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A Randomized, Placebo-Controlled Study of High-Dose Baclofen in Alcohol-Dependent Patients—The ALPADIR Study

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Abstract

Aims: Alcohol dependence is a major public health issue with a need for new pharmacological treatments. The ALPADIR study assessed the efficacy and safety of baclofen at the target dose of 180 mg/day for the maintenance of abstinence and the reduction in alcohol consumption in alcohol-dependent patients.

Methods: Three hundred and twenty adult patients (158 baclofen and 162 placebo) were randomized after alcohol detoxification. After a 7-week titration, the maintenance dose was provided for 17 weeks, then progressively decreased over 2 weeks before stopping.

Results: The percentage of abstinent patients during 20 consecutive weeks (primary endpoint) was low (baclofen: 11.9%; placebo: 10.5%) and not significantly different between groups (OR 1.20; 95%CI: 0.58 to 2.50; $P = 0.618$). A reduction in alcohol consumption was observed from month 1 in both groups, but the difference of 10.9 g/day at month 6 between groups, in favour of baclofen, was not statistically significant ($P = 0.095$). In a subgroup of patients with high drinking risk level at baseline, the reduction was greater with a difference at month 6 of 15.6 g/day between groups in favour of baclofen ($P = 0.089$). The craving assessed with Obsessive-Compulsive Drinking Scale significantly decreased in the baclofen group ($P = 0.017$). No major safety concern was observed.

Conclusions: This study did not demonstrate the superiority of baclofen in the maintenance of abstinence at the target dose of 180 mg/day. A tendency towards a reduction in alcohol consumption and a significantly decreased craving were observed in favour of baclofen.

Short summary: Baclofen was assessed versus placebo for maintenance of abstinence and reduction in alcohol consumption in alcohol-dependent patients. This study did not demonstrate the superiority of baclofen in the maintenance of abstinence. A tendency towards a reduction in alcohol consumption and a significantly decreased craving were observed in favour of baclofen.

INTRODUCTION

Alcohol use disorders (AUDs), including alcohol dependence, are a major public health problem. A 3.4% of the European population suffers from alcohol dependence (Wittchen *et al.*, 2011; Rehm *et al.*, 2015). A few pharmacological treatments are approved and marketed for alcohol dependence: disulfiram, acamprosate and naltrexone for the maintenance of abstinence, and recently nalmefene for the reduction in alcohol consumption in high drinking risk level patients. Due to the heterogeneity of patients with AUD, these treatments show an efficacy of limited effect size and are not widely prescribed (Litten *et al.*, 2016).

Baclofen is a lipophilic analogue of gamma aminobutyric acid (GABA), is an agonist of the $GABA_B$ receptor and able to cross the blood–brain barrier. It is marketed since the 1970s for the relief of muscle spasticity. Baclofen has been shown to reduce alcohol intake in different animal models of AUD (Agabio and Colombo, 2014). Randomized controlled trials versus placebo have assessed the effectiveness of baclofen in alcohol-dependent patients (Addolorato *et al.*, 2002, 2007, 2011; Garbutt *et al.*, 2010; Ponizovsky *et al.*, 2015). The low number of patients, the short duration of studies and the low dosage (30, 50 or 60 mg/day) may explain the divergent outcomes, which did not allow any definitive conclusion regarding the efficacy of baclofen in AUD. Recently, two randomized placebo-controlled studies with high-dose baclofen have been published and reported contradictory results. In the first, Muller *et al.* (2015) reported positive results with a baclofen dose up to 270 mg/day, in a 3-month follow-up study: abstinence rate and cumulative abstinence duration were significantly higher with baclofen compared to placebo (68.2% vs. 23.8% and 67.8 days vs. 51.8 days, respectively). In the second, Beraha *et al.* (2016) compared the efficacy of low-dose baclofen (30 mg/day), high-dose baclofen (up to 150 mg/day) and placebo after a 4- to 21-day detoxification period: time to first relapse (=first heavy drinking day, HDD) was not statistically different between low-dose baclofen, high-dose baclofen and placebo patients; results were also comparable between groups for secondary outcomes: total alcohol consumption (TAC), percentage of patients that relapsed, abstinence rate and cumulative abstinence duration.

Observational studies with long-term data (one or two years) are in favour of a positive effect of baclofen on the prevention of alcohol relapses or the reduction in alcohol consumption (de Beaurepaire, 2012; Rigal *et al.*, 2012).

Comorbid mental disorders (e.g. mood and anxiety disorders) are frequently associated with AUD (Bradizza *et al.*, 2006; Shield *et al.*, 2013) and may influence the effectiveness of baclofen.

