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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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ABSTRACT

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.

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 ϒ-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 Parhhem 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 are 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

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to be easily manageable and demonstrated no addictive properties (Addolorato, Leggio, Abenavoli, et al., 2006; Addolorato, Leggio, Agabio, et al., 2006; Johnson et al., 2005). It has recently been shown (Addolorato et al., 2007) that owing to its safe side-effect profile with low 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, RCTs 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 being 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-Coccossis, Liappas, Tzavellas, et al., 2007; Rosenbloom, Sullivan, Sassoon, et al., 2007; Saarni, 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, & Blumenthal, 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, Duersteler-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, Flaum, 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 both to 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 $\geq$5 drinks per day; women $\geq$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