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

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Summary

Background **Intervention to achieve alcohol abstinence represents the most effective treatment for alcohol-dependent patients with liver cirrhosis; however, anticraving drugs might worsen liver disease. We aimed to investigate the effectiveness and safety of baclofen in achieving and maintaining alcohol abstinence in patients with liver cirrhosis.**

Methods **Between October, 2003, and November, 2006, 148 alcohol-dependent patients with liver cirrhosis were referred to the Institute of Internal Medicine, Rome, Italy. 84 were randomly allocated either oral baclofen or placebo for 12 weeks. Primary outcome was proportion of patients achieving and maintaining alcohol abstinence. Measures of this outcome were total alcohol abstinence and cumulative abstinence duration, which were assessed at outpatient visits. Relapse was defined as alcohol intake of more than four drinks per day or overall consumption of 14 or more drinks per week over a period of at least 4 weeks. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00525252.**

Findings **Of 42 patients allocated baclofen, 30 (71%) achieved and maintained abstinence compared with 12 (29%) of 42 assigned placebo (odds ratio 6·3 [95% CI 2·4–16·1]; p=0·0001). The number of dropouts (termination of treatment) did not differ between the baclofen (6/42 [14%]) and placebo (13/42 [31%]) groups (p=0·12). Cumulative abstinence duration was about twofold higher in patients allocated baclofen than in those assigned placebo (mean 62·8 [SE 5·4] *vs* 30·8 [5·5] days; p=0·001). No hepatic side-effects were recorded.**

Interpretation **Baclofen is effective at promoting alcohol abstinence in alcohol-dependent patients with liver cirrhosis. The drug is well tolerated and could have an important role in treatment of these individuals.**

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Introduction

Alcohol remains the most frequent cause of liver cirrhosis in developed countries.[1] Persistent alcohol intake in people with alcoholic cirrhosis is associated with high mortality.[2] The most effective management strategy for these individuals is to achieve total alcohol abstinence, since medical and surgical treatments for alcoholic liver disease have limited success when drinking continues.[1]

In the past few decades, several drugs have been assessed for their ability to reduce alcohol craving and, consequently, to increase abstinence and prevent alcohol relapse.[3] However, at present, no formal pharmacological trials are in progress that aim to reduce alcohol intake in people with alcoholic cirrhosis.[1] In trials of anticraving drugs, individuals with high amounts of aminotransferases, advanced liver disease, or both are typically excluded[4,5] because these agents undergo extensive liver metabolism and drug-related liver damage is possible. In particular, naltrexone is contraindicated in people with liver disease owing to its hepatic metabolism and reports of drug-related hepatic injury.[6] Findings of a preliminary study[7] suggested that acamprosate administered for 1 day was well tolerated in patients with Child-Pugh class A and B cirrhosis. However, as far as we are aware, no trials of prolonged treatment with this drug in people with cirrhosis have been undertaken. Topiramate is a promising agent. However, to our knowledge, no trials of this drug have been done in individuals with cirrhosis. Topiramate might induce hyperammonaemia,[8] and important changes in hepatic function tests have been noted.[9]

Baclofen, a γ aminobutyric acid (GABA) B-receptor agonist, represents a promising drug for treatment of craving in alcohol-dependent patients.[10] In accordance with data from preclinical experiments,[11] preliminary findings showed that the drug reduced alcohol craving and intake and enhanced abstinence in alcohol-dependent patients.[12,13] Baclofen has low liver metabolism (about 15%) and is mainly eliminated unmodified by the kidney.[14] No hepatic side-effects of the drug have been reported either in patients dependent on alcohol[12,13,15] or those with neurological disorders.[14] As a result, baclofen could represent a useful drug to augment alcohol abstinence in individuals affected by alcoholic liver cirrhosis. The aim of our study was to assess the effectiveness and safety of baclofen administration in achieving and maintaining alcohol abstinence in alcohol-dependent patients with liver cirrhosis.

Methods

Patients

Between October, 2003, and November, 2006, all alcohol-dependent patients affected by liver cirrhosis consecutively referred to the Institute of Internal Medicine of the

Catholic University in Rome, Italy (which has both a liver unit and an alcohol addiction unit), were assessed for eligibility for our study. Inclusion criteria were: age-range 18–75 years; diagnosis of alcohol dependence according to DSM-IV (diagnostic and statistical manual of mental disorders, 4th revision) criteria; diagnosis of liver cirrhosis; an alcohol intake of at least two heavy drinking days per week on average (men ≥5 drinks per day; women ≥4 drinks per day) and an average overall consumption of 21 drinks per week or more for men and 14 drinks per week or more for women during the 4 weeks before enrolment (one standard drink is equal to 12 g absolute alcohol); and presence of a referred family member able to assist with drug administration and monitoring. Exclusion criteria were: severe heart or lung disease; abnormal renal function, hepatorenal syndrome, or both; malignant disease; metabolic diseases; hepatic encephalopathy; treatment with interferon or corticosteroids within the past 60 days; psychopathological illness treated with psychoactive drugs; epilepsy; and addiction to drugs other than nicotine.