The objectives of the ALPADIR study were to assess the efficacy and safety of baclofen at a target dose of 180 mg per day for the maintenance of abstinence after alcohol detoxification and the reduction in alcohol consumption in alcohol-dependent patients.

METHODS AND MATERIALS

Patients

This randomized, double-blind, placebo-controlled study recruited patients from 39 specialized hospital centres in France. The detoxification was performed on an out- or in-patient basis before randomization. During the study, patients were followed on an outpatient basis. Eligible patients were adult men or non-pregnant, non-breastfeeding women, with a diagnosis of alcohol dependence according to DSM-IV (American Psychiatric Association, 2000), who had experienced at least one previous abstinence attempt, and had been fully abstinent for 3–14 days before randomization; this range of 3–14 days was established in order to allow patients needing in-patient detoxification to participate in the study. Comorbid psychiatric diseases were assessed according to the investigator's judgment. The main non-inclusion criteria were: need for a prolonged residential treatment after detoxification; need for an intensive psychosocial intervention during follow-up; history of baclofen intake by prescription or by self-medication; epilepsy or history of epilepsy; concomitant treatment with one or several drugs for the maintenance of abstinence; concomitant treatment with psychotropic medications, except antidepressants at stable dose for at least 2 months, diazepam and oxazepam; severe renal, cardiac or pulmonary disorders; severe psychiatric conditions (schizophrenia and bipolar disorder); clinically significant cognitive disorders; hepatic encephalopathy; suicidal risk or history of suicide; other current dependence except nicotine. A screening was performed by the investigators before inclusion according to the inclusion and non-inclusion criteria of the protocol. Data on non-eligible patients were not kept for research purposes nor was additional information collected on non-eligible patients.

The study was conducted in accordance with Good Clinical Practice, French regulations, and the ethical and scientific principles of the Declaration of Helsinki, approved by an ethics committee and authorized by French competent authorities. Written informed consent was obtained from each included patient. The study was registered in ClinicalTrials.gov (NCT01738282).

Randomization and blinding

Patients were randomly assigned to baclofen or placebo in a 1:1 ratio, according to a computer generated randomization list (blocks size of 4). The allocation sequence was centralized via an Interactive Web Response System.

The identical aspect of verum (20 mg coated scored baclofen tablet) and placebo tablets allowed a double-blind design. Sealed code envelopes were sent to the investigator centres with the corresponding study treatments. Access to the randomization codes and unblinding could only be performed in case of emergency.

Treatment administration and study procedures

Patients were randomized at the inclusion visit. Fourteen follow-up visits were then planned over a 30-week period. BRENDA sessions (Starosta *et al.*, 2006) were provided during each visit to support patients in changing their behaviour and to enhance adherence to treatment.

The study treatment was administered over 26 weeks comprising three periods: (a) a 7-week titration period during which the daily dose was gradually increased from 1 to 9 tablets; the initial dose was provided twice a day (10 mg morning and evening) for 2 days, then three times a day and the dose increased by 10 mg every four days; (b) a 17-week maintenance period at the dose reached at the end of the titration period and (c) a 2-week tapering-off period. The last follow-up visit was conducted 4 weeks after the end of study treatment. During the titration and maintenance periods, the dose could be reduced in case of persistent somnolence; a return to the higher dose was tried after a 3-day period of stability and satisfactory tolerance. Patients who did not reach the target dose of 180 mg/day participated in the study at their maximum tolerated dose.

At the inclusion visit, daily drinking data were retrospectively collected over the month (= 28 consecutive days) prior to

detoxification using the timeline follow back method (Sobell and Sobell, 2012). This data were considered as the baseline drinking risk level according to the World Health Organization classification (WHO, 2000). Severity of alcohol dependence was assessed at inclusion with the Alcohol Dependence Scale (Skinner and Allen, 1982). Patients reported daily their alcohol consumption, i.e. the number of standard drinks per day (one standard drink = 10 grams of alcohol) on a paper diary.

Outcome measures

The primary outcome measure was the rate of abstinent patients during 20 consecutive weeks from Day 29 (start of the 5th week of the titration period) to Day 168 (end of the maintenance period). A grace period was authorized from Day 1 (start of study treatment) to Day 28. According to the EMA (2010) and FDA (2015) guidelines, the primary endpoint can be assessed after a pharmacologically justified grace period; at day 28 of the study, the daily dose of 90 mg was considered as high enough to be able to maintain abstinence.

The secondary outcome measures regarding alcohol consumption were the change from baseline in TAC (g/day) and HDD (days/month) to month 6, defined as the last 28-day period of study treatment at maintenance dose.

