Le malattie da abuso da bevande alcoliche;
Modena, 28 Aprile 2007

Nuove frontiere nella terapia dell'abuso alcolico

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Università Cattolica del Sacro Cuore

• Alcoholism is characterized by: craving, loss of control, tolerance and physical dependence

Gianoulakis, Alcohol Alcoholism 1996

• The main objectives of treatment are to control AWS symptoms, to maintain abstinence and to prevent relapse and drop out

• Psychological approach and counselling are essential components of therapy

- Efficacy by Alcoholics Anonymous: 5-15% in U.S.A.

Erikson, Alcohol Alcoholism 1996

- Efficacy by short and long-term intervention: 7-39%.

Edwards and Rollnick, Addiction 1997

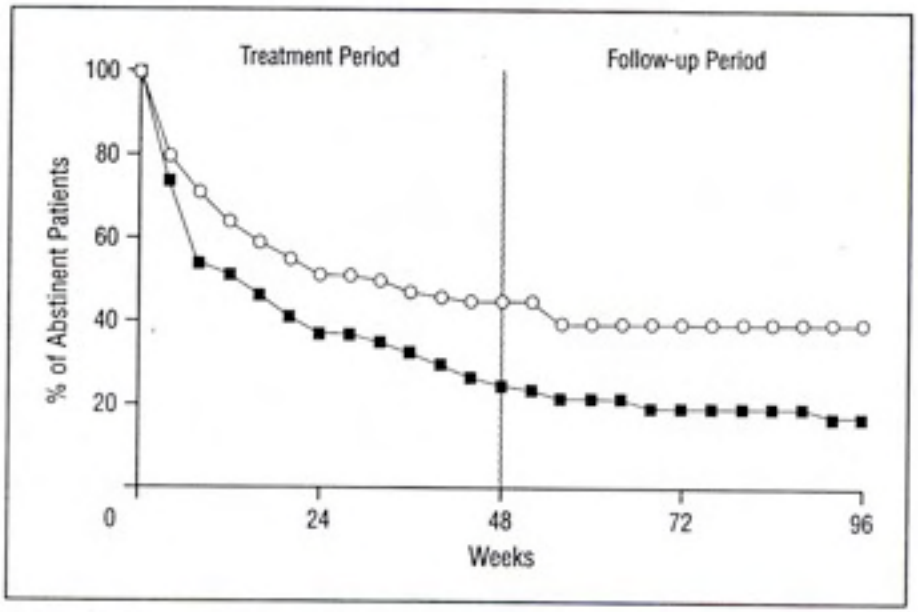
• Pharmacotherapy may be necessary in treating individuals who are not helped by psychological therapies alone

USEFUL DRUGS TO MAINTAIN ABSTINENCE

- DISULFIRAM (ANTABUSE®; ETILTOX®)
- ACAMPROSATO (CAMPRAL®)
- NALTREXONE (NALOREX®)
- GHB (ALCOVER®)
- BACLOFEN (LIORESAL®)
- TOPIRAMATO (TOPAMAX®)
- SSRI (FLUOXEREN®, SEROXAT®, ETC)
- NATURAL SUBSTANCES (*Salvia milthiorriza, Radix*

Acamprosate

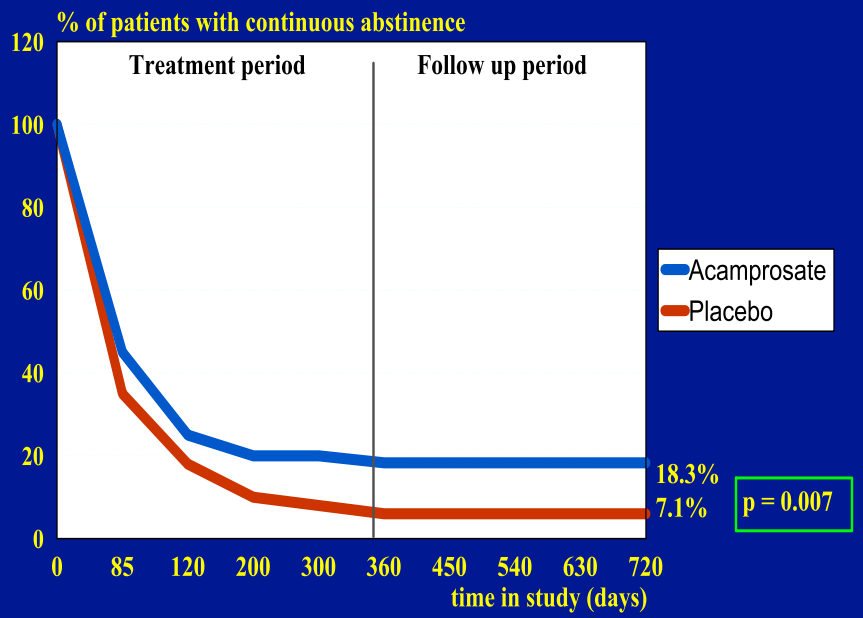
- N-metil-D-aspartate and glutamate receptor antagonist
- reduce the glutamatergic stimulation



Kaplan-Meier survival analysis (survival function estimate). Continuous abstinence for the treatment and follow-up periods. Curve with open circles indicates acamprosate treatment; curve with shaded squares, placebo treatment.

Sass et al, Arch Gen Psych 1996

Comparison of acamprosate and placebo in long-term treatment of alcohol dependence



Whitworth AB et al., Lancet, 1996

Withworth et al, Lancet 1996

Acamprosate

Studies evaluating large sample of alcoholic patients show that acamprosate is effective in reducing alcohol relapse and in increasing the alcohol abstinence rate, although with modest efficacy

Kranzler, Alcohol Alcohol 2000

Johnson & Ait-Daoud, Psychopharmacology 2000

- **Opioid receptor antagonist**

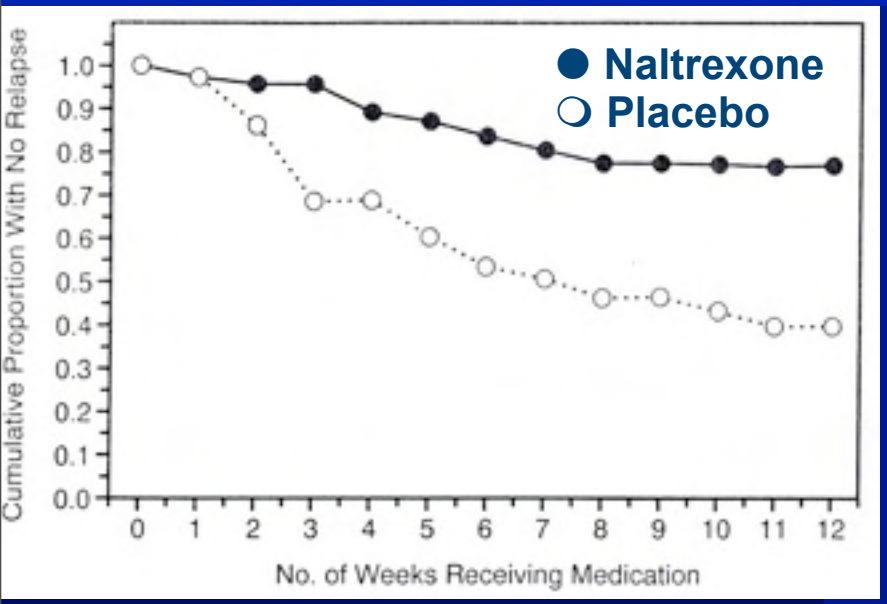
- **"Extinction" mechanism: progressive decrease of alcohol seeking behaviour related to a decrease of alcohol reward sensation**

