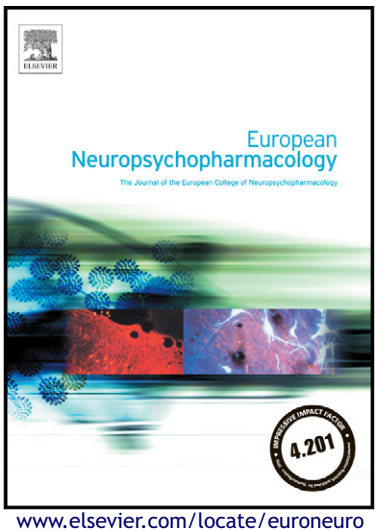

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High-Dose Baclofen for the Treatment of Alcohol Dependence (BACLAD Study): A Randomized, Placebo-Controlled Trial

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Abstract

Previous randomized, placebo-controlled trials (RCTs) assessing the efficacy of the selective γ-aminobutyric acid (GABA)-B receptor agonist baclofen in the treatment of alcohol dependence have reported divergent results, possibly related to the low to medium dosages of baclofen used in these studies (30-80 mg/d). Based on preclinical observations of a dose-dependent effect and positive case reports in alcohol-dependent patients, the present RCT aimed to assess the efficacy and safety of individually titrated high-dose baclofen for the treatment of alcohol dependence. Out of 93 alcohol-dependent patients consecutively screened, 56 were randomly assigned to a double-blind treatment with individually titrated baclofen or placebo using dosages of 30-270 mg/d. The multiple primary outcome measures were 1) total abstinence and 2) cumulative abstinence duration during a 12-week high-dose phase. More patients of the baclofen group maintained total abstinence during the high-dose phase than those receiving placebo (15/22, 68.2 % vs. 5/21, 23.8 %, p = 0.014). Cumulative abstinence duration was significantly higher in patients given baclofen compared to patients of the placebo group (mean 67.8 (SD 30) vs. 51.8 (SD 29.6) days, p = 0.047). No drug-related serious adverse events were observed during the trial. Individually titrated high-dose baclofen effectively supported alcohol-dependent patients in maintaining alcohol abstinence and showed a high tolerability, even in the event of relapse. These results provide further evidence for the potential of baclofen, thereby possibly extending the current pharmacological treatment options in alcohol dependence.

Keywords: Alcohol dependence - pharmacotherapy - high-dose baclofen

Introduction

Alcohol use disorders (AUDs) are chronic and widespread diseases accounting for 44.4 % of the years of life lost (YLLs) attributable to mental and substance use disorders worldwide (Whiteford et al., 2013). In the vast majority of alcohol-dependent patients, the clinical course is characterized by multiple relapses to drinking after detoxification treatment, with relapse rates ranging from 75 % to 85 % (Boothby and Doering, 2005; Bottlender et al., 2007). Besides attendance at self-help groups, and psychosocial and psychotherapeutic treatment approaches, only a few specific pharmacological interventions for alcohol-dependent patients exist to date. Since 1948, only 4 substances have been approved by the Federal Drug Administration (FDA), namely the aldehyde dehydrogenase inhibitor disulfiram, the putative glutamate modulator acamprosate (recent findings suggest a calcium-related mechanism of action) (Spanagel et al., 2014), and the opioid antagonist naltrexone (2 formulations, oral and injectable) (Zindel and Kranzler, 2014). In Europe, the opioid antagonist nalmefene has also been approved by the European Medicines Agency (EMA) for the reduction of alcohol consumption in alcohol-dependent patients (EMA, 2013). Although several, but not all, of these compounds have repeatedly been shown to be effective in clinical trials (Anton et al., 2006; Mann et al., 2013; Rosner et al., 2010a; Rosner et al., 2010b; Suh et al., 2006), the observed effects were only modest; for instance, acamprosate has been shown to reduce the risk of relapse by 14 % and to increase cumulative abstinence duration by 11 % compared to placebo in a meta-analysis (Rosner et al., 2010a). Naltrexone was found to reduce the risk of heavy drinking by 17 % compared to placebo, heavy drinking days by 3 %, drinking days by 4 % and the amount of alcohol consumed per drinking day by 11 grams (Rosner et al., 2010b). Therefore, further clinical evaluation of new pharmacological strategies is crucial to optimize treatment of alcohol-dependent patients.

In recent years, animal studies have suggested that the GABA-B receptor system is involved in alcohol-related behaviors (Colombo et al., 2004). The GABA-B receptor is located within several brain areas including the so-called mesolimbic reward system of the brain, and has

been hypothesized to modulate dopaminergic neurotransmission (Bowery et al., 1987; Fadda et al., 2003), which plays an important role in the development and maintenance of alcohol dependence (Heinz, 2002; Koob and Volkow, 2010). The selective GABA-B receptor agonist baclofen is approved for the treatment of spasticity resulting from various neurological conditions. There is preclinical evidence from studies in rats that baclofen suppresses the acquisition and maintenance of alcohol drinking behavior as well as an increase in alcohol intake after a period of alcohol abstinence (Agabio and Colombo, 2014).

In alcohol-dependent patients, a few RCTs using baclofen have been published to date (Addolorato et al., 2002; Addolorato et al., 2011; Addolorato et al., 2007; Garbutt et al., 2010). These studies reported a high tolerability of baclofen (including in patients with comorbid liver cirrhosis) (Addolorato et al., 2007), but conflicting results in terms of efficacy (Caputo et al., 2014; Muller et al., 2014). Given the low ability of baclofen to cross the blood brain barrier (Taira, 2009), these inconsistent findings might be related to the rather low dosages of baclofen used in these trials (30-80 mg/d). Based on preclinical observations of a dose-dependent effect of baclofen on alcohol consumption in rodents treated with dosages up to 3 mg/kg (Colombo et al., 2003), as well as positive case reports in alcohol-dependent patients receiving high-dose baclofen up to 270 mg/d (Ameisen, 2005), the present RCT aimed to investigate the efficacy and safety of individually titrated high-dose baclofen (up to 270 mg/d) in alcohol-dependent patients using a 2-arm, parallel-group, double-blind, randomized and placebo-controlled design.

