Baclofen as Add-On to Standard Psychosocial Treatment for Alcohol Dependence: a Randomized, Double-Blind, Placebo-Controlled Trial With 1 Year Follow-Up

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A B S T R A C T

Background: Limited clinical trials and case-reports yielded conflicting results regarding the efficacy of baclofen (a GABAB agonist) in the treatment of alcohol dependence. The aim of this study was to test the efficacy and tolerability of baclofen in alcohol dependent patients in Israel.

Methods: The study was a double-blind, placebo-controlled, randomized trial comparing 50 mg/day of baclofen to placebo over 12 weeks, in addition to a standard psychosocial intervention program, with 26-week and 52-week follow-up observations. The percentages of heavy drinking days and abstinent days were the primary outcome measures, and craving, distress and depression levels; self-efficacy; social support from different sources; and health-related quality of life (HRQL) were secondary outcomes. Tolerability was also examined.

Results: Sixty-four patients were randomized; 62% completed the 12-week trial and 37% completed the 52-week follow-up. No between group differences were found in the percentages of heavy drinking and abstinent days. A significant reduction in levels of distress, depression and craving and improved HRQL occurred for both arms, whereas self-efficacy and social support remained unchanged in both groups. No adverse events were observed.

Conclusions: Unlike previous positive trials in Italy, and similarly to a negative trial in the USA, we found no evidence of superiority of baclofen over placebo in the treatment of alcohol dependence. However, the high placebo response undermines the validity of this conclusion. Therefore, more placebo-controlled trials are needed to either verify or discard a possible clinical efficacy of baclofen for alcohol dependence.

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1. Introduction

Among pharmacological agents for the treatment of alcohol dependence that have demonstrated some efficacy in reducing alcohol withdrawal symptoms as well as alcohol craving and relapse rates (Müller et al., 2014; Zindel & Kranzler, 2014), baclofen takes a particular place (Addolorato, Caputo, Capristo, et al., 2002; Addolorato, Leggio, Abenavoli, et al., 2006, Addolorato, Leggio, Agabio, et al., 2006; Addolorato, Leggio, Ferrulli, et al., 2007; Bucknam, 2007) because the medication is widely prescribed off-label in alcohol dependence, although evidence for its recommendation is insufficient (Liu & Wang, 2013). Baclofen—a potent, stereoselective γ-aminobutyric acid B (GABAB) receptor agonist—proved to be effective in suppressing alcohol withdrawal signs in alcohol dependent patients both in open-label and controlled clinical trials (Muzyk, Rivelli, & Gagliardi, 2012). Moreover, baclofen was found to be effective in relapse prevention due to its ability to maintain abstinence from alcohol reducing alcohol craving and consumption in alcoholic patients (Addolorato, Leggio, Abenavoli, et al., 2006; Addolorato, Leggio, Agabio, et al., 2006; Addolorato et al., 2002; Addolorato et al., 2011; Brennan, Leung, Gagliardi, et al., 2013; Bucknam, 2007; Colombo, Addolorato, Agabio, et al., 2004; Cousins, Roberts, & de Wit, 2002; Flannery, Garbutt, Cody, Renn, et al., 2004; Heilig & Egli, 2006; Johnson, Swift, Addolorato, et al., 2005). Baclofen (brand names Kemstro and Lioresal, manufacturer Parhjem Trading, Ltd.) is a muscle relaxant and antispastic medicine, whose primary indication is the treatment of spasticity resulting from a number of degenerative neurological disorders, including multiple sclerosis (Davidoff, 1985). Adverse events associated with baclofen use (drowsiness; dizziness; weakness and fatigue; confusion; insomnia; hypotension; nausea; constipation, and urinary frequency) have generally been transient and of mild-to-moderate severity (Garbutt, Kampov-Polevoy, & Gallop, 2010; Muzyk et al., 2012). The central nervous system depressant effects of baclofen may be additive to those of alcohol and other central nervous system (CNS) depressants. Importantly, in previous clinical trials baclofen proved
to be easily manageable and demonstrated no addictive properties (Addolorato, Leggio, Abenavoli, et al., 2006; Addolorato, Leggio, Agabio, et al., 2007; Johnson et al., 2005). It has recently been shown (Addolorato et al., 2007) that owing to its safe side-effect profile with lower liver toxicity baclofen can be used for the maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis. However, this study had some limitations, including limited external validity due to narrow inclusion and exclusion criteria as well as problems with statistical inference related to missing data (Brennan et al., 2013).