- **The drug should be administered in actively drinking patients**

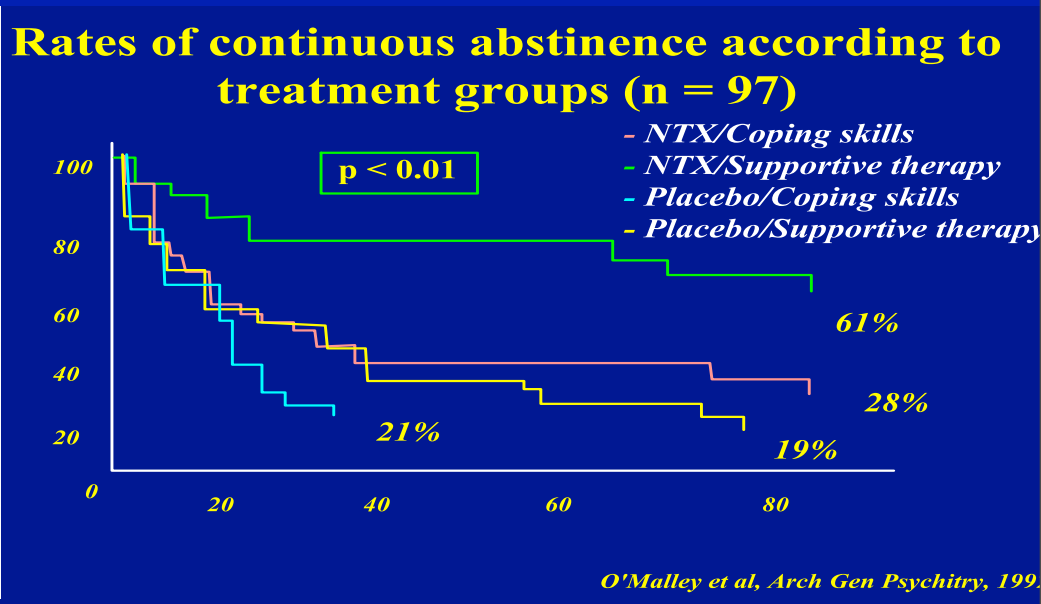
Sinclair et al, Alcohol Alcohol 2001

Naltrexone

FDA approved the drug for alcohol dependence on 1994



Volpicelli et al, Arch Gen Psychiat 1992



O'Malley et al, Arch Gen Psychiat 1992


Patented Mar. 17, 1931 1,796,977

DISULFIRAM

UNITED STATES PATENT OFFICE

Naltrexone

No significant difference **between naltrexone 50 mg/day and placebo in a 3 or 12 months of treatment in a double blind randomized multicentric US study**

Naltrexone for 3 months (short term) or 12 months (long term) v placebo for alcohol dependence‡

Outcomes at 13 weeks	Comparison	Means	Difference between groups (95% CI)
Number of days to relapse	Short or long term v placebo	72.3 v 62.4	9.9 (-3.0 to 22.8)
Outcomes at 52 weeks			
Percentage of drinking days	Long term v placebo	15.1 v 18.0	-2.9 (-7.7 to 1.9)
	Short term v placebo	19.4 v 18.0	1.4 (-3.6 to 6.5)
Number of drinks per drinking day (NDPDD)§	Long term v placebo	9.6 v 9.3	0.3 (-1.8 to 2.4)
	Short term v placebo	10.5 v 9.3	1.2 (-0.5 to 2.9)

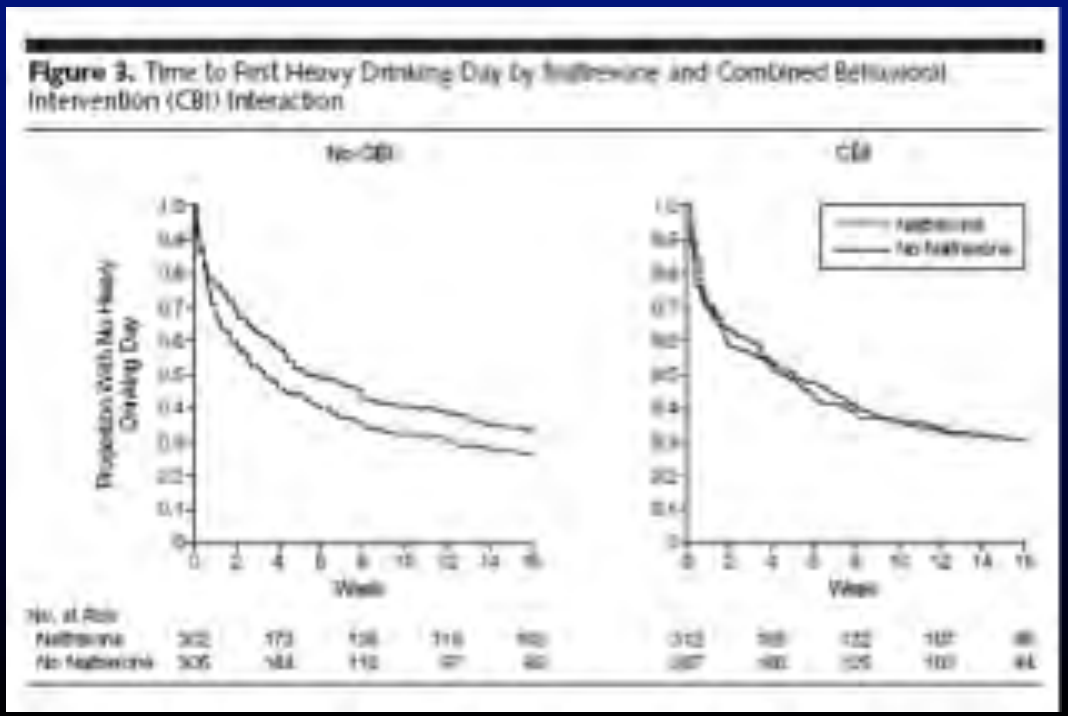
‡CI defined in glossary. None of the mean differences is statistically significant. §NDPDD was evaluated for the 66% of patients who consumed alcohol during follow up.

Krystal et al, N Engl J Med 2001

ORIGINAL CONTRIBUTION

Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence

The COMBINE Study: A Randomized Controlled Trial



Anton et al. JAMA 2006

Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis

"…..the two medications appear to provide a comparable but modest effects on the likelihood of a patient's maintenance of abstinence…."