Experimental procedures

Setting and Patients

This study was conducted at the outpatient unit of the Department of Psychiatry and Psychotherapy at the Campus Charité Mitte of the Charité - Universitätsmedizin Berlin. Patients were recruited from our in- and outpatient department as well as by spontaneous referral at the study site. The first patient was recruited in March 2011, and the last visit was completed in May 2014. Inclusion criteria for men and women were: a) age of ≥ 18 and < 65 years; b) diagnosis of alcohol dependence according to ICD-10 (WHO, 1994) and DSM-IV-TR ((APA), 2000); c) an alcohol consumption of at least 2 heavy drinking days per week on average (men ≥ 5 drinks per day; women ≥ 4 drinks per day; 1 standard drink is equal to 12 g absolute alcohol) and an average overall alcohol intake of 21 drinks per week or more for men and 14 drinks per week or more for women during the 4 weeks before detoxification; d) a completed in- or outpatient detoxification before randomization; e) last alcohol consumption within 7 to 21 days before randomization; and f) sufficient German language skills. Exclusion criteria were significant internal, psychiatric (axis I diagnoses other than alcohol or nicotine dependence) or neurological conditions; current treatment with psychotropic drugs that could affect study outcome (i.e. sedatives, alcohol relapse prevention such as acamprosate, disulfiram, naltrexone, antidepressants, antipsychotics, anticonvulsants); epilepsy or epileptiform convulsions; pregnancy and/or currently breastfeeding; intolerance to baclofen; terminal renal failure; alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) values 5 times the upper normal limit, bilirubin > 1.9 mg/dl, International Normalized Ratio (INR) > 1.6; gastrointestinal ulcera; and treatment mandated by a legal authority.

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and approved by the local ethics committee, the ethics committee of the state of Berlin (Landesamt für Gesundheit und Soziales Berlin) and the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). Written informed consent was obtained from all patients.

Procedures

The 24-week trial consisted of four intervals, i.e., the titration phase (up to 4 weeks, depending on the individually tolerated high-dose), high-dose phase (12 weeks), tapering phase (up to 4 weeks) and follow-up (4 weeks after termination of study medication). The study design is shown in Figure 1. Thirteen to 17 visits were performed throughout the study (depending on the individually titrated high-dose): screening and baseline (both visits could be combined), 1-3 weekly visits during the titration phase, 1 visit after reaching the individual high-dose, 6 bimonthly visits during the high-dose phase, 1-3 visits during the tapering phase, 1 visit after termination of study medication, and 1 follow-up visit 4 weeks after termination of study medication. Additionally, telephone visits were performed during the titration and tapering phases after each dosing step to assess treatment adherence, occurrence of relapses, and adverse events. Furthermore, pill count was performed to assess medication adherence. All patients received the standardized supportive therapy previously used in the COMBINE study (Anton et al., 2006) (Medical Management, MM) (Pettinati et al., 2004), which focuses on psychoeducation and enhancement of motivation and adherence. Starting from baseline, up to 9 sessions were performed within the consecutive clinical visits.

Figure 1: BACLAD trial profile.

Randomisation and masking

Following screening, patients were randomly assigned at the baseline visit to double-blind treatment with baclofen or placebo in a 1:1 ratio according to a computer-generated randomization list (in blocks of 4; stratification with regard to sex). The randomization list was kept by the biometrician and the study pharmacist who prepared the study medication packages. The study pharmacist did not have any further role in the trial. Sealed envelopes

containing study medication details were kept at the outpatient unit to be opened by a staff member in case of a study drug-related emergency. During the whole study, no unblinding was necessary.

According to a detailed medication plan, all patients received boxes containing between 11 and 50 capsules each in dosages of 5, 10 or 30 mg of baclofen or placebo (depending on the respective clinical visit). For the first 3 days, patients received baclofen or placebo in identical capsules in a dose of 5 mg t.i.d.; subsequently, the daily dose of baclofen/placebo was increased to a maximum of 90 mg t.i.d. within 4 weeks (titration phase). In case of intolerance, the dosage could be reduced to a minimum of 10 mg t.i.d. Patients received the maximum tolerated dosage of baclofen or placebo for 12 consecutive weeks (high-dose phase). Medication was then gradually tapered over a maximum of 4 weeks (tapering phase). In the event of alcohol consumption, study medication was subsequently tapered (as a requirement of the competent authority) according to the dose titration schedule (Table 1).

Table 1: Dose titration schedule.

Assessments

During the trial the following examinations and assessments were performed:

- Physical examination (psychiatric, neurologic, internal) at the screening visit, after reaching the individual high-dose, after termination of the study medication, and at the follow-up visit.
- Clinical visits including assessment of adverse events, vital signs, breathalyzer test, Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1976), Hamilton Depression Scale (HAM-D) (Hamilton, 1960), Visual Analogue Scale of Craving (VASC) (Mottola, 1993), Obsessive Compulsive Drinking Scale (OCDS-G) (Nakovics et al., 2008), Timeline Followback (TLFB) (Sobell and Sobell, 1992) conducted weekly from the screening

visit to the time point of reaching the individual high-dose, thereafter bimonthly until the tapering phase, then again weekly; 1 follow-up visit 4 weeks after termination of study medication. The Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and the Alcohol Dependence Scale (ADS) (Skinner and Horn, 1984) were assessed at the baseline visit.

- Blood chemistry testing at the screening visit, subsequently monthly until termination of study medication. Serum levels of the study medication were assessed 2 weeks after reaching the individual high-dose.
- Electrocardiogram at screening visit and after termination of study medication.
- Telephone visits after each increase or decrease in the dose.

Outcome Measures

The multiple primary outcome measures were 1) total abstinence and 2) cumulative abstinence duration during the high-dose phase. Abstinence was defined as negative subjective report plus negative breathalyzer test as well as a level of carbohydrate-deficient transferrin (CDT) within the normal range, or, if increased, lower compared to the baseline level. Based on previously published trials (Addolorato et al., 2007; Johnson et al., 2007) and our own clinical experience, we chose a conservative approach assuming for data analysis that all patients who dropped out of the study had relapsed. Drop-out was defined as termination of treatment before study end.

