National Conference of the Association for Addictive Diseases of the Czech Medical Association, Špindlerův Mlýn, April 25- 29, 2010

GABAergic medications in the treatment of alcohol addiction: Role of GHB and Baclofen

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DIPARTIMENTO POLITICHE ANTIDROGA

0145-6008/05/2902-0248$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 29, No. 2
February 2005

Safety and Efficacy of GABAergic Medications for Treating Alcoholism

Bankole A. Johnson, Robert M. Swift, Giovanni Addolorato, Domenic A. Ciraulo, and Hugh Myrick

This article highlights the proceedings of a symposium presented at the 27th Annual Scientific Meeting of the Research Society on Alcoholism in Vancouver, British Columbia, Canada, June 29, 2004. The organizers and co-chairs were Bankole A. Johnson, MD, PhD, and Robert M. Swift, MD, PhD. The presentations included (1) Introduction, by Bankole A. Johnson; (2) Safety, Tolerability, and Efficacy of γ-Hydroxybutyric Acid and Baclofen in the Treatment of Alcohol Addiction, by Giovanni Addolorato; (3) Safety of Gabapentin in Treating Alcoholism, by Hugh Myrick; (4) New Data on the Safety and Effectiveness of Topiramate in the Treatment of Alcohol Dependence, by Bankole A. Johnson; (5) Evaluating the Risk of Benzodiazepine Prescription to Alcohol-Dependent Individuals, by Domenic A. Ciraulo; and (6) Safety and Efficacy of GABAergic Agents in Treating Alcoholics: Discussion, by Robert M. Swift.

Key Words: Alcoholism, Alcohol Withdrawal, Craving, γ-Aminobutyric Acid, Topiramate.

This presentation will review the clinical studies focused on:

- Gamma Hydroxybutiric Acid (GHB)

- BACLOFEN

GAMMA HYRDOXYBUTYRIC ACID (GHB) ($C_4H_8O_3$)

IT IS A SHORT-CHAIN 4-CARBON FATTY ACID PHISIOLOGICALLY PRESENTS IN THE HYPOTHALAMUS AND BASAL GANGLIA

Snead OC III. N Engl J Med 2005

Gamma Hydroxybutiric Acid (GHB)

- It interpheres with the brain activity of some neurotransmitter systems

  Gessa et al. J Neurochem 1968; Maitre. Prog Neurobiol 1997

- It shares several similarities with the pharmacological profile of ethanol

  Colombo et al. Physiol Behav 1998; Poldrugo & Addolorato. Alcohol Alcohol 1998

- It is effective both in inhibiting ethanol consumption and in suppressing ethanol withdrawal syndrome in rats

  Fadda et al. Alcohol Alcohol 1998; Gessa et al. Alcohol 1998

Gamma Hydroxybutiric Acid (GHB)

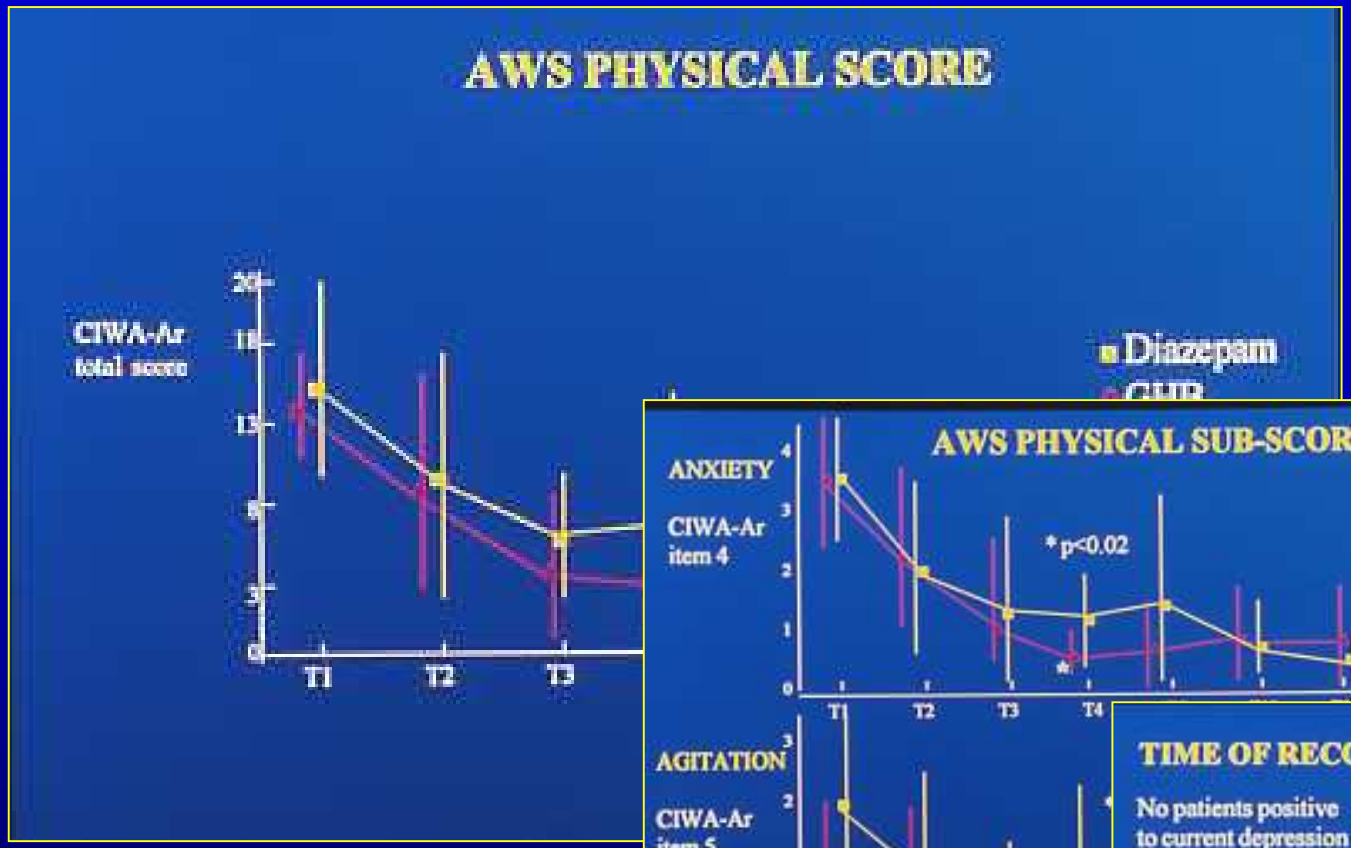
- In the US, through a limited distribution program, the FDA approved GHB (Xerem ®) as a Schedule III Controlled Substance, to treat a small subset of patients with narcolepsy who have episodes of weak or paralyzed muscles (i.e., cataplexy).

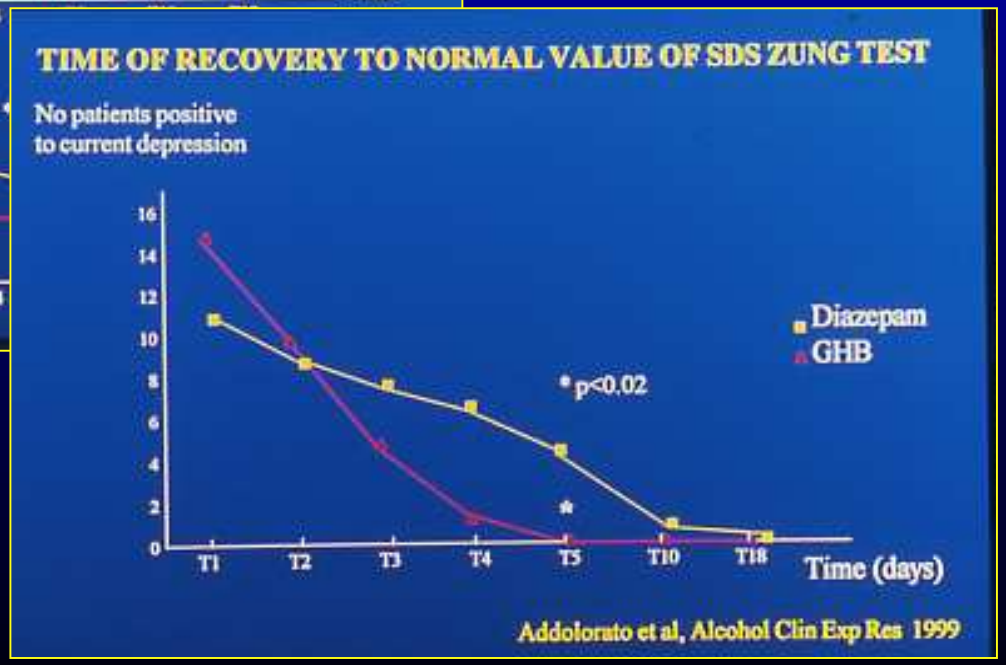
- In Italy and Austria, GHB (Alcover ®) is approved for the treatment of alcohol dependence