Reference (n for naltrexone/n for placebo)	Drinks/drinking day	Percentage drinking days	Percentage abstinent	Percentage relapse	Percentage retention
Volpicelli et al. (1992) (35/35)		-0,533*	0,114	-0,323	0,089
O'Malley et al. (1992) (46/51)	-0,102	-0,285*	0,245*		
Oslin et al. (1997) (23/21)		-0,454*		-0,236	0,104
Volpicelli et al. (1997) (48/49)		-0,163*	0,093	-0,178	-0,006
Hersh et al. (1998) (31/33)	-0,013	-0,042	0,154	0,029	0,071
Kranzler et al. (1998) (15/5)	-0,113	-0,132	0,182	-0,2	
Anton et al. (1999) (68/63)	-0,218*	-0,191*	0,14	-0,221*	0,118
Kranzler et al. (2000) (60/63)	0,104	0,108	-0,058	-0,018	-0,221*
Chck et al. (2000) (90/85)			0,017		

Kranzler & Van Kirk, ACER 2001

Gamma Hydroxybutiric Acid (GHB)

- GHB is a short-chain 4-carbon fatty acid

- It is present in particular in the hypothalamus and basal ganglia.

Snead & Moreley. Brain Res 1981

- 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, Alcohol 2000

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

Fadda et al. Life Sci 1983; Gessa et al. Alcohol 2000

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%)
- drug 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 Alcoholism 1996

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 benefit from greater fractioning of the dose

Addolorato et al. Lancet 1998

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

Addolorato et al. Lancet 1998

GHB FRACTIONING EFFICACY

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- 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%)

- 66 (72.5%) abstinent

• 91 Phase 1

- 25 (27.5%) not-abstinent

Phase 2

- 19 (76%) abstinent

- drug abuse: no

Addolorato et al. Lancet 1998

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

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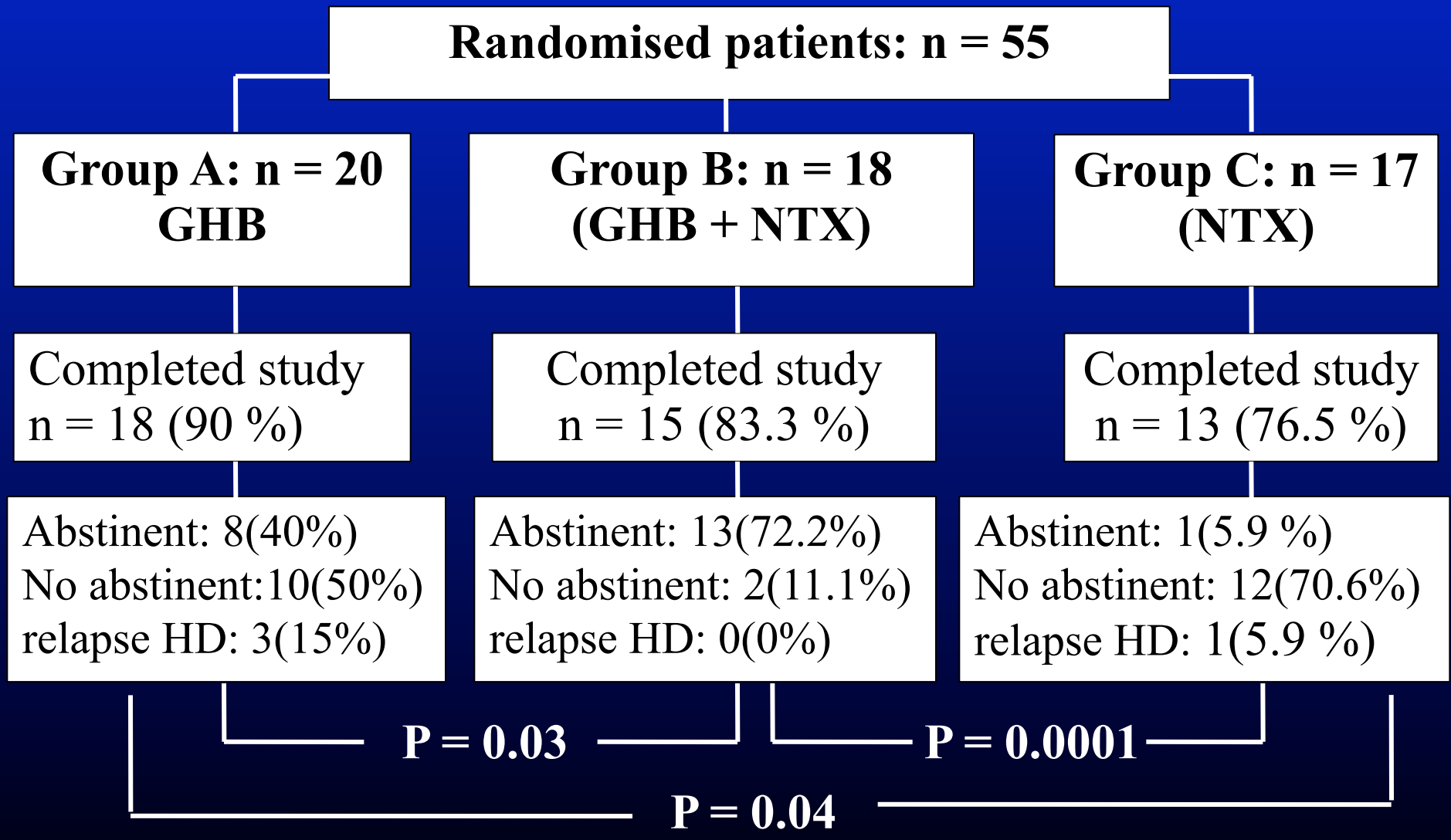
Abstract

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

COMPAIRING AND COMBINING GHB AND NALTREXONE



Caputo et al. Eur Neuropsychopharmacol *in press*

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

- It must be used under strict medical surveillance

Addolorato & Gasbarrini. New Engl J Med 2005

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

Addolorato et al. Alcohol 2000

BACLOFEN

- β-(4-chlorophenyl)-γ-aminobutiric acid
- $GABA_B$ receptor agonist
- present clinical use: to control spasticity

Davidoff, Ann Neurol 1985

BACLOFEN AND RELAPSE PREVENTION

• *in alcohol sP rats*

- reduce voluntary alcohol intake

Colombo et al, Alcohol Clin Exp Res 2000

- reduce alcohol deprivation effect

Colombo et al, Drug Alcohol Depend 2003

- suppress the stimulation of alcohol intake induced by morphine Colombo et al, Eur J Pharmacol 2004

• *in alcohol addicted patients*

- reduce alcohol craving and intake (open studies)

Addolorato et al, Alcohol Clin Exp Res 2000
Flannery et al, Alcohol Clin Exp Res 2004

DOUBLE BLIND STUDY

- 39 subjects affected by current alcoholism (DSM IV)
  - 20 (51.3%) baclofen
  - 19 (48.7%) placebo

- Baclofen or placebo administered per os for 4 weeks
  - 15 mg/day fractioned in 3 times day for the first 3 day
  - 30 mg/day fractioned in 3 times day for the 27 day