Other secondary outcome measures were: Obsessive-Compulsive Drinking Scale (OCDS) (Anton *et al.*, 1995) to assess craving, Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) (Guy, 1976), Hospital Anxiety and Depression (HAD) scale (Zigmond and Snaith, 1983), 9-item alcohol dependence quality of life (AlQoL9) (Malet *et al.*, 2006) and hepatic biomarkers, gamma glutamyltransferase (GGT) and carbohydrate deficient transferrin (CDT).

The safety profile was assessed by recording adverse events (AEs) and vital signs at each visit, safety laboratory tests and electrocardiogram at inclusion and at the last visit. An Independent Data Safety Monitoring Board assessed safety data continuously and in a blinded manner during the study.

Sample size

Based on a systematic review reporting an abstinence rate of approximately 25% with placebo (Mann *et al.*, 2004) and anticipating a rate of 45% with baclofen, a sample size of 158 patients per treatment group was required, assuming a type I error of 5% and a power of 90%.

Statistical analysis

The following datasets were prespecified in the study protocol:

The safety population, defined as patients having received at least one dose of study treatment, and considered for safety purpose;

The full analysis set population, defined as randomized patients, having received at least one dose of study treatment and having reported at least one data regarding alcohol consumption in their diary, which is the main population for efficacy assessments;

The per-protocol population, defined as patients without protocol violation, i.e. failure to comply with inclusion/non-inclusion criteria and the use of prohibited treatments.

Three methods of imputation were used for the management of missing data related to alcohol consumption:

Multiple imputation with a placebo pattern mixture model (assuming that the alcohol consumption of dropped out patients was the same as those in the placebo group) was the main imputation method; it is one of the recommended method for handling missing data in alcohol clinical trials (Hallgren and Witkiewitz, 2013; Witkiewitz *et al.*, 2014).

Most plausible outcome (for abstinence endpoint only): for patients who did not report any alcohol consumption during the 20 consecutive weeks and had at least one missing data during the period, their profiles were reviewed by 2 blinded medical experts who filled in the missing data;

Worst case: missing data were imputed to alcohol intake.

Primary endpoint analyses: the abstinence rate was compared between the two groups using a logistic regression model adjusted on baseline drinking risk level and centres. Patients with at least one alcohol-containing drink during the 20-week period were considered as failures. The main analysis was performed on the full analysis set population with the multiple imputation method. Three sensitivity analyses were performed: on the full analysis set population using the most plausible outcome and the worst case methods; on the per-protocol population using the multiple imputation method. All patients withdrawn before Day 29 were considered as failures.

Secondary endpoints analyses: change from baseline in TAC and HDD to month 6 were analysed using a mixed model for repeated measures with as fixed factors, treatment group, baseline drinking risk level and centres.

RESULTS

Patient disposition and baseline characteristics

Three hundred and twenty patients were randomized, 158 in the baclofen group and 162 in the placebo group. One hundred and thirty patients withdrew prematurely from the study: 59 (37.3%) in the baclofen group and 71 (43.8%) in the placebo group; for 14 patients (5 baclofen and 9 placebo), the drop-out occurred before the end of the grace period. The main reason was the withdrawal of consent for the baclofen group ($n = 17$) and the lack of efficacy for the placebo group ($n = 20$) (Fig. 1). Mean time (SE) to withdrawal did not differ between groups: 156.3 (5.3) days for baclofen and 151.9 (5.5) days for placebo ($P = 0.312$).

Demographic and baseline characteristics are presented in Table 1. No relevant difference was observed between the two treatment groups. The percentage of patients with at least a high drinking risk level was 68.4% in the baclofen group and 70.4% in the placebo group. Alcohol consumption characteristics at baseline were comparable in both groups except a higher percentage of women with medium and low drinking risk level in the baclofen group (35.1% vs. 27.1% in the placebo group). The mean value of GGT at baseline was higher in the placebo group than in the baclofen group. The median duration of abstinence before randomization was 7 days for both groups.

Eighty-six baclofen patients (65.6%) and 119 placebo patients (88.8%) reached the maximum daily dose of 180 mg (9 tablets). In the baclofen group, the mean (SD) daily maintenance dose was 153.5 (40.5) mg. The maintenance dose was <120 mg/day, ≥120 and <160 mg/day, and ≥160 mg/day for 17%, 16% and 67% of patients, respectively. Approximately 10% and 35% of the patients also suffered from anxiety and depression, respectively. HAD scores were relatively low without relevant difference between the two groups.

