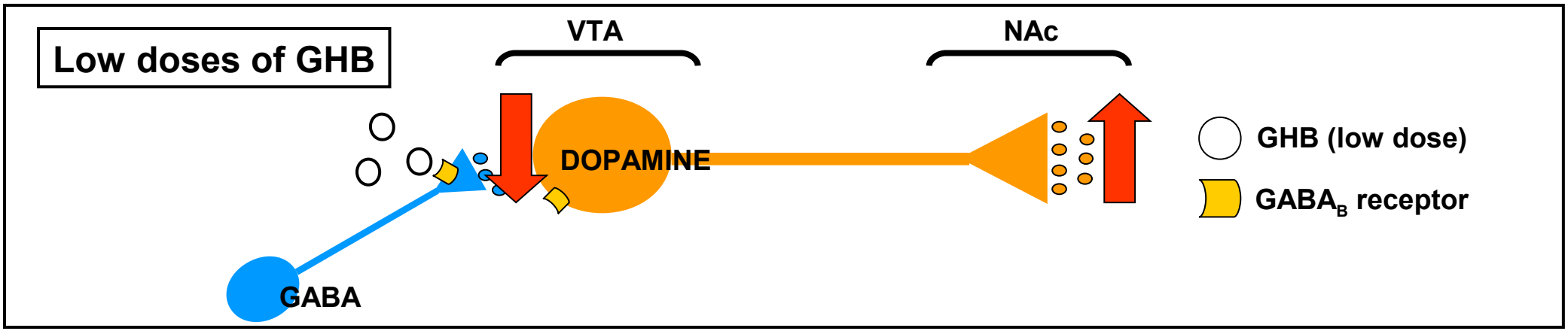
50 mg / kg / die per os

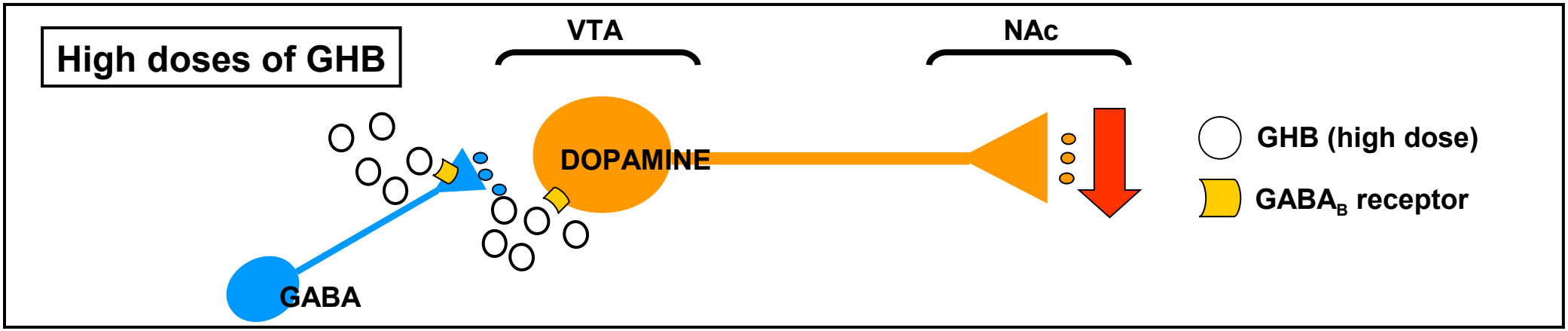
frazionato in 3 o 6 dosi giornaliere

paziente di 70 kg di peso corporeo

3.5 g/die = 21 ml/die (7 ml x 3/die)

Adodolorato et al., *Exp Opin Invest Drugs, 2009*
Caputo et al., Lancet, 2005, 2009
Caputo, Curr Pharm Des, 2010





Adapted from: Cruz et al., Nature Neurosci. 7:153-159, 2004

GHB had no effects on attention, vigilance, alertness, short-term memory or psychomotor co-ordination; adverse effects were limited to slight subjective feelings of dizziness and dullness, which disappeared 30-60 min after administration of the dose.
Lorazepam caused impairment of psychometric functions.
Therefore, GHB does not influence the ability to drive or work.

(Ferrara et al., 1999)

Table 1 Summary of significant peak subjective effects measures relative to placebo and high-dose comparisons between 0.5 mg/70 kg triazolam and 4.5 g/70 kg sodium oxybate

Subjective effect	Drug vs. placebo comparison[a]		High-dose comparison[b]
	TRZ vs. PL	SXB vs. PL	
Drug effect	+	+	NS
Sedating or depressant	+	+	NS
Limbs heavy or rigid	+	+	NS
Lightheaded or dizzy	+	+	NS
Fatigued or weak	+	+	NS
Confused or disoriented	+	+	NS
Difficulty concentrating	+	+	NS
Forgetful	+	+	NS
Dry mouth	+	+	NS
Speech slurred	+	NS	NS
Numbness or tingling	+	+	NS
Dislike drug effect	+	+	NS
Energetic	−	NS	TRZ>SXB
Alert	−	−	TRZ>SXB
Sleepy	+	+	TRZ>SXB
Tired or lazy	+	+	TRZ>SXB
Easy going or mellow	+	NS	TRZ>SXB
Mentally slowed down	+	+	TRZ>SXB
Limp or loose	+	NS	TRZ>SXB
Blurred vision	+	+	TRZ>SXB
Unsteady	+	+	SXB>TRZ
Queasy	NS	+	SXB>TRZ
Bad effects	+	+	SXB>TRZ

[a] These columns show the results of simple contrasts between placebo and doses of triazolam (TRZ) and sodium oxybate (SXB) on peak effects data. Symbol (+ or −) indicates that at least one dose of drug was significantly different from placebo ($p<0.05$) and the direction of the drug effect. NS indicates that no dose of that drug was different from placebo

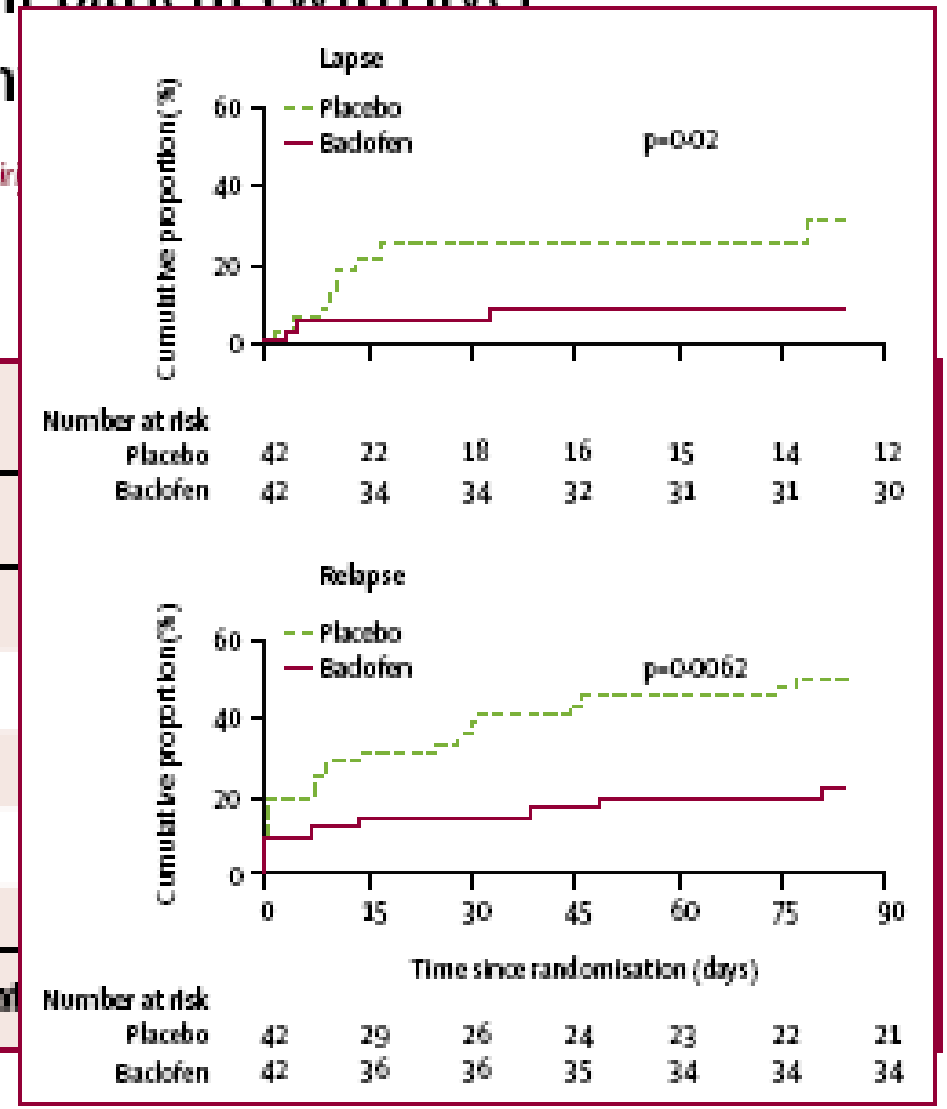
[b] This column shows the results of simple contrasts between the largest dose of triazolam (0.5 mg/70 kg) and sodium oxybate (4.5 g/70 kg). The drug to the left of the > symbol produced a significantly greater effect ($p<0.05$). NS indicates that the effects produced by the two doses were not significantly different

Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind con

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

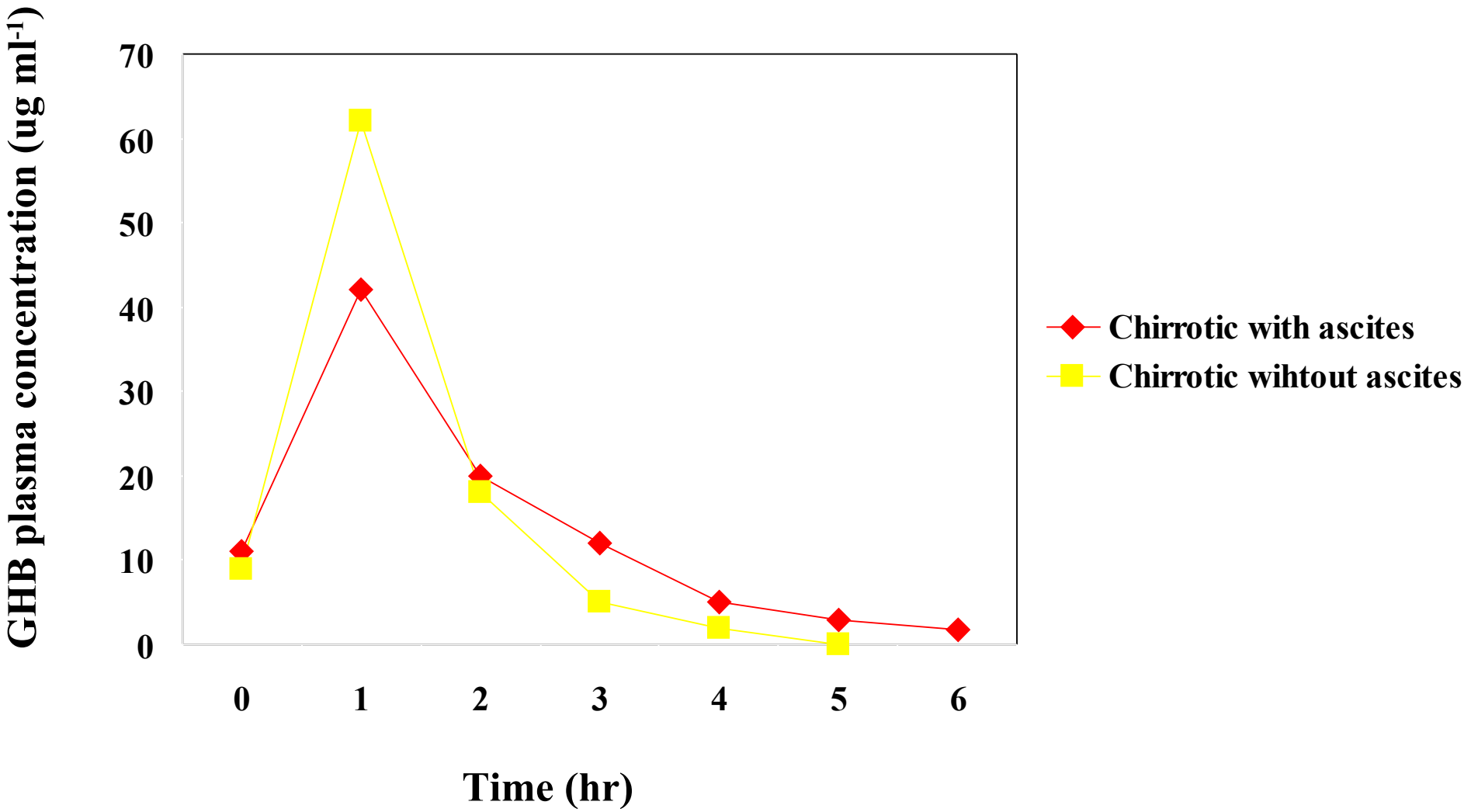
	Total alcohol abstinence (n [%])	
	Placebo	Baclofen
Child-Pugh A	1/6 (17)	3/4 (75)
Child-Pugh B	5/20 (25)	12/20 (60)
Child-Pugh C	6/16 (38)	15/18 (83)
Total	12/42 (29)	30/42 (71)