- 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

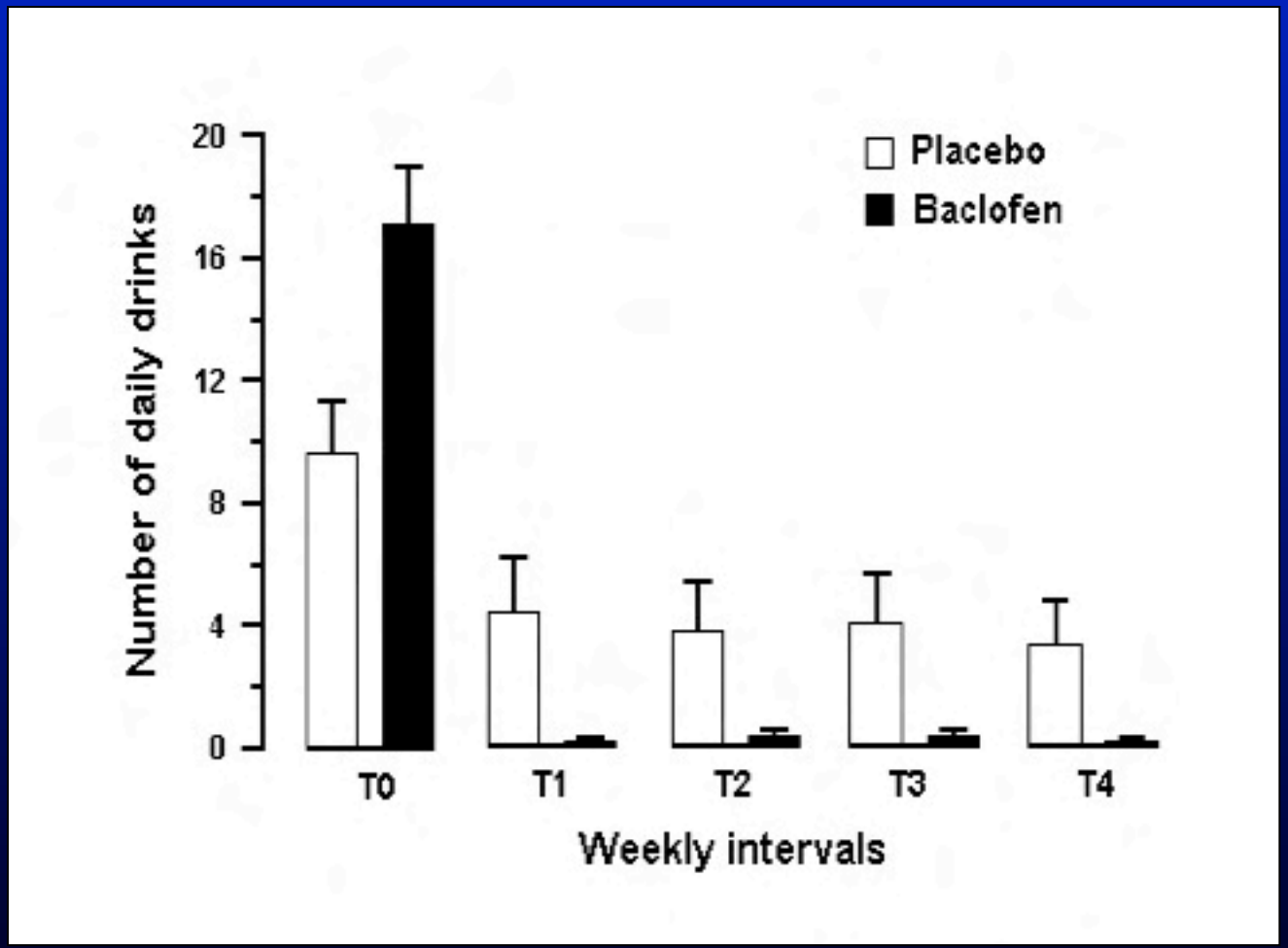
Anton et al, Arch Gen Psychiatry 1996

- Supportive therapy: AA

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	

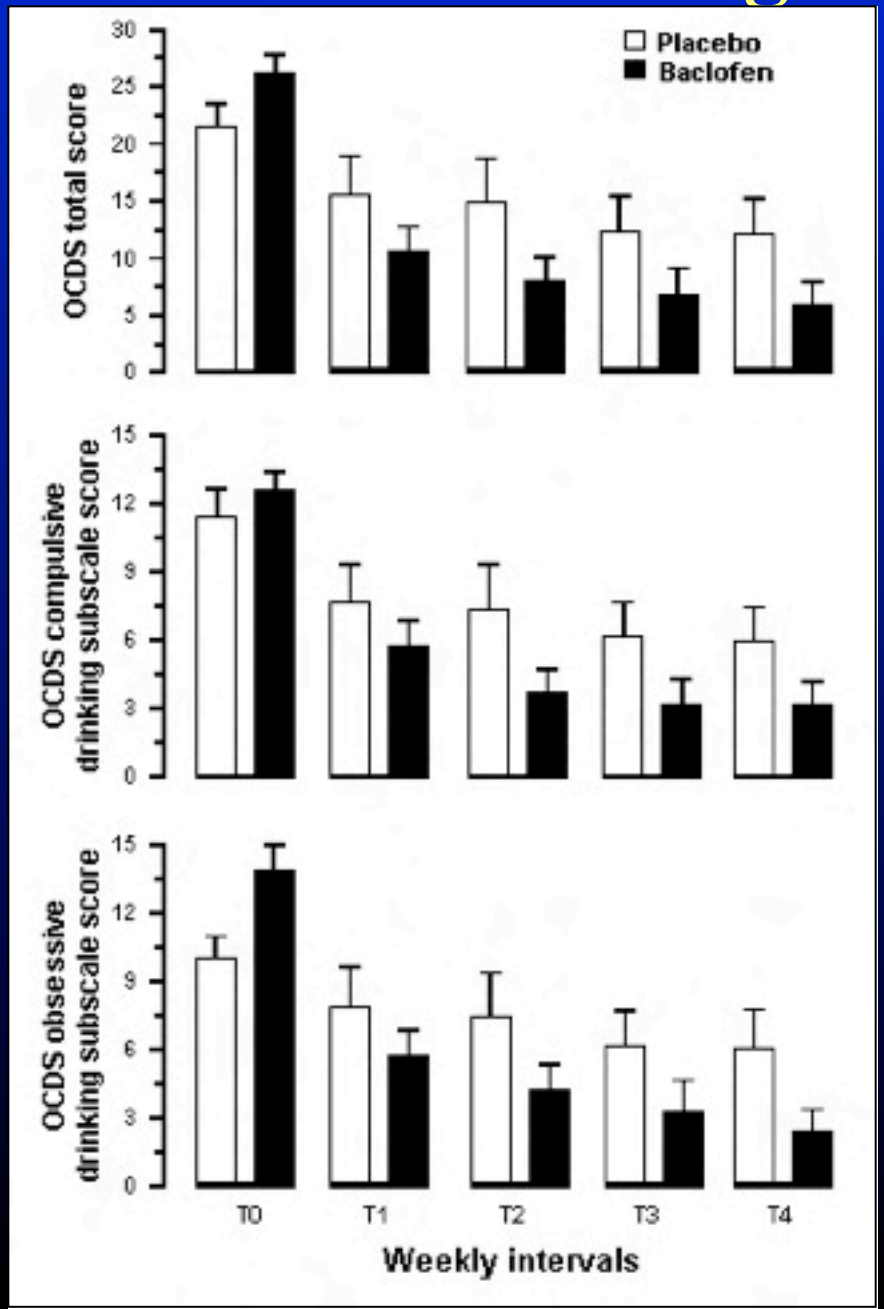
Suppression of alcohol consumption by baclofen



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

Addolorato et al, Alcohol Alcohol 2002

Reduction of craving for alcohol by baclofen



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

SIDE EFFECTS

- **tolerability was fair in all patients; no patients discontinued the drug**
  - **side effects (resolved after 1-2 weeks of treatment)**
    - sleepiness,
    - abdominal symptoms
    - headache
    - vertigo
    - hypotension

- **no euphoria or other pleasant effects**
- **no craving for the drug**
- **at the drug discontinuation: no *BWS* or side effects**
- **tolerance to baclofen's sedative effect in alcohol addiction both**
  - **in animals** **Besheer et al, Psychopharmacol 2004**
  - **in humans** **Addolorato et al, Psychopharmacol 2004**

Vol. 31, No. 1
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The γ-Aminobutyric Acid-B Receptor Agonist Baclofen Attenuates Responding for Ethanol in Ethanol-Dependent Rats

Brendan M. Walker and George F. Koob

Background: γ-Aminobutyric acid-B ($GABA_B$) receptor agonists have been shown to suppress operant self-administration of ethanol in nondependent rats. However, little work has focused on the effects of $GABA_B$ receptor agonists on self-administration of ethanol in dependent animals.