We diagnosed liver cirrhosis on the basis of histological findings, physical examination, or both, laboratory tests, and imaging studies; liver biopsy was not undertaken in 29 patients with severe coagulation disorders. We graded the clinical condition of patients at the time of enrolment according to the Child-Pugh classification. We investigated concomitant chronic viral hepatitis B and C infections. Patients with HBsAg, hepatitis C virus antibodies, or both were included in the study only if they met DSM-IV criteria for alcohol dependence and had a large alcohol intake (according to the inclusion criteria). Individuals with other causes of liver cirrhosis (ie, hereditary haemochromatosis, Wilson disease, primary biliary cirrhosis, autoimmune hepatitis) were excluded from the study on the basis of clinical, biochemical, serological, and histological hallmarks.

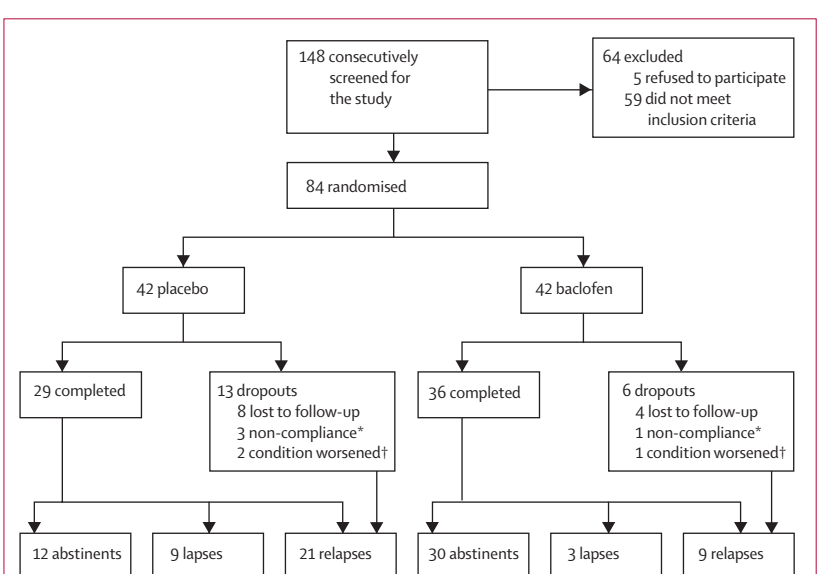

Figure 1: **Trial profile**
*Missed many appointments or failed to attend, or did not return tablet bottle, even at a subsequent visit. †Judged unrelated to study drug but rather to progression of liver disease.

The study protocol fully adhered to guidelines of the ethics committee of the Università Cattolica in Rome, Italy, where the study was done. Eligible patients provided written informed consent to take part in the study after receiving information on the characteristics, dosing rate, and possible side-effects of baclofen and on the possibility of dropping out of the study at any time.

Procedures

Every patient was admitted to hospital for 3–4 days. Admission was a research requirement to undertake biochemical, serological, and histological examinations and to treat potential alcohol withdrawal syndrome. We treated this disorder (diagnosed according to the clinical institute withdrawal assessment for alcohol—revised scale) when it arose with diazepam. In such individuals, baclofen or placebo administration was started after diazepam discontinuation.

As previously described,[12] eligible patients who provided informed consent were randomly allocated either oral baclofen or placebo. The randomisation sequence was generated by the pharmacist who prepared drug and placebo. Randomisation was balanced with blocks. The pharmacist did not have any further role in the study. Participants and investigators were unaware of treatment assignment. To maintain masking, the randomisation code was concealed in a safe box in the pharmacy. For the duration of the study (including also the 4 weeks of follow-up), the pharmacist or another employee of the same pharmacy could be contacted at any time to open the safe box in the case of a specific emergency. No such incident arose. We administered treatment in a double-blind fashion for 12 consecutive weeks. Placebo tablets were identical in size, colour, shape, and taste to baclofen. Tablets were entrusted to a family member, who was asked to administer every dose and monitor the patient for side-effects. Family members received information about possible side-effects and reported them at every outpatient visit. For the first 3 days, baclofen was given at a dose of 5 mg three times a day; subsequently, the dose was increased to 10 mg three times per day. We chose the prescribed dose on the basis of previous data.[12]

We strongly advised all patients against use of other agents capable of affecting craving for alcohol,[3] including benzodiazepines and antidepressants. Alcohol-sensitising drugs (ie, disulfiram) were not allowed during the study and subsequent follow-up period.