Secondary outcomes were safety and tolerability of the study drug, drop-out rate, and changes in psychiatric assessments compared to baseline (HAM-A, HAM-D, VASC and OCDS-G).

Sample Size Calculations and Statistical Analyses

The sample size was calculated for the multiple endpoint 1) total abstinence and 2) cumulative abstinence duration during the high-dose phase according to the principle of ordered hypotheses, which allows for testing every single endpoint with the full α-level (Maurer et al., 1995). Based on a previous report of an abstinence rate of 71.4 % for baclofen and 28.6 % for placebo as well as an effect size of 0.906 for the cumulative abstinence duration (Addolorato et al., 2007), and assuming an error of the first kind = 5 % (two-sided), a power of 80 %, and a drop-out rate of about 20 %, we calculated (nQuery Advisor® Release 7.0, Stat. Solutions Ltd. & South Bank, Crosse's Green, Cork, Ireland) a total sample size of 56 patients, each for both endpoints.

Results were expressed as arithmetic mean ± standard deviation (SD), median with quartiles, or frequencies [%], as appropriate. Because of the limited sample sizes and/or non-symmetrically distributed observations, we applied only nonparametric statistics. Differences between the two treatment groups in terms of relevant clinical parameters were tested by using the non-parametric exact Wilcoxon-Mann-Whitney test as well as the exact Chi-square test.

Time-to-event data were analyzed applying Kaplan-Meier estimations of the survival curves with subsequent Log-Rank tests and multivariate Cox regressions, respectively. Treatment group, age, and number of previous detoxifications (the latter two have been identified as risk factors for alcohol relapse in previous studies) (Beck et al., 2012; Muller et al., 2010) were included into the regression analyses as risk factors. Hazard ratios (HR) with 95 % confidence intervals were determined.

In order to investigate particular data with repeated measurements over time, such as HAM-A, HAM-D, VASC and OCDS-G as well as laboratory values, we applied a nonparametric multivariate analysis of longitudinal data in a two-factorial design (1st factor: treatment, 2nd factor: time) [nonparametric MANOVA] (Brunner et al., 2002), after adjusting for baseline measurements. A two-tailed p-value < 0.05 was considered statistically significant. All

numerical calculations were performed with IBM© SPSS© Statistics, Version 22, © Copyright 1989, 2010 SPSS Inc., an IBM Company, and SAS, Version 9.1, © Copyright by SAS Institute, Inc., Cary, NC, USA.

Results

Patients

The CONSORT diagram of the trial is shown in Figure 2. Ninety-three patients were initially screened, and 56 met the study criteria and were randomized to treatment with baclofen (n = 28) or placebo (n = 28). Table 2 shows demographic and clinical characteristics of the patients included. The mean rate of medication adherence during the high-dose phase (defined as number of pills taken divided by number of pills prescribed) was 85.8 % in the baclofen group and 85.9 % in the placebo group (U = 172, p = 0.325). Ten patients (35.7 %) of the baclofen group reached the maximum dose of 270 mg/d, compared to 19 patients (67.9 %) of the placebo group (χ^2 = 15.37, df = 7, p = 0.013). Mean dose of study medication during the high-dose phase was 180 mg/d (SD 86.9) in the baclofen group and 257.1 mg/d (SD 33.6) in the placebo group (U = 114.5, p = 0.001), mean serum levels of baclofen were 747.41 ng/ml (SD 354.09). The mean maximum dose reached was 191.8 mg/d (SD 69) in the baclofen group and 240 mg/d (SD 54.8) in the placebo group (U = 239.5, p = 0.007).

Four patients had slightly shorter or longer durations of abstinence before randomization (0-23 days instead of 7-21 days), but were included in the study at their own request nevertheless. These patients were included to prevent a severe relapse in the days until a later study inclusion. One patient was unintentionally given a study medication designated to another patient; this patient decided to terminate the participation in the study thereafter.

Figure 2: CONSORT diagram of the trial. A total of 93 alcohol-dependent patients were screened for study eligibility. After exclusion of 37 patients, 56 patients were randomized resulting in n = 28 for placebo and n = 28 for baclofen. Subsequently, patients either reached the high-dose phase (grey boxes, n = 43 in total; n = 21 for placebo; n = 22 for baclofen) or relapsed/dropped out under medication before reaching that phase (n = 13 in total; n = 7 for placebo; n = 6 for baclofen). All patients (n = 56) were included in the analysis of the complete medication phase as shown in the white boxes at the bottom row.

Table 2: Demographic and clinical characteristics of the study participants by treatment group.

Outcomes

During the 12-week high-dose phase, significantly more patients assigned to baclofen remained abstinent compared to those assigned to placebo (15/22, 68.2 % vs. 5/21, 23.8 %, $\chi^2 = 8.6$, df = 2, p = 0.014). Cumulative abstinence duration during the high-dose phase was significantly higher in the group of patients allocated to baclofen, showing an increase of 30.9 % compared to patients receiving placebo (mean 67.8 (SD 30) vs. 51.8 (SD 29.6) days; U = 150, p = 0.047). The number of drop-outs during this interval did not differ between the baclofen and placebo groups (3/22, 13.6 % vs. 5/21, 23.8 %; $\chi^2 = 0.83$, df = 2, p = 0.743).

Analysis of the whole medication phase (i.e., titration phase, high-dose phase and tapering phase) revealed that significantly more patients also maintained alcohol abstinence in the baclofen group compared to placebo (12/28, 42.9 % vs. 4/28, 14.3 %; $\chi^2 = 5.6$, df = 1, p = 0.037). Cumulative abstinence duration during the complete medication phase was higher in the baclofen group (mean 82.9 (SD 49) vs. 66.8 (SD 41.9) days), but fell short of statistical

significance (U = 320.5, p = 0.241). The number of drop-outs did not differ between the baclofen and placebo groups during this interval (6/28, 21.4 % of each group).

The Kaplan-Meier survival analysis revealed a significantly greater chance of maintaining abstinence for patients allocated to baclofen during the high-dose phase (χ^2 = 6.5, df = 1, p = 0.011) and complete medication phase (χ^2 = 3.98, df = 1, p = 0.046) compared to patients receiving placebo (Figure 3a + b). Multivariate Cox regression analysis (including treatment group, age and number of previous detoxifications) showed an HR of 0.3 (95 % CI 0.1-0.7; p = 0.009) for relapse or drop-out during the high-dose phase for patients receiving baclofen, and an HR of 0.5 (95 % CI 0.2-0.9; p = 0.022) for relapse or drop-out during the complete medication phase.