GHB in the treatment of alcohol dependent individuals

- **ALCOHOL WITHDRAWAL SYNDROME**
- **MAINTAINING ALCOHOL ABSTINENCE**

GHB vs Diazepam

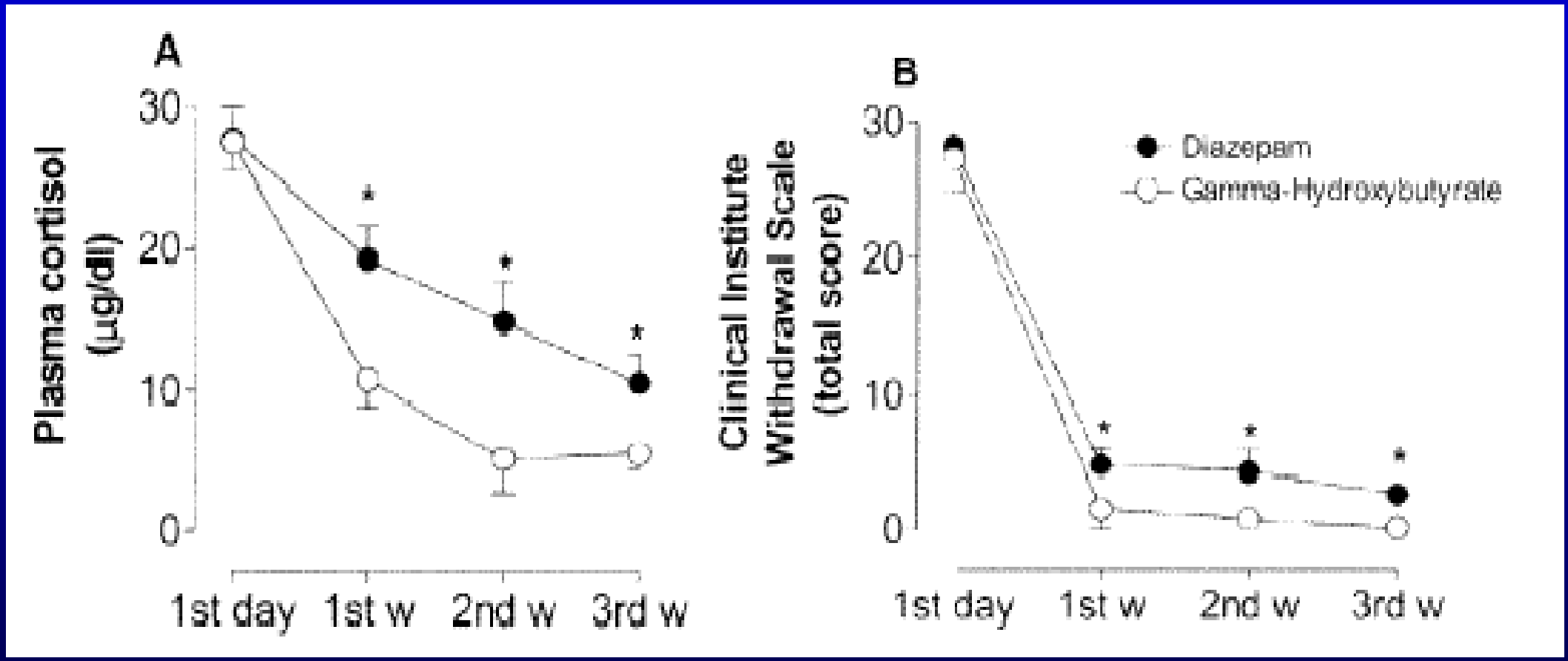




Diazepam 0.5-0.75 mg/kg body weight
GHB 50 mg/kg body weight

Addolorato et al, Alcohol Clin Exp Res, 1999

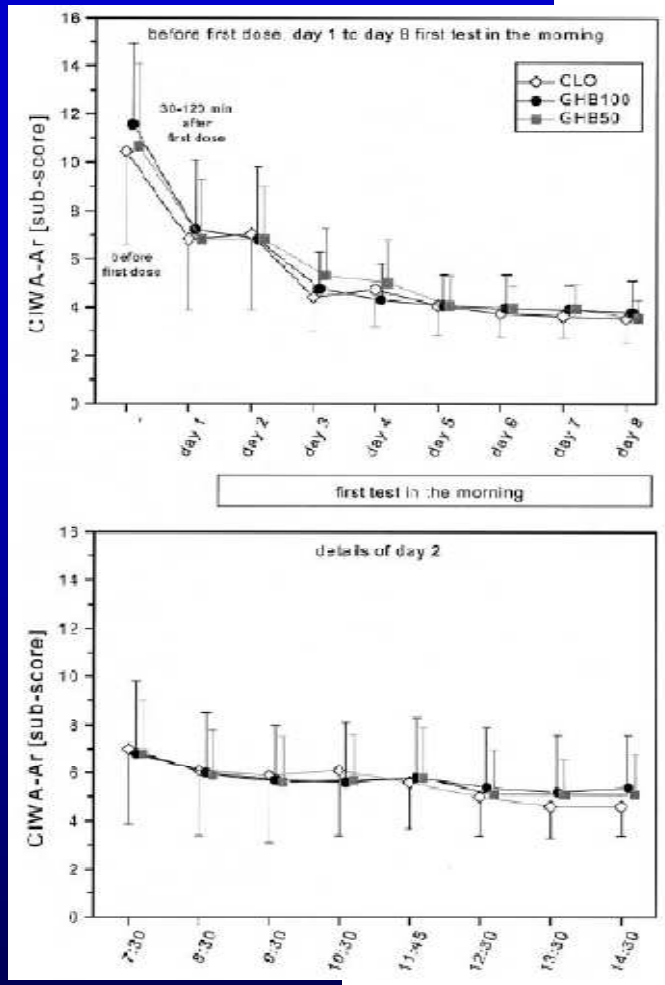
GHB vs Diazepam



Diazepam 0.5 mg/kg body weight
GHB 50 mg/kg body weight

Nava et al. Am J Drug Alcohol Abuse 2007

Alcohol & Alcoholism Vol. 37, No. 1, pp. 67–73, 2002



DOUBLE-BLIND CONTROLLED TRIAL OF γ-HYDROXYBUTYRATE AND CLOMETHIAZOLE IN THE TREATMENT OF ALCOHOL WITHDRAWAL

AMANDA A. NIMMERRICHTER*, HENRIETTE WALTER[1], KARIN E. GUTIERREZ-LOBOS[1] and OTTO M. LESCH[1]

Anton-Proksch-Institute, Vienna and [1]Department of Psychiatry, University Clinic, Vienna, Austria

(*Received* 24 *July* 2000; *in revised form* 25 *May* 2001; *accepted* 19 *July* 2001)

	Group					
	GHB_{50}		GHB_{100}		CLO	
	No. of patients	No. of complaints	No. of patients	No. of complaints	No. of patients	No. of complaints
Vertigo	9	17	17	32	7	9
Rhinitis	2	2	3	3	1	1
Nausea	1	1	2	2	0	0
Diarrhoea	4	4	3	3	3	3
Total	16		25		14	

Nimmerrichter et al. Alcohol Alcohol 2002

GHB

ALCOHOL WITHDRAWAL SYNDROME

50 – 100 mg / kg / day orally for 6-10 days

fractioned into 3 or 6 daily doses

i.e.: patient with 70 kg of body weight

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

Gallimberti et al. Lancet 1989
Addolorato et al. Alcohol Clin Exp Res 1999
Nimmerrichter et al. Alcohol Alcohol 2002
Korniger & Lesch. Acta Med Austriaca 2003
Nava et al. Am J Drug Alcohol Abuse 2007

GHB in the treatment of alcohol dependent individuals

- **ALCOHOL WITHDRAWAL SYNDROME**
- **MAINTAINING ALCOHOL ABSTINENCE**

GHB EFFICACY IN ALCOHOLISM THERAPY

Short-term GHB administration studies:

- efficacy in increasing the number of abstinent days and reducing the number of daily drinks in alcoholics

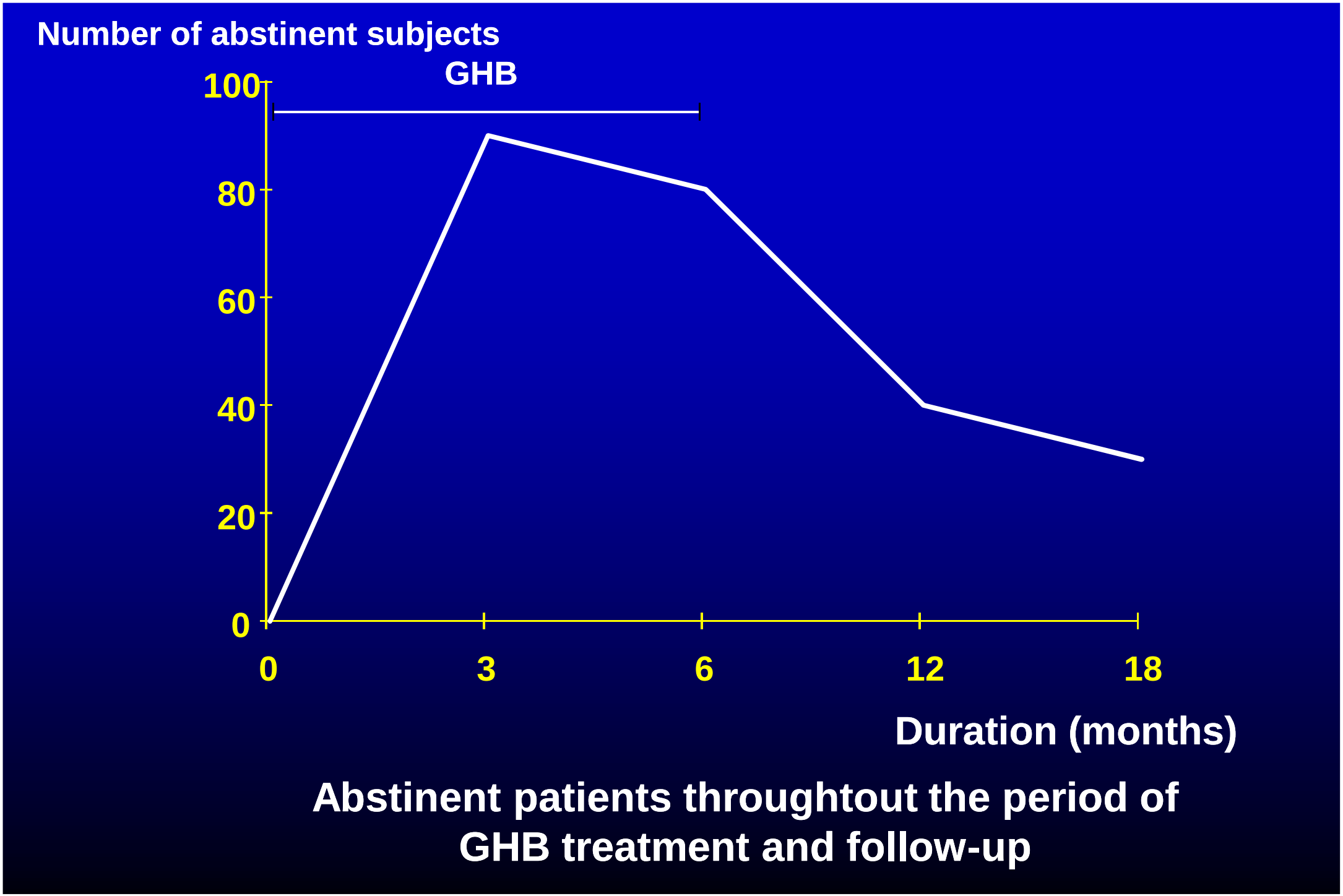
Gallimberti et al. Alcohol Clin Exp Res 1992

Medium-term GHB administration studies:

- 179 alcohol dependent patients treated (50 mg/kg/day on 6 months)
- 109 completed the study (60.9%); totally abstinent: 84 (78%)
- GHB abuse: 11 (10.2%); 6-7 times the dose

		Craving score		
Patients	*n*	Start	End	
Total sample	109	9.01±2.64	3.72±2.84	<0.001
Abstinent	84	9.16±2.71	3.09±2.53	<0.001
Not abstinent	25	8.51±2.32	5.75±2.95	<0.001

Addolorato et al. Alcohol Alcohol 1996



Abstinent patients throughtout the period of GHB treatment and follow-up

GHB reduces Alcohol Intake and Craving

Comparing treatments of alcoholism on craving and biochemical measures of alcohol consumptions

Felice Nava, M.D., Ph.D.[a], Stefania Premi[b], M.D., Ezio Manzato, M.D.[c], Alfio Lucchini, M.D.[d]

	T0			T1		
	GHB group	NTX group	DSF group	GHB group	NTX group	DSF group
All patients that completed the trial						
	n = 22	n = 18	n = 19	n = 22	n = 18	n = 19
AI	11.3 ± 2.8	10.5 ± 2.9	10.5 ± 2.8	0.6 ± 1.3*	0.8 ± 1.4*	0.9 ± 1.3*
ACS	8.2 ± 1.3	7.3 ± 1.1	7.8 ± 0.9	1.7 ± 0.7*[a]	3.6 ± 1*	3.1 ± 0.8*
MCV (fl)	97.1 ± 1.6	97.5 ± 2	97.7 ± 1.9	85.3 + 4.7*[b]	92.2 ± 4.5*	92.2 ± 3.6*
GGT (U/l)	96.3 ± 13.2	97.1 ± 8.1	96.3 ± 15.5	24.4 ± 3.8*[c]	32.4 ± 10*	38 ± 9.2*
AST (U/l)	45.9 ± 9.2	42.3 ± 5.6	48.1 ± 9.2	25.1 ± 7.3*[d]	32.6 ± 4.6*	33.6 ± 5.5*
ALT (U/l)	44.1 ± 10.4	46.7 ± 8.9	47.6 ± 7.3	22.2 ± 3.3*[e]	36.5 + 7.3*	38.6 + 5.1*

Nava et al. J. Psychoactive Drugs 2006

GHB EFFICACY IN ALCOHOLISM THERAPY

- **The rate of non-responders to GHB is 30-40%**

- **In most studies the drug (50 mg/kg) was divided into 3 daily administrations**

- **The half-life of GHB is relatively short**

Ferrara et al. Br J Clin Pharmacol 1992

- **Non-responder to GHB could benefit from a greater fractioning of the dose and we tested this hypothesis**

GHB FRACTIONING EFFICACY

- 119 alcoholic patients enrolled
- Phase 1 (8 weeks) 50 mg/kg x 3/day per os
- Phase 2 (following 8 weeks)
  - abstinent patients: same dose at same intervals
  - not abstinent patients: same dose fractioned in 6 times/day

- drop-out: 28 (23.5%)

• 91 Phase 1

- 66 (72.5%) abstinent

- 25 (27.5%) not-abstinent

Phase 2

- 19 (76%) abstinent

- GHB abuse: none

Addolorato et al. Lancet 1998

The alcohol craving score of subjects treated with GHB

		Craving score Phase 1			Craving score Phase 2		
Patients	***n***	**Start**	**End**	***P***	**Start**	**End**	***P***
Whole group	**91**	**10.4±3.1**	**3.8±2.1**	**<0.001**	**3.8±2.1**	**2.0±1.9**	**<0.005**
Group A	**66**	**10.6±2.9**	**1.6±1.9**	**<0.001**	**1.6±1.9**	**1.7±1.8**	**ns**
			<0.001			**ns**	
Group B	**25**	**9.7±3.2**	**5.7±3.1**	**<0.005**	**5.7±3.1**	**1.9±1.4**	**<0.005**
			<0.001				

Group A: subjects treated with GHB 3 times/day both in the first 8 weeks (phase 1) and in the second 8 weeks (phase 2); Group B: subjects not abstinent throughout phase 1 with GHB 3 times/day and treated with GHB 6 times/day in phase 2.