Table 4: Total alcohol abstinence by Child-Pugh classificat

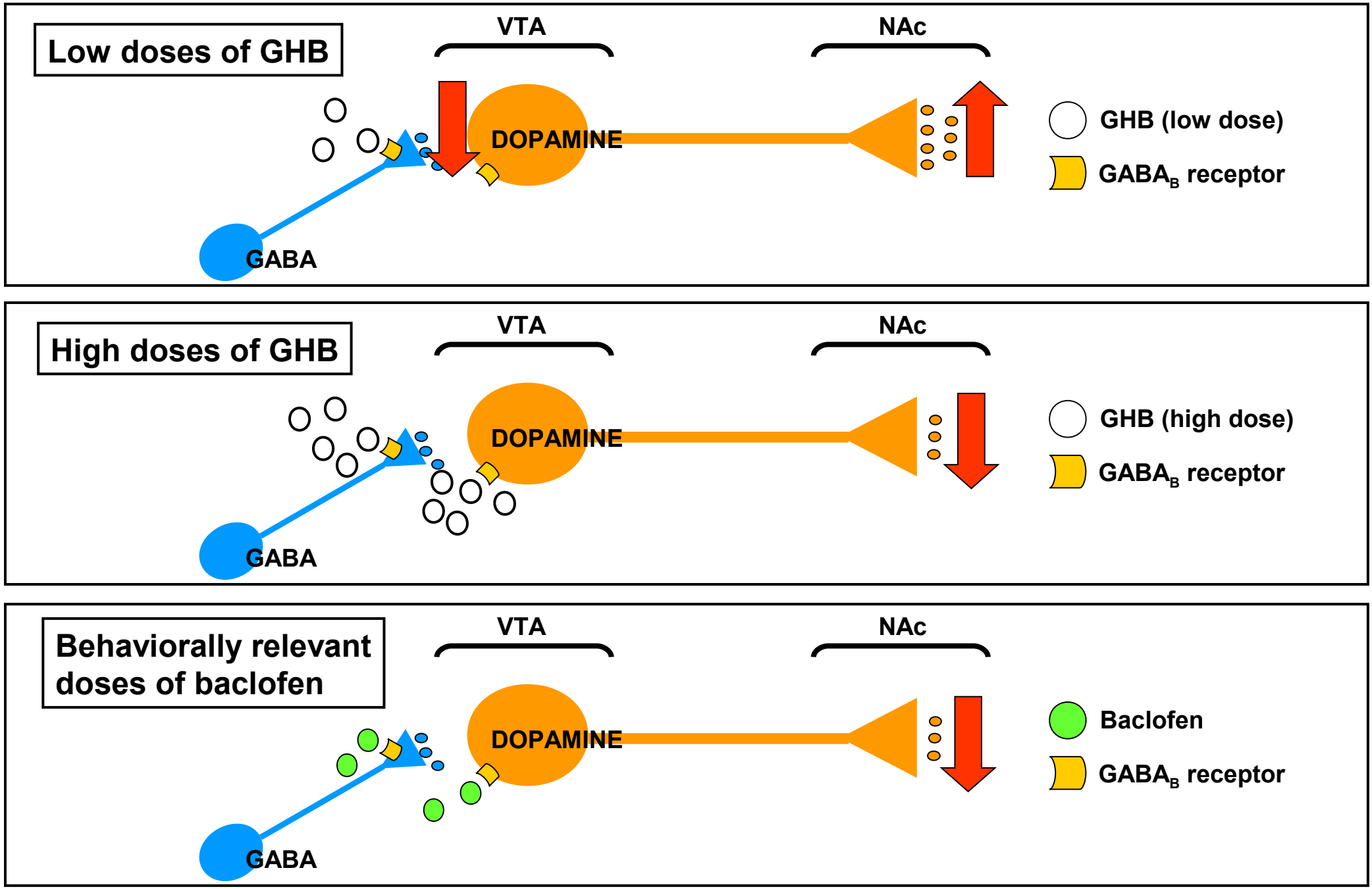


(Addolorato et al, Lancet, 2007)

GHB and LIVER CHIRROSIS

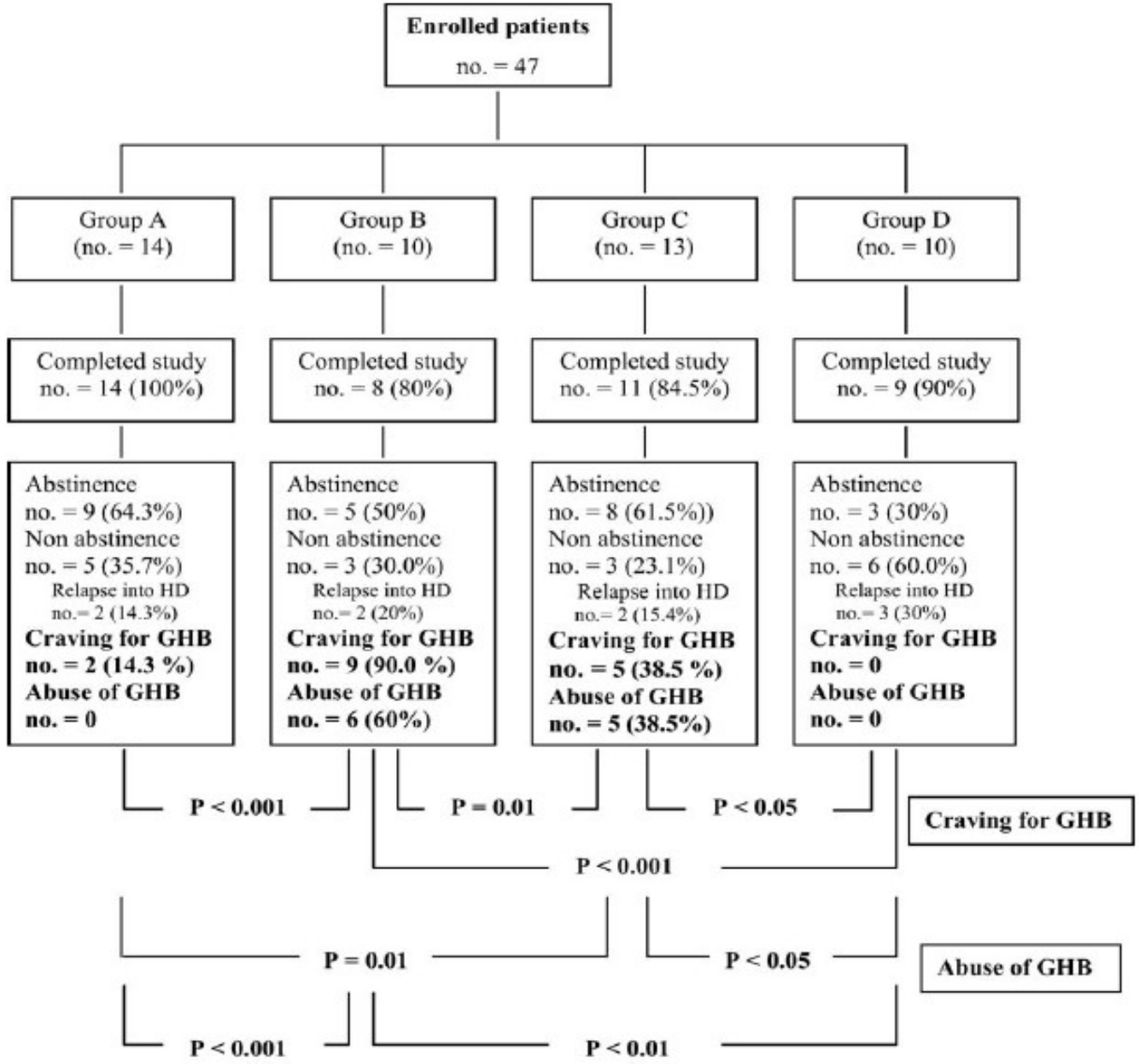


(Ferrara et al., Eur J Clin Pharmacol, 1996)