After termination of the study medication (follow-up), two patients of the baclofen and one patient of the placebo group relapsed.

Figure 3a and b: Kaplan-Meier survival analyses for the high-dose and the complete medication phase.

Figure 4 shows the distribution of individually titrated dosages during the high-dose phase. A direct effect of individual doses on maintenance of abstinence could not be found for baclofen (U = 35, p = 0.212).

Figure 4: Distribution of individually titrated high-dose in the baclofen group with regard to abstinence vs. relapse.

Except for an effect of time on the OCDS-G compulsive subscale score during the high-dose phase, no effects of treatment or time on mean craving scores, (OCDS-G, VASC), HAM-D

and HAM-A total scores during the high-dose or the complete medication phase were found by a nonparametric two-factorial analysis of longitudinal data (see Table 3).

Table 3: Laboratory values, craving, anxiety and depression scores in both treatment groups during the trial.

Safety and Tolerability

Tolerability of the study medication was fair in all study participants, and no deaths or drug-related serious adverse events occurred. Table 4 shows the reported adverse events in both treatment groups. Two patients of the baclofen group terminated treatment due to side effects (fatigue). With regard to laboratory values, no effect of treatment or time was found for AST, ALT, GGT and CDT with the exception of MCV showing a significant effect of both treatment and time without a significant treatment by time interaction (Table 3). No reports of euphoric or stimulating effects of baclofen were recorded, and no patients receiving baclofen reported craving for the study medication after drug discontinuation.

Table 4: Adverse events with an occurrence of ≥ 10 %.

Discussion

Baclofen has recently received temporary approval in France for the treatment of alcohol-dependent patients for dosages up to 300 mg/d (ANSM, 2014). This is noteworthy, since only case reports/series and open studies using high-dose baclofen have been available to date (de Beaurepaire, 2012; Pastor et al., 2012), without results of RCTs. To the best of our knowledge, this is the first randomized, placebo-controlled trial assessing the efficacy and safety of individually titrated high-dose baclofen (30-270 mg/d) in alcohol-dependent patients. We found that baclofen supported patients in maintaining abstinence more effectively than placebo during the 12-week high-dose phase as well as during the complete medication phase (including titration and tapering). Thus, our study adds further evidence for the efficacy of baclofen in the treatment of alcohol dependence shown in previous clinical trials (Addolorato et al., 2002; Addolorato et al., 2007).

Compared to previous studies, the mean dosage of baclofen was relatively high in the present study (180 mg/d), possibly contributing to the superiority of baclofen compared to placebo, which was not found in a larger trial using lower dosages (30 mg/d) (Garbutt et al., 2010). However, contrary to the prior assumption of a possible dose-response effect (Addolorato et al., 2011; Ameisen, 2005; Garbutt et al., 2010), the individually titrated dose of baclofen did not differ between abstainers and relapsers in our trial. Studies with larger sample sizes should further explore dose-response effects on alcohol abstinence.

Approximately two-thirds of the baclofen group compared to one-third of the placebo group did not reach the maximum dose of 270 mg/d. This result was not expected, as in our clinical experience baclofen was used in dosages up to 270 mg/d in single cases and could have been used in comparable dosages in the baclofen group, which (as our post-hoc analysis shows) was not the case.

Interestingly, we could not observe an effect of baclofen on craving and anxiety as found in previous studies (Addolorato et al., 2002; Addolorato et al., 2007), possibly suggesting a mechanism of action that does not primarily involve these syndromes in alcohol dependence. Currently, there are two psychopharmacological modes of baclofen mainly discussed: partial

substitution (Rolland et al., 2013) and modulation of dopaminergic transmission within the mesolimbic reward system (Pastor et al., 2012). Regarding the partial substitution hypothesis, one would expect that the continuous administration of high-dose baclofen might clinically result in alcohol-mimicking effects and evoke withdrawal symptoms during dose reduction or discontinuation. However, consistent with findings of previous RCTs (Addolorato et al., 2002; Garbutt et al., 2010), none of our patients reported ethanol-like effects from the study medication; moreover, neither craving nor withdrawal symptoms after discontinuation of baclofen were observed in our study. Furthermore, it is currently unclear if or to what extent ethanol directly targets GABA-B receptors in the human brain (Harris et al., 2008).

Preclinical findings suggest that GABA-B receptor agonists such as baclofen may directly modulate dopaminergic transmission via inhibition of dopaminergic neurons projecting from the ventral tegmental area to the nucleus accumbens, a key component of the mesolimbic reward system (Westerink et al., 1996). Thus, an ethanol- or (alcohol-associated) cue-induced increase of dopaminergic transmission within the mesolimbic reward system (Di Chiara and Bassareo, 2007) might be inhibited by baclofen. The low ability of baclofen to cross the blood brain barrier (Taira, 2009) may help to explain why higher dosages are needed in some patients to achieve such effects on the central nervous system, which can be further explored in imaging studies.

With regard to the safety and tolerability of baclofen, our results underline the favourable safety profile reported in previous studies (Addolorato et al., 2007; Garbutt et al., 2010). In the baclofen group, only two patients terminated treatment due to adverse effects (fatigue) and no serious drug-related adverse events were recorded. In line with findings of a laboratory study (Evans and Bisaga, 2009), no drug-related serious adverse events occurred in the case of relapse during administration of baclofen. In contrast, several cases of intended baclofen intoxication in alcohol-dependent patients have recently been reported (Franchitto et al., 2014); hence, the administration of baclofen in patients with psychiatric comorbidities and/or previous suicide attempts should be critically evaluated.