We assessed all patients as an outpatient every week for the first month and then every 2 weeks. At every visit, review of drinking, overall functioning, difficulties with treatment adherence, and adverse effects were addressed. Pill counts served as the primary marker of

treatment adherence, which was calculated as the total number of tablets dispensed minus the number returned divided by the total number of tablets dispensed. Only tablets that were returned were included in these pill counts. We also provided routine psychological support counselling at every visit. Counselling was undertaken by the same trained professional staff (SC, AM, and CD'A) in individual sessions of 30 min, directed mainly at identification of the difficulties related to alcohol dependence that the individual found hard to resolve in daily life. Counselling sessions were identical in content and counsellors were unaware of treatment allocated. We encouraged attendance at support groups (eg, Alcoholics Anonymous).

The primary outcome of our study was the proportion of patients achieving and maintaining alcohol abstinence. Primary outcome measures were total abstinence from alcohol and cumulative abstinence duration. We assessed abstinence from alcohol at every visit, on the basis of a patient's self-evaluation (reporting alcohol intake as the mean number of standard drinks consumed per day, where one standard drink is equal to 12 g of absolute alcohol), and family-member interview.[12,16] Where reports conflicted, the highest estimate was used. Patients and family members were instructed carefully about the amount of different alcoholic beverages corresponding to a standard drink. Moreover, to confirm alcohol consumption, we measured the alcohol content of blood, urine, or both. We calculated cumulative abstinence duration as the total number of days abstinent from alcohol. Alcohol relapse was defined as a daily alcohol intake of more than four drinks or an overall consumption of 14 drinks or more per week during at least 4 weeks.[16] We deemed alcohol lapse as any episode of alcohol consumption not classified as relapse. After drug discontinuation, we recorded the presence of possible side-effects attributable to drug withdrawal every week for the first 4 weeks by outpatient visits.

The secondary outcome of our study was the difference in craving measures between groups. Craving level was ascertained by the Italian version of the obsessive compulsive drinking scale (OCDS)[17] at the start of the study (T0) and at every visit (T1–T12). This validated scale consists of two subscales that measure both the obsessive and compulsive components of craving. OCDS total score and the obsessive and compulsive subscale scores were considered separately.

We measured liver enzymes and biological markers of alcohol abuse (ie, amounts of aspartate aminotransferase, alanine aminotransferase, γ glutamyltranspeptidase, and total bilirubin; international normalised ratio; and mean cellular volume), concentrations in blood of creatinine and ammonia, and the number connection test at T0, T4, T6, T8, T10, and T12. Amounts of albumin in serum were assessed at T0, T4, T8, and T12.

Statistical analysis

We calculated the sample size by considering the proportion of patients maintaining total alcohol abstinence as the primary outcome measure and differences in craving measures as secondary outcomes. At least 40 individuals were needed for each group. This estimate incorporated a standardised effect size of 0·50, nine timepoints (T0, T1–T4, T6, T8, T10, and T12), a correlation of 0·6 constant over time,[18] and a power of 0·80 for a two-tailed hypothesis test with an α of 0·05. Accordingly, we included 42 people in each group to allow for dropouts. With this sample size, a difference in proportion of abstinent patients between groups of almost 0·31 was judged significant, assuming that the proportion of success in the placebo group was 0·20.[12,19] We regarded $p<0·05$ as significant.

We assumed for this analysis that all patients who terminated treatment before the end of the study had relapsed. For these individuals, cumulative abstinence duration was calculated with data available at the time of the last outpatient visit. We compared the number of abstinent patients in the two treatment groups with the two-sided Fisher's exact test. The same analysis was used to compare the number of dropouts. Dropouts were defined as those patients who terminated treatment before the end of the study.

	Excluded patients (n=64)
Demographic characteristics	
Age (years)	56·0 (45·5–62·0)
Men	23 (64)
Married	33 (52)
Education >13 years	21 (33)
Employed	48 (75)
Addiction characteristics	
Duration of daily consumption of alcohol (years)	18·0 (10·5–23·0)
Duration of alcohol abuse by DSM criteria (years)	23·5 (18·0–32·5)
Liver cirrhosis characteristics	
Child-Pugh class	
A	8 (13)
B	14 (22)
C	42 (66)
Reasons for exclusion*	
Refusal to participate	5 (8)
Severe heart or lung disease	6 (9)
Renal dysfunction, hepatorenal syndrome, or both	33 (52)
Hepatic encephalopathy	27 (42)
Metabolic diseases (including diabetes)	11 (17)
Psychopathological illness treated with psychoactive drugs	19 (30)
Addiction to drugs other than nicotine	8 (13)
Malignant disease (including hepatocellular carcinoma)	19 (30)
Epilepsy or epileptiform convulsions	1 (2)

Data are number of individuals (%) or median (IQR). *Sum exceeds 100% since some individuals were excluded for more than one reason.