Addolorato et al. Lancet 1998

INTERIM SUMMARY

- The administration of GHB 6 times/day led to the abstinence in a great percentage of non-responders
- The increase division of GHB can induce a significant reduction in craving (intervals: 4 hr)
- These findings could be related to the short half-life of the drug

Addolorato et al. Lancet 1998

- We confirmed our observation in a large number of patients

Addolorato et al. Drug Alcohol Depend 1998

- Our data have been confirmed

in animals — Agabio et al. Alcohol Alcohol 1998

in humans — Maremmani et al. Alcoholism 1998

GHB

MANTAINANCE OF ABSTINENCE

50 mg / kg / day orally for 3-6 months

fractioned into 3-6 daily doses

i.e.: patient with 70 kg of body weight

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

Gallimberti et al. Lancet 1989
Addolorato et al. Alcohol Alcohol 1996
Addolorato et al. Drug Alcohol Depend 1998
Maremmani et al. J Psychactive Drugs 2001
Addolorato et al. Expert Opin Investig Drugs 2009

GHB vs NTX

GHB 50 mg/kg body weight/day
NTX 50 mg/day

ELSEVIER

Drug and Alcohol Dependence 70 (2003) 85–91

DRUG and ALCOHOL DEPENDENCE

www.elsevier.com/locate/drugalcdep

Gamma-hydroxybutyric acid versus naltrexone in maintaining alcohol abstinence: an open randomized comparative study

F. Caputo [a,*], G. Addolorato [b], F. Lorenzini [a], M. Domenicali [a], G. Greco [c], A. del RE [a], G. Gasbarrini [b], G.F. Stefanini [d], M. Bernardi [a]

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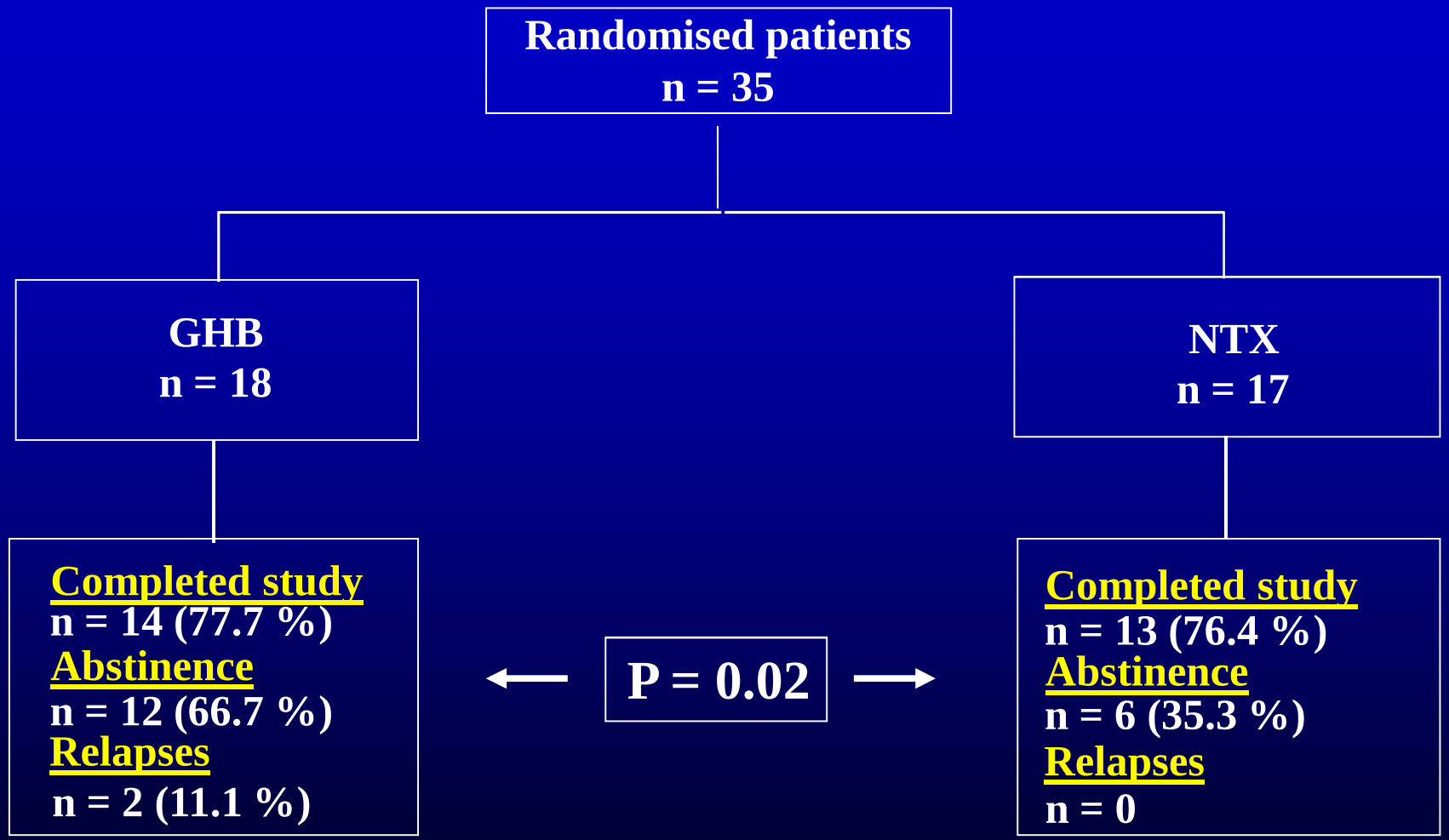
Received 6 August 2002; received in revised form 8 November 2002; accepted 14 November 2002

Abstract

Maintaining abstinence from alcohol is the main goal in the treatment of alcohol dependence. Naltrexone (NTX) and γ-hydroxybutyric acid (GHB) have proved able to maintain alcohol abstinence in alcoholic subjects. The aim of our study was to evaluate the efficacy of GHB compared with NTX in maintaining abstinence from alcohol after 3 months of treatment. A total of 35 alcohol-dependent outpatients were randomly enrolled in two groups: the GHB group consisted of 18 patients treated with oral doses of GHB (50 mg/kg of body weight t.i.d) for 3 months; the NTX group consisted of 17 patients treated with oral doses of NTX (50 mg/day) for 3 months. At the end of the study, a statistically significant difference ($P = 0.02$) was found in the number of abstinent patients between the GHB and the NTX groups. In patients who failed to be abstinent, no relapses in heavy drinking were observed in the NTX group, while in the GHB group all patients relapsed. The results of the present study show that GHB is more effective than NTX in maintaining abstinence from alcohol in a short-term treatment period; on the other hand, NTX confirmed its ability to reduce alcohol relapses.

Keywords: Pharmacotherapy; γ-Hydroxybutyric acid; Naltrexone; Maintaining abstinence from alcohol

GHB vs NTX


Randomised patients
n = 35
GHB
n = 18
NTX
n = 17
Completed study
n = 14 (77.7 %)
Abstinence
n = 12 (66.7 %)
Relapses
n = 2 (11.1 %)
P = 0.02
Completed study
n = 13 (76.4 %)
Abstinence
n = 6 (35.3 %)
Relapses
n = 0

GHB plus Naltrexone

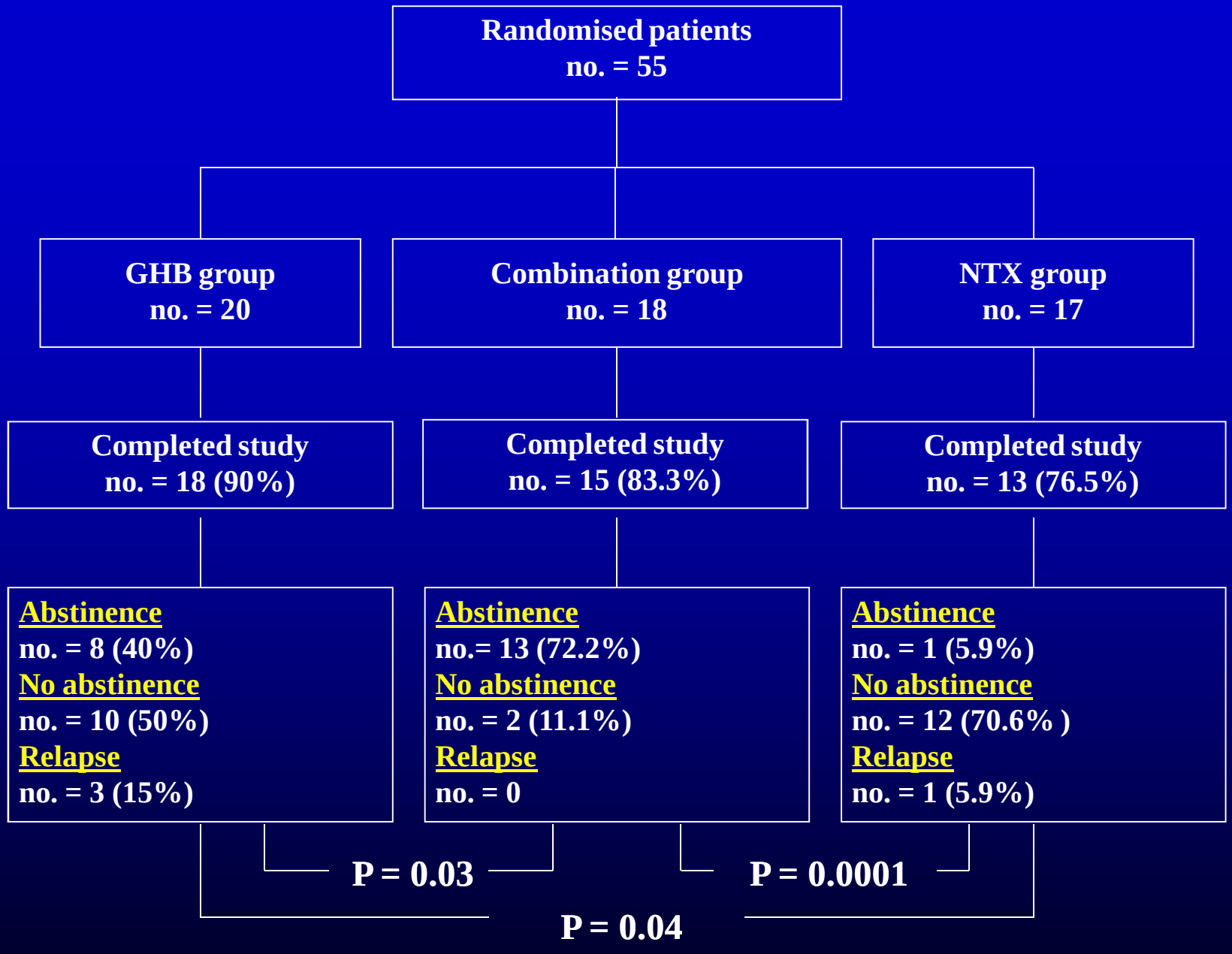
The association between GHB + NTX increase the efficacy of both drugs and reduce the risk of GHB abuse

European Neuropsychopharmacology (2007) 17, 781–789

www.elsevier.com/locate/euroneuro

Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: An open randomised comparative study

Fabio Caputo [a,b,*,1], Giovanni Addolorato [c], Michela Stoppo [a], Sara Francini [a], Teo Vignoli [a], Francesca Lorenzini [a], Arfedele Del Re [b], Claudio Comaschi [b], Pietro Andreone [a], Franco Trevisani [a], Mauro Bernardi [a], Alcohol Treatment Study Group [2]


Randomised patients
no. = 55
GHB group
no. = 20
Combination group
no. = 18
NTX group
no. = 17
Completed study
no. = 18 (90%)
Completed study
no. = 15 (83.3%)
Completed study
no. = 13 (76.5%)
Abstinence
no. = 8 (40%)
No abstinence
no. = 10 (50%)
Relapse
no. = 3 (15%)
Abstinence
no.= 13 (72.2%)
No abstinence
no. = 2 (11.1%)
Relapse
no. = 0
Abstinence
no. = 1 (5.9%)
No abstinence
no. = 12 (70.6%)
Relapse
no. = 1 (5.9%)
P = 0.03
P = 0.0001
P = 0.04