Methods: In the present experiment, the $GABA_B$ receptor agonist baclofen was tested for the ability to modulate both fixed- (FR) and progressive-ratio (PR) responding for ethanol in rats while nondependent and subsequently after ethanol dependence induction. Following the acquisition and stabilization of baseline operant ethanol self-administration and after dependence induction, baclofen (0.0, 0.5, 1, 2, and 4 mg/kg, intraperitoneal [IP]) was tested on FR-4 responding for ethanol. The ability of baclofen (2.0 mg/kg) to affect responding under a PR schedule of reinforcement was also evaluated. Dependence was induced in the animals by subjecting them to a 1-month intermittent vapor-exposure period in which animals were exposed to ethanol vapor for 14 h/d. Following the 1-month period, the vapor-exposed animals resumed FR-1 and PR baclofen drug testing (doses as described above) in the operant chambers at a time point corresponding to the animals being 6 hours into withdrawal (i.e., 6 hours after the ethanol vapor had been discontinued for that day).

Results: Baclofen (0.0, 0.5, 1, 2, and 4 mg/kg, IP) dose-dependently decreased ethanol self-administration in both nondependent and dependent rats on a FR schedule of reinforcement. However, the dose of baclofen that significantly reduced responding for ethanol was shifted to the left in the ethanol vapor-exposed animals, indicating an increased sensitivity to baclofen in animals that were chronically exposed to ethanol. When tested using a PR schedule of reinforcement, there was a significant increase in the breakpoint for the vapor-exposed animals (i.e., the animals were willing to work more in a dependent state). Baclofen (2.0 mg/kg, IP) suppressed intake for both nondependent and dependent animals.

Conclusions: Ethanol dependence produced increased self-administration of ethanol as reflected in increased ethanol intake and increased responding on a PR schedule of reinforcement. As baclofen suppressed ethanol self-administration and showed evidence of increased potency in dependent animals, the present experiment suggests that the $GABA_B$ receptor could be a potential pharmacotherapeutic target for the treatment of chronic alcoholism.

Key Words: Self-Administration, Intermittent Ethanol Vapor Exposure, Acute Withdrawal, Dependence, Baclofen.

Alcoholic patients with liver cirrhosis

- The only effective strategy for alcoholic patients with liver cirrhosis is total alcohol abstinence, since medical and surgical treatments for ALD and its complications have limited success when drinking continues Yates et al, Alcohol Alcoholism 1998

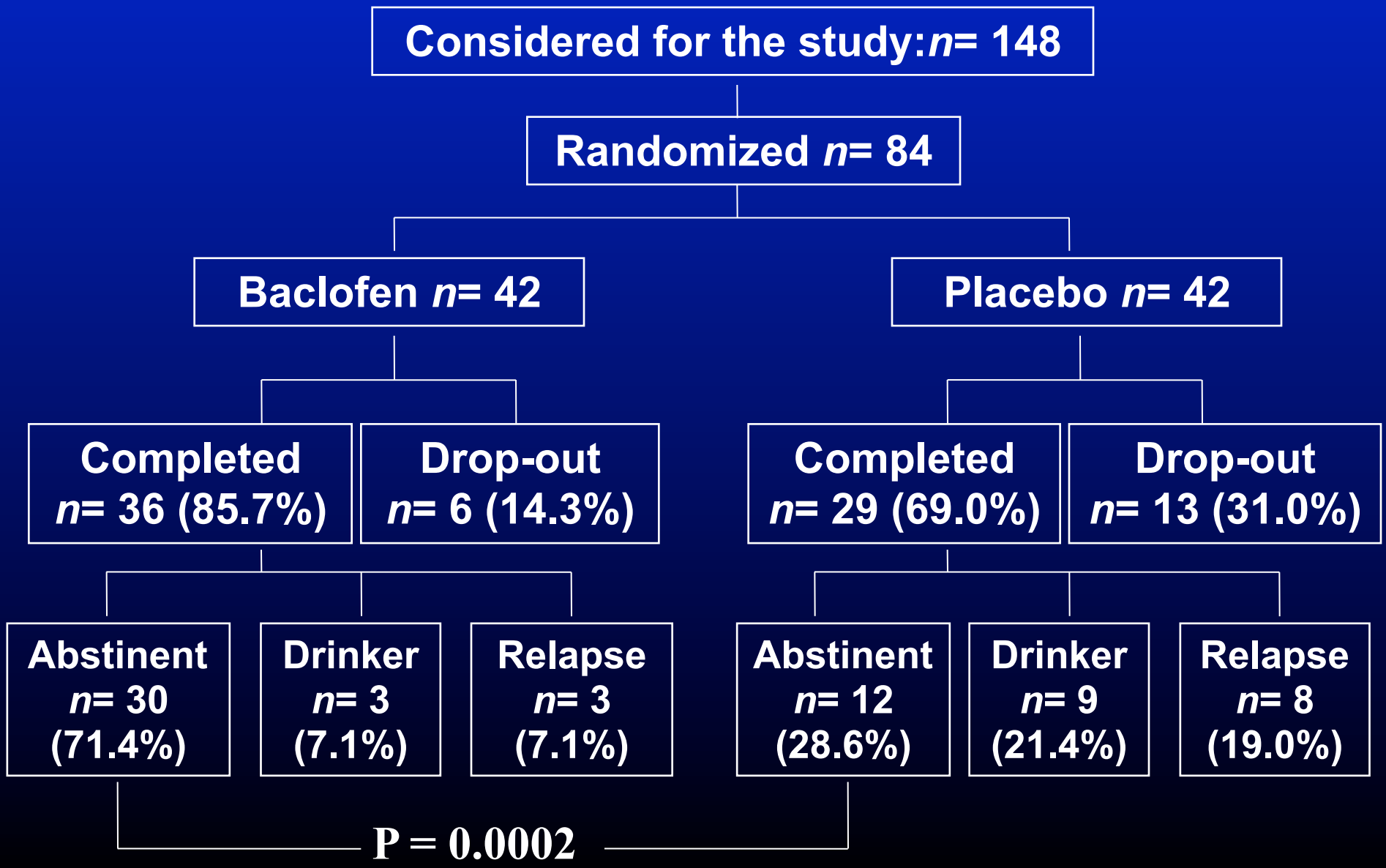
- Only total alcohol abstinence is able to improve survival and the clinical outcome of patients with ALD