The following limitations of our study need to be addressed. First, the sample size of this clinical trial was too small to draw final conclusions regarding the future role of baclofen in the treatment of alcohol dependence (a power of 81 % for total abstinence, but only 48 % for cumulative abstinence duration); larger studies are needed to confirm our findings. Second, our study was conducted at a single site; therefore, a bias with regard to patients´ and setting characteristics might have influenced our results. On the other hand, this design avoids potential between-centre variabilities. Third, since methods to detect recent alcohol consumption reliably are limited, we cannot exclude that single lapses in both treatment groups have not been detected. Fourth, we only assessed the effects of baclofen on maintaining abstinence; it remains unclear if baclofen is also effective in reducing alcohol consumption in alcohol-dependent patients who do not seek abstinence.

In summary, we found that individually titrated high-dose baclofen supported alcohol-dependent patients effectively in maintaining alcohol abstinence and was well tolerated overall, even in the case of relapse. The current findings suggest that baclofen´s efficacy does not depend on a clear cut-off dose, therefore dosing can probably be conducted individually. However, since results of larger trials regarding its safety are lacking, such individual dosing needs to be performed carefully and include close monitoring. Based on our results, baclofen does not seem to exert its effects primarily via reduction of craving or anxiety; the underlying psychopharmacological mechanisms of baclofen need to be studied in further trials. Taken together, our results strengthen the notion that baclofen medication can promote abstinence in some patients, thereby possibly extending the currently available pharmacological treatment options in alcohol dependence.

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Table 1: Dose titration schedule.

Days of Treatment	Total Daily Dose	5 mg-Capsules	10 mg-Capsules	30 mg-Capsules
Day 1 – 3	15 mg	1-1-1	-	-
Day 4 – 6	30 mg	-	1-1-1	-
Day 7 – 9	60 mg	-	2-2-2	-
Day 10 – 12	90 mg	-	-	1-1-1
Day 13 – 15	120 mg	-	1-1-1	1-1-1
Day 16 – 18	150 mg	-	2-2-2	1-1-1
Day 19 – 21	180 mg	-	-	2-2-2
Day 22 – 24	210 mg	-	1-1-1	2-2-2
Day 25 – 27	240 mg	-	2-2-2	2-2-2
Day 28 – 114	270 mg	-	-	3-3-3
Day 115 – 117	240 mg	-	2-2-2	2-2-2
Day 118 – 120	210 mg	-	1-1-1	2-2-2
Day 121 – 123	180 mg	-	-	2-2-2
Day 124 – 126	150 mg	-	2-2-2	1-1-1
Day 127 – 129	120 mg	-	1-1-1	1-1-1
Day 130 – 132	90 mg	-	-	1-1-1
Day 133 – 135	60 mg	-	2-2-2	-
Day 136 – 138	30 mg	-	1-1-1	-
Day 139 - 141	15 mg	1-1-1	-	-

Table 2: Demographic and clinical characteristics of the study participants by treatment group.

Characteristics	Placebo	Baclofen	p value
Sex [n (%)]			
Male	19 (67.9)	20 (71.4)	n.s.[b]
Female	9 (32.1)	8 (28.6)	
Age [mean ± SD (range)]	45.6 ± 7 (29–64)	47.4 ± 7 (32–59)	n.s.[a]
Highest school qualification [n (%)]			n.s.[b]
Secondary modern school-leaving certificate, year 5 to 9	1 (3.6)	0 (0)	
Secondary modern school-leaving certificate, year 5 to 10	1 (3.6)	1 (3.6)	
University-entrance diploma	1 (3.6)	2 (7.1)	
Technical college	15 (53.6)	21 (75)	

University degree	10 (35.7)	4 (14.3)	
Employment status [n (%)]			n.s.[b]
Employed	15 (53.6)	17 (60.7)	
Unemployed	13 (46.4)	11 (39.3)	
Marital status [n (%)]			n.s.[b]
Married	11 (39.3)	5 (17.9)	
Separated	0 (0)	3 (10.7)	
Divorced	4 (14.3)	8 (28.6)	
Unmarried	13 (46.4)	12 (42.9)	
Smoker [n (%)]	18 (64.3)	17 (60.7)	n.s.[b]
Years of hazardous alcohol consumption [mean (SD)]	11.5 (7.3)	13.9 (10.1)	n.s.[a]
Alcohol consumption (grams) per day	191.6 (94.8)	206.2 (94.1)	n.s.[a]

before inclusion [mean (SD)]			
Days of abstinence at study inclusion (Baseline) [mean (SD)]	12 (4.9)	12.4 (4.6)	n.s.[a]
Number of previous detoxifications [n (%)]			n.s.[b]
One	7 (25)	11 (39.3)	
2 to 5	16 (57.1)	12 (42.9)	
More than 5	5 (17.9)	5 (17.9)	
Positive family history regarding alcohol dependence (first-degree relatives) [n (%)]	15 (53.6)	18 (64.3)	n.s.[b]
ADS [mean (SD)]	15.8 (5.1)	16.6 (6.2)	n.s.[a]

[a]Exact Mann-Whitney U test.

[b]Exact Chi-Square test.

		Placebo	Baclofen	p value[a]	MANOVA	
					DF	p value
Laboratory values	**Aspartate aminotransferase (AST) in U/l [mean (SD)]**				Drug 1.00	0.292
	Baseline	34.2 (18.4)	38.0 (21.1)	0.269	Time 2.45	0.471
	After termination of study medication	25.7 (0.6)	22.5 (5.8)	0.304	Drug x Time 2.45	0.069
	Alanine aminotransferase (ALT) in U/l [mean (SD)]				Drug 1.00	0.150
	Baseline	42.8 (37.1)	43.1 (28)	0.486	Time 2.26	0.439
	After termination of study medication	18.7 (2.5)	21.1 (8.3)	1.00	Drug x Time 2.26	0.143
	γ glutamyltransferase (GGT) in U/l [mean (SD)]				Drug 1.00	0.266
	Baseline	123.8 (125.2)	104.8 (100)	0.926	Time 1.69	0.419
	After termination of study medication	39.0 (23.6)	21.8 (14.7)	0.094	Drug x Time 1.69	0.508
	Mean cellular volume (MCV) in fl [mean (SD)]				Drug 1.00	**0.026**