GHB ABUSE AND DEPENDENCE IN ALCOHOLICS

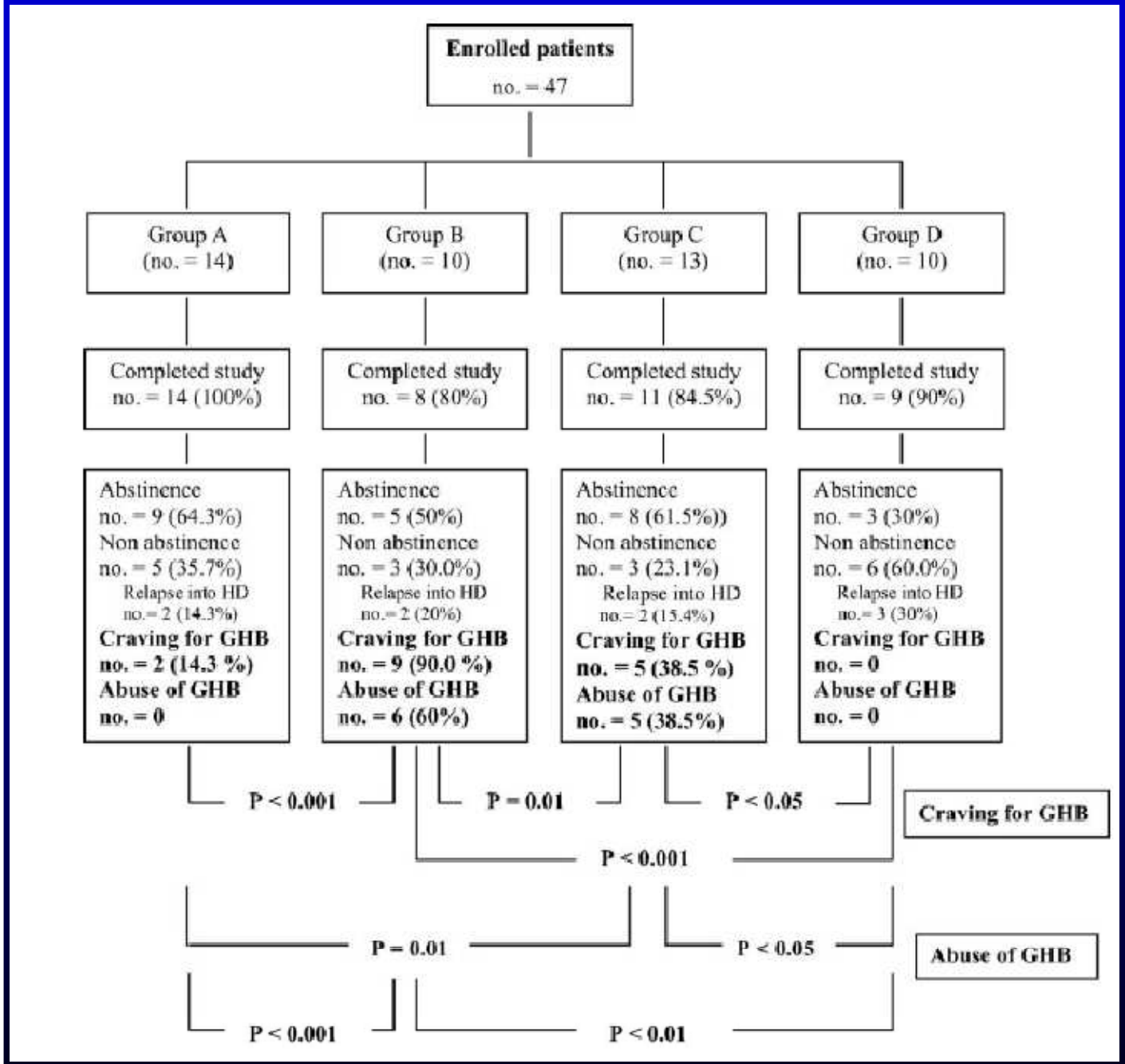
- A craving development for the drug was reported

- From 10% to 15% of patients abused of GHB (6-7 times the dose)
  - psychotropic effects
  - temporary reduction in craving

Addolorato et al. Alcohol Alcohol 1996
Gallimberti et al. Alcohol 2000

- No case of GHB abuse/dependence was reported with the greater fractioning

Addolorato et al. Lancet 1998
Addolorato et al. Drug Alcohol Depend 1998
Maremmani et al. Alcoholism 1998



Subgroups of alcoholics at risk of GHB abuse

A: pure alcoholics

B: alcoholics with a sustained full remission from cocaine dependence

C: alcoholics with a sustained full remission from heroin dependence

D: alcoholics with heroin dependence in a methadone maintainance treatment

Caputo et al. J Psychopharmacol 2009

GHB ABUSE IN NON-ALCOHOLICS

- In 1990, GHB appeared in the U.S. on the commercial market
- by November 1990, 57 cases of GHB poisoning were reported

FDA. JAMA 1991

- FDA issued a ban which removed GHB from the market
- GHB continued to be illegaly produced and sold

Carter et al. Morb Mortal Wkly Rep 1997

GHB ABUSE IN NON-CLINICAL SELF ADMINISTRATION

- inappropriate use in body-builders — Takahara et al. JCEM 1977
- used as diet aid — Tunnicliff et al. Toxicol Clin Toxicol 1997
- to treat insomnia — Chin et al. West J Med 1992
- as an euphoriant and as a recreational drug — Louagie et al. Toxicol Clin Toxicol 1997
- in the U.S. and U.K. it is sold clandestinetely — Anonymous. Druglink 1994

- names :

LIQUID ECSTASY

SALTY WATER

GRIEVOUS BODILY HARM

SOAP

G-RIFFICK

GEORGIA HOME BOY

LIQUID X

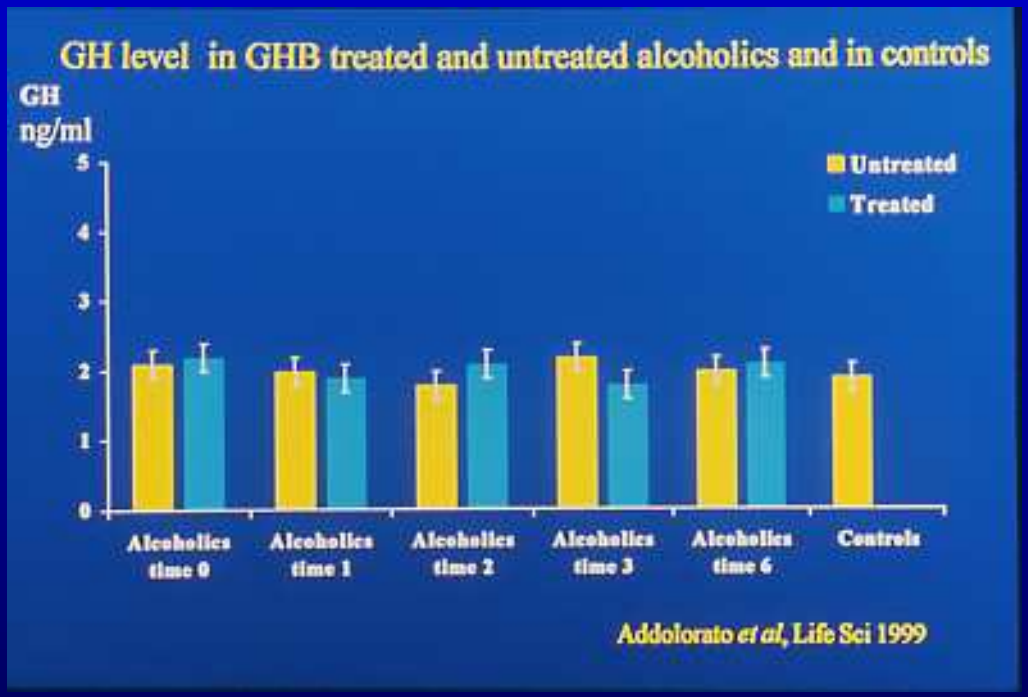
CHERRY MENT

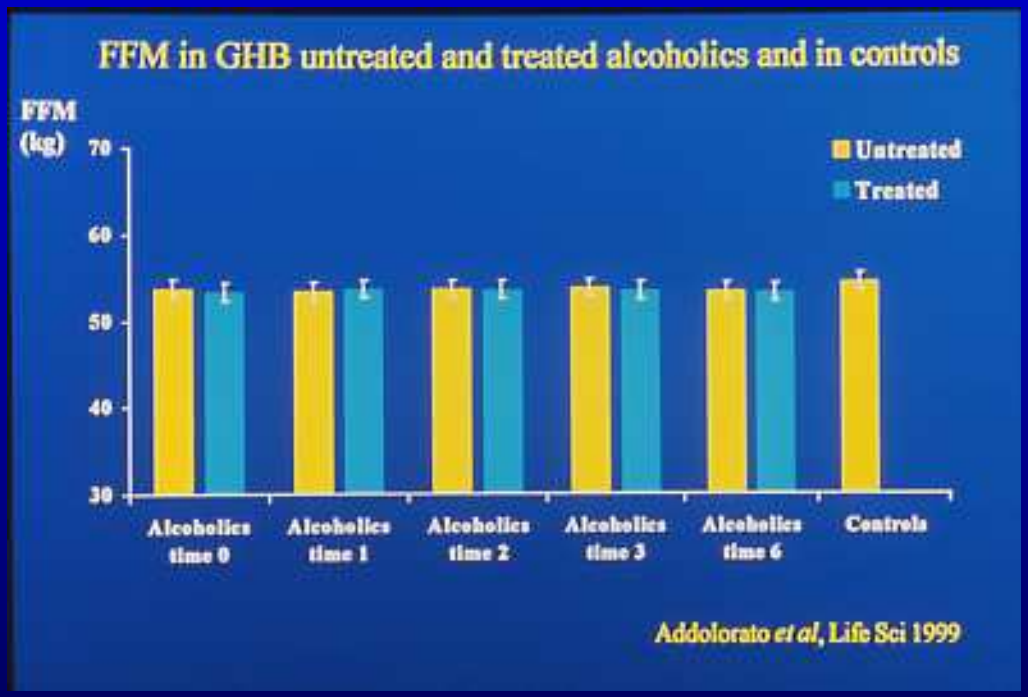
- Doses of 2.5 g to 30 g
- in a single administration
- alone or associated with other recreational drugs

Marwick. JAMA 1997

GHB and body composition in alcoholisc

• In alcoholics, long-term administration of therapeutic doses of GHB did not influence GH release and body composition





• The lack of anabolic effects in alcoholics suggest a further general safety of the drug in the treatment of alcohol addiction

Addolorato et al. Life Sci 1999

Summary

In alcoholism

- GHB is effective in alcoholism therapy: rationale like methadone in heroin addiction

  Colombo & Gessa. Addict Biol 2000

- Cases of craving for GHB with abuse and possible dependence may occur during treatment

  Addolorato et al. Addiction 1997

- These observations support the similarity between GHB and alcohol

  Colombo et al. Physiol Behav 1998

- GHB must be used under strict medical surveillance

  Addolorato et al. Alcohol 2000

Summary

In alcoholism

- In non-responders: increase the fractioning, not the dose

Addolorato et al. Lancet 1998

- GHB dependence does not occurr at the therapeutic dosage

Addolorato et al. Drug Alcohol Depend 2005

- GHB abuse appears to be a limited phenomenon that should not undetermine its medical use….

Colombo & Gessa. Addict Biol 2000

….at least in “pure alcoholics”; it shoud be avoided in some subgroups of alcoholic patients

Caputo et al. J Psychopharmacol 2009

Summary

GHB abuse in other conditions (non clinical self-administration)

- higher risk in some countries in which the use of GHB is increasing for its euphoric and anabolic effects (UK, USA)

- the GHB utilised is synthetised in undergound uncontrolled laboratories; the GHB concentration in the bottle can greatly vary (3 to 20 g)

  Louagie et al. Clin Toxicol 1997

- the danger of GHB toxicity, overdose and dependence may be greater

- the abuse of GHB mainly occurs acutely in a single self administration

Summary

These observations may justify:

- the different severity of the side effects related to GHB abuse;
- the different severity of the symptoms at the abrupt GHB suspension

- in subjects who use GHB for alcoholism therapy

Gallimberti et al. Lancet 1989; Alcohol Clin Exp Res 1992;

Addolorato et al. Alcohol Alcohol 1996; Alcohol Clin Exp Res 1997

- in subjects who take the "street version"

Chin et al. West J Med 1992;

Galloway et al. Lancet 1994; Addiciton 1997;

Carter et al. Morb Mortal Wkly rep 1997;

Marwick. JAMA 1997;

Louagie et al. Toxicol Clin Toxicol 1997;

Thomas et al. BMJ 1997

GHB, $GABA_B$ and GHB receptors

- There is evidence that GHB might have GABA-mimetic effects *in vivo*

  Hosli et al. Neurosci Lett 1983

- GHB might act at $GABA_B$ receptors both directly as a partial agonist and indirectly through GHB-derived GABA

  Wong et al. Trends Pharmacol Sci 2004

- A GHB receptor has been cloned and characterized in both rat and human brain

  Andriamampandry et al. FASEB J 2003; FASEB J 2007

- GHB receptors have large functional (and probably structural) homologies with the $GABA_B$ receptors.