Another recent double-blind randomized clinical trial (RCT) (Garbutt et al., 2010) was conducted to assess the efficacy and safety of a total daily dose of 30 mg of baclofen for alcohol dependence. The primary outcomes of that study were number of heavy drinking days and proportion of abstinence between groups, and secondary outcomes included percentage of abstinent days, time to usage, craving, anxiety, depression, and safety information. Although the study did not show any difference between baclofen and placebo groups in both primary and secondary outcomes, and thus failed to demonstrate any benefit of baclofen, it was found that the drug was well tolerated and had no significant reported adverse events. Thus, RCIs conducted to date yielded conflicting results that require additional research to establish whether baclofen does or does not have any therapeutic efficacy in alcohol dependence.

Noteworthy, to date a traditional clinical approach to establish treatment efficacy persists in the field of substance use disorders. This approach takes into consideration mainly the effect of treatment agents on the objective clinical outcomes of substance use disorder such as retention in treatment programs, frequency and amount of the substance used in post-treatment compared to pre-treatment. At the same time, it pays insufficient attention to the assessment of subjective efficacy indicators of the medication under trial. Only recently, quality of life (QOL) measures have been recognized as important prognostic variables of benefit from treatment (Testa & Simonson, 1996). In medical health care there is consensus that QOL should reflect the subjective perception of a patient's well-being and functioning, pertaining to physical, emotional and social aspects as well as everyday life activities (Wilson & Cleary, 1995). The QOL concept has been acknowledged as an important tool in the evaluation of substance abuse programs (Torrens, San, Martinez, et al., 1997; Torrens, Domingo-Salvany, Alonso, et al., 1999). However, to date there have been few efforts to evaluate the effects of alcohol dependence and its treatment on the QOL of alcoholic patients (Anton & Randall, 2005; Donovan, Mattson, Cisler, et al., 2005; Ginieri-Coccosis, Liappas, Tzavellas, et al., 2007; Rosenbloom, Sullivan, Sasson, et al., 2007; Saarini, Suvisaari, Sintonen, et al., 1995; Stewart, Hutson, & Connors, 2006; UKATT Research Team, 2005). In their recent review, Luquiens, Reynaud, Falissard, and Aubin (2012) pointed out that the use of many different instruments makes it difficult to compare quality-of-life improvement between trials. They found that of eight different quality-of-life instruments used as outcome measures in 18 studies, only the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumthalt, 1993) demonstrated a significant difference between intervention groups at all endpoints in one clinical trial (Johnson, Ait-Daoud, Akhtar, & Ma, 2004).

Although both acute and chronic stress have been linked with drug and alcohol abuse, with acute stress being one of the main triggers of relapse in detoxified alcohol addicts (Sinha & Li, 2007; Walter, Gerhard, Duerster-MacFarland, et al., 2006; Zywiak, Stout, Longabaugh, Dyck, et al., 2006), none of the clinical trials with baclofen tested how the clinical efficacy and side-effect profile affect important determinants of patient’s behavior, such as well-being, self-perceptions of social support and self-efficacy. Importantly, in other areas of clinical psychiatry, it has been shown that subjective QOL and associated factors (self-efficacy and social support) play an important role in re-adaptation to the social environment (Koivumaa-Honkanen, Honkanen, Antikainen, et al., 1999), compliance with treatment and its effectiveness (Ho, Nopoulos, Flum, et al., 1998; Ponizovsky, Grinshpoon, Margolis, et al., 2006; Ritsner, Ponizovsky, Endicott, et al., 2002).