	Baseline	96.8 (5.3)	96.4 (4.9)	0.857	Time 2.53	**0.000**
	After termination of study medication	89.0 (2.6)	90.7 (2.8)	0.556	Drug x Time 2.53	0.152
	CDT in % [mean (SD)]				Drug 1.00	0.215
	Baseline	2.3 (0.9)	2.6 (0.9)	0.075	Time 1.68	0.427
	After termination of study medication	1.6 (0.2)	1.5 (0.2)	0.598	Drug x Time 1.68	0.445
Craving	**OCDS total score**				Drug 1.00	0.856
	Baseline	21.9 (8)	20 (9)	0.479	Time 3.18	0.260
	End of study	2.3 (3.2)	9.3 (8.8)	0.294	Drug x Time 3.18	0.830
	OCDS obsessive subscale				Drug 1.00	0.872
	Baseline	10.9 (4.3)	9.3 (4.9)	0.144	Time 3.36	0.429
	End of study	1.7 (2.1)	5.3 (4.5)	0.336	Drug x Time 3.36	0.719
	OCDS compulsive subscale				Drug 1.00	0.441
	Baseline	11.1 (4.6)	10.7 (4.5)	0.917	Time 3.46	0.110
	End of study	0.7 (1.2)	4 (4.6)	0.301	Drug x Time 3.46	0.859
	VASC				Drug 1.00	0.796
	Baseline	10.3 (16.9)	7.9 (12.7)	0.413	Time 3.88	0.202
	End of study	7 (6.6)	6.7 (9.2)	0.773	Drug x Time 3.88	0.512
Craving during the high-dose phase	**OCDS total score**				Drug 1.00	0.711
	After reaching high-dose phase	13.6 (12.1)	10 (9.3)	0.394	Time 3.32	0.918
	End of high-dose phase	8.8 (17.5)	10.5 (11)	0.402	Drug x Time 3.32	0.498
	OCDS obsessive subscale				Drug 1.00	0.978

	After reaching high-dose phase	6.3 (6.1)	4.6 (5)	0.221	Time 3.43	0.315
	End of high-dose phase	5 (9)	5.9 (5.8)	0.475	Drug x Time 3.43	0.228
	OCDS compulsive subscale				Drug 1.00	0.295
	After reaching high-dose phase	7 (6.8)	5.4 (5.1)	0.598	Time 3.41	**0.043**
	End of high-dose phase	3.8 (8.5)	4.6 (5.6)	0.391	Drug x Time 3.41	0.627
	VASC				Drug 1.00	0.603
	After reaching high-dose phase	2.6 (3.1)	4.4 (4.7)	0.265	Time 4.22	0.288
	End of high-dose phase	2.4 (3.4)	6.3 (13.1)	0.757	Drug x Time 4.22	0.300
Anxiety	**HAM-A**				Drug 1.00	0.961
	Baseline	3 (3.5)	2.1 (2.3)	0.536	Time 3.05	0.114
	End of study	0 (0)	1.9 (5)	1.00	Drug x Time 3.05	0.669
Depression	**HAM-D**				Drug 1.00	0.925
	Baseline	3.1 (3.2)	2.6 (2.6)	0.506	Time 2.81	0.126
	End of study	0 (0)	2.1 (5.4)	1.00	Drug x Time 2.81	0.676

[a]Exact Mann-Whitney U test.

Table 4: Adverse events with an occurrence of ≥ 10 %.

Adverse Event	**Placebo** [n (%)]	**Baclofen** [n (%)]	**Total** [n (%)]	**p value** (Exact Chi-square test)
Headache	7 (25.0)	4 (14.3)	11 (19.6)	0.503
Fatigue	7 (25.0)	13 (46.4)	20 (35.7)	0.162
Sleep disturbances	4 (14.3)	9 (32.1)	13 (23.2)	0.205
Muscle weakness	3 (10.7)	6 (21.4)	9 (16.1)	0.469
Vertigo/dizziness	0 (0)	5 (17.9)	5 (8.9)	0.051
Visual disturbances	2 (7.1)	5 (17.9)	7 (12.5)	0.422
Muscle pain	3 (10.7)	0 (0)	3 (5.3)	0.236
Fasciculations	1 (3.6)	4 (14.3)	5 (8.9)	0.352
Common cold/infection	11 (39.3)	1 (3.6)	12 (21.4)	**0.002**
Depressed mood/anxiety	2 (7.1)	3 (10.7)	5 (8.9)	1.00
Gastrointestinal symptoms	3 (10.7)	1 (3.6)	4 (7.1)	0.611
Urgency	0 (0)	4 (14.3)	4 (7.1)	0.111
Hypertension	2 (7.1)	3 (10.7)	5 (8.9)	1.00
Tingling sensation	0 (0)	3 (10.7)	3 (5.3)	0.236
Pain (diverse)	8 (28.6)	4 (14.3)	12 (21.4)	0.329

Figure 1: BACLAD trial profile.