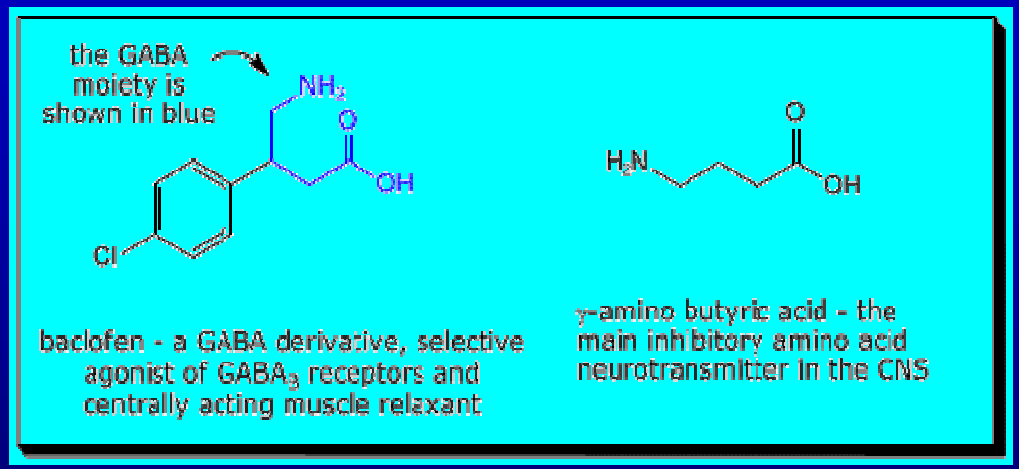
  Kemmel et al. Neurosci Lett 1983J Comp Neurol 2006

…..moving forward….

- **There is evidence that GHB might have GABA-mimetic effects *in vivo*.**
- **GHB might act at $GABA_B$ receptors both directly as a partial agonist and indirectly through GHB-derived GABA.**
- **A GHB receptor has been cloned and characterized in both rat and human brain.**
- **GHB receptors have large functional (and probably structural) homologies with the $GABA_B$ receptors. However, GHB receptors are able to bind GHB and some structurally related analogs, but not GABA.**

Baclofen

β-(4-chlorophenyl)-γ-aminobutyric acid



$GABA_B$ receptor agonist, FDA-approved for spasticity

Davidoff RA. Ann Neurol 1985

BACLOFEN AND RELAPSE PREVENTION

- *in animal models*

- **daily alcohol intake in alcohol-experienced rats**

  Colombo et al. Alcohol Clin Exp Res 2000

- **extra-amount of alcohol consumed after a period of abstinence**

  Colombo et al. Drug Alcohol Dep 2003

- **motivational properties of alcohol**

  Colombo et al. Psychopharmacology 2003

- **self-administration of alcohol**

  Liang et al. Neuropharmacology 2006
  Walker & Koob. Alcohol Clin Exp Res 2007

- **severity of ethanol withdrawal**

  Colombo et al. Alcohol Clin Exp Res 2000
  Knapp et et al. Alcohol Clin Exp Res 2007

Baclofen in open-label clinical studies

0145-6008/00/2401-0067$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH
Vol. 24, No. 1
January 2000

Ability of Baclofen in Reducing Alcohol Craving and Intake: II—Preliminary Clinical Evidence

Giovanni Addolorato, Fabio Caputo, Esmeralda Capristo, Giancarlo Colombo, Gian Luigi Gessa, and Giovanni Gasbarrini

0145-6008/04/2810-1517$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH
Vol. 28, No. 10
October 2004

Baclofen for Alcohol Dependence: A Preliminary Open-Label Study

Barbara A. Flannery, James C. Garbutt, Meghan W. Cody, William Renn, Kathy Grace, Michael Osborne, Ken Crosby, Mary Morreale, and Amy Trivette

DOUBLE BLIND STUDY

- 39 subjects affected by current alcoholism (DSM IV)
  - 20 (51.3%) baclofen
  - 19 (48.7%) placebo
- Baclofen (30 mg/day) or placebo administered per os for 4 weeks
- Outpatients control: at the start (T0) and every control (T1-T4)
  - abstinence: markers and counselling (patient and relatives)
  - self-reported drinks consumed per day
  - craving: OCDS
  - State anxiety: STAY test
- Supportive therapy: AA

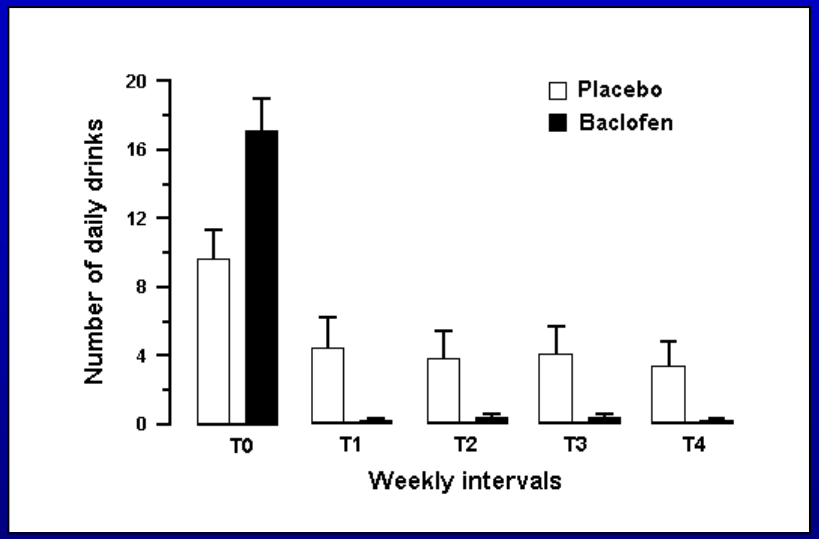
Addolorato et al. Alcohol Alcohol 2002

RESULTS

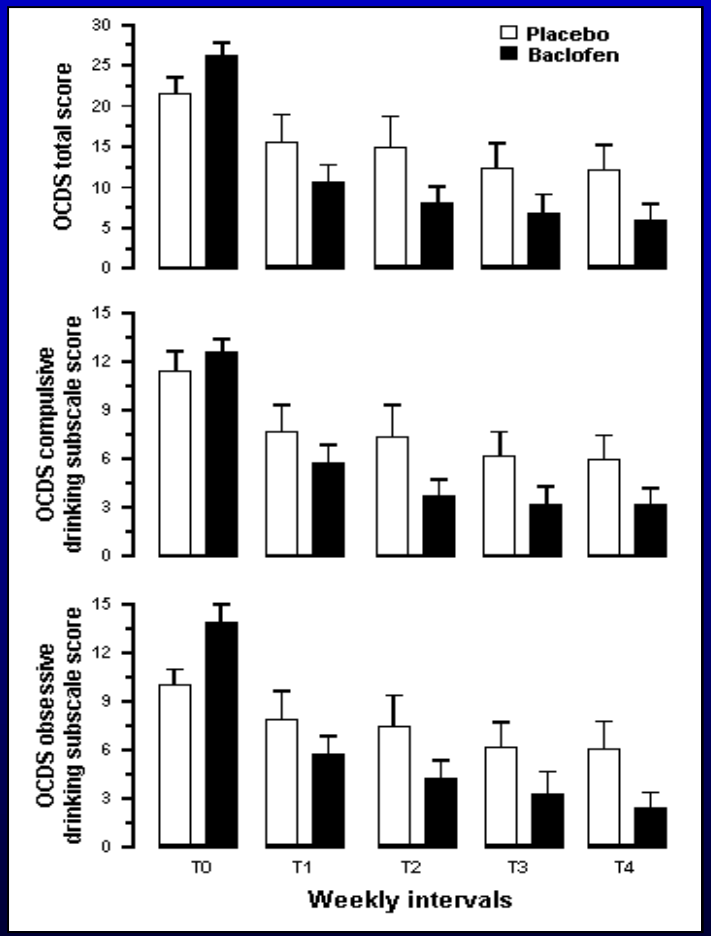
- **Drop-out:**
  - **baclofen 3 (15.0%)**
  - **p = 0.06**
  - **placebo 8 (42.1%)**
- **Completed the study**
  - **baclofen 17 (85.0%)**
  - **p = 0.06**
  - **placebo 11 (57.9%)**
- **Totally abstinent**
  - **baclofen 14 (70.0%)**
  - **p < 0.005**
  - **placebo 4 (21.1%)**
- **CAD**
  - **baclofen 19.6 ± 2.6**
  - **p < 0.005**
  - **placebo 6.3 ± 2.4**

DOUBLE BLIND STUDY

Effective to suppress alcohol intake and to reduce alcohol craving



ANCOVA results
$F_{treat}(1,78)=10.71$
$p<0.005$



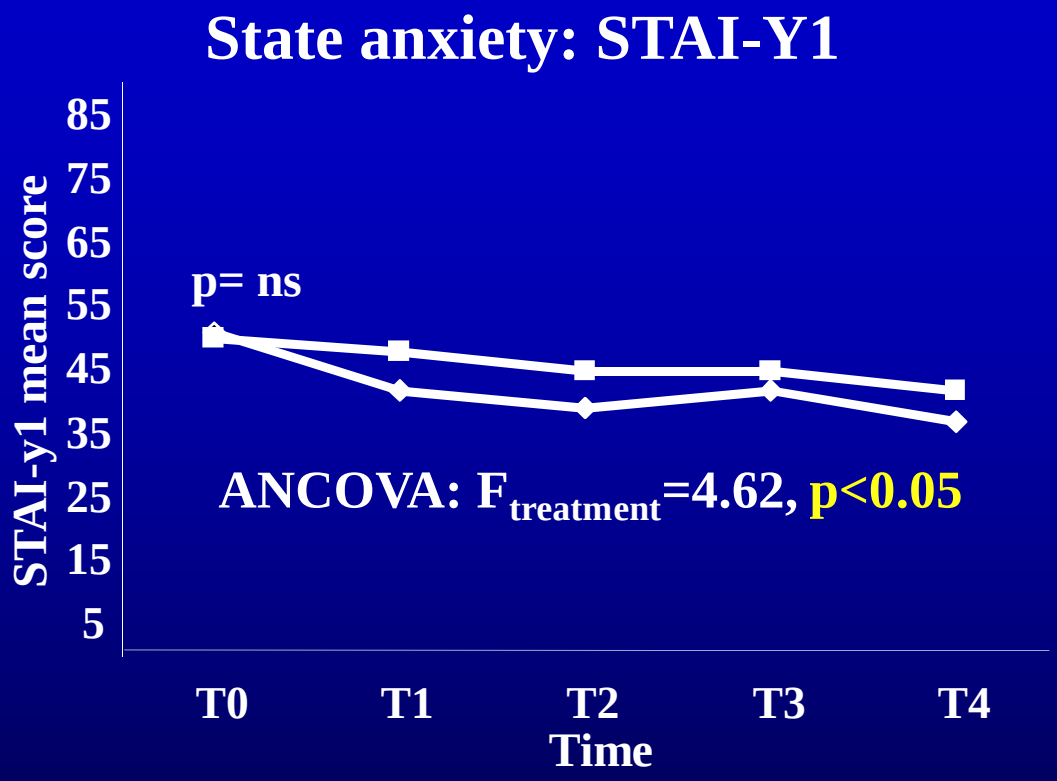
ANCOVA results
$F_{treat}(1,78)=5.65$
$p<0.05$

ANCOVA results
$F_{treat}(1,78)=4.60$
$p<0.05$

ANCOVA results
$F_{treat}(1,78)=5.06$
$p<0.05$

Addolorato et al, Alcohol Alcohol 2002

Baclofen efficacy in reducing state anxiety



Addolorato et al. Alcohol Alcohol 2002

Baclofen efficacy in reducing state anxiety

- This result is probably related to the ability of baclofen to achieve both a rapid detoxification and a decrease in craving, resulting in a rapid reduction of physical and psychological symptoms

- This is consistent with the data suggesting that craving and anxiety are supposed to share common mechanisms

Swift & Stout. J Subst Abuse 1992

Review TRENDS in Pharmacological Sciences Vol.26 No.1 January 2005

Don't worry 'B' happy!: a role for $GABA_B$ receptors in anxiety and depression

John F. Cryan and Klemens Kaupmann

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GABA, the main inhibitory neurotransmitter in the brain, regulates many physiological and psychological processes. Thus, dysfunction of the GABA system is implicated in the pathophysiology of several neuropsychiatric disorders, including anxiety and depression. However, the role of $GABA_B$ receptors in behavioural processes related to these disorders has not been resolved. $GABA_B$ receptors are G-protein-coupled receptors that function as heterodimers of $GABA_{B(1)}$ and $GABA_{B(2)}$ subunits. In addition to highly selective agonists and antagonists, novel $GABA_B$ receptor tools have been developed recently to further assist elucidation of the role of $GABA_B$ receptors in CNS function. These include mice that lack functional $GABA_B$ receptors, and novel positive modulators of the $GABA_B$ receptor. In this review, we discuss evidence that points to a role of $GABA_B$ receptors in anxiety and depression.

development of novel pharmacological and genetic tools that have advanced knowledge on the role of $GABA_B$ receptors in emotional disorders such as anxiety and depression.