Tilg & Day, Nature Clin Pract Gatsroenterol Hepatol 2007

- However these patients are usually excluded from trials investigating the efficacy of anti-craving drugs because of fear to worsen liver disease

- Baclofen is manageable and it has a kidney elimination

Efficacy and safety of baclofen in alcoholic patients with liver cirrhosis

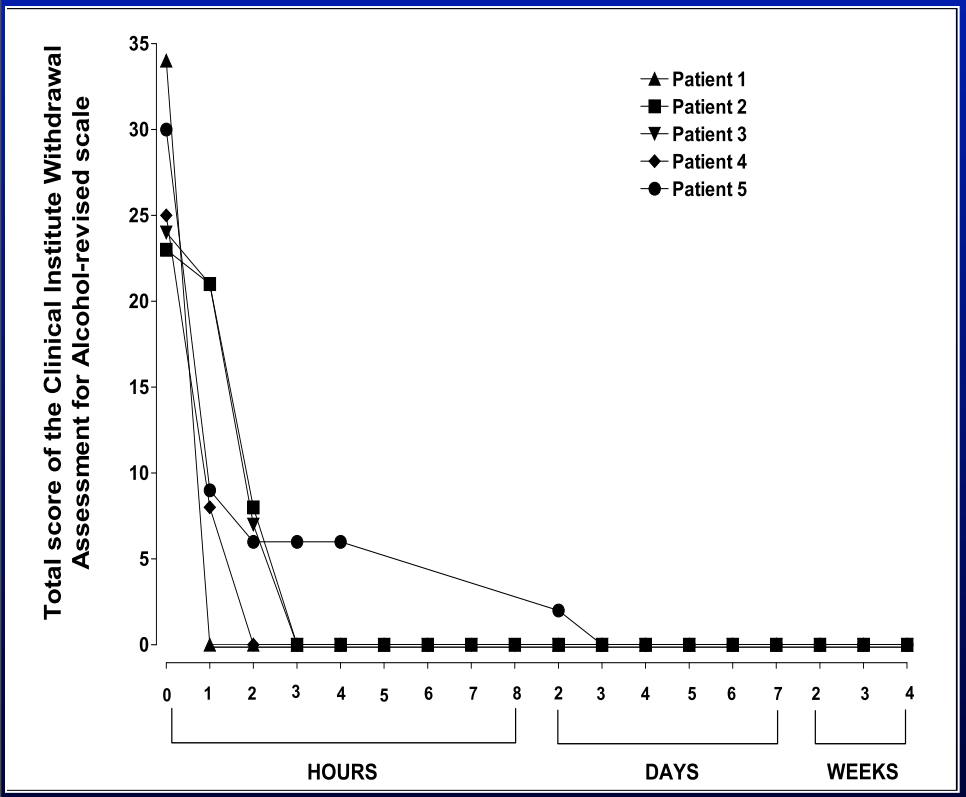


AST, ALT, GGT values in patients treated with placebo or baclofen (n=36) at different times of the study and statistical significance at the post-hoc analysis (Newman-Keuls test)

		AST			ALT			GGT	
	Placebo N=29	Baclofen N=36	P	Placebo N=29	Baclofen N=36	P	Placebo	Baclofen N=36	P
T0	96.6 ± 11.1	91.1 ± 9.1	*P*=0.71	95.7 ± 12.3	85.6 ± 9.9	*P*=0.45	251.8 ± 41.9	264.1 ± 49.7	*P*=0.69
T4	75.1 ± 9.2	65.7 ± 6.6	*P*=0.04	68.3 ± 8.8	55.9 ± 5.3	*P*=0.05	181.3 ± 35.0	144.9 ± 27.1	*P*=0.03
T6	64.2 ± 6.4	58.1 ± 5.3	*P*=0.20	63.4 ± 7.6	46.8 ± 4.4	*P*=0.001	148.9 ± 29.0	96.1 ± 12.6	*P*=0.00
T8	56.9 ± 5.9	48.0 ± 4.3	*P*=0.24	62.1 ± 7.0	40.7 ± 3.7	*P*=0.00	125.8 ± 24.2	74.5 ± 11.3	*P*=0.03
T10	53.8 ± 5.1	41.1 ± 3.4	*P*=0.04	58.7 ± 7.0	38.7 ± 4.1	*P*=0.001	114.7 ± 24.4	62.4 ± 9.6	*P*=0.02
T12	50.4 ± 4.9	36.9 ± 3.7	*P*=0.02	61.0 ± 7.4	38.4 ± 5.0	*P*=0.001	110.1 ± 24.6	54.9 ± 10.0	*P*=0.01

Suppressing effect of baclofen on alcohol withdrawal and delirium tremens syndrome in alcohol dependent patients

10 mg every 8 hours



Addolorato et al, Am J Med 2002

25 mg every 8 hours

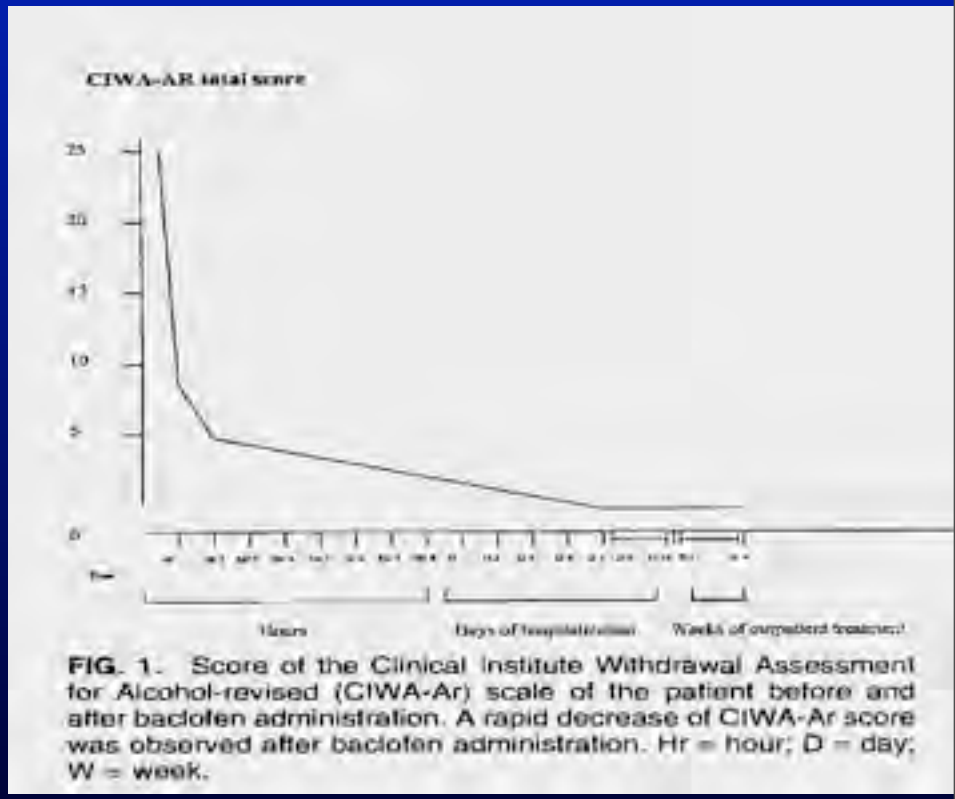


FIG. 1. Score of the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scale of the patient before and after baclofen administration. A rapid decrease of CIWA-Ar score was observed after baclofen administration. Hr = hour; D = day; W = week.