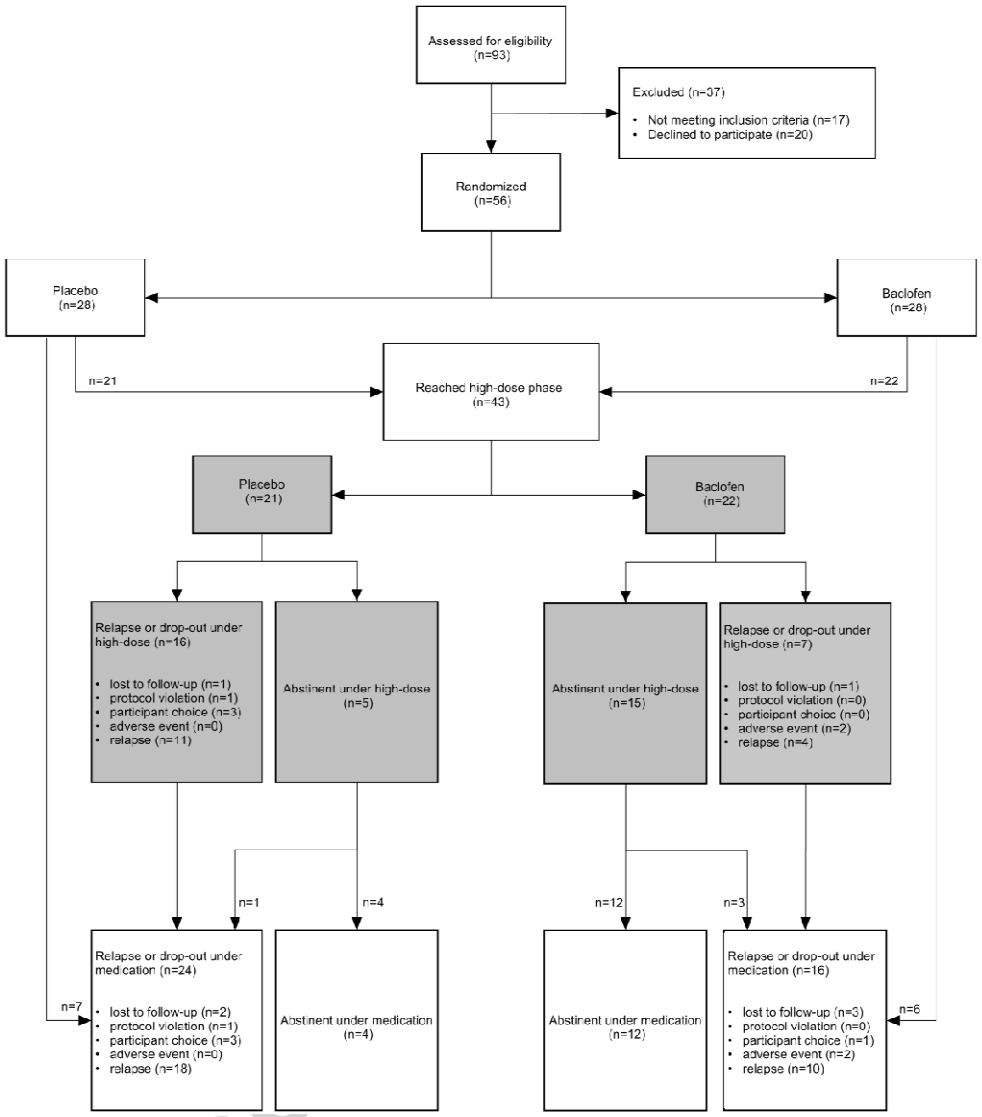
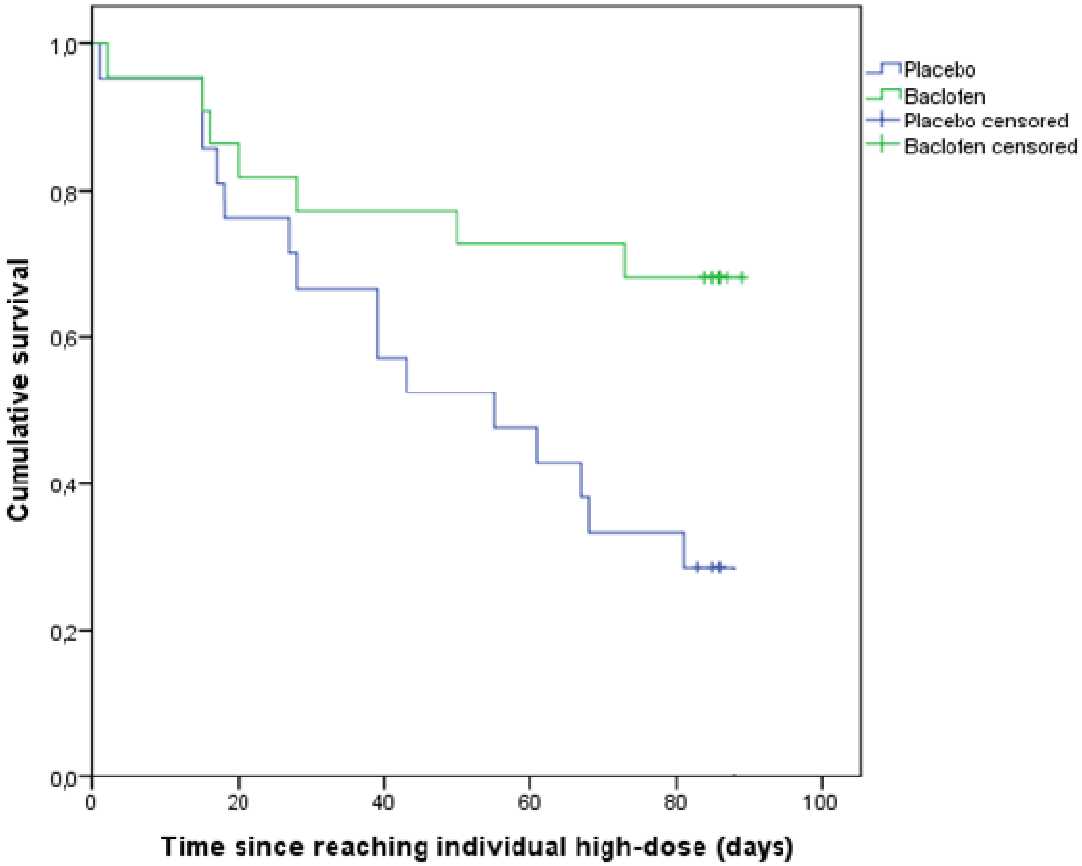


Figure 2: CONSORT diagram of the trial. A total of 93 alcohol-dependent patients were screened for study eligibility. After exclusion of 37 patients, 56 patients were randomized resulting in n = 28 for placebo and n = 28 for baclofen. Subsequently, patients either reached the high-dose phase (grey boxes, n = 43 in total; n = 21 for placebo; n = 22 for baclofen) or relapsed/dropped out under medication before reaching that phase (n = 13 in total; n = 7 for placebo; n = 6 for baclofen). All patients (n = 56) were included in the analysis of the complete medication phase as shown in the white boxes at the bottom row.