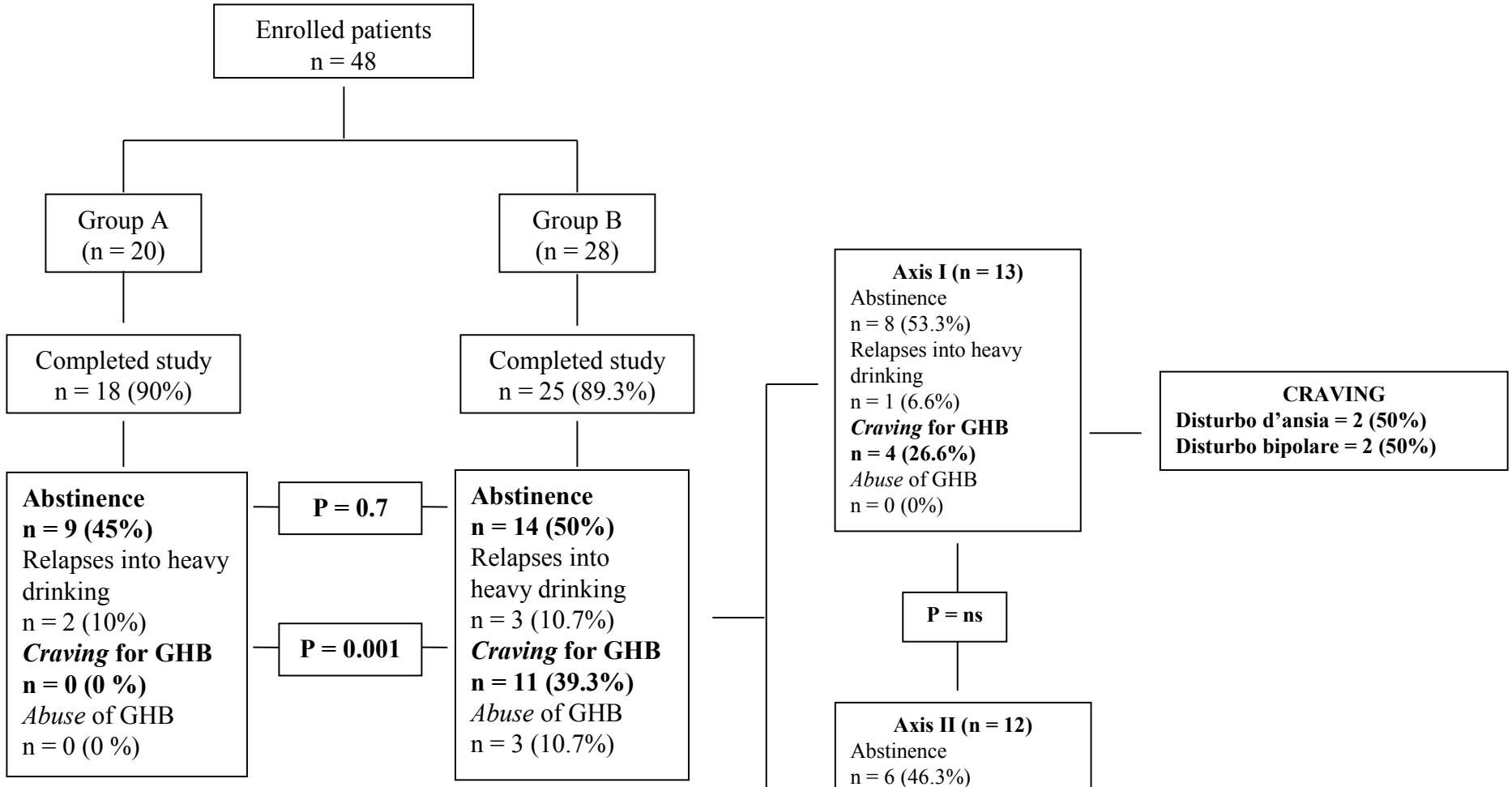


Adapted from: Cruz et al., Nature Neurosci. 7:153-159, 2004

CRAVING E ABUSO PER GHB

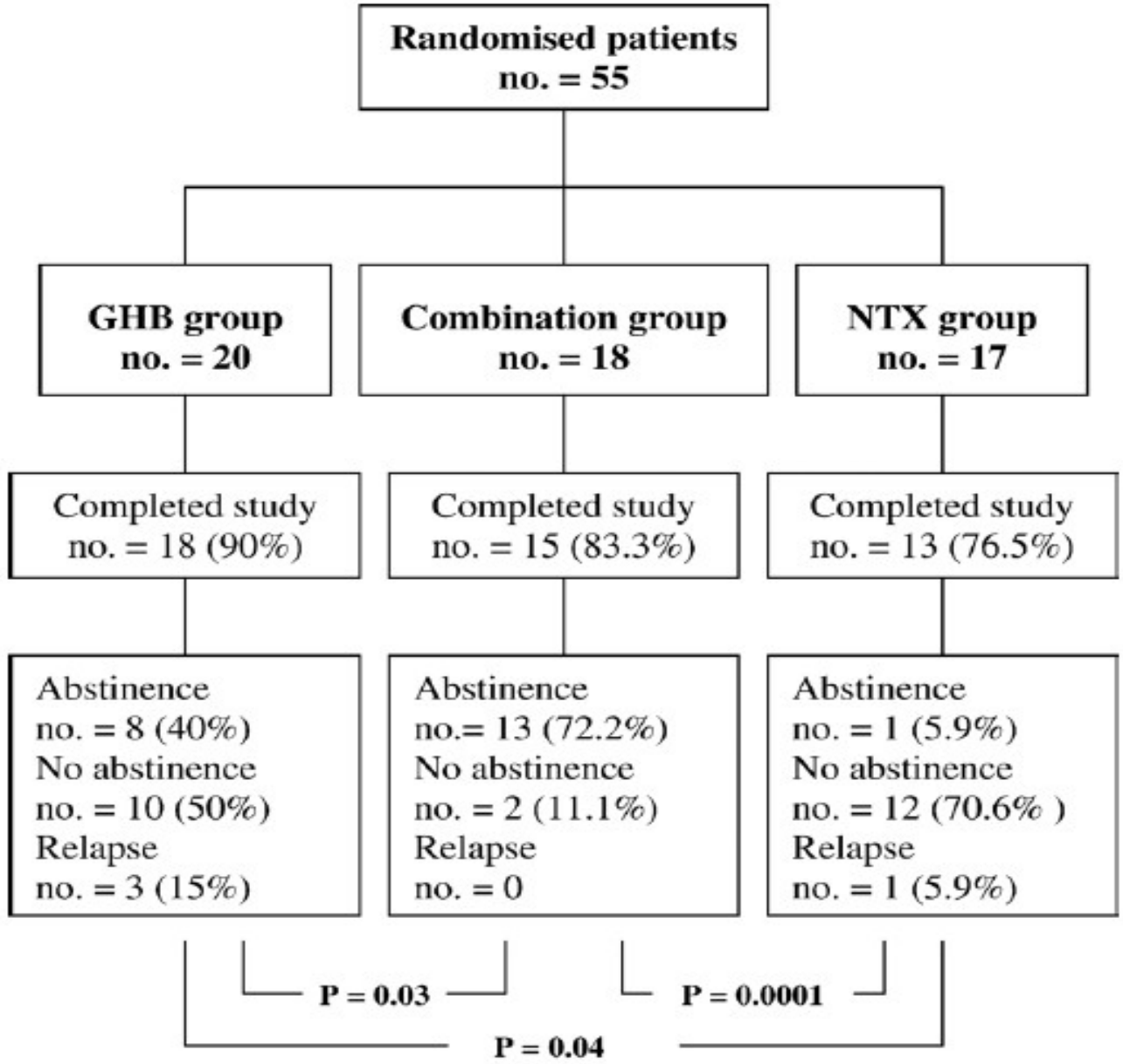


(Caputo et al, J Psychopharmacol, 2009)



(data not published)

COMBINAZIONE FARMACOLOGICA



(Caputo et al, Eur Neuropsychopharmacol, 2007)

Table 3 Adverse events during the treatment period. Fifteen patients showed adverse effects: 2 patients (GHB group), 9 patients (combination group) and 4 patients (NTX group)

	GHB group	Combination group	NTX group
Vertigo	2 (3%)	5 (27.7%)	
Headache	1 (1.5%)	2 (11.1%)	
"Sense of drunkenness"	1 (1.5%)		
Nausea		4 (22.2%)	2 (11.8%)
Appetite reduction		1 (5.5%)	
Sweating		1 (5.5%)	
Sedation		1 (5.5%)	1 (5.9%)
"Uncertainty in daily activities"		1 (5.5%)	
Abandonment of treatment due to adverse events	1 (5%)	3 (16.7%)	1 (5.9%)

Each value expresses the number of patients who manifested adverse effects.