Table 1: **Characteristics of individuals excluded from study**

	Placebo (n=42)	Baclofen (n=42)
Demographic characteristics		
Age (years)	49·5 (44·0–60·0)	49·0 (43·0–61·0)
Men	29 (69)	32 (76)
Married	24 (57)	27 (64)
Education >13 years	9 (21)	12 (29)
Employed	31 (74)	33 (79)
Addiction characteristics		
Duration of daily consumption of alcohol (years)	16·0 (13·0–23·0)	16·0 (12·0–24·0)
Duration of alcohol abuse (years)	22·0 (17·0–26·0)	22·0 (17·0–27·0)
Obsessive compulsive drinking scale (OCDS) scores		
OCDS total	25·0 (22·0–29·0)	28·0 (23·0–32·0)
Compulsive subscale	9·5 (8·0–12·0)	12·0 (9·0–14·0)
Obsessive subscale	15·0 (14·0–18·0)	16·5 (14·0–20·0)
Alcohol withdrawal syndrome treated by diazepam	11 (26)	13 (31)
Liver cirrhosis characteristics		
Child-Pugh score	9·0 (8·0–11·0)	9·0 (8·0–11·0)
Child-Pugh class		
A	6 (14)	4 (10)
B	20 (48)	20 (48)
C	16 (38)	18 (43)
Hepatitis B virus positive	10 (24)	3 (7)
Hepatitis C virus positive	12 (29)	12 (29)

Data are number of patients (%) or median (IQR).

Table 2: **Baseline characteristics of study participants**

	Placebo (n=42)	Baclofen (n=42)
Mean cellular volume (fL)	98·7 (91·4–103·0)	98·2 (90·0–104·7)
γ glutamyltransferase (U/L)	200·5 (99·0–290·0)	159·5 (89·0–333·0)
Aspartate aminotransferase (U/L)	84·0 (50·0–121·0)	79·0 (48·0–121·0)
Alanine aminotransferase (U/L)	98·0 (52·0–127·0)	77·5 (49·0–111.0)
Bilirubin (g/L)	2·6 (2·1–3·3)	2·6 (2·1–3·3)
Albumin (g/L)	29·0 (26·0–32·0)	29·5 (27·0–32·0)
International normalised ratio	2·1 (2·0–2·6)	2·1 (2·0–2·7)
Creatinine (g/L)	0·9 (0·8–1·0)	0·9 (0·8–1·0)

Data are median (IQR).

Table 3: **Baseline biological measures of alcohol misuse and liver and kidney function in study participants**

	Total alcohol abstinence (n [%])		Odds ratio (95% CI)	p
	Placebo	Baclofen		
Child-Pugh A*	1/6 (17)	3/4 (75)	10·3 (0·4–939·7)	0·2381
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)	0·0001

*Point and interval odds ratio estimates and relative p values were calculated using exact logistic regression.

Table 4: **Total alcohol abstinence by Child-Pugh classification**

We estimated survival functions with the Kaplan-Meier approach for each treatment group, taking the first episode of abstinence failure (lapse or relapse) as the event of interest. The difference between groups was measured by log-rank test. We used Cox's proportional-hazards regression model to analyse predictors of lapse and relapse. The assumption of proportional hazards was measured by testing the significance of interactions between every covariate and time.[20]

Our analysis was done by intention to treat, insomuch that we assumed every patient took the drug allocated to them and counted them in that group.[21] To take into account repeated measures for the same individual, an ANCOVA mixed model was fitted, including as fixed effects: treatment group; time; interaction between treatment group and time; and baseline measure of response variable.[22] We tested the assumption of homogeneity effect of baseline in each group with the interaction term between baseline measure×group. This approach allows us to use all available data since it can be applied adequately to unbalanced data and to repeated measurements taken at unequal timepoints.[23] Moreover, the ANCOVA model is a more powerful technique than ANOVA to detect change from baseline.[24] To define the correlation between repeated measurements, we selected a covariance pattern between observations (spatial power law), which was specific for unequally spaced data.[25] F tests were based on Kenward-Roger's adjusted degrees of freedom, an approach specifically proposed for small sample setting.[26] Moreover, between-patient variability was regarded in the model as a random effect. When between-group differences of craving levels and liver function tests were measured, we assumed that missing data were missing at random; in other words, missing data depend on observed outcomes but not unobserved outcomes. Under this assumption, estimates will be valid and fully efficient provided that the model assumed for the data distribution is correct.[27] All calculations were done with some procedures of SAS version 8.2.