We report here the results of a randomized, double-blind, placebo-controlled study that was performed to determine the efficacy of the administration of baclofen for 12 weeks, as add-on therapy to standard psychosocial treatment for mild alcohol dependence, on alcohol craving, consumption and abstinence from alcohol (objective clinical indicators) alongside with health-related quality of life and self-perceptions in patients suffering from alcohol use disorder. Based on the literature reviewed, we hypothesized that: (1) baclofen has a beneficial effect on the objective clinical indicators of alcoholism and (2) treatment with baclofen would improve the patient’s health-related quality of life and associated self-perceptions. Both 6-month and 1-year follow-up observations aimed to test the stability of the efficacy of baclofen over time.

2. Methods

2.1. Study design

This paper reports the results of a 12-week, randomized, double-blind, placebo-controlled trial with 1-year follow-up. The trial was conducted from 1 January 2009 to 31 December 2010 at 15 outpatient medical centers for alcohol dependence treatment across Israel. All the centers belong to both the Ministry of Health and Ministry of Welfare and are regularly audited by the Department for the Treatment of Substance Abuse. The study protocol was approved by the Institutional Review Board of Sha’ar Menashe MHC and all eligible patients provided written informed consent after receiving information on baclofen treatment and potential side-effects, dosage and on the possibility to quit the trial at any time.

2.2. Participants

Male and female patients were eligible if they met the following inclusion criteria before randomization: (1) aged 18 to 60 years; (2) had an ICD-10 diagnosis of alcohol dependence (F10.10; World Health Organization, 1993); (3) had sought treatment to stop alcohol consumption; (4) had an alcohol intake of at least two heavy drinking days (HDD) per week (men ≥5 drinks per day; women ≥4 drinks per day) and average overall consumption of 21 drinks per week or more for men and 14 drinks per week or more for women during the month preceding recruitment (one standard drink is defined as 12 g absolute alcohol); (5) had no more than 6 total abstinent days (ABS) per month on average, and (6) had a reliable family member able to help with drug administration and monitoring. Exclusion criteria were: a detoxification treatment for acute alcohol withdrawal syndrome (requiring hospitalization) during the month before randomization, chronic use of psychotropic medication before randomization, dependence on psychoactive substances other than nicotine, liver cirrhosis, acute alcohol psychosis, severe depression, organic brain syndromes, pregnancy and lactation. Thus, the study population could be defined as mild alcohol use disorder according to DSM 5 criteria (305.00; American Psychiatric Association, 2013).

2.3. Procedures

Eligible patients who gave informed consent were randomly assigned to either oral baclofen or placebo (Fig. 1). Randomization was performed by the pharmacist who prepared drug and placebo by using a random number generator (Rosenberger & Lachin, 2002), with the only restriction that the groups should be of equal size. The medicine was administrated in a double-blind manner over 12 consecutive weeks. Placebo tablets were identical in all organoleptic characteristics to baclofen. Either baclofen or placebo was entrusted to a referred family member, who was asked to administer every dose to the patient and monitor his/her for side-effects. Family members were informed about possible side-effects and reported them at each outpatient visit. For the first 3 days, baclofen 15 mg/day was administered in 3 divided doses; then baclofen dosage was increased to 50 mg/day in 2 divided
doses (taken at 9 AM and 4 PM), which is half of the maximum daily dose according to the manufacturer’s guidelines. The dose of 50 mg/day was chosen since it is within the range (30–60 mg/day) demonstrated to be effective in reducing daily alcohol intake in alcohol-dependent subjects (Addolorato et al., 2011). During the last 3 days of the treatment protocol, the dose of baclofen was again decreased to 15 mg/day in 3 divided doses. This dosage schedule is somewhat greater than the minimum therapeutic dosage recommended by the medication manufacturer in order to avoid adverse events.