(Caputo et al, Eur Neuropsychopharmacol, 2007)

Medications Acting on the Gaba System in the Treatment of Alcoholic Patients

Fabio Caputo* and Mauro Bernardi[1]

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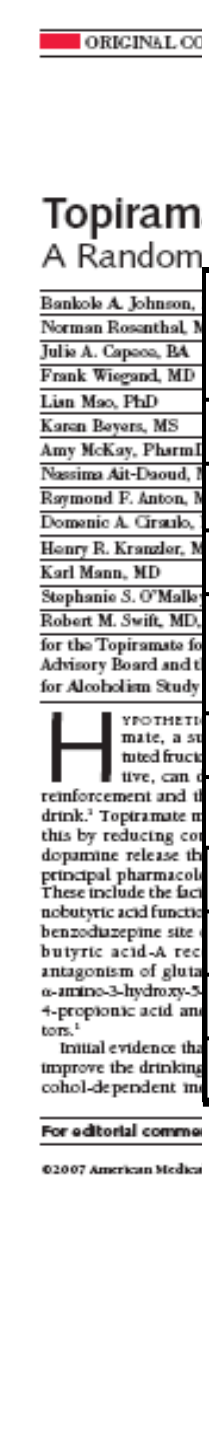
Abstract: Gamma aminobutyric acid (GABA) represents the major inhibitory neurotransmitter of the central nervous system. Ethanol as well as benzodiazepines (BDZs) and some anticonvulsant drugs directly affect $GABA_A$ receptors inducing similar anxiolytic, sedative-hypnotic, and anticonvulsant effects. Since BDZs have proven their efficacy in ameliorating symptoms and in decreasing the risk of seizures and delirium tremens, they are the drugs of choice for the treatment of alcohol withdrawal syndrome (AWS). However, due to their addictive potential and lack of safety when combined with alcohol, BDZs are usually not recommended for the maintenance of alcohol abstinence. Other GABA-ergic medications represent potentially promising drugs useful in the treatment of AWS and in maintaining alcohol abstinence. Indeed, available studies have demonstrated that clomethiazole, gabapentin and gamma hydroxybutyrate (GHB) present a similar efficacy to BDZs in suppressing AWS. In addition, current evidence also indicates that gabapentin and GHB do not have significant interactions with ethanol that render them safe to use in maintaining alcohol abstinence. Moreover, gabapentin and valproic acid may be beneficial in maintaining alcohol abstinence in alcoholics with psychiatric co-morbidity. Pregabalin, neurosteroids, tiagabine, and vigabatrin need further clinical evidence of efficacy, safety and tolerability. Thus, given the importance of GABA-ergic mechanisms in the development and maintenance of alcohol dependence, and the very interesting results currently achieved, more research on GABA-ergic agents is warranted.

Keywords: Alcoholism; alcohol withdrawal syndrome; maintenance of abstinence from alcohol; benzodiazepines; gabapentin; gamma hydroxybutyrate; valproic acid.



Selected Adverse Events During Treatment Occurring in ?10% of Subjects in the Topiramate Group

Adverse Event	No. (%) of Participants: Topiramate (n = 183)	No. (%) of Participants: Placebo (n = 188)
Paresthesia	93 (50.8%)	20 (10.6%)*
Taste perversion	42 (23.0%)	9 (4.8%)*
Anorexia	36 (19.7%)	13 (6.9%)*
Difficulty with concentration/attention	27 (14.8%)	6 (3.2%)*
Somnolence	22 (12.0%)	19 (10.1%)
Difficulty with memory	23 (12.6%)	13 (6.9%)
Dizziness	21 (11.5%)	10 (5.3%)*
Pruritus	19 (10.4%)	2 (1.1%)*
Fatigue	41 (22.4%)	33 (17.6%)
Headache	44 (24.0%)	60 (31.9%)

*P<0.05, chi-square test. If a subject experienced more than one adverse event within a category, the subject is counted once under that category. Subjects with more than one occurrence of an adverse event are summarized under the most related category.

Courtesy of Professor Bankole Johnson

(Johnson et al., JAMA, 2007)

- **TPM impaired cognitive test performance, whereas gabapentin had minimal effects. The effects of TPM were of sufficient magnitude potentially to affect daily and occupational function (Salinsky et al., Neurology, 2003).**
- **The cognitive effects of TPM are slightly worse overall than volproic acid in patients who tolerate therapy over several months (Meador et al., Neurology, 2005).**
- **Lamotrigine produces significantly fewer untoward cognitive and behavioral effects compared to topiramate (TPM) (Meador et al., Epilepsia, 2003).**

ORIGINAL ARTICLE

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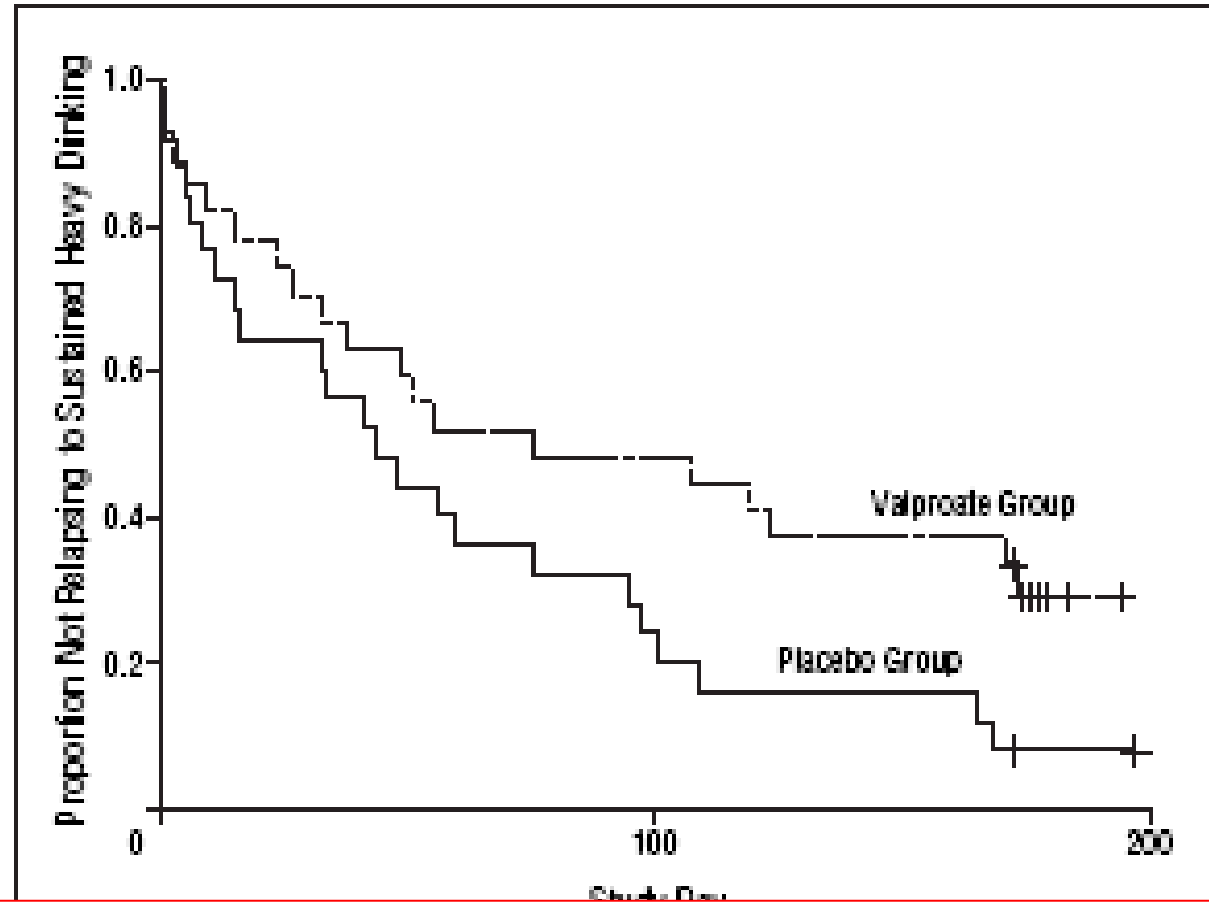

Valproate therapy decreases heavy drinking in patients with comorbid bipolar disorder and alcohol dependence.
The results of this study indicate the potential clinical utility of the anticonvulsant mood stabilizer, valproate, in bipolar disorder with co-occurring alcohol dependence.