This study is registered with ClinicalTrials.gov, number NCT00525252.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Of 148 alcohol-dependent patients initially screened for the study, 64 did not meet study criteria. Table 1 reports characteristics of excluded individuals and reasons for exclusion. 84 people met study criteria and were randomly allocated either placebo or baclofen. Table 2 shows study participants' baseline demographic, addiction, and liver cirrhosis characteristics. Table 3 reports baseline biological measures of alcohol misuse and liver and kidney function.

More patients allocated baclofen achieved and maintained alcohol abstinence throughout the study

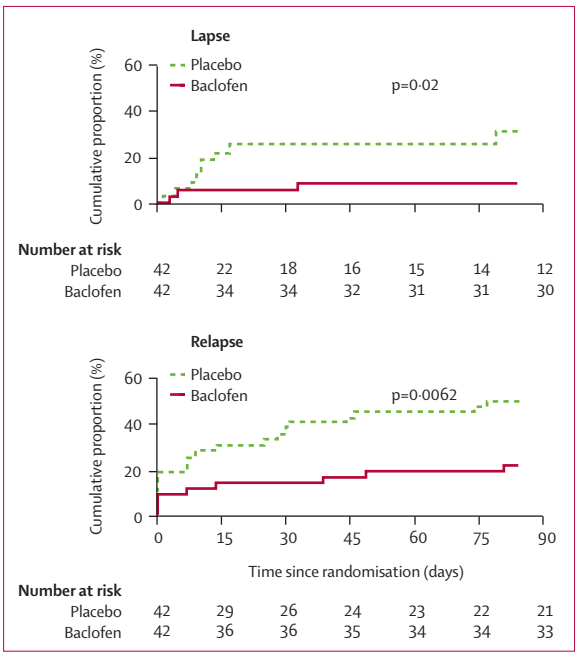

Figure 2: **Kaplan-Meier survival analysis of proportion of lapse and relapse**
Number at risk refers to proportion remaining free of lapse and relapse.

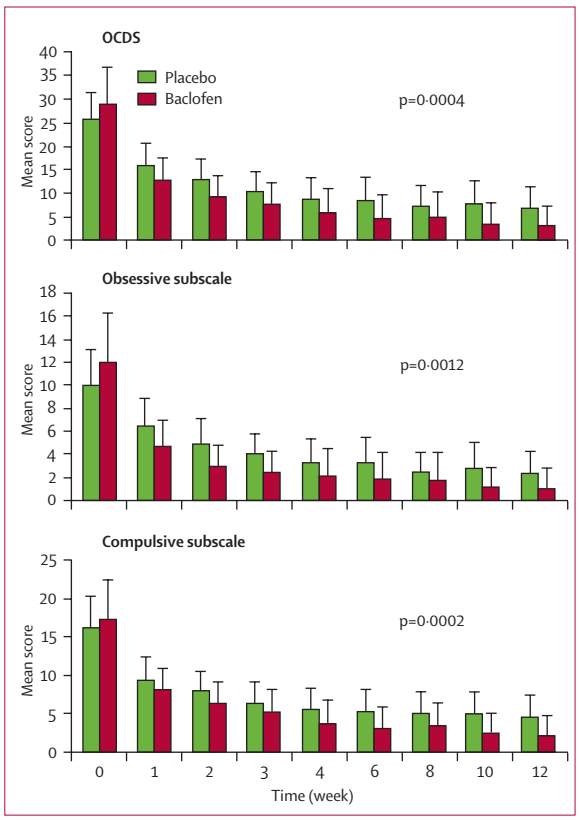

Figure 3: **Mean total craving score (OCDS) and compulsive and obsessive subscale scores in the two treatment groups at different observation times**
Error bars represent SD.

period (30/42 [71%]) than did those assigned placebo (12/42 [29%]; odds ratio 6·3 [95% CI 2·4–16·1]; p=0·0001). Table 4 shows the breakdown for total alcohol abstinence by Child-Pugh classification. More individuals were totally abstinent from alcohol in the baclofen group than in the placebo group for both class B and C.