At baseline, all patients were instructed not to use any drugs potentially suppressing craving for alcohol (benzodiazepines, antidepressants, metadone, naltrexone, acamprosate, γ-hydroxybutyric acid, and varenicline), alcohol-sensitizing (e.g., disulfiram) and potentiating (e.g., antihistaminic) drugs during the study and follow-up period. Each patient was checked on a weekly basis throughout the trial for drinking, overall functioning, problems with adherence and adverse events. Medication compliance was measured with pill counts calculated by the formula: the total number of dispensed minus the number returned divided by the total number of tablets dispensed. At every center, professional staff provided a standard psychosocial intervention program for the treatment of alcoholism. This program includes weekly support counseling following the principles of motivational interviewing, education and therapy, based on cognitive behavioral therapy (CBT) principles addressing problems contributing to or resulting from alcoholism, and teaching skills to cope with alcohol dependence over time, similar to the principles of the BRENDA therapy (Starosta, Leeman, & Volpicelli, 2006). In each treatment group twelve individual and six group counseling sessions were provided during the medication period, and 9 individual and 6 group counseling sessions during the follow-up period.

2.4. Outcome measures

The primary outcome of the study was the proportion of heavy drinking days (%HDD) and, correspondingly, the proportion of total abstinent days (%ABS), which were assessed at week 6 (T1), week 12 (T2) of the medication period and at week 26 (T3) and week 52 (T4) of the follow-up period. These proportions were calculated on the basis of (1) a patient’s self-report of alcohol intake as the mean number of standard drinks per day for each period by the Time Line Follow-Back (TLFB; Sobell, Sobell, Leo, & Cancilla, 1988) interview administered by the study coordinator; and (2) family member report of the mean number of abstinence days for each period. In cases of discrepancies between the reports, the highest estimate was used. The information about HDD and ABS at T0 referred to 6 weeks of alcohol consumption before the enrollment to the study.

The secondary outcomes were the between-group differences in craving, depression, emotional distress, self-efficacy, perceived social support and quality of life at T1, T2, T3 and T4. These were measured, respectively, by the Obsessive–Compulsive Drinking Scale (OCDS; Anton, Moak, & Latham, 1995); abridged Beck Depression Inventory (BDI; Beck & Beamesderfer, 1974); General Health Questionnaire (GHQ-12, Goldberg & Williams, 1988); General Self-Efficacy Scale (GSES; Schwarzer & Jerusalem, 1995), Multidimensional Scale of Perceived Social Support (MSPSS; Zimet, Dahlem, Zimet, et al., 1988), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993).

The OCDS was used to evaluate self-reported alcohol craving. It has 14-items that provide a total as well as two subscale scores—obsessive drinking (OD) and compulsive drinking (CD). The abridged BDI is an extensively validated self-report measure of the severity of 13 depressive symptoms (sadness, pessimism, past failure, loss of pleasure, guilt feelings, self-dislike, suicidal thoughts or wishes, loss of interest, indecisiveness, change in appearance, loss of energy, fatigue, and changes in appetite). Each symptom is scored from 0 (absence) to 3 (extreme severity). Total scores range from 0 to 4 (none or minimal depression), from 5 to 7 (mild depression), from 8 to 15 (moderate depression), and 16 and over (severe depressive symptoms).

Psychological distress was measured using the GHQ-12 which assesses whether the respondent has recently experienced a particular symptom or behavior. Responses are rated on a 4-point Likert scale, ranging from “Much less than usual” (score 0) to “Much more than usual” (score 3). Total scores range from 0 to 36 and vary by study population: total scores of about 11–12 are typical, and a score higher than 20 suggests severe problems and psychological distress.

The GSES measures one’s belief in his/her ability to cope with stressful situations. The scale consists of 10 items (e.g. “Usually I am able to control a situation” or “In unexpected situations, I always know how I must behave myself”). Responses are rated on a 4-point Likert-scale.
ranging from “absolutely not true” (weighted as 1) to “absolutely true” (weighted as 4), where the higher GSES total scores indicate stronger self-efficacy beliefs.

The MSPSS is a self-report instrument for assessment of emotional help and the level of satisfaction with the social support obtained from three sources—family, friends and significant others. The scale includes 12 items, each of which refer to the people to whom the respondent would turn if he/she had problems of a personal, health or family nature, as well as financial and employment problems. Responses are scored on a 7-point scale from 1 (‘completely disagree’) to 7 (‘completely agree’). The MSPSS index and three subscales—family, friends and significant others—are computed. MSPSS total score ranged from 12 to 84, with a higher score indicating greater satisfaction with total support.