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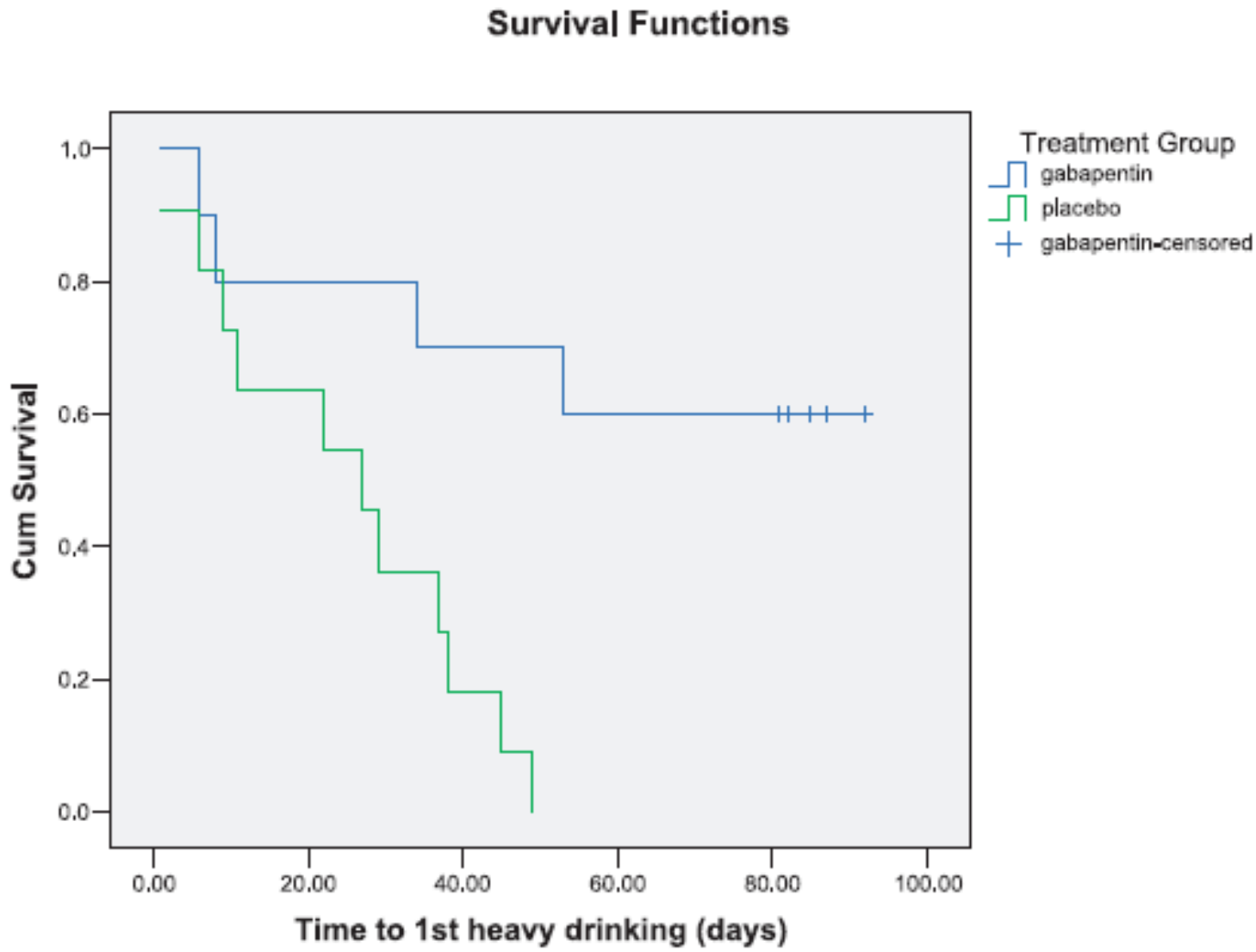
August 2008

A Randomized Double-Blind Pilot Trial of Gabapentin



Naltrexone and Disulfiram in Patients with Alcohol Dependence and Comorbid Psychiatric Disorders

Ismene L. Petrakis, James Poling, Carolyn Levinson, Charla Nich, Kathleen Carroll, Bruce Rounsaville, and the VA New England VISN I MIRECC Study Group

						Treatment Contrasts		
	Disulfiram/Naltrexone (*n* = 65)	Disulfiram/Placebo (*n* = 66)	Naltrexone (*n* = 59)	Placebo (*n* = 64)	Change over time	DN vs. DP or N	DP vs. N	Any med vs. P
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*z*, *p*	*F*, *p*	*F*, *p*	*F*, *p*
Self-reported drinking								
Consecutive days of abstinence	69.2 (24.0)	70.5 (24.1)	67.2 (25.5)	61.0 (30.3)		.01, .94	.17, .68	4.49, .04
% Days abstinent	96.6 (8.7)	96.6 (10.5)	95.4 (11.8)	93.5 (14.0)		.14, .71	.36, .55	2.78, .10
% Heavy drinking days	3.1 (8.1)	3.2 (10.5)	4.0 (11.4)	5.9 (12.9)		.10, .76	.20, .65	2.48, .12
Subjects with total abstinence, *n*	46 (70.8)	51 (77.3)	38 (64.4)	42 (65.6)		.00, .95	2.55, .11	.67, .41

A modest advantage for the use of disulfiram and naltrexone for this group of dually diagnosed alcohol-dependent individuals but did not suggest an advantage in the combination

Naltrexone and Disulfiram in Patients With Alcohol Dependence and Current Depression

Ismene Petrakis, MD, Elizabeth Ralevski, PhD, Charla Nich, Carolyn Levinson, MPH, Kathleen Carroll, PhD, James Poling, PhD, and Bruce Rounsaville, MD and the VA VISN I MIRECC Study Group

	Disulfiram/ Naltrexone		Disulfiram/ Placebo		Naltrexone		Placebo		By Psychiatric Diagnosis	Interaction (Treatment Contrast × Depression)		
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	*df* = 1 F, *P*	DN vs DP (F, *P*)	DP vs N (F, *P*)	Any Medication vs P (F, *P*)
Alcohol Use Outcomes												
Maximum consecutive days of abstinence												
Depression	69.3 (25.0)	28	73.5 (22.8)	43	67.2 (25.0)	34	61.5 (29.8)	34	0.56, 0.46	0.26, 0.61	0.80, 0.37	0.06, 0.80
No depression	69.1 (23.6)	37	64.8 (25.8)	23	67.2 (26.8)	25	60.4 (31.4)	30				
% Days abstinent												
Depression	99.0% (2.6%)	28	97.1% (10.3%)	43	95.2% (13.9%)	34	94.6% (11.1%)	34	1.72, 0.19	1.06, 0.30	0.27, 0.60	0.05, 0.82
No depression	94.9% (11.1%)	37	95.5% (11.1%)	23	95.8% (8.4%)	25	92.1% (16.9%)	30				
% Heavy drinking days												
Depression	0.9% (2.2%)	28	2.8% (10.3%)	43	4.2% (13.7%)	34	4.5% (10.3%)	34	1.29, 0.26	0.99, 0.32	0.23, 0.63	0.02, 0.88
No depression	4.5% (10.3%)	37	4.1% (11.1%)	23	3.6% (7.4%)	25	6.4% (14.6%)	30				

The results suggest that disulfiram and naltrexone are safe pharmacotherapeutic agents for dually diagnosed individuals with depression for the treatment of alcohol use disorders

Naltrexone and Disulfiram in Patients with Alcohol Dependence and Comorbid Post-Traumatic Stress Disorder