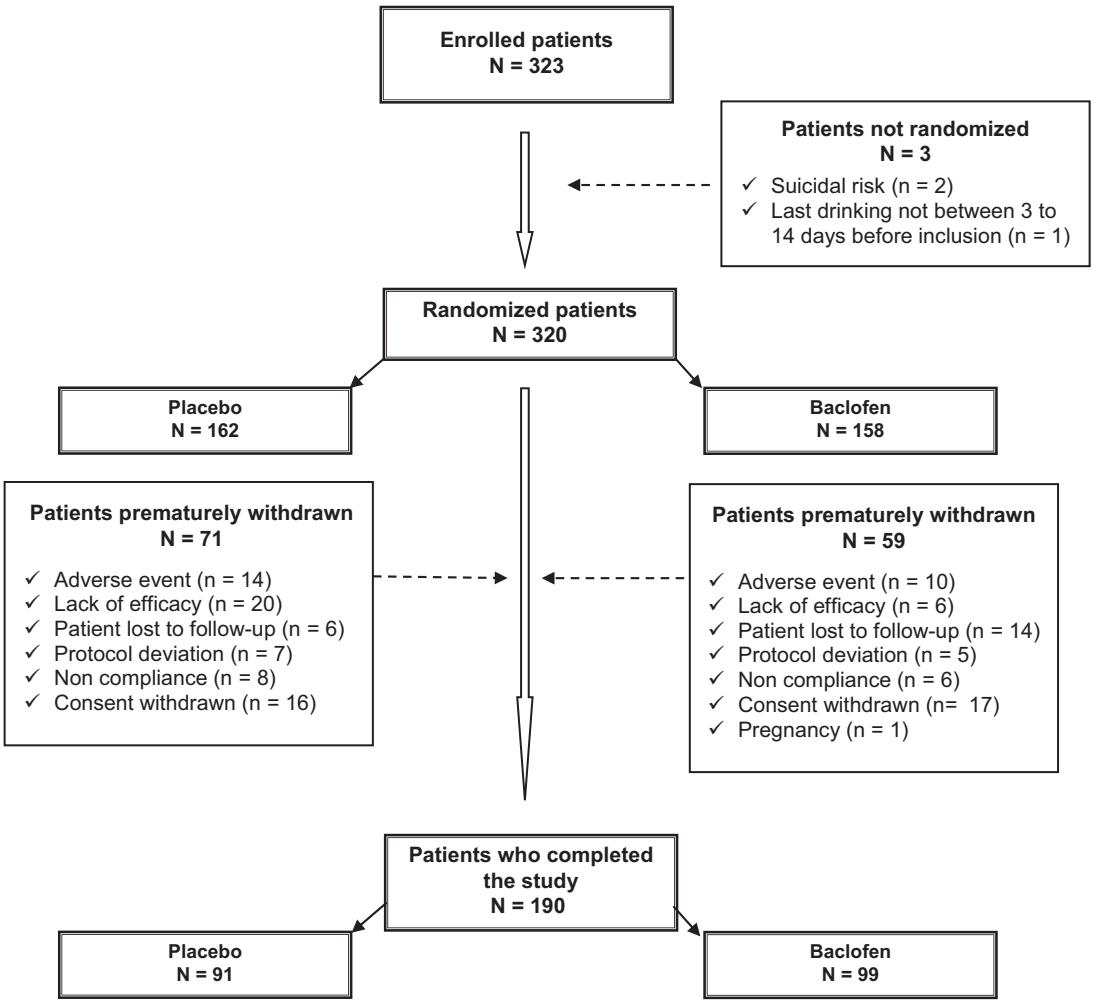

Fig. 1. Patient disposition.

Efficacy

The main analysis provided an estimated percentage of abstinent patients during 20 consecutive weeks of 11.9% in the baclofen group and 10.5% in the placebo group. The logistic regression model gave a treatment p value of 0.619, and an OR (odds ratio) [95%CI] of 1.20 [0.58; 2.50]. The sensitivity analyses confirmed these results.

Interestingly two initially planned subgroup analyses provided statistically significant results on abstinence in favour of baclofen: (a) female subgroup (n = 85; OR [95%CI] = 10.56 [1.22; 91.87]; P = 0.032) and (b) subgroup of patients with a detoxification period ≤7 days (n = 165 patients; OR [95%CI] = 6.48 [1.12; 37.49]; P = 0.037). However, it is important to note the overlap between these two subgroups, given the overrepresentation of patients with a detoxification period ≤7 days (63.5%) in the female subgroup.

A reduction of TAC was observed in both groups at month 6 compared to baseline using the multiple imputation method: –55.1 g/day in the baclofen group [95%CI: −64.9; −45.2] and −44.2 g/day in the placebo group [95%CI: −54.1; −34.3]; the difference of 10.9 g/day in favour of baclofen [95%CI: −23.7; 1.9] was not statistically significant (P = 0.095).