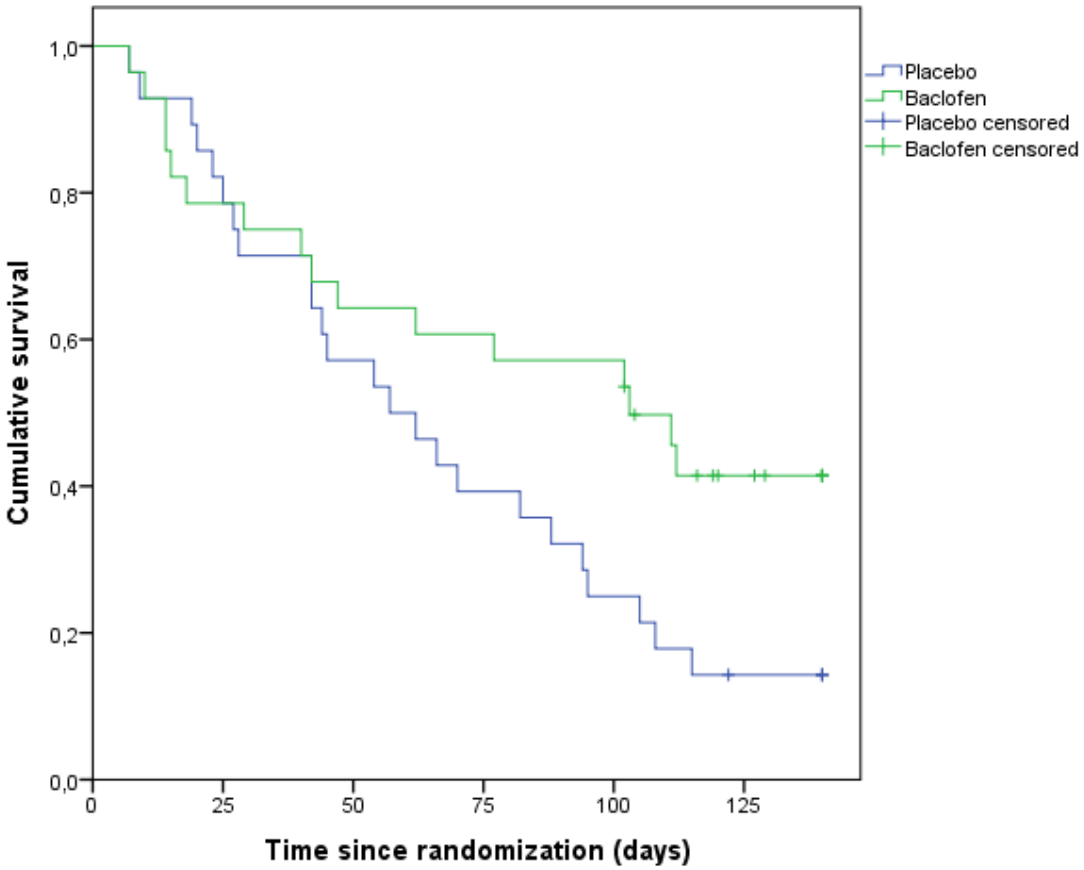


Figure 3a and b: Kaplan-Meier survival analyses for the high-dose and the complete medication phase.

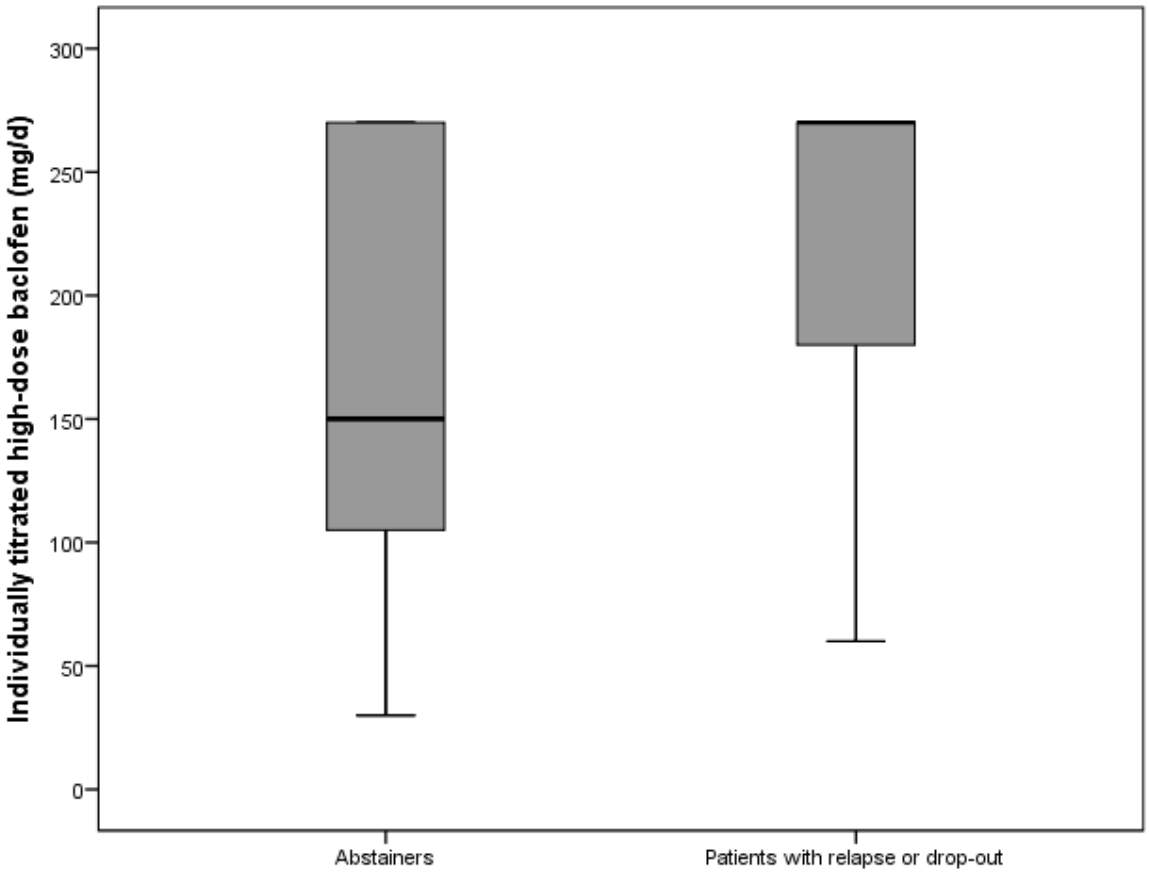


Figure 4: Distribution of individually titrated high-dose in the baclofen group with regard to abstinence vs. relapse.