	Disulfiram/ Naltrexone	Disulfiram/ Placebo	Naltrexone	Placebo	By Psychiatric Diagnosis	Interaction (tx contrast PTSD)[a]		
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	*df* = 1 *F*, *p*	DN vs DP *F*, *p*	DP vs N *F*, *p*	Any med vs P *F*, *p*
Maximum consecutive days of abstinence								
No PTSD (*n* = 161)	69.6 (21.9)	67.1 (25.6)	66.0 (27.2)	66.1 (26.9)	.23, .63	.73, .39	.40, .53	6.10, .01
PTSD (*n* = 93)	68.2 (28.6)	75.7 (21.0)	68.7 (23.8)	49.7 (34.7)				
% Days abstinent								
No PTSD	96.1% (9.8%)	95.9% (10.7%)	96.5% (7.5%)	95.2% (11.0%)	1.55, .20	.32, .57	1.00, .32	2.79, .10
PTSD	97.8% (5.7%)	97.7% (10.5%)	94.1% (15.7%)	89.7% (19.0%)				
% Heavy drinking days								
No PTSD	3.5% (9.3%)	4.0% (10.6%)	2.8% (6.7%)	3.5% (8.8%)	.52, .47	.41, .52	1.27, .26	3.92, .05
PTSD	1.7% (4.4%)	2.2% (10.5%)	5.4% (15.5%)	9.6% (17.6%)				
Abstinent for entire study period[a]	*n* (%)	*n* (%)	*n* (%)	*n* (%)	x^2, *p*	x^2, *p*	x^2, *p*	x^2, *p*
No PTSD	29 (65.9)	29 (72.5)	21 (63.6)	31 (70.5)	.60, .44	.02, .89	.10, .75	.01, .92
PTSD	17 (81.0)	22 (84.6)	17 (65.4)	11 (55.0)				

The results of this study suggest that disulfiram and naltrexone are effective and safe for individuals with PTSD and comorbid alcohol dependence

Alcoholism: Clinical and Experimental Research

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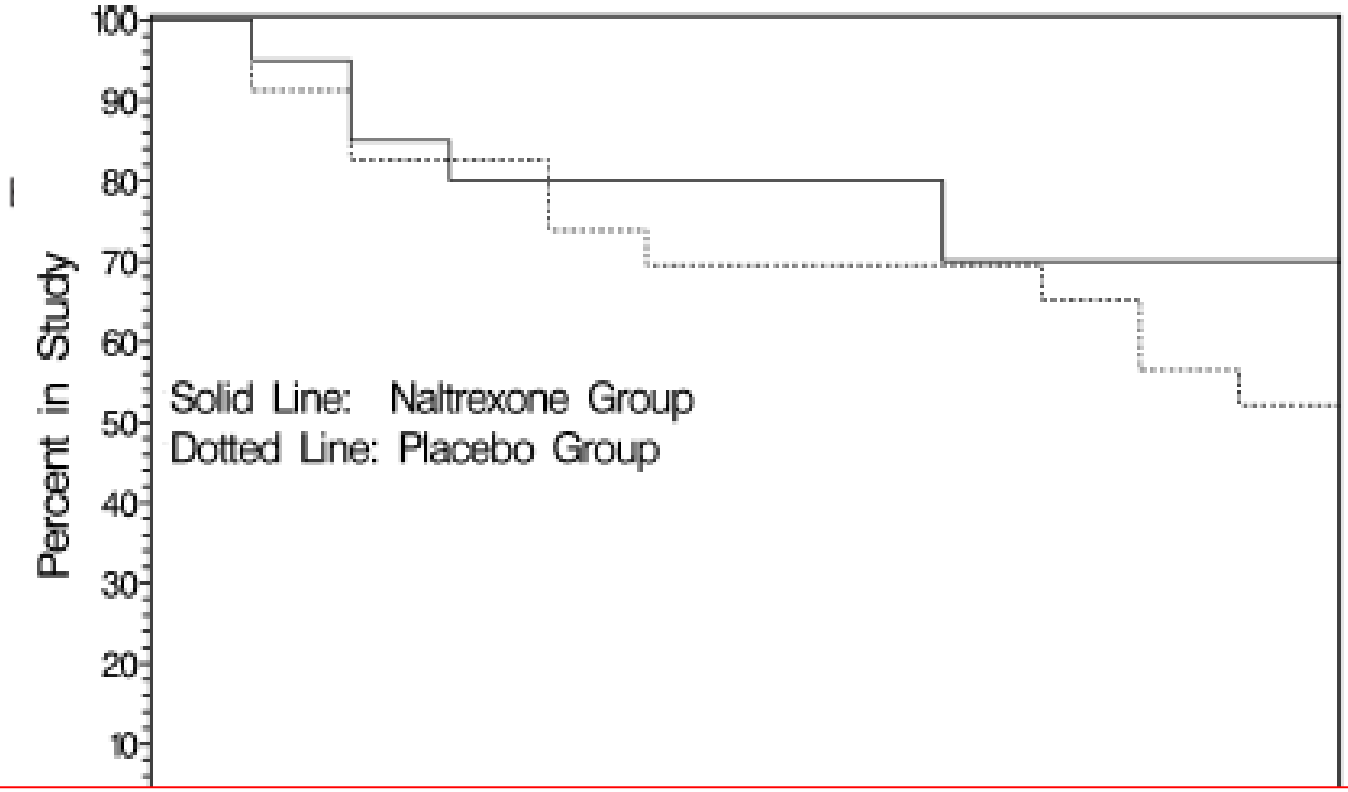
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Naltrexone in Outpatients With Bipolar



Results suggest the potential value and acceptable tolerability of naltrexone for alcohol dependence in bipolar disorder patients; a larger trial is needed to establish efficacy.

	Disulfiram/ naltrexone Mean (SD)	Disulfiram/ placebo Mean (SD)	Naltrexone Mean (SD)	Placebo Mean (SD)	Personality group df = 1 F, *p*	Contrasts*			Interactions†
						DN v. DP *p*	DP v. N *p*	Any med v. P *p*	*p*
Maximum consecutive weeks of abstinence									
No BPD (n = 68)	9.5 (3.4)	10.4 (3.2)	9.7 (3.8)	8.8 (4.3)	.001, .97	.56	.37	.008	.45
BPD (n = 157)	10.7 (3.3)	9.4 (3.9)	9.3 (3.4)	8.3 (4.3)					
No ASPD (n = 95)	10.1 (3.0)	10.0 (3.7)	8.7 (3.9)	8.2 (4.5)	1.17, .28	.72	.95	.004	.43
ASPD (n = 130)	9.6 (3.7)	11.1 (2.3)	10.3 (3.3)	8.3 (4.5)					
Average number of drinks per week									
No BPD (n = 68)	.28 (.63)	.20 (.67)	.36 (.93)	.53 (1.1)	.022, .88	.44	.46	.76	.25
BPD (n = 157)	.19 (.71)	.43 (1.0)	.32 (.60)	.40 (.97)					
No ASPD (n = 95)	.28 (.65)	.32 (.95)	.56 (1.1)	.64 (1.1)	1.9, .16	.83	.80	.39	.80
ASPD (n = 130)	.27 (.71)	.18 (.45)	.12 (.25)	.48 (1.0)					
Percent heavy drinking days									
No BPD (n = 68)	2.6 (6.5)	2.2 (7.8)	3.6 (10.8)	5.1 (11.1)	.16, .68	.55	.94	.27	.64
BPD (n = 157)	2.0 (8.0)	4.4 (11.6)	2.8 (5.8)	3.5 (9.1)					
No ASPD (n = 95)	2.6 (6.9)	3.5 (11.1)	5.6 (12.7)	5.5 (11.3)	1.9, .16	.78	.89	.13	.58
ASPD (n = 130)	2.6 (7.3)	2.0 (5.2)	.91 (1.9)	4.7 (10.9)					
Average number of drinks per drinking day									

Diagnosis of personality disorder did not adversely affect alcohol outcomes; patients with ASPD or BPD did not have a poorer response to medication than patients without diagnosis of ASPD or BPD.