The Q-LES-Q is a self-report form composed of 16 items, each rated on a 5-point scale that indicates the degree of enjoyment or satisfaction with: physical health; social relations; ability to function in daily life; ability to get around physically; mood; family relations; sexual drive and interest; ability to work on hobbies, work, leisure time activities; economic status; household activities; and living/housing situation. A total score of 1 to 15 items was computed, while item 16 assessing “overall life satisfaction” was not included to avoid exaggerated scores.

Time frame for all instruments was the week preceding the visit. For all tools used, Cronbach’s alpha coefficients (internal consistency) ranged from 0.83 to 0.92.

2.5. Adverse events monitoring

All adverse effects spontaneously reported by the study participants were assessed for severity and relationship to study medication.

2.6. Statistical analysis

All outcome variables for patients who discontinued treatment before the end of the medication period were computed with the registers of the visit preceding discontinuation (last observation carried forward), which were compared between the treatment groups by Fisher’s exact test. Based on the assumption that every patient took the allocated drug, intention to treat analysis was made (Hallgren & Witkiewitz, 2013). All randomized patients were analyzed (intent-to-treat). Significance of between-group differences in baseline demographic characteristics (age, sex, marital status, education, religious affiliation, and immigrant and employment status) and alcohol history variables (duration of harmful alcohol consumption, number of prior inpatient detoxification) was assessed using χ² for categorical parameters and two-tailed t-tests for continuous parameters. The statistical significance of changes in the primary and secondary outcome estimates from baseline throughout week 12 (the medication period) and from week 12 to week 26 to week 52 (the follow-up periods) within each treatment arm was evaluated by ANCOVA and between the arms by two-tailed t-tests. A mixed model was used, including as fixed effects: treatment group, time, and their interaction; and baseline score of outcome variable. Under the assumption that missing data were missing at random, i.e., that outcome estimates were dependent on missing-data patterns, pattern-mixture models (Hedeker & Gibbons, 2006) were used, which provide overall estimates of effects by averaging over the various missing-data patterns.

For all analyses, the level of statistical significance was established at p < .05. All analyses were performed by SAS version 9.1 (SAS Institute Inc, Cary, NC). This study is registered with ClinicalTrials.gov, number NCT01002105.

3. Results

Out of the 75 screened, 11 patients were excluded (4 refused and 7 did not fully meet the inclusion criteria) and 64 patients (48 male and 16 female) were randomly assigned either to baclofen (n = 32) or placebo (n = 32) in a double-blind study design.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Baclofen</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 32)</td>
<td>(n = 32)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.7 ± 8.7</td>
<td>42.6 ± 9.6</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td>24 M/8 F</td>
<td>24 M/8 F</td>
<td>ns</td>
</tr>
<tr>
<td>Married</td>
<td>59%</td>
<td>48%</td>
<td>ns</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.7 ± 3.7</td>
<td>11.5 ± 1.2</td>
<td>ns</td>
</tr>
<tr>
<td>Employed</td>
<td>38.5%</td>
<td>43.7%</td>
<td>ns</td>
</tr>
<tr>
<td>Religious affiliation (Jewish)</td>
<td>62%</td>
<td>61%</td>
<td>ns</td>
</tr>
<tr>
<td>Immigrants</td>
<td>59%</td>
<td>66%</td>
<td>ns</td>
</tr>
<tr>
<td>Age at first alcohol consumption (years)</td>
<td>18.9 ± 4.1</td>
<td>19.1 ± 4.4</td>
<td>ns</td>
</tr>
<tr>
<td>Age at first binge (years)</td>
<td>23.6 ± 6.3</td>
<td>24.2 ± 8.7</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of harmful alcohol consumption (years)</td>
<td>14.1 ± 1.0</td>
<td>15.1 ± 1.6</td>
<td>ns</td>
</tr>
<tr>
<td>No. of prior inpatient detoxification</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>1</td>
<td>22%</td>
<td>26%</td>
<td>ns</td>
</tr>
<tr>
<td>2+</td>
<td>19%</td>
<td>24%</td>
<td>ns</td>
</tr>
<tr>
<td>%HDD</td>
<td>69.0 (±23.5)</td>
<td>66.0 (±21.4)</td>
<td>ns</td>
</tr>
<tr>
<td>%ABS</td>
<td>19.0 (±7.8)</td>
<td>15.0 (±10.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Drinks/drinking day</td>
<td>8.2 ± 1.6</td>
<td>7.4 ± 1.5</td>
<td>ns</td>
</tr>
</tbody>
</table>