$GABA_B$ receptors

The first $GABA_B$ receptor cDNAs were isolated in 1997 [6]. The identification of a second $GABA_B$ receptor protein soon after led to the discovery that native $GABA_B$ receptors are heterodimers of two subunits, $GABA_{B(1)}$ and $GABA_{B(2)}$ (Figure 1) (reviewed in [7,8]). In the brain, two predominant, differentially expressed isoforms are transcribed from the *Gabbr1* gene, $GABA_{B(1a)}$ and $GABA_{B(1b)}$, which are conserved in different species including humans [6,9,10]. In the rat brain $GABA_{B(1a)}$ is the prevalent isoform at birth whereas $GABA_{B(1b)}$ is more abundant in adult brain tissue [9]. Transcription of these isoforms is driven by different promoters and does not

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Alcohol 43 (2009) 559–563

ALCOHOL

Role of the $GABA_B$ receptor system in alcoholism and stress: focus on clinical studies and treatment perspectives

Giovanni Addolorato[a,*], Lorenzo Leggio[a,b], Silvia Cardone[a], Anna Ferrulli[a], Giovanni Gasbarrini[a]

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Received 17 December 2008; received in revised form 6 May 2009; accepted 12 August 2009

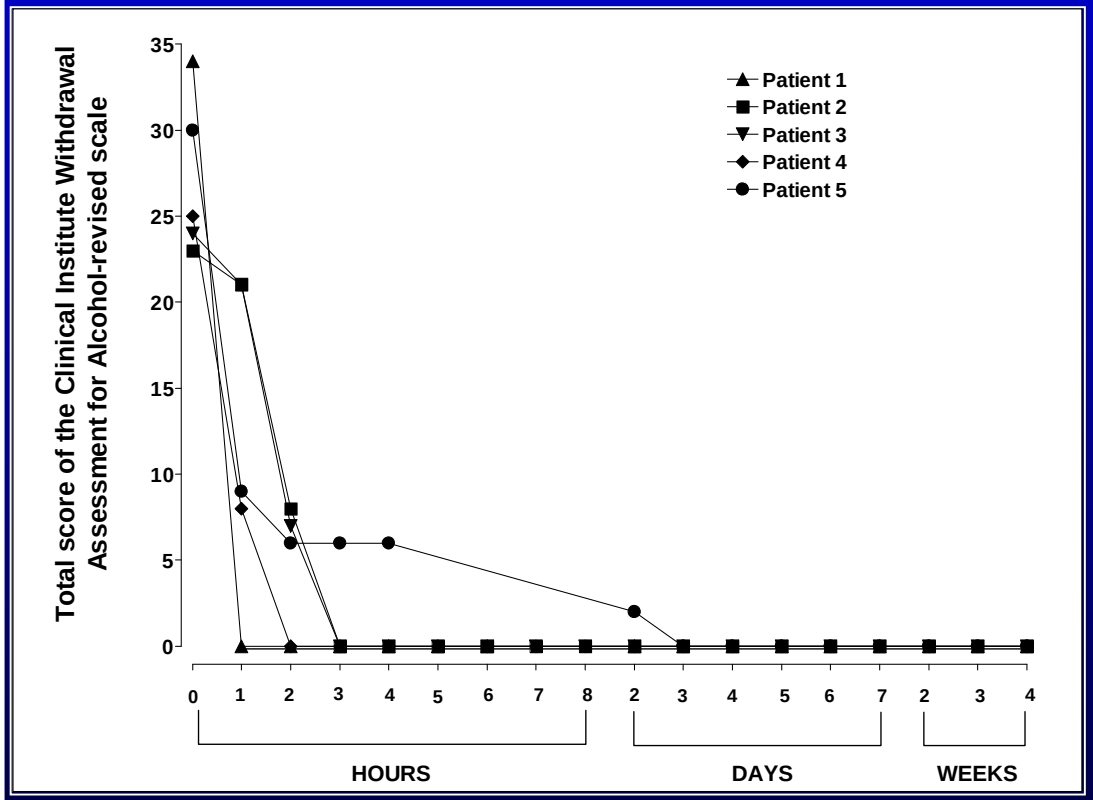
Abstract

Alcoholism and stress share some common neurobiological circuits, including the GABAergic system. In particular, the $GABA_B$ receptor seems to play an important role. The $GABA_B$ receptor agonist baclofen has been studied as a treatment for alcohol-dependent subjects. Baclofen administration in alcohol-dependent patients was able to promote abstinence, inducing the remission of withdrawal symptoms, reducing alcohol craving, and reducing alcohol intake. Baclofen also reduced anxiety in alcohol-dependent subjects, probably acting on brain stress circuitry and/or on other neuroendocrine systems. Baclofen also showed excellent safety and tolerability, even in alcohol-dependent patients with advanced liver disease (i.e., cirrhosis). Future studies should investigate which alcoholic subtype may better benefit of the administration of baclofen in the treatment of alcohol dependence.

Keywords: Alcohol dependence; Stress; Anxiety; Craving; GABA; Baclofen

Baclofen suppression of withdrawal syndrome and delirium tremens in alcoholic patients

10 mg in 3 daily administration



Addolorato et al. Am J Med 2002

25 mg in 3 daily administration

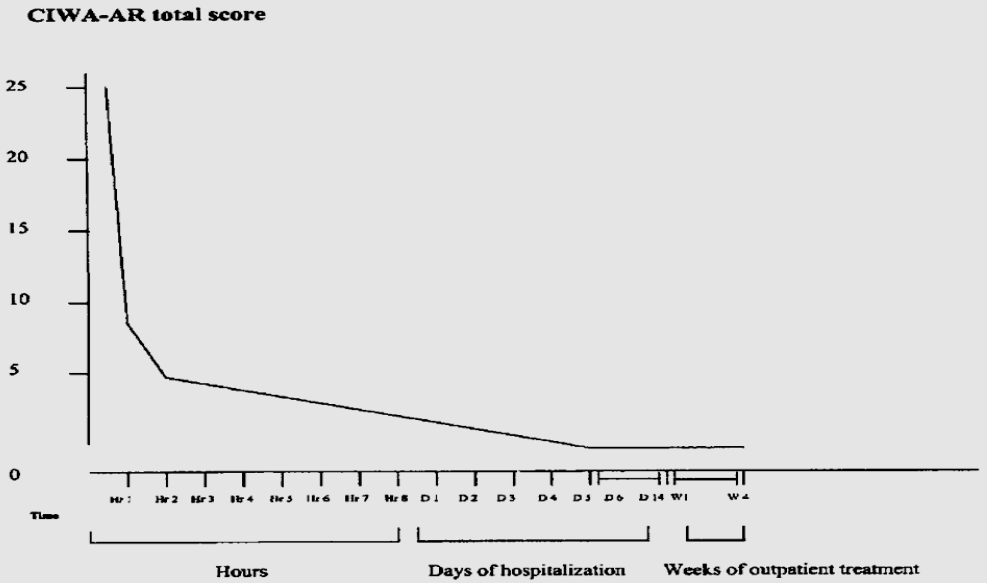


FIG. 1. Score of the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scale of the patient before and after baclofen administration. A rapid decrease of CIWA-Ar score was observed after baclofen administration. Hr = hour; D = day; W = week.

Addolorato et al. Clin Neuropharmacol 2003

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

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THE AMERICAN JOURNAL of MEDICINE ®

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]

130 "active" alcoholics (DSM IV)

- **Patients enrolled only if CIWA-Ar score ≥ 10**
- **CIWA-Ar administered once a day before the first daily administration**
- **CIWA-Ar administered "blinded" on days 1,2, 3, 4, 5, and 10**

93 excluded
- **81 did not develop m/s AWS**
- **12 refused to partecipate**

37 randomized

19 allocated to *diazepam*

19 received treatment 0.75 mg/kg in 6 times/day

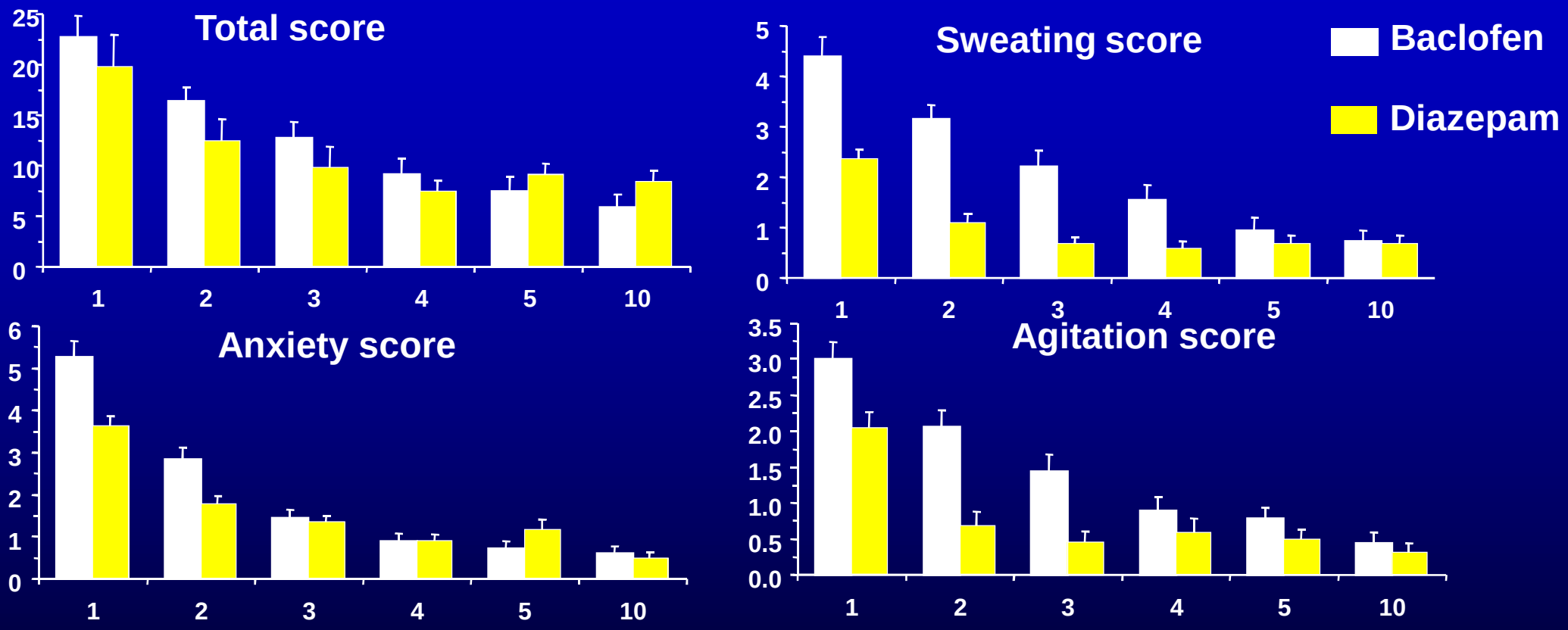
19 completed trial

18 allocated to *baclofen*

18 received treatment 30 mg in 3 times/day

18 completed trial

Suppressing effect of baclofen on alcohol withdrawal: a comparative study versus 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

Baclofen and liver cirrhosis

Baclofen showed its safety and efficacy in achieving and maintaining alcohol abstinence in alcohol-dependent patients with liver cirrhosis

Articles

THE LANCET

Volume 370 · Number 9603 · December 8–14, 2007

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

Giovanni Addolorato, Lorenzo Leggio, Anna Ferrulli, Silvia Cardone, Luisa Vonghia, Antonio Mirijello, Ludovico Abenavoli, Cristina D'Angelo, Fabio Caputo, Antonella Zambon, Paul S Haber, Giovanni Gasbarrini

Alcohol and Liver Cirrhosis

- **Alcohol is the most frequent cause of liver cirrhosis in the Western world**

  Tilg & Day. Nat Clin Pract Gastroenterol Hepatol 2007

- **Persistent alcohol intake has been associated with increased mortality in patients with liver cirrhosis**