A decrease in the number of HDD was also observed at month 6 compared to baseline in both groups using the multiple imputation method: –9.9 days in the baclofen group [95%CI: −11.7; −8.3] and −8.7 days in the placebo group [95%CI: −10.3; −7.1]; the difference of 1.3 days in favour of baclofen [95%CI: −3.4; 0.8], was not statistically different (P = 0.228).

The reduction of TAC was observed as of month 1 in both groups and during each consecutive 4-week period following randomization, and was always greater in the baclofen group, but without reaching statistical significance (Fig. 2). A similar trend was observed for the number of HDD during the course of the study.

A decrease of OCDS total score was observed in both groups, and the change from baseline to month 6 was statistically greater with baclofen (mean adjusted difference: –2.86; P = 0.017). The standardized effect size was 0.41—this decrease was observed in both obsessive and compulsive sub-scores (Table 2).

All other scores improved over time in both groups (decreased for HAD and CGI, and increased for AlQoL9). There was a slightly greater improvement for baclofen patients, but without reaching statistical significance. An initially planned subgroup analysis was conducted according to HAD score at baseline (≤10 or >10) and did not evidence any relevant difference between baclofen and placebo for the endpoints related to alcohol consumption.

Table 1. Demographic and baseline characteristics

Full analysis set population $n = 310$	Placebo $n = 155$	Baclofen $n = 155$
Sex		
Male	107 (69.0%)	118 (76.1%)
Female	48 (31.0%)	37 (23.9%)
Age (years)	49.8 (9.8)	49.0 (10.7)
Current smoker (yes)	99 (63.9%)	109 (70.3%)
Duration of alcohol dependence (years)	14.2 (9.4)	12.8 (10.1)
Family history of alcohol dependence (yes)	95 (61.3%)	107 (69.5%)
Alcohol Dependence Scale		
Total score (0–47)	16.4 (6.9)	15.6 (6.0)
Comorbid mental disorders		
Anxiety	16 (10.3%)	23 (14.8%)
Depression	55 (35.5%)	51 (32.9%)
Drinking risk level (WHO classification)[a]		
Low	24 (15.5%)	21 (13.5%)
Medium	22 (14.2%)	28 (18.1%)
High	41 (26.5%)	46 (29.7%)
Very high	68 (43.9%)	60 (38.7%)
TAC (g/day)	93.6 (65.5)	95.5 (75.6)
HDD/month	17.6 (10.0)	17.9 (10.2)
OCDS total score (0–40)	19.2 (7.3)	19.5 (6.6)
Obsessive score (0–20)	8.0 (3.8)	8.1 (3.9)
Compulsive score (0–20)	11.2 (4.2)	11.4 (3.8)
CGI severity score (1–7)	2.9 (1.5)	2.8 (1.5)
HAD total score (0–42)	11.6 (4.0)	11.9 (3.8)
Anxiety score (0–21)	5.7 (1.6)	5.8 (1.5)
Depression score (0–21)	6.0 (3.4)	6.1 (3.1)
AlQoL9 total score (9–41)	23.8 (3.9)	24.0 (3.3)
GGT (IU/l)	148.9 (249.2)	113.3 (140.6)
CDT (%) (≤1.7%)	2.3 (2.3)	2.1 (2.3)

Data are mean (SD) or number of patients (%). Cut off values of questionnaires/scales and CDT are in brackets.

[a]WHO (World Health Organization) classification of drinking risk levels: low (≤40 g/day for males and ≤20 g/day for females), medium (>40 and ≤60 g/day for males and >20 and ≤40 g/day for females), high (>60 g/day and ≤100 g/day for males and >40 g/day and ≤60 g/day for females), very high (>100 g/day for males and >60 g/day for females).

GGT decreased from baseline to last visit in both groups with a greater reduction in baclofen patients. To address the large variability of GGT values, an analysis of log transformation data was conducted and the difference in the change from baseline to last visit was found statistically in favour of baclofen ($P = 0.012$).

A small decrease of CDT values was observed in the baclofen group from baseline to the last visit, whereas there was no change in the placebo group. The difference between groups was close to significance ($P = 0.077$).