#### 3.1. Demographic and clinical characteristics

Table 1 presents and compares the 32 patients on placebo versus the 32 on baclofen by demographic and clinical characteristics. As can be seen, the groups were quite comparable on all characteristics studied, including the ICD-10 diagnosis of mild alcohol dependence in both groups.

#### 3.2. Percent completers

Out of the 32 randomized patients for each group, only 23 patients (72%) completed the 12-week treatment with placebo and 17 patients (53%) with baclofen; no significant baclofen effect was found (χ² = 0.55, p = .46). The corresponding figures for completers of the 52 week follow-up period were 11 patients (34%) and 13 patients (41%), respectively; also with no significant baclofen effect (χ² = 0.12, p = .76).

#### 3.3. Effect of baclofen on percent heavy drinking days (HDD)

Fig. 2 shows that there was a significant time effect (t = 8.57; p < .001) on %HDD which decreased more than 3 times during the medication period for both placebo and baclofen arms. However, no baclofen effect was found for %HDD during both treatment (19.9% ± 3.5% for placebo
and 20.1% ± 2.7% for baclofen; t = 0.25, p = .79) and follow-up (28.3 ± 5.1% and 27.5 ± 4.7%, respectively; t = 0.65, p = .51) periods.

3.4. Effect of baclofen on percent abstinent days (ABS)

Fig. 3 shows a significant time effect on %ABS which increased more from distinct sources for both treatment and baclofen groups across the study periods. As can be seen, a significant baclofen effects were found for %ABS during both treatment (47.5 ± 7.5% for placebo and 46.1 ± 5.3% for baclofen; t = 0.86, p = .39) and follow-up (40.7 ± 2.5% and 41.9 ± 3.1%, respectively; t = 1.69, p = .09) periods.

3.5. Effect of baclofen on craving, distress and depression

Table 2 summarizes the secondary outcomes for the placebo and baclofen groups across the study periods. As can be seen, a significant time effect on reduction in craving (p < .001), distress (p < .01) and depression (p < .05) scores was detected in both groups, whereas there were no significant between-group differences in these variables during the medication and follow-up phases of the study.

3.6. Effect of baclofen on self-efficacy and social support

Table 2 also shows no significant time and baclofen effects on self-efficacy and social support from distinct sources for both treatment and followup periods.

3.7. Effect of baclofen on health-related quality of life (HRQL)

We found significant time effects for the improvement in HRQL scores in both the placebo and baclofen groups (F = 15.86 and F = 11.48, respectively; both p < 0.001) and for both phases of the study, but again no baclofen effect was found (t = 0.01, p = 0.99).

3.8. Tolerability and safety of baclofen

Baclofen was well tolerated. Only two side effects were registered: drowsiness and headache. The former was reported by 2 patients on baclofen (5%) and 3 patients on placebo (8%) treatment; and the latter was reported by one patient on baclofen (3%) and two patients on placebo (3%). These effects were transient and mild in nature. No serious adverse events, related to the study drug or placebo, were reported.

4. Discussion

To date RCTs have reported conflicting results about the efficacy of baclofen in the treatment of alcohol dependence. Although patients randomized to baclofen experienced higher rates of abstinence from alcohol than those receiving placebo in three RCTs (Addolorato et al., 2002, 2007, 2011), the largest available RCT (Garbutt et al., 2010) failed to find any differences between baclofen and placebo for the treatment of alcohol dependence. Our study examined more secondary outcomes and over a longer follow-up period than previous RCTs did, but we also found that efficacy of baclofen for alcohol dependence did not surpass that of placebo.