  Pessione et al. Liver Int 2003

- **Cessation of alcohol consumption or a reduction in alcohol intake improves histology and/or survival of patients with any stage of alcohol liver disease (ALD)**

  Tilg & Day. Nat Clin Pract Gastroenterol Hepatol 2007

Alcohol and Liver Cirrhosis

- **Medical and surgical treatments for ALD have limited success when drinking continues**

- **The most effective management strategy for alcoholics with liver cirrhosis is to achieve total alcohol abstinence**

Nespor, Zima & Csémi. Cas Lek Cesk 2005

- **At present there are no formal trials on drugs aimed at reducing alcohol intake in these patients since meds currently available might worsen liver disease**

Tilg & Day. Nat Clin Pract Gastroenterol Hepatol 2007

Drugs effective in alcoholic patients and ALD

DISULFIRAM → **Hepatotoxicity, fulminant liver failure**

Mason. DICP 1989

NALTREXONE → **Hepatotoxicity, contraindicated in ALD**

Atkinson et al. Clin Pharm Ther 1985

Mosby's Drug Consult 2005

GHB
ACAMPROSATE → ***Hyperammoniemia***

Laborit et al, Int J Neuropharmacol 1964

Ahboucha et al. Metab Brain Dis 2004

Baclofen and Liver function

Baclofen **is metabolized only for 15% in the liver and it is mainly eliminated unmodified by kidney excretion**

Wuis et al. Eur J Clin Pharmacol 1989

No hepatic side-effects of the drug have been reported either in patients for:

- **Alcohol-dependence** — **Addolorato et al. Alcohol Alcohol 2002**; **Flannery et al. Alcohol Clin Exp Res 2004**
- **Neurological disorders** — **Davidoff. Ann Neurol 1985**

A significant reduction in AST, ALT, GGT value was found in treated alcoholic patients; it was related to the reduction of alcohol intake and to the safety of the drug

PATIENTS

- **Evaluated for the study 148 consecutive alcohol dependent patients affected by liver cirrhosis (2003-2006)**

- **Patients were admitted to our hospital for 3-4 days**
  - **to perform clinical examinations**
  - **to treat possible AWS**
  - **to inform the patients on the study (informed consent)**

- **84 patients were randomized**

- ***Baclofen*** **and** ***Placebo*** **were orally administered in a double-blind fashion for 12 consecutive weeks, at a dose of**

  - **15 mg/die fractioned in 3 doses for the first 3 days**
  - **30 mg/die fractioned in 3 doses for the other days**

METHODS

- Routine psychological support counselling was provided at each visit
- Counselling was undertaken by the same trained professional staff in individual sessions of 30 min
- The attendance at support groups (AA) was encouraged
- Liver enzymes and biological markers of alcohol abuse (AST, ALT, GGT, total bilirubin, INR, MCV), creatinine, ammonia were measured at T0, T4, T6, T8, T10 and T12. Serum albumin was assessed at T0, T4, T8, and T12