Addolorato et al, Clin Neuropharmacol 2003

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

THE AMERICAN JOURNAL of MEDICINE®

ELSEVIER

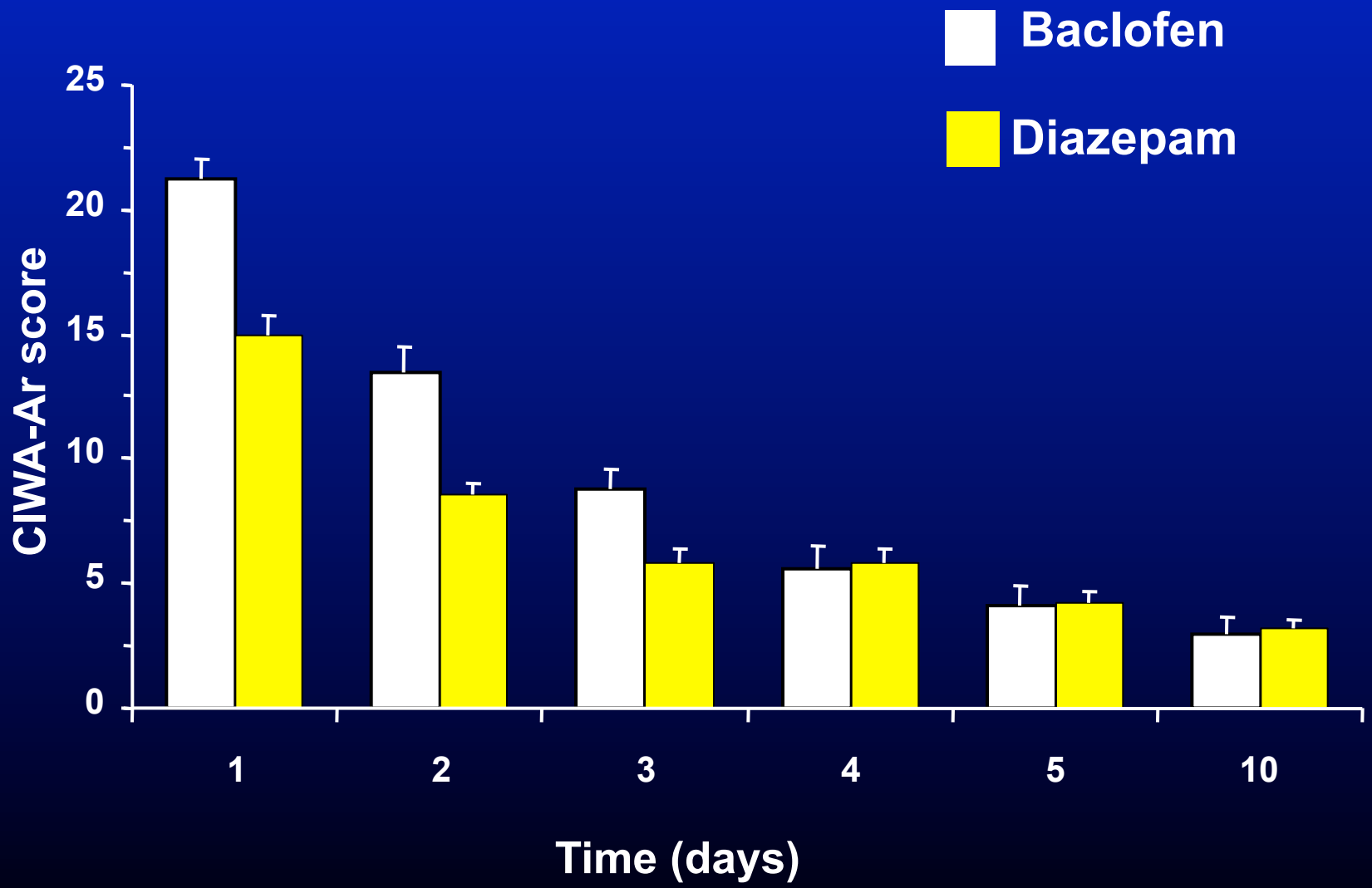
BRIEF OBSERVATION

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. Beasley" 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

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



Addolorato et al, Am J Med 2006

SUMMARY

• Baclofen administration in human alcoholics have a significant efficacy

- to induce alcohol abstinence
- to reduce alcohol intake
- to reduce alcohol craving
  - in obsessive component
  - in compulsive component
- to induce the remission of
  - alcohol withdrawal syndrome
  - delirium tremens

• Baclofen seems to be very manageable also showing general safety, even when administered to patients with severe liver disease

"In progress" study

IBIS

International Baclofen Intervention Study

IBIS 1

- Giovanni Addolorato & Giovanni Gasbarrini, Rome
- Roberta Agabio & Giancarlo Colombo, Cagliari

- Jonathan Chick, Edimburgh
- Anne Lingford-Hughes, Bristol

- Otto M. Lesch, Wien

- Paul Haber, Sidney

IBIS 2

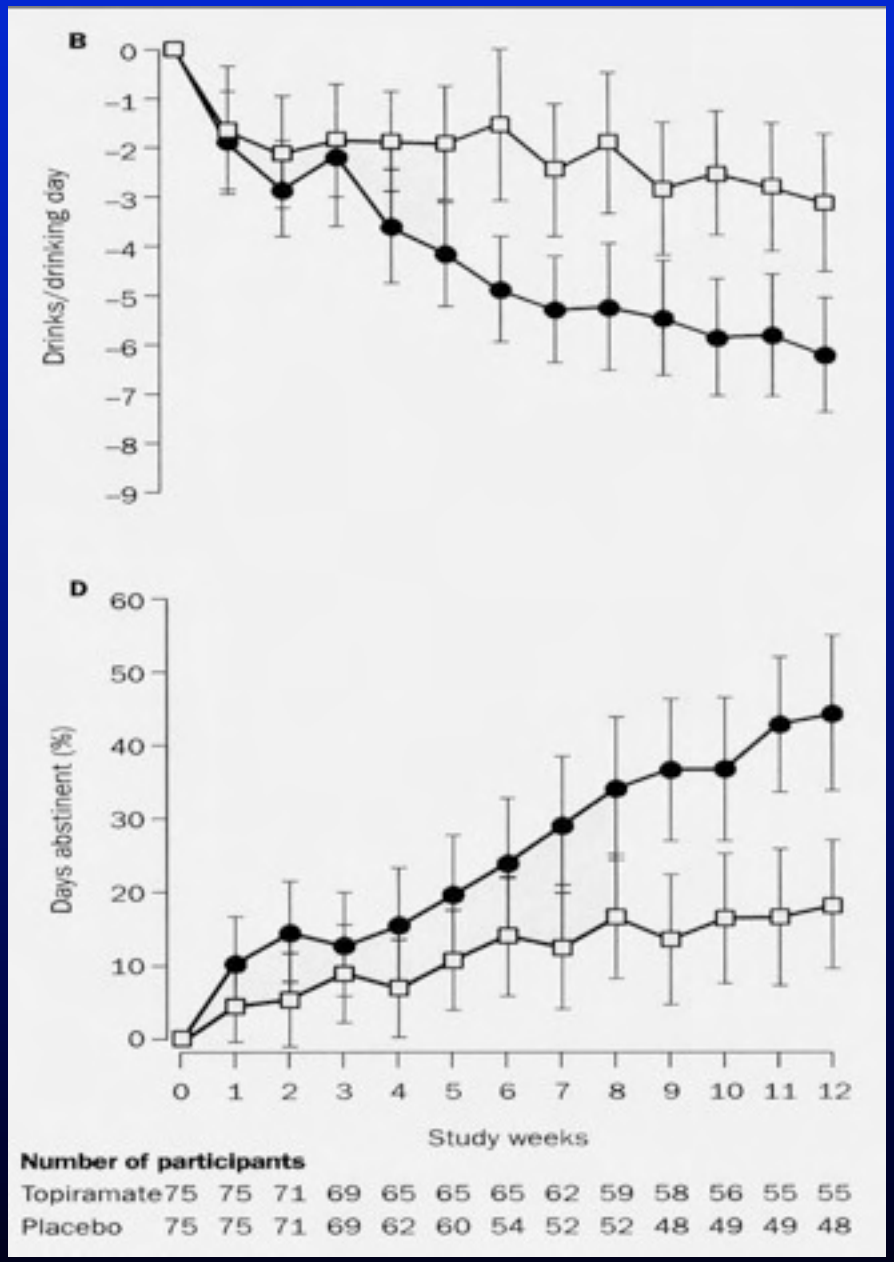
- James C. Garbutt, Chapel Hill
- Barbara Flannery, Baltimore