However, given the high placebo (psychosocial treatment) response in our study, the conclusion of the ineffect of baclofen should be taken with caution. Thus, in order to validate our findings more placebo-controlled trials are needed to either verify or discard a possible clinical efficacy of baclofen for alcohol dependence. Such large-scale, long-term (> 1 year), placebo-controlled studies in patients with moderate-severe (rather than mild) alcohol dependence should include, in addition to placebo, other compounds that were shown to be effective in the treatment of alcohol dependence, such as acamprosate or naltrexone.

Unlike in previous studies, the purpose of our study was to assess the efficacy of baclofen addition to standard psychosocial treatment for alcohol dependence. In this respect, our study failed to demonstrate that baclofen addition improves the outcomes of on-going psychosocial treatment for patients with mild alcohol dependence. Unlike previous positive RCTs carried out in Italy (Addolorato et al., 2002, 2007, 2011), and in accordance with Garbutt et al.'s study in the USA (Garbutt et al., 2010), we found no evidence for efficacy of baclofen for alcohol dependence.

Table 2

Summary of secondary outcomes.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baclofen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCDS</td>
<td>28.7 ± 9.8</td>
<td>17.4 ± 9.2</td>
</tr>
<tr>
<td>OD</td>
<td>11.4 ± 4.8</td>
<td>6.9 ± 4.3</td>
</tr>
<tr>
<td>CD</td>
<td>17.3 ± 6.8</td>
<td>10.6 ± 5.9</td>
</tr>
<tr>
<td>GHQ</td>
<td>17.7 ± 5.7</td>
<td>15.1 ± 5.1</td>
</tr>
<tr>
<td>BDI</td>
<td>16.2 ± 7.9</td>
<td>12.3 ± 6.5</td>
</tr>
<tr>
<td>GSES</td>
<td>25.4 ± 6.9</td>
<td>24.1 ± 5.8</td>
</tr>
<tr>
<td>MSPSS</td>
<td>55.1 ± 18.3</td>
<td>59.6 ± 19.4</td>
</tr>
<tr>
<td>Family</td>
<td>19.4 ± 5.9</td>
<td>20.3 ± 6.6</td>
</tr>
<tr>
<td>Friends</td>
<td>15.6 ± 8.3</td>
<td>18.2 ± 7.6</td>
</tr>
<tr>
<td>Others</td>
<td>20.1 ± 7.0</td>
<td>21.3 ± 6.7</td>
</tr>
<tr>
<td>Q-LES-Q</td>
<td>2.8 ± 3.8</td>
<td>10.8 ± 3.8</td>
</tr>
</tbody>
</table>

Mean scores ± SD are shown

OCDS = Obsessive–Compulsive Drinking Scale; OD = Obsessive Drinking subscale; CD = Compulsive Drinking subscale.
GHQ = General Health Questionnaire; BDI = Beck Depression Inventory; GSES = General Self-Efficacy Scale.
MSPSS = Multidimensional Scale of Perceived Social Support; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.
T0 = baseline; T1 = 6 weeks; T2 = 12 weeks; T3 = 26 weeks; T4 = 52 weeks.
* p < 0.05.
** p < 0.01.
*** p < 0.001.
dependence on the primary outcome measure—%HDD. However, a highly significant psychosocial treatment effect was found for both medication and placebo groups, indicating that psychosocial treatment by itself was efficacious in reducing heavy drinking as well as in prolonging abstinence.

Likewise, no evidence of baclofen effect was revealed on the secondary outcomes, such as craving for alcohol, HRQL, psychological distress and depression, though again a significant psychosocial treatment effect was noted in both groups. Finally, neither baclofen nor psychosocial treatment effects were found for other secondary outcomes, such as feelings of self-efficacy and perceived social support from any source.

Taken together, these data do not support our hypotheses that baclofen has an additional beneficial effect on the objective clinical indicators of alcohol dependence and that baclofen addition may improve the HRQL and associated self-perceptions among these patients more than standard psychosocial treatment alone. However, our findings must be considered in the context of the overall clinical trial evidence with particular attention to variations across trials, possibly due to the effectiveness of the psychosocial treatment rather than the medication effect (Litten, Castle, Falk, et al., 2013; Litten, Ryan, Fertig, et al., 2013).