METHODS: *OUTCOMES*

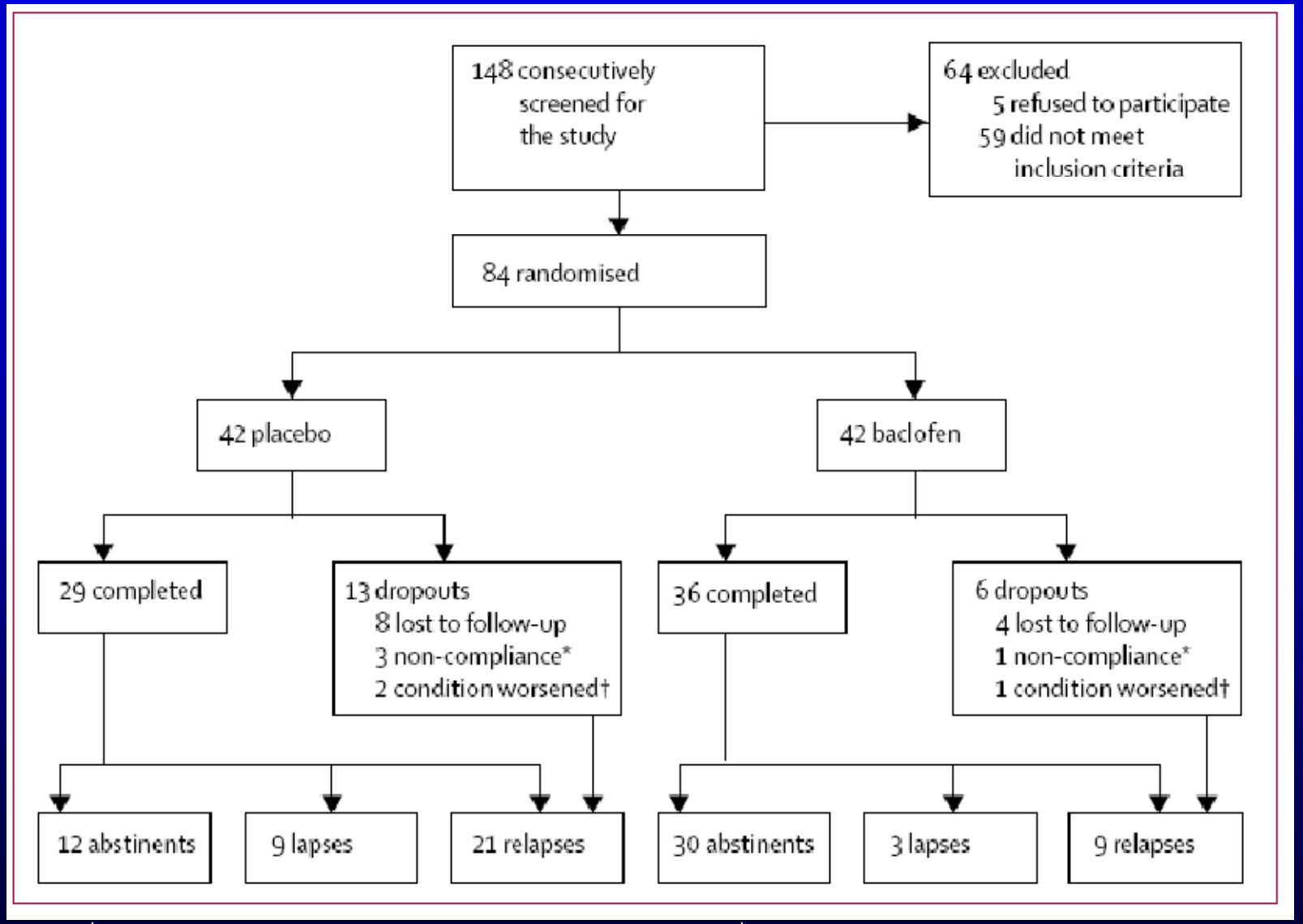
PRIMARY OUTCOMES

- **Total alcohol abstinence**
- **Cumulative Abstinence Duration (CAD)**

SECONDARY OUTCOMES

- **Craving reduction**
- **Improvement of biological parameters**

Trial profile



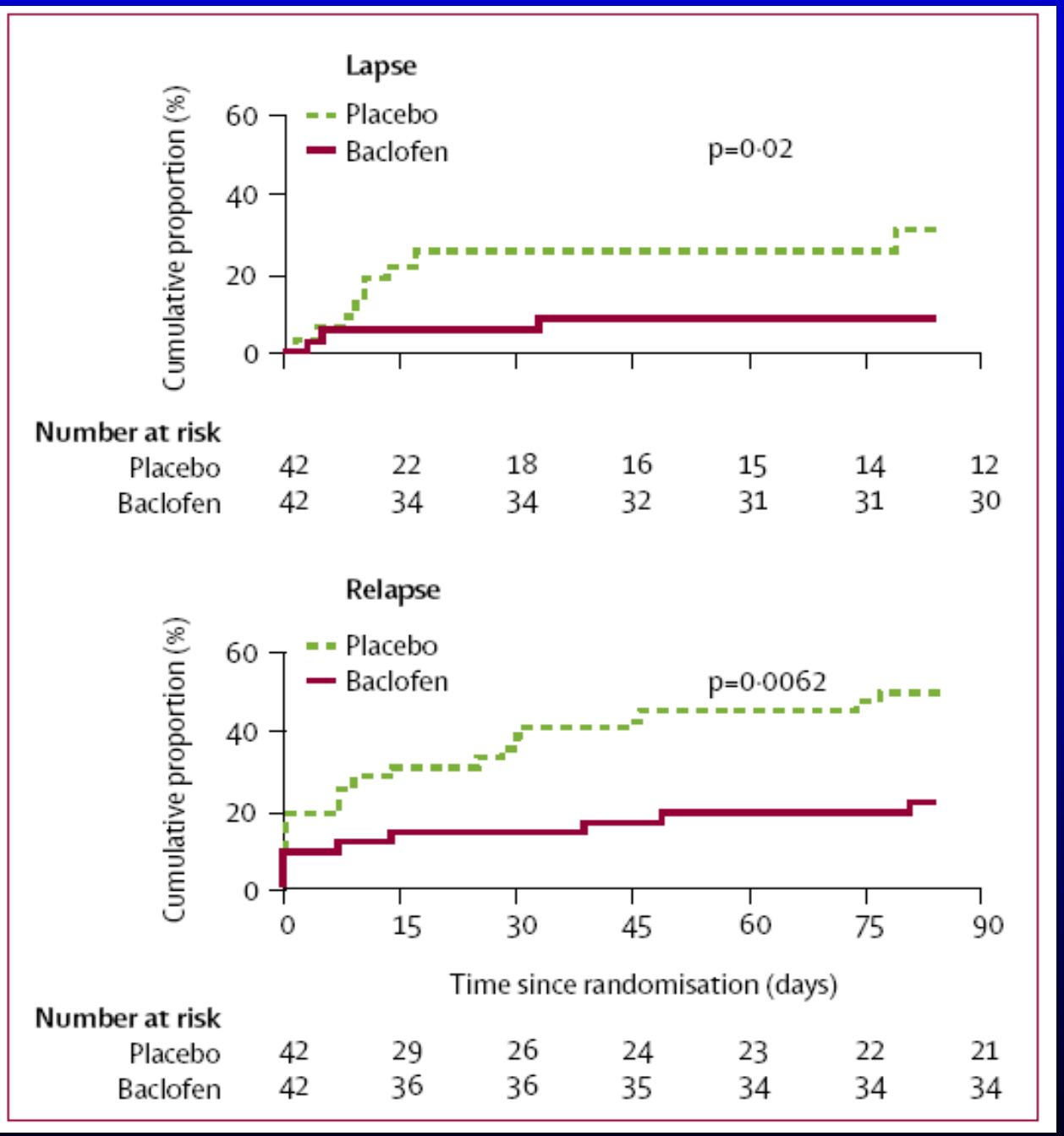
p = 0.0002

CAD: 30.8 ± 5.5 — **p = 0.001** — **CAD: 62.8 ± 5.4**

Total alcohol abstinence by Child-Pugh classification

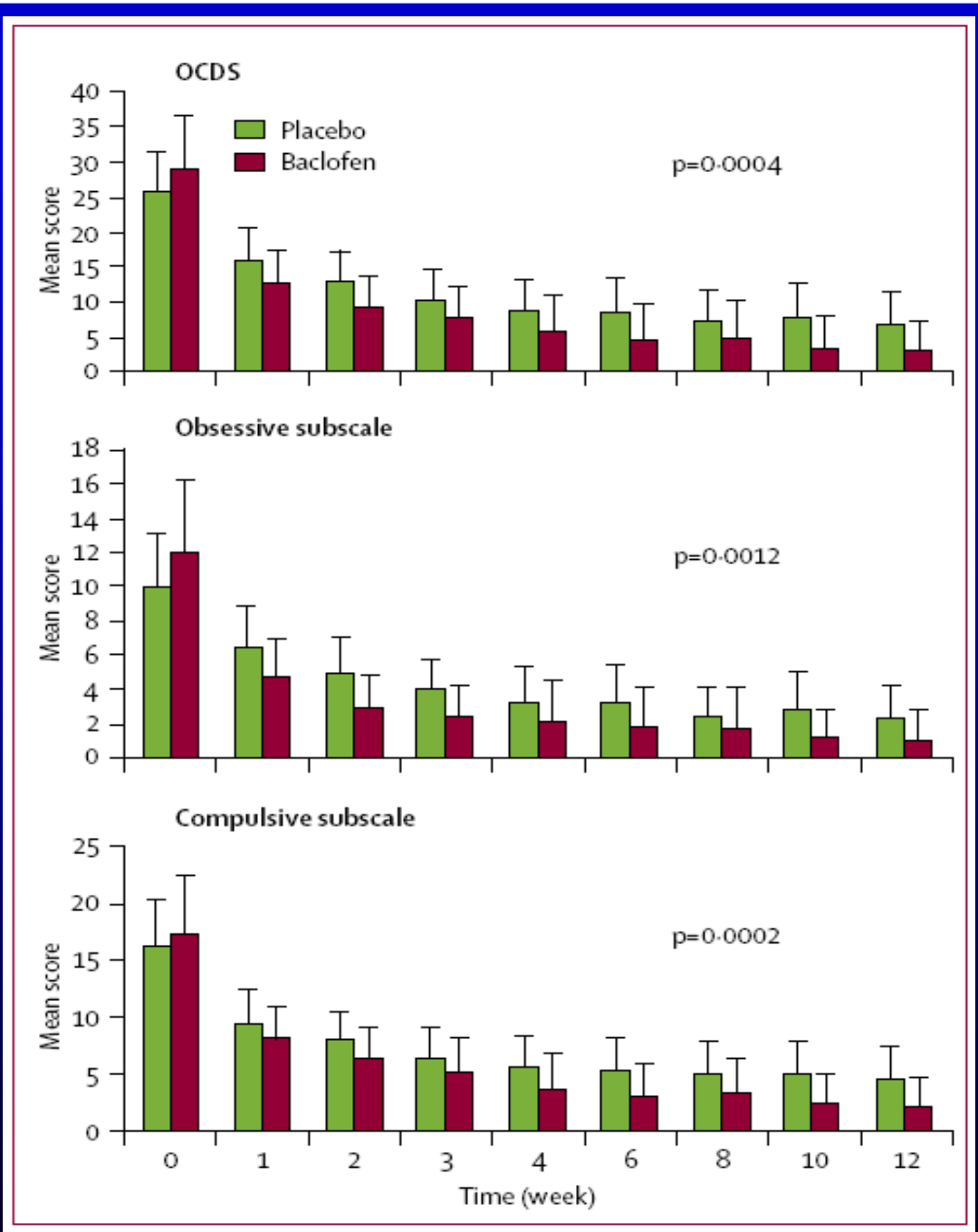
	Total alcohol abstinence (n [%])		Odds ratio (95% CI)	p
	Placebo	Baclofen		
Child-Pugh A	1/6 (17)	3/4 (75)	15·0 (0·7–339·5)	0·09
Child-Pugh B	5/20 (25)	12/20 (60)	4·5 (1·2–17·4)	0·03
Child-Pugh C	6/16 (38)	15/18 (83)	8·3 (1·7–41·3)	0·0094
Total	12/42 (29)	30/42 (71)	6·3 (2·4–16·1)	0·000

Table 4: Total alcohol abstinence by Child-Pugh classification



Kaplan–Meier survival analysis of proportion of lapse and relapse

Number at risk refers to proportion remaining free for *lapse* and *relapse*



Craving score

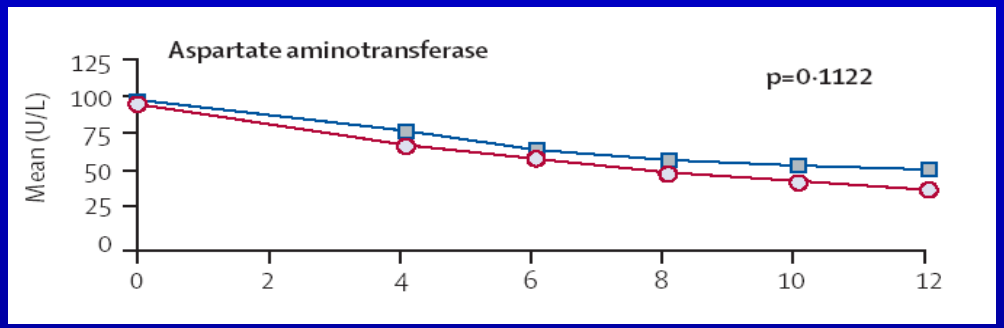
total OCDS
***p= 0.0004**

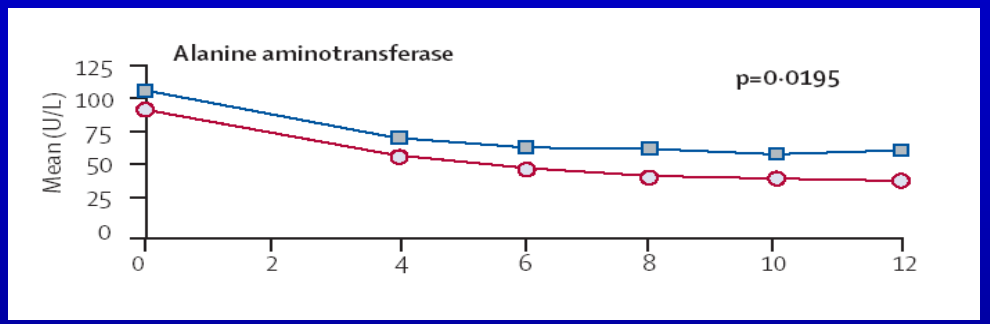
ODS (obsessive craving)
***p= 0.0012**

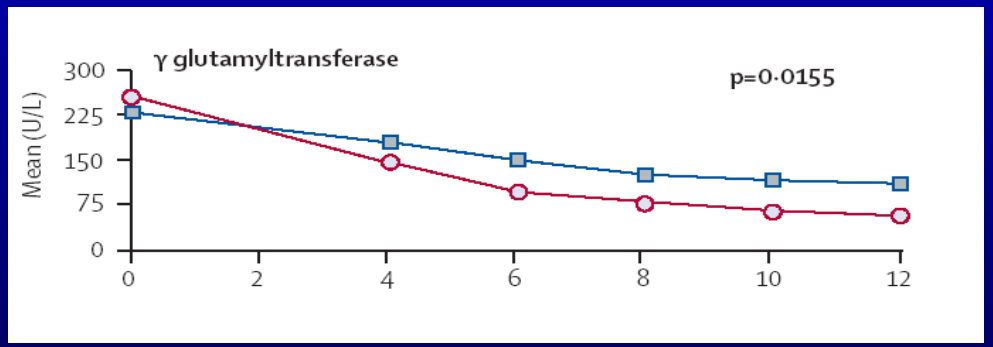
CDS (compulsive craving)
***p= 0.0002**

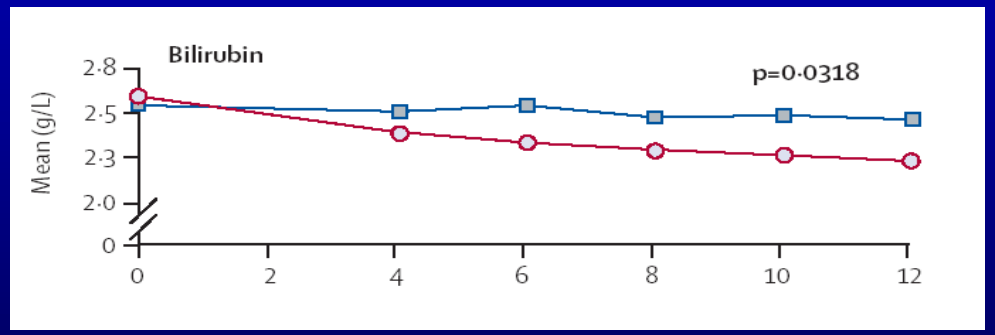
****ANCOVA mixed-model***

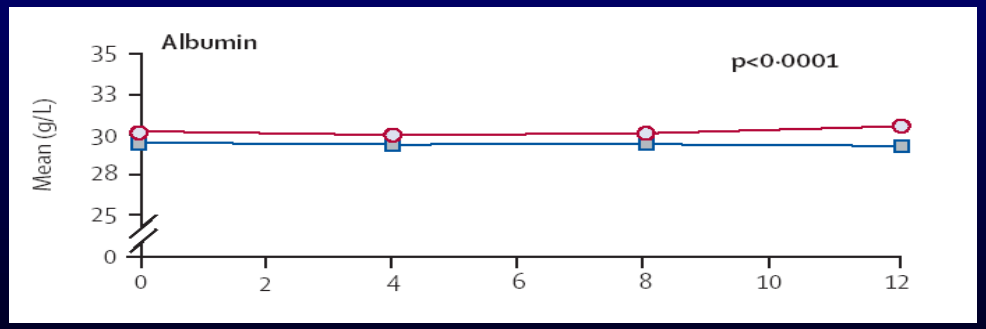
Biochemical markers

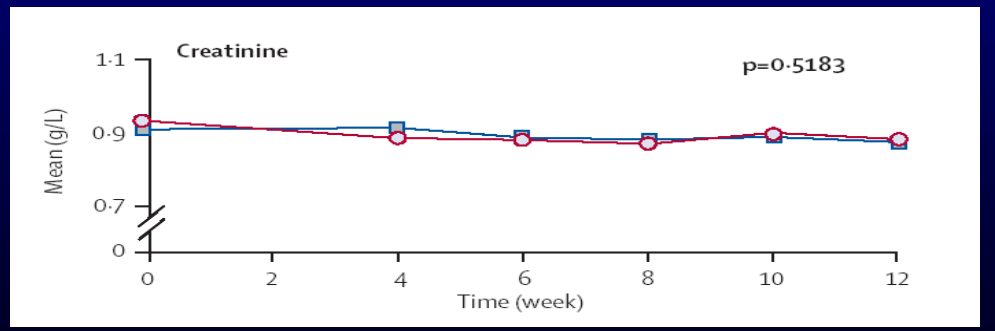












Placebo
Baclofen

Side effects

Baclofen group	Placebo group
headache (n=4)	headache (n=4)
tiredness (n=1)	tiredness (n=1)
vertigo (n=2)	vertigo (n=1)
sleepiness (n=1)	

- No patients discontinued treatment because of a side effect
- No serious adverse events leading to drug cessation were reported
- No patients showed encephalopathy/hyperammonaemia during the study period

CONCLUSIONS - Baclofen Efficacy

- **Baclofen was significantly more effective than placebo at achieving and maintaining alcohol abstinence in alcohol-dependent patients with liver cirrhosis**
- **This effect could be related to the higher effectiveness of the drug than placebo in reducing alcohol craving**
- **The fewer number of dropouts in the baclofen group also confirms the drug efficacy**

CONCLUSIONS - Baclofen Efficacy

- **Effectiveness of baclofen was especially evident in patients with advanced liver cirrhosis (Child-Pugh B and C)**
  - **more motivated patients**
  - **motivation and psychological support not enough**
  - **baclofen allowed to achieve total abstinence**

- **Baclofen could play a role in liver transplantation (OLTx) taking into account the concerns regarding the risk of recurrent alcohol consumption before and/or after OLTx, so that total alcohol abstinence is required before OLTx**

CONCLUSIONS - Baclofen Safety

- **Baclofen was well tolerated by individuals with Child-Pugh class A, B, and C cirrhosis: absence of hepatic and renal side effects**

- **Patients did not show encephalopathy during the study, probably because baclofen is a selective $GABA_B$ receptor agonist ($GABA_A$ receptors agonist can increase risk for hepatic encephalopathy)**

Anboucha et al. Metab Brain Dis 2004

- **Baclofen is the first anti-craving drug with proved efficacy and safety in alcoholic patients with advanced liver disease**

Final remarks

- **Trials testing medications for alcoholism usually exclude severely ill patients**

- **This exclusion improves the homogeneity of the sample population but reduces external validity of trials**

  Garbutt & Flannery. Lancet 2007

- **If confirmed by future larger studies, these results get the basis for treating with an anti-craving medication a wide population of alcoholic patients, including those with severe medical comorbidities as advanced liver damage**

  Gache & Hadengue. J Hepatol 2008

Clinical Studies with Baclofen: SUMMARY

- **Baclofen administration in alcoholics is able to:**
  - **induce alcohol abstinence**
  - **reduce alcohol craving and intake**
  - **induce the remission of withdrawal syndrome**

- **Baclofen is very manageable, also in alcoholic patients with liver chirrosis**

- **Baclofen reduces state anxiety in alcohol abstinence and withdrawal**

Financial Support

European Research Advisory Board (ERAB)

Italian Ministry for University, Scientific and Technological Research (MURST)

Acknowledgements

L. Leggio, MD; A. Ferrulli, MD; S. Cardone, MD; L. Vonghia, MD;
A. Mirijello, MD; C. D'Angelo, MD; A. Nesci, MD, V. Leso, MD

My best production: my twins Andrea e Matteo

Thank you for you attention