The number of dropouts did not differ between the baclofen and placebo groups (6/42 [14%] *vs* 13/42 [31%]; p=0·12). Cumulative abstinence duration was about twofold higher in patients allocated baclofen than in those assigned placebo (mean 62·8 [SE 5·4] *vs* 30·8 [5·5] days; p=0·001). Survival analysis indicated a significantly greater chance of remaining free of lapse and relapse to alcohol consumption in individuals allocated baclofen (figure 2). At 30 days after randomisation, six (14%) alcohol-dependent patients in the group allocated baclofen had relapsed compared with 16 (38%) assigned placebo. At 60 days, eight (19%) and 19 (45%) relapses, respectively, were recorded. Findings of the Cox's proportional-hazards regression analysis showed a hazard ratio of 0·2 (95% CI 0·1–0·9) for lapse and of 0·4 (0·2–0·8) for relapse in patients allocated baclofen. Adding to this model age, sex, duration of alcohol abuse, Child-Pugh class, average alcohol daily consumption, and liver function measures did not predict lapse (data not shown). International normalised ratio was inversely associated with probability of relapse (hazard ratio 0·2; [95% CI 0·1–0·5]).

Figure 3 shows the mean total craving score (OCDS) and compulsive and obsessive subscale scores in the two treatment groups at different observation times. Baclofen significantly reduced craving scores. Findings of the ANCOVA mixed model showed a significant effect of both treatment and time on total OCDS and compulsive and obsessive subscale scores (table 5). Interaction of treatment effects by time was significant only for the compulsive subscale score.

Figure 4 shows mean values of biological liver variables measured during the 12-week study period. Individuals allocated baclofen had significantly reduced alanine aminotransferase, bilirubin, international normalised ratio, and γ glutamyltransferase from baseline and significantly increased albumin (table 5). A significant effect of the interaction between treatment and time on biochemical values was noted only for albumin values. No difference was seen in aspartate aminotransferase, mean cellular volume, and creatinine values between baclofen and placebo group.

No patients had encephalopathy during the study period. Further, none showed hyperammonaemia or a relevant change in number connection test performance (data not shown). No serious systemic or single-organ event leading to drug cessation was reported and no patient discontinued treatment because of a side-effect. Tolerability was fair in all individuals. Side-effects in the baclofen group were headache (n=4), tiredness (1), vertigo (2), and sleepiness (1), and in the placebo group