The improvements in treatment outcomes may result from a complex interplay of patients, RCT staff, and treatment environment factors rather than from the direct effect of the medication (Finniss, Kapchuk, Miller, & Benedetti, 2010). The beneficial effect of the on-going psychosocial treatment makes it especially difficult in clinical trials to detect a specific effect of psychiatric medications. Noteworthy, the reported placebo response in alcohol trials even greater than that observed in depression and schizophrenia trials (Anton, O’Malley, Ciraulo, et al., 2006; Fertig, Ryan, Falk, et al., 2012; Khan, Detke, Khan, & Mallinckrodt, 2003; Kirsch, Deacon, Hueno-Medina, et al., 2008; Kobak, Leuchter, DeBota, et al., 2010; Mallinckrodt, Zhang, Prucka, & Millen, 2010). It may be explained by either an increased suggestibility of alcohol dependent patients compared with other psychiatric patients or their greater optimism and expectations about the experimental medications’ effect (Weiss, O’Malley, Hosking, et al., 2008).

Although our study failed to demonstrate any benefit from baclofen, the drug was well tolerated with no reported significant adverse events. Despite ongoing alcohol consumption by many individuals, we observed no significant alcohol–baclofen interactions. Consistent results on tolerability obtained across all RCTs and case studies available to date (Ameisen, 2005; Brennan et al., 2013; Bucknam, 2007) suggest that baclofen is feasible for safe use in further trials even with higher doses of the drug.

The similarity of characteristics of our sample (in terms of age, gender, and alcohol consumption) with those of the Garbutt study (2010) could explain comparable outcomes of both studies. In contrast, including more severely alcohol dependent patients in the Addolorato studies (2002; 2007) could account for the differences in our outcomes. It is likely that baclofen might have a stronger impact on more severely dependent patients (Brennan et al., 2013). Another possible explanation is that a 50 mg/day dose of baclofen might be an insufficient dose for most patients. There are case reports suggesting that substantially higher doses may be required for obtaining efficacy in some patients. For instance, Ameisen (2005) reported suppression of alcohol consumption and reduction in craving and anxiety from a dose of 120 mg/day, and Bucknam (2007) reported improvement in alcohol consumption accompanied by relaxation from a dose of 100–140 mg/day of baclofen. These reports suggest the possibility of a dose–response relationship for baclofen at least for some patients with alcohol dependence, which should be examined in future flexible dose studies.

Limitations of this study are common with other RCTs (Addolorato et al., 2002; Garbutt et al., 2010): the exclusion of patients with severe neurological and psychiatric comorbidities may limit external validity of our study and generalization of its findings to patient groups with these comorbidities. The small sample size increases the probability that a small effect could be missed, particularly in more severe cases of alcohol dependence than in our population. Other limitations are: the multi-site design of the trial that often shows a large inter-site variability; the high rate of attrition the relatively low dosage of baclofen (50 mg/day) and its administration in two divided doses rather than 3 times a day. It is of note that baclofen has a short half-life (ranging from 2 to 6 hours), therefore it is possible that during the experimental treatment, patients spent the second half of the day without coverage from the active medication. However, despite the difference in treatment methodology (e.g., Garbutt and colleagues used baclofen at a total dose of 30 mg, divided in three doses daily), the results of the two studies were substantially similar.

The strengths of the present study are its randomized, placebo-controlled trial nature and the use of a standard assessment methodology; the administration of pills by family members and control of compliance with drug treatment by pill count, as well as the “real world” nature of the trial setting.

5. Conclusions

We suggest that further studies should be performed with flexible dose regimens, comparing baclofen not only with placebo but simultaneously with other active compounds, before arriving at a final conclusion concerning the efficacy of baclofen as add-on therapy for alcohol dependence.

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Contributors

AMP and PR conceived of the project with input on the design from AG. EA and AMP conducted the statistical analysis. AMP wrote the first draft of the manuscript and PR and AW provided significant input in redrafting. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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