A post hoc analysis was performed in a subgroup of 215 patients (106 baclofen and 109 placebo) with high/very high drinking risk level at baseline (heavy drinkers). Their baseline characteristics were similar to the global population, except a higher mean (SD) TAC [123.6 (75.9) g/day for baclofen patients, and 118.9 (62.0) g/day for placebo patients] and a greater mean (SD) number of HDD per month [23.8 (5.4) for baclofen patients and 22.8 (6.2) for placebo patients]. An important reduction of TAC and an important decrease in the number of HDD were observed in both groups at month 6 compared to baseline using the multiple imputation method. The reduction in TAC was −89.3 g/day for the baclofen group [95%CI: −102.8; −75.9] and −73.7 g/day for the placebo group [95%CI: −87.1; −60.4]. The reduction in HDD was −17.5 days/month for the baclofen group [95%CI: −19.7; −15.3] and −15.8 days/month for the placebo group [95%CI: −17.9; −13.7]. The difference between groups was in favour of baclofen (TAC −15.6 g/day [95%CI: −33.6; 2.4]; HDD −1.72 days/month [95%CI: −4.6; 1.1]), but not statistically significant for TAC ($P = 0.089$) nor HDD ($P = 0.236$). A decrease in the OCDS score was observed in both groups; the mean adjusted difference (−3.8) [95%CI: −6.5; −1.2] for total score in the change from baseline to month 6 was statistically significant in favour of baclofen ($P = 0.005$). The standardized effect size was 0.56.

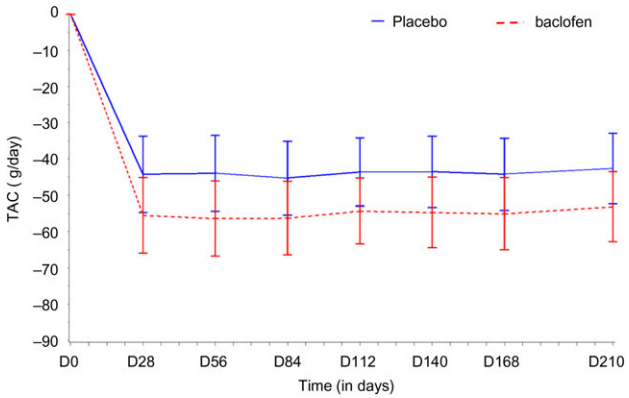

Fig. 2. Mean change in TAC (g/day) from baseline.

Safety

More than 90% of patients in each group experienced at least one AE: 96.8% in the baclofen group and 91.8% in the placebo group. In both the baclofen and placebo groups, most AEs were of mild (59.8% and 65.5%, respectively) or moderate (31.6% and 27.8%, respectively) intensity. The number of AEs was higher in the baclofen group ($n = 1245$) compared to the placebo group ($n = 863$). The system organ classes most frequently involved were Nervous system, Psychiatric and General disorders. The most common AEs were the same in both groups: somnolence, sleep disorders, asthenia and dizziness, but the incidence was higher in baclofen patients. 60% of AEs in the placebo group and 46% in the baclofen group were considered not related to study treatment by the investigators. AEs reported by at least 5% of patients in at least one treatment group are listed in Table 3. The majority of AEs started during the titration period and usually lasted over the treatment period, except the AE 'anxiety' whose frequency increased over time in the baclofen group. The percentage of patients who reported anxiety was 7% during titration, 10.2% during maintenance period and 16% during the 2-week tapering-off period. In the placebo group, the percentage of patients with anxiety was stable over the three periods (7–8%).

Twenty-four patients prematurely withdrew from the study due to AEs: 10 in the baclofen group and 14 in the placebo group.

Twenty baclofen patients and 26 placebo patients experienced 40 and 43 serious adverse events (SAEs), respectively. A 70% of these SAEs were considered not related to study treatment by the investigators. The most frequent SAEs in both groups were hospitalization for alcohol detoxification (9 in the baclofen group and 11 in the placebo group), fall (4 in the baclofen group and 2 in the placebo group), suicidal ideation (1 in the baclofen group and 4 in the placebo group),

Table 2. OCDS scores—change from baseline to month 6

Full analysis set population	Placebo		Baclofen		Difference to placebo	*P*
Score	*n*	Mean (SD)	*n*	Mean (SD)	Means difference [95%CI]	
Total score						
Baseline	84	17.4 (7.2)	87	19.4 (6.7)		
Change	84	−7.5 (8.4)	87	−11.7 (9.6)	−2.86 [−5.22 ; −0.51]	0.017
Obsessive items score						
Baseline	93	7.7 (3.9)	98	8.1 (3.6)		
Change	93	−3.3 (4.6)	98	−4.8 (4.7)	−1.16 [−2.24 ; −0.091]	0.034
Compulsive items score						
Baseline	85	10.2 (4.2)	89	11.3 (3.8)		
Change	85	−4.6 (4.9)	89	−7.0 (5.5)	−1.53 [−2.82 ; −0.24]	0.020

Mixed model with baseline, treatment group and centres as covariates. Only patients with documented visits are taken into account.