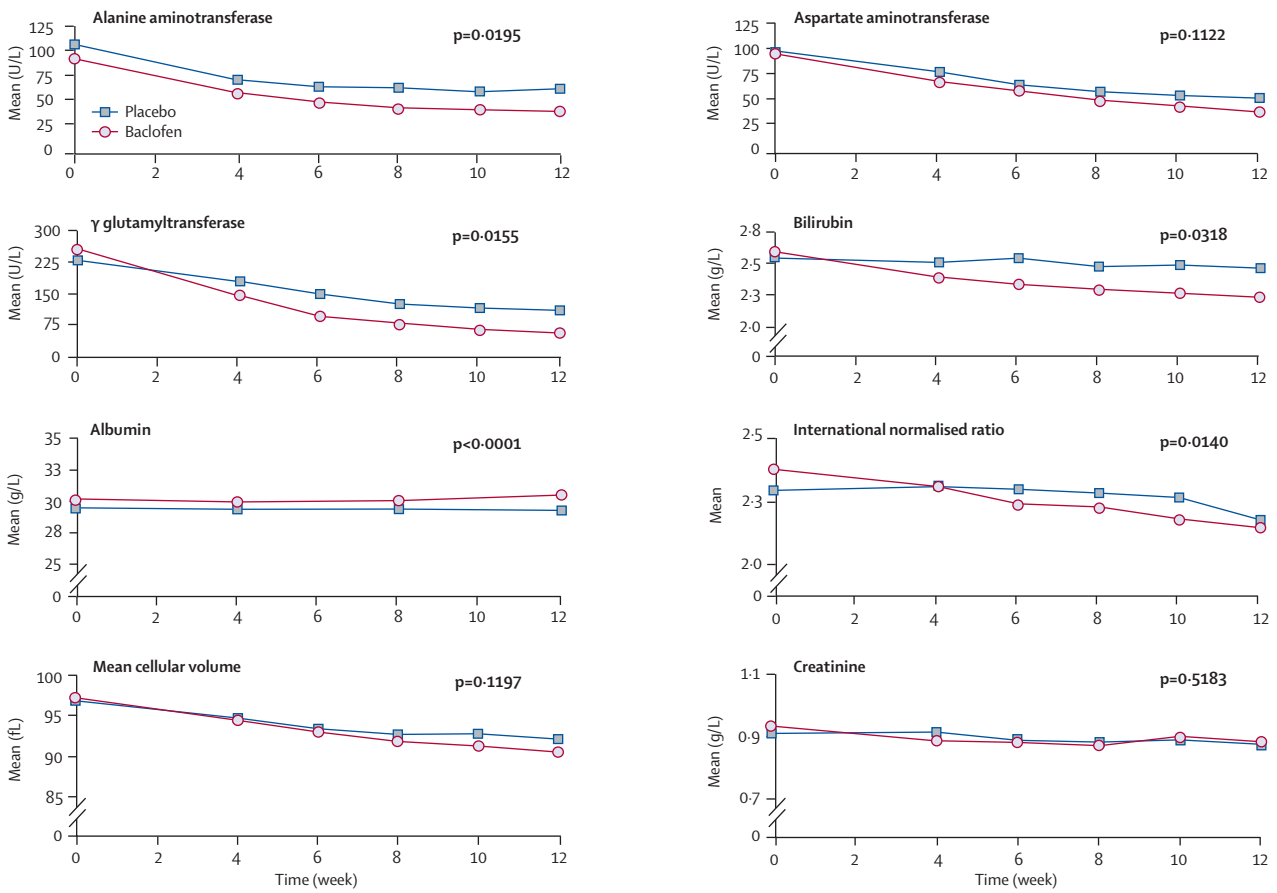

Figure 4: **Mean values of biological liver variables in the two treatment groups during the study period**

	Drug		Time		Drug time	
	F	p	F	p	F	p
OCDS	13·7	0·0004	61·5	<0·0001	1·9	0·0704
Compulsive subscale	15·4	0·0002	47·5	<0·0001	2·1	0·0388
Obsessive subscale	11·5	0·0012	50·4	<0·0001	1·6	0·1218
Alanine aminotransferase	5·7	0·0195	4·3	0·0023	0·7	0·6134
Aspartate aminotransferase	2·6	0·1122	14·0	<0·0001	0·4	0·8028
γ glutamyltransferase	6·2	0·0155	16·2	<0·0001	0·4	0·7766
Bilirubin	4·8	0·0318	2·3	0·0556	1·8	0·1346
Albumin	17·4	<0·0001	1·4	0·2581	4·5	0·0138
International normalised ratio	6·4	0·0140	4·1	0·0031	0·6	0·6761
Mean cellular volume	2·5	0·1197	19·7	<0·0001	1·1	0·3732
Creatinine	0·4	0·5183	1·8	0·1375	0·8	0·5585

Table 5: **Effects of drug, time, and interaction on addiction and laboratory variables, estimated by ANCOVA mixed models**

headache (4), tiredness (1), and vertigo (1). No patient allocated baclofen reported euphoria or other pleasant effects attributed to the drug, and no reports were noted of craving for baclofen. Treatment adherence did not differ between groups, with individuals allocated placebo taking a mean of 79·5% (SD 10·2) of their dose compared with 82·8% (11·6) for those allocated baclofen (p=0·1699).

During the 4 weeks after drug discontinuation, one lapse and two relapses in the placebo group and one lapse and one relapse in the baclofen group were recorded. Neither a drug withdrawal syndrome nor any side-effects attributable to drug suspension were noted.

Discussion

Our results show that oral administration of baclofen is significantly more effective than placebo at achieving and maintaining alcohol abstinence and at increasing cumulative abstinence duration in alcohol-dependent patients with liver cirrhosis. This reduction in self-reported alcohol use was associated with significant reductions in clinical markers of liver injury (alanine aminotransferase, γ glutamyltransferase, bilirubin, and international normalised ratio), findings that confirm self-reported data and suggest that the reduction in alcohol consumption was sufficient to lessen liver injury.

As previously reported, the higher effectiveness of baclofen compared with placebo at achieving and maintaining alcohol abstinence could be related to effectiveness of the drug at rapid reduction of alcohol craving,[12,13] in particular in its compulsive and obsessive components.[12] This observation is confirmed by the significant reduction in both total OCDS score and compulsive and obsessive subscale scores in individuals allocated baclofen. Although significantly lower in the baclofen group, craving scores were also reduced with placebo, probably owing to medical management and supportive treatment. In the baclofen group, the higher reduction of craving could also account for the fewer dropouts. Although not significant, the higher number of dropouts in the placebo group could be related to low placebo effectiveness—an observation that is in line with findings of previous pharmacological trials in psychiatric patients[28] and with preliminary data for baclofen effectiveness in alcohol-dependent individuals.[12]

Notwithstanding that alcohol abstinence and relapse prevention represent the main objectives in treatment of alcohol-dependant patients with liver cirrhosis,[1] such individuals are usually excluded from trials of anticraving drugs[1] because of concerns that these agents might worsen liver disease. The safety profile of baclofen[12–15] enabled us to test this drug on alcohol-dependent patients with liver cirrhosis. To our knowledge, our trial represents the first study in which effectiveness and safety of an anticraving drug has been investigated in such individuals with advanced liver disease.