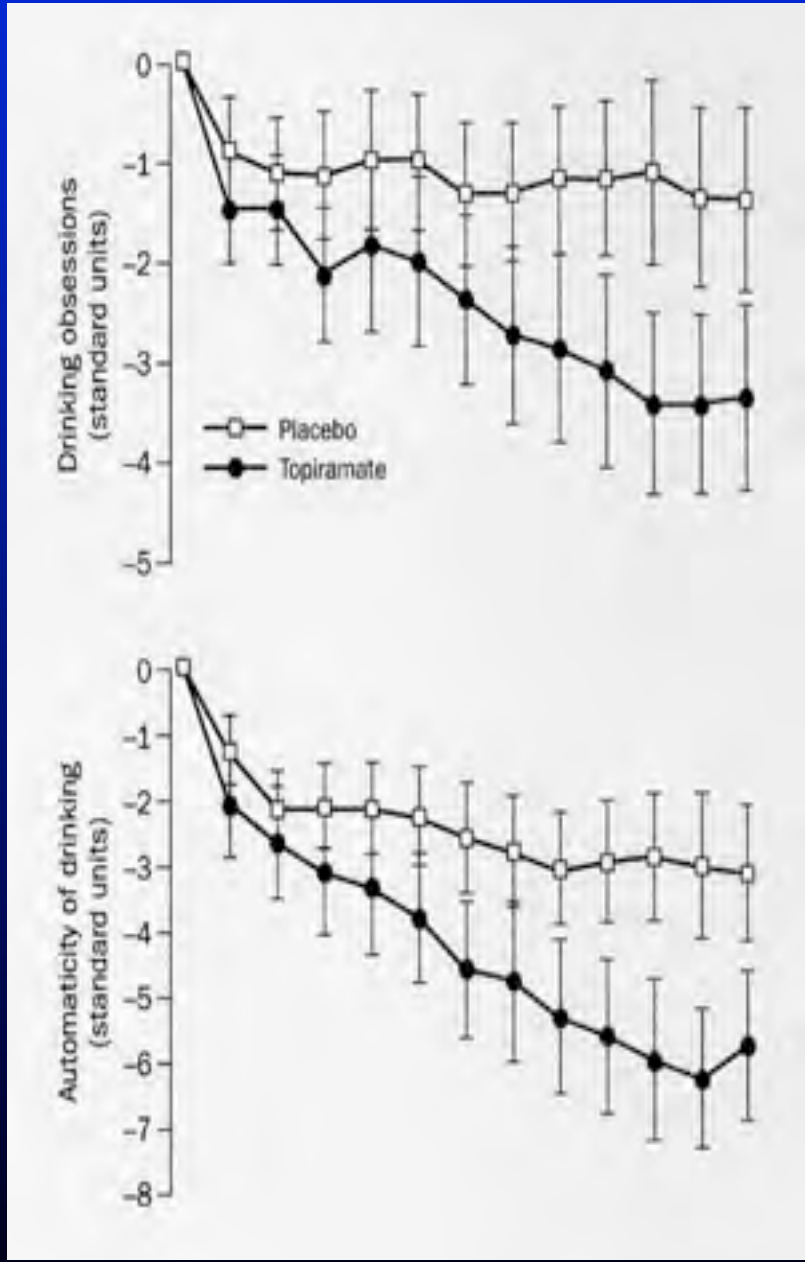
Coordinator Center : Rome
g.addolorato@rm.unicatt.it

Topiramate

- $GABA_A$ receptor agonist
- In a clinical trial, topiramate, compared with placebo, was efficacious at reducing craving and heavy drinking and improving abstinence among alcohol-dependent individuals; dose: 25 to 300 mg day
- Safety: no serious adverse events at study end
- No evidence of an interaction between alcohol and topiramate's adverse events profile at these dose levels

Johnson BA et al. Lancet. 2003





Johnson et al, Lancet 2003

27th Annual Scientific Meeting of the Research Society on Alcoholism
June 29, 2004; Vancouver, Canada

0145-6008/05/2902-0248$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH
Vol. 29, No. 2
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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.

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Hypothesis for the employment of different drugs for different types of alcohol dependent patients in relation to different craving profiles

Drug	Characteristics of the drug	Characteristics of the patient for the specific drug	Craving Pathway
Naltrexone	Opioid receptor antagonist	HD, PD, EOA; patients with binge drinking, inability to abstain; Lesch III and IV typology	*Reward*
Acamprosate	Ca^{++} acetyl homotaurinate	Lesch I and II typology; LOA; patients with withdrawal symptoms and reactive drinking	*Relief*
GHB	Alcohol mimetic with endogenous receptor	Patients with withdrawal symptoms and reactive drinking (patients have to be followed under strict medical control)	*Relief and Reward*
Baclofen	$GABA_B$ receptor agonist	Patients with withdrawal symptoms; patients with obsessive-compulsive drinking; patients with anxiety disorder	*Relief and Obsessive; Reward?*
Topiramate	$GABA_A$ receptor agonist	Patients with drinking obsessions, automaticity of drinking and interference due to drinking; LOA and EOA; Lesch III and IV typology?	*Obsessive; Reward?*
Fluoxetine, sertraline, citalopram	Selective Serotonin Reuptake Inhibitors	Patients with depression; patients with compulsive drinking?, loss of control? and alcohol related diseases?; LOA. Lesch III typology?	*Obsessive ?*
Ondansetron	5HT3 antagonist	EOA; Lesch IV typology?	*Obsessive*

HD: hazardous drinkers; PD: problematic drinkers;
LOA: Late-Onset Alcoholics; EOA: Early-Onset Alcoholics.

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