The findings suggest that naltrexone and disulfiram can be safely and effectively used with patients who have comorbid diagnoses of Axis I and Axis II disorders

IPOTESI DI TRATTAMENTO FARMACOLOGICO: TIPOLOGIE DI ETILISTI

- **SINDROME DA ASTINENZA (approvati):**
  - BENZODIAZEPINE (diazepam, oxazepam, lorazepam e clordiazepossido):
    - prevenzione convulsioni e delirium tremens
  - SODIO OXIBATO:
    - stessa efficacia, se non superiore, alla benzodiazepine
    - prevenzione convulsioni e delirium tremens (?)
- **SINDROME DA ASTINENZA (non approvati):**
  - BACLOFENE e PREGABALIN:
    - efficacia (?!?)
    - alcolisti epatopatici
  - GABAPENTIN:
    - efficacia inferiore alle BDZs
    - numerosi episodi pregressi di sindrome da astinenza
  - ACIDO VALPROICO:
    - efficacia inferiore alle BDZs
    - alcolisti non epatopatici

IPOTESI DI TRATTAMENTO FARMACOLOGICO: TIPOLOGIE DI ETILISTI

- **MANTENIMENTO DELL'ASTINENZA (approvati):**
  - SODIO OXIBATO:
    - alcolisti senza preclusione di tipologia
    - più efficace del disulfiram e naltrexone
    - ESTREMA CAUTELA IN
      - poli-assuntori
      - disturbi psichiatrici d'ansia e bipolari (Asse I)
      - borderline di personalità (Asse II)
  - DISULFIRAM:
    - non epatopatici gravi o con neuropatia
    - Asse I e II (disulfiram: in trattamento farmacologico per stabilità psichica?!)
  - NALTREXONE:
    - se obiettivo è la riduzione del consumo ("heavy drinkers", "binge drinkers")
    - Asse I e II
  - SODIO OXIBATO + NALTREXONE:
    - craving per sodio oxibato
    - maggior efficacia nel mantenimento astinenza (effetto sinergico); effetti collaterali (limite?)
  - NALTREXONE + DISULFIRAM:
    - non migliorano l'efficacia
    - Asse I e II (disulfram: in trattamento farmacologico per stabilità psichica?!)
  - SODIO OXIBATO + DISULFIRAM (???)
  - NALMEFENE:
    - se obiettivo è la riduzione del consumo ("heavy drinkers", "binge drinkers")

IPOTESI DI TRATTAMENTO FARMACOLOGICO: TIPOLOGIE DI ETILISTI

- **MANTENIMENTO DELL'ASTINENZA (non approvati):**
  - BABLOCFENE:
    - alcolisti cirrotici
  - TOPIRAMATO:
    - alcolisti senza preclusione di tipologia
    - lento effetto
    - numerosi effetti collaterali: minimo dosaggio efficace (?)
  - GABAPENTIN:
    - alcolisti con disturbo post-traumatico da stress
    - alcolisti con disturbi del sonno
  - ACIDO VALPROICO:
    - alcolisti con disturbo bipolare (Asse I)
  - PREGABALIN:
    - alcolisti con sindrome ansiosa (Asse I)
    - alcolisti con ostilità e psicoticismo

- Double-blind, double dummy evaluation of the efficacy of GHB versus benzodiazepine in the acute alcohol detoxification
  - (protocol GHB CR00/1 – GATE 1 Study)
- Multinational, multicentre, double-blind, placebo controlled evaluation of the efficacy of GHB in the long-term maintenance of abstinence
  - (protocol GHB CR00/2 – GATE 2 Study)
- Nalmefene efficacy study II: randomised, double-blind, placebo-controlled, parallel-group, efficacy study of 20 mg nalmefene, as needed use, in patients with alcohol dependence
  - (protocol study 12023A)

Caravaggio – Bacco

- **S.B. donna, 62, pensionata, vedova da 10 anni, una figlia**
- **AF: nonno materno alcolista, tumore intestino madre e padre**
- **APR: ipertensione arteriosa; sindrome depressiva (già prima dell'insorgenza dell'abuso di alcol)**
- **AT: ex fumatrice (sospensione 10 anni fa); alcol inizio uso età di 15 anni, abuso (circa 16-18 unità alcoliche/die di vino) da circa 14 anni, prima volta che decide di intraprendere un trattamento per PAC e non ha mai partecipato a gruppi di auto-aiuto**
- **EO: eritema del volto con congiuntive umettate; epatomegalia; PA = 180/90; FC = 65 bpm; peso: 80 kg (sovrappeso); altezza: 1.56**
- **Laboratorio: incremento MCV, GGT, GOT, GPT, trigliceridi e colesterolo**
- **CAGE: +-+-**
- **DSM-IV positivo per dipendenza**
- **CIWA-Ar: 14 punti**
- **Terapia domiciliare: Atenololo ¼ cp/die; Delorazepam 0.5 mg ½/ al bisogno ed Escitalopram 10 mg/die.**

- **-Alcover sciroppo: 10 ml x 5/die (ore 8, 12, 16, 20 e 23) per 3 gg., poi passa a 10 ml x 3/die (ore 11, 18, e 22) in mantenimento (dopo 15 gg., ridotto per insorgenza di vertigini a 7.5 x 3/die);**
- **-Atenololo 100 mg cp: ½ cp x 2/die (ore 8 e 20);**
- **-Cipralex 10 mg cp: 1 cp/die (ore 8);**
- **-Delorazepam 1 mg cp: 1/2 cp/die (ore 22);**
- **-Folina cp: 1 cp/die (ore 12) per 30 gg., poi sospende;**
- **-counselling motivazionale / CBT.**

COMPLETA ASTINENZA DA CIRCA 3 MESI

- **S.M. uomo, 42, disoccupato**
- **AF: padre etilista**
- **APR: sindrome ansiosa (Asse I); disturbo borderline di personalità (Asse II); epatite cronica HCV; pregresso dipendenza da oppiacei (sospeso uso del metadone 1 anno fa); uso saltuario di cocaina e cannabis; tabagista**
- **AT: alcol inizio uso età di 15 anni, abuso (circa 16-18 unità alcoliche/die di vino) da circa 20 anni; già trattato con disulfiram senza successo; non ha mai partecipato a gruppi di auto-aiuto**
- **EO: epatomegalia; PA = 130/80; FC = 80 bpm; peso: 75 kg; altezza: 1.80**
- **Laboratorio: incremento MCV, GGT, GOT, GPT, trigliceridi e colesterolo**
- **CAGE: ++++**
- **DSM-IV positivo per dipendenza**
- **CIWA-Ar: 20 punti**
- **Terapia domiciliare: En gtt.: 5 gtt. x 2/die.**

- **Alcover sciroppo: 10 ml x 6/die (ore 7, 10, 13, 16, 19 e 22) per 3 gg., poi passa a 10 ml x 3/die (ore 7, 13, e 19) in mantenimento e poi sospeso 2 giorni prima della dimissione e sostituito con Baclofene 10 mg x 3/die (ore 8, 16 e 20);**
- **Idratazione con 2000 cc/24 h per 3 gg.;**
- **Tiamina 100 mg fl. i.m.: 1 fl/die per 3 gg., poi 300 mg/die per os;**
- **Lyrica 75 mg cp: 1 cp x 3/die (ore 8, 16 e 20);**
- **riaffidato al Ser.T. per continuare terapia (gruppi AA? terapia epatite cronica HCV?)**