Table 3. Adverse events reported by at least 5% of patients

Safety population *n* = 316 Number of patients (%)	Placebo *n* = 159	Baclofen *n* = 157
Somnolence	39 (24.5%)	73 (46.5%)
Sleep disorders[a]	49 (30.8%)	61 (38.8%)
Asthenia	54 (34.0%)	60 (38.2%)
Dizziness	20 (12.6%)	47 (29.9%)
Headache	24 (15.0%)	42 (26.7%)
Anxiety	21 (13.2%)	30 (19.1%)
Paraesthesia	7 (4.4%)	26 (16.6%)
Nausea	12 (7.5%)	21 (13.4%)
Diarrhoea	23 (14.5%)	20 (12.7%)
Tinnitus	3 (1.9%)	18 (11.5%)
Myalgia/musculoskeletal pain	9 (5.7%)	18 (11.5%)
Back pain	9 (5.7%)	17 (10.8%)
Muscle spasms[b]	6 (3.8%)	17 (10.8%)
Hyperhidrosis	5 (3.1%)	16 (10.2%)
Nasopharyngitis	9 (5.7%)	14 (8.9%)
Disturbance in attention	6 (3.8%)	14 (8.9%)
Arthralgia	10 (6.3%)	13 (8.3%)
Dry mouth	8 (5.0%)	12 (7.6%)
Decreased appetite	7 (4.4%)	11 (7.0%)
Fall	9 (5.7%)	11 (7.0%)
Depression	10 (6.3%)	11 (7.0%)
Irritability	9 (5.7%)	11 (7.0%)
Dysgeusia/ageusia	2 (1.3%)	11 (7.0%)
Tremor	12 (7.5%)	10 (6.4%)
Memory impairment	5 (3.1%)	9 (5.7%)
Abdominal pain	22 (13.8%)	9 (5.7%)
Influenza	8 (5.0%)	9 (5.7%)
Weight decreased	4 (2.5%)	8 (5.1%)
Muscular weakness	5 (3.1%)	8 (5.1%)
Vomiting	6 (3.8%)	8 (5.1%)
Constipation	10 (6.3%)	7 (4.5%)
Alcohol detoxification	10 (6.3%)	5 (3.2%)

[a]Initial insomnia, middle insomnia, insomnia and sleep disorders

[b]Muscle involuntary contractions, muscle rigidity, muscle spasms, muscle twitching, muscle stiffness, clonus, myoclonus.

depression (3 in each treatment group), overdose (3 in the baclofen group). One placebo patient died during the study from a pancreatic carcinoma and hepatic metastases.

No relevant changes over time or differences between groups were observed for other safety variables: vital signs, laboratory tests and electrocardiograms.

DISCUSSION

Our study did not demonstrate the superiority of baclofen in the maintenance of abstinence at the target dose of 180 mg/day. The abstinence rate during 20 weeks was low in both groups and very far from the initial hypothesis. No relevant subgroup of patients was identified for maintenance of abstinence.

However, a reduction in alcohol consumption was observed in both groups in terms of TAC (g/day) and number of HDD per month; but the difference with placebo in the change from baseline did not reach statistical significance in neither the global population, nor the heavy drinkers. It should be kept in mind that the sample size was calculated for the endpoint of 'continuous abstinence' and therefore, our study was not powered for the criteria of reduction in alcohol consumption; it can be anticipated that a higher number of high drinking risk level patients would have made the difference statistically significant for the latter. A possible shift of patient's expectations from abstinence towards reduction in alcohol consumption, reinforced by the current French media context (Rolland *et al.*, 2012) regarding the use of baclofen in AUD may explain, at least in part, the low abstinence rates and very high placebo effect for the criteria of reduction in alcohol consumption.

Our study design with a dose titration based on safety reporting may also have negatively affected the results; the negative outcomes could be partly explained by the fact that patients did not reach an effective dose for safety reason.

Furthermore, the 3–14 days duration of abstinence period may have contributed to the results; indeed, patients able to sustain a long abstinence period without medication are more likely to have a less severe AUD and perhaps a lesser requirement for pharmacotherapy. On the other hand, patients not able to maintain a long abstinence period may need additional support to improve their outcome; reducing the duration of detoxification before treatment could minimize the placebo effect (Gueorguieva *et al.*, 2014).

The statistically significant superiority of baclofen compared to placebo in decreasing OCDS scores is consistent with previously published data. The anti-craving effect of baclofen was also reported in a pharmacokinetic/ pharmacodynamic study conducted in 67 alcohol-dependent adult volunteers (Imbert *et al.*, 2015). Surprisingly, the important reduction in craving observed by Muller *et al.* (2015) and Beraha *et al.* (2016) was not different between high-dose baclofen and placebo patients. The exact mechanism of the anti-craving action of $GABA_B$ agonists is still under investigation. Different pharmacological mechanisms of action have been suggested, such as the inhibition of alcohol-induced dopamine release in the mesolimbic system involved in the

reward system (Colombo *et al.*, 2004; Mirijello *et al.*, 2015); a partial substitution effect has also been proposed (Chick and Nutt, 2012; Rolland *et al.*, 2013).