In our study, only five people who were eligible refused to participate. The previous scarcity of available anticraving drugs for alcohol-dependent patients with cirrhosis could have been an incentive for participation.

Although total alcohol abstinence was not a rare event in this study, effectiveness of baclofen was especially evident in people with advanced cirrhosis, such that the odds ratio to maintain abstinence compared with placebo exceeded 4 in individuals classified with Child-Pugh B cirrhosis and 8 for Child-Pugh C disease. Possibly, patients affected by severe liver injury had the most motivation to stop their drinking behaviour, but as shown by the modest rate of abstinence in the placebo group, motivation, psychological support, and regular follow-up visits alone were not enough.

Total alcohol abstinence represents the most effective strategy for alcohol-dependent patients affected by liver cirrhosis. Findings of meta-analyses have shown that even low doses of daily alcohol intake are associated with increased risk of cirrhosis.[29] Total abstinence from alcohol consumption enhances the clinical outcome of all stages of alcoholic liver disease.[1] As a result, achieving total alcohol abstinence should represent the main aim in management of patients affected by any stage of liver cirrhosis. Abstinence can lead to substantial regression of fibrosis and, possibly, early cirrhosis.[1] Continued alcohol abuse is a risk factor for cirrhosis-related complications, including hepatocellular carcinoma,[1] and represents an absolute contraindication to liver transplantation in these patients.[30]

Liver transplantation is now an established treatment for end-stage alcoholic cirrhosis, although concerns remain about risk for recurrent alcohol abuse.[31] Strategies to reduce this risk in patients both before and after transplantation can help to avoid harmful alcohol relapse.[31] From this point of view, baclofen could have a role in this setting, taking into account both its effectiveness and safety, although long-term follow-up studies are needed to address these points.

No hepatic side-effects were noted in patients, and baclofen was well tolerated by individuals with Child-Pugh class A, B, and C cirrhosis. The absence of hepatic side-effects was lent support by the decrease in aminotransferase concentrations. Specifically, measures of liver function, including amounts of γ glutamyltransferase, fell significantly in patients allocated baclofen. This outcome was presumably attributable to suspension or reduction of alcohol intake, but the parallel diminution in indices of hepatocellular damage further points to the safety of the drug, even in the event of relapses to heavy drinking. The absence of hepatotoxic effects could be related to low liver metabolism of baclofen, which is mainly excreted unmodified by the kidney.[14]

No renal side-effects were recorded. Specifically, no patients had increased creatinine concentrations. Our present observations indicate that baclofen is safe in individuals with cirrhosis, at least in those without kidney diseases, hepatorenal syndrome, or both.

No serious side-effects were reported, a feature in line with previous data.[12] The absence of serious side-effects was also noted by Shoptaw and colleagues[32] in cocaine-dependent patients treated with doses of baclofen higher than those used in our study. The safety of baclofen can account, at least partly, for the scarcity of dropouts attributable to drug side-effects. Moreover, the safety of baclofen enabled us not to compromise the masked fashion of the trial.

Researchers have suggested that GABA drugs, in particular those acting on GABA A-receptors, can increase risk for hepatic encephalopathy.[33] However, our patients did not show encephalopathy during the study, probably because baclofen is a selective GABA B-receptor agonist. This aspect could further act in favour of this drug as an anticraving treatment for alcohol-dependent patients with liver cirrhosis.

Our study has some limitations. First, alternate standardised methods to monitor drinking (such as the time-line follow-back) are scarce. Second, we assumed a missing-at-random mechanism for analysis of missing data. We are not able to exclude a missing-not-at-random mechanism in our data, and this possibility could have biased our estimates. However, methods that attempt to account for a missing-not-at-random mechanism need strong assumptions that are difficult to validate.[34] Third,

differences between cumulative prevalence frequency at 30 and 60 days for lapses were potentially affected by the low number of events recorded.

In conclusion, our results suggest that baclofen, because of its anticraving action and safety, could have an important role for treatment of alcohol-dependent patients with advanced liver disease. We have shown that a pharmacological agent can promote alcohol abstinence and prevent alcohol relapse in individuals with alcoholic liver disease. Further studies are needed to define the best duration of treatment, to assess possible tolerance to baclofen in a more prolonged regimen, and to define the role of baclofen in clinical practice.

Contributors

GA thought of the neuroscientific basis and rationale for the study. GA, LL, and GG designed the protocol and wrote the report. GA, LL, AF, LV, and LA did the research. AZ and PSH participated in statistical analysis and interpretation of data and helped to write the report. SC, AM, and CD'A provided psychological support counselling. FC assisted with interpretation of data. All investigators contributed to report revision.

Conflict of interest statement

We declare that we have no conflict of interest.

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