Our study did not reveal any relevant benefit of baclofen compared to placebo on anxiety nor depression based on HAD scores. It should be kept in mind that baselines scores were low leaving little room for improvement. In terms of generalizability of the present findings, it is important to note that the lack of available data on patients screened but not enrolled prevented us for any comparison with the patients who were enrolled.

The concept of high-dose baclofen was first mentioned by Dr Olivier Ameisen, an alcohol-dependent French physician who, in 2005, published his own experience with baclofen up to 270 mg/day to treat his dependence; he reported the suppression of craving and the relief of anxiety (Ameisen, 2005). This new concept was reinforced by the publication of 1- and 2-year observational, open-label and non-comparative studies (de Beaurepaire, 2012; Rigal *et al.*, 2012) and had a huge national impact in France, not only among some addiction specialists, but also among patients potentially interested in this new treatment (Rolland *et al.*, 2012). Moreover, given that baclofen poorly crosses the blood-brain barrier, the need for high-dose baclofen can be justified for some patients. In March 2014, the French Medicines Agency, facing a strong increase in off-label prescriptions (Rolland *et al.*, 2014) and a genuine expectation from patients and physicians, regulated the use of baclofen for the treatment of alcohol dependence with a Temporary Recommendation for Use (TRU) for 3 years (Rolland *et al.*, 2016). The TRU was implemented, assuming a positive benefit/ risk ratio, taking into account available data.

To date, the results of randomized clinical trials using high-dose baclofen are ambivalent. Muller *et al.* (2015) reported positive results with high-dose baclofen (up to 270 mg/day) in the maintenance of abstinence during 12 weeks; whereas our study had negative results for this same criterion over 20 weeks with a lower target dose of 180 mg/day and Beraha *et al.* (2016) did not report any difference in terms of time to first relapse and abstinence rates at the dose of 150 mg/day, 30 mg/day or with a placebo. Earlier, Addolorato *et al.* (2002, 2007) reported a similar percentage of abstinent patients during 4 or 12 weeks as in Muller's study (Muller *et al.*, 2015), i.e. around 70% of abstinent patients with baclofen and 20–30% with placebo, but using a baclofen dose of 30 mg/day only.

The heterogeneity of the AUD population and the different designs and methodologies, in terms of dose, duration of treatment, duration of detoxification, intensity of psychosocial support, endpoints and sample size, may explain the inconsistent results of these baclofen randomized studies. Furthermore, it is suggested that baclofen is likely to be more beneficial for more severe AUD patients and/or patients with high or very high drinking risk level. (Leggio *et al.*, 2010; Muller *et al.*, 2015). As a dose-response effect has not been established, the need to adapt the dose to each patient is anticipated (as is already the case for spastic patients), and the daily maintenance dose would therefore be a balance between optimal efficacy and acceptable tolerance. The dose should be progressively increased until the therapeutic objective is achieved. In addition, a specific potential interest must be underlined for patients with hepatic impairment due to the fact that the liver does not play a significant role in the metabolism of baclofen.

The safety results observed in this study were consistent with the known safety profile of baclofen in terms of nature of events, but with a higher frequency. Our study is the largest randomized controlled trial versus placebo assessing a high-dose of baclofen in an alcohol-dependent population to be published to date.

Our study did not demonstrate the superiority of baclofen compared to placebo in the maintenance of abstinence after detoxification. However, a tendency towards a reduction in alcohol consumption was observed from the first month of treatment, particularly in the heavy drinkers subgroup, but without reaching statistical significance compared to placebo, probably due to a sub-optimal study design. The French media context around baclofen has probably strongly influenced the outcomes with an important placebo effect on the reduction in alcohol consumption. The study does confirm the previously published anti-craving effect of baclofen.

Alcohol dependence is a worldwide health issue with a need for new pharmacological treatments. Baclofen is probably one of them, able to reduce alcohol consumption, especially for the patients whose craving leads to excessive alcohol consumption, and probably with a dose adapted to each patient. High-dose baclofen still needs further investigations.

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M.R., H.J.A., F.P. and M.D. designed the study. F.T. and B.Z. (Ethypharm SAS) were involved in the study design, data collection, data management, statistical analysis and drafted the manuscript. All authors have reviewed and commented the manuscript. All authors have read and approved the final version.

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