# BACLOFEN IN THE TREATMENT OF ALCOHOL USE DISORDER

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# BACLOFEN IN THE TREATMENT OF ALCOHOL USE DISORDER

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This is a collection on use of the GABA-B agonist Baclofen in the use of alcohol use disorder. The articles center around efficacy of Baclofen ranging from acute withdrawal to maintenance of abstinence, address the issue of dosing and indications and variation of Baclofen use worldwide.

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# Editorial: Baclofen in the Treatment of Alcohol Use Disorder

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**Keywords: alcohol use disorder, baclofen, prescription, safety, mode of action**

**Editorial on the Research Topic**

**Baclofen in the Treatment of Alcohol Use Disorder**

Alcohol use disorder (AUD) is a severe illness for which available treatments are of limited efficacy. Over the last 20 years, baclofen has progressively emerged as a potentially useful treatment for AUD, but our knowledge on the best way to prescribe it, on potential influencing factors on its effects, and on its mechanism of action in AUD is still limited. Knowledge on its efficacy is also debated. As all three of us—RB, MH, and RA—have a long practice of baclofen use in the treatment of AUD, we thought of writing a special issue on this topic, and were delighted when *Frontiers in Psychiatry* accepted to give us this opportunity [two of us, RB and MH, have previously participated in the writing of a book on the same topic (1, 2)]. The realization of this new special issue has proved to be a kind of adventure we did not expect at the start.

We aimed at joining our competencies to provide a shared description of the methods to obtain an optimal therapeutic effect of baclofen in the treatment of AUD. We were aware that to obtain its therapeutic effect, the required dose of baclofen may largely vary among patients, certain patients requiring low doses and other high or very high doses. In other words, our experience showed that patients require "personalized doses" of baclofen that allow them to say "well, at this dose I have no more craving for alcohol, I do not experience craving when I see bottles or people who drink," meaning that, following Olivier Ameisen's words, the patient has reached a state of "indifference towards alcohol" (3).

Our special issue had three goals. The first was to give a general view of baclofen use for AUD treatment in different countries. The second was to provide joined information on the methods to prescribe baclofen in the treatment of AUD. The third was to obtain recent data from different research teams involved in various aspects of baclofen use in the treatment of AUD. To achieve these goals, we solicited the participation of a large number of baclofen prescribers worldwide.

For our first goal, Garbutt describes the use of baclofen in the US. According to this contribution, there is a limited use of baclofen to treat AUD in the US. However, Garbutt points out that there is, in general, a very low rate of medication use for the treatment of AUD in the US, largely due to a lack of knowledge of physicians and patients about the potential value of medications. Regarding baclofen, the results of meta-analyses showing that its efficacy is equivocal, the concerns of tolerability, and the fact that its prescription remains off label are all elements that may deter clinicians and patients. Garbutt nevertheless mentions that there are no accurate data on the use of baclofen in AUD in the US, making it difficult to know if clinicians prescribe it. These remarks probably apply to most other countries, except France, which is the only country where baclofen has an official approval from Health Authorities in the treatment of AUD, and where baclofen is more widely prescribed.

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For our second goal, we convened a large group of international experts, representative of researchers and physicians who contributed to the recent studies on baclofen and AUD. This group of experts achieved a consensus on the use of baclofen to treat AUD—"the Cagliari Statement"—published by *Lancet Psychiatry* in 2018 (4). After this concise and rigorous document, the group decided to provide a more detailed description of the different methods used to administer baclofen in the treatment of AUD (de Beaurepaire et al.). In detail, we describe how, especially in experimental studies, baclofen is usually administered in fixed doses to evaluate the efficacy and safety of each specific dose whereas, in clinical practice, baclofen is usually administered in flexible doses. In other words, the dose is gradually increased until the patient achieves the desired effects or side effects that prevent a further increase in dose. In this article, other than this description of the methods adopted for baclofen administration, there is also an unprecedented exhaustive review of published studies, approved by 26 authors coming from seven different countries (Australia, France, Germany, Great Britain, Italy, The Netherlands, and the US).

For our third goal, several innovative reports dealing with baclofen prescription and use, pharmacokinetics, preclinical research, and clinical investigations aiming to understand its potential mechanisms of action in AUD are published in the special issue. Reports on baclofen prescription and use include a long-term retrospective study (Pinot et al.); a research report on the response to baclofen in patients receiving antidepressants (Heng et al.); reviews on the effects of baclofen in alcohol withdrawal syndrome (AWS) (Cooney et al.), on the adverse effects of baclofen (Rolland et al.), and on the management of self-poisoning with baclofen (Franchitto et al.); and reviews focused on comorbidities—with liver cirrhosis (Mosoni et al.) and other mental disorders (Agabio and Leggio). In a 3-year retrospective study, Pinot et al. have followed 144 patients with AUD receiving tailored doses of baclofen (50 to 520 mg/day; average dose, 211 mg/day), and the treatment was successful in 63.3% of the patients (according to the WHO classification criteria) (Pinot et al.), a percentage of success grossly similar to that reported in other previously published observational studies. Depression and antidepressant treatment are common features in patients with AUD, and it was important to search for a potential interaction between baclofen and antidepressants. Heng et al. show that in patients on long-term treatment with antidepressants prior to starting baclofen, a beneficial effect on drinking outcomes can be shown like in patients who are not using antidepressants. However, there was a trend to an interaction between the two that needs further investigations (baseline tobacco use or alcohol liver disease may interfere with the interaction) (Heng et al.). The effectiveness of baclofen in the treatment of AWS is controversial, and Cooney et al., in their review, confirm that the evidence does not support the use of baclofen as a first-line treatment of AWS. Adverse effects too often limit or circumvent baclofen treatment, and this issue must be seriously considered. Rolland et al. propose a thoughtful review on baclofen adverse effects, separating the common and benign ones (sedation, insomnia, dizziness, and tinnitus) from the rare but potentially dangerous ones (seizures, mania, and sleep apnea), and point that concurrent consumption of alcohol, benzodiazepines, and other sedatives may worsen many adverse effects. These considerations have consequences on baclofen treatment management in terms of prevention of adverse effects and obtaining an optimal response (Rolland et al.). Cases of intentional or non-intentional baclofen self-poisoning have increased in parallel with the increasing use of baclofen in AUD. These cases present with particular clinical features that clinicians must be aware of. Franchitto et al. review the literature on that subject and address the management of this condition. AUD is often associated with liver cirrhosis and/or mental illnesses. AUD is difficult to treat in patients with liver cirrhosis because approved AUD medications may impair liver function. Baclofen is attractive because it has no liver toxicity, and Mosoni et al. review the clinical trials investigating the effect of baclofen in patients with AUD associated with liver disease. The results show a very favorable effect of baclofen in these patients, although the most appropriate dose of the drug remains to be determined (Mosoni et al.). Mental illness may alter the outcome in baclofen-treated patients. Agabio and Leggio address this issue by using a narrative analysis of all clinical and human laboratory studies of baclofen treatment in patients with AUD with or without mental illness. The most frequent psychiatric comorbidities are anxiety and depression. Further work is needed to determine if these comorbidities interfere with baclofen treatment outcome (Agabio and Leggio).

Reports on baclofen pharmacokinetics include two studies by Simon et al. In their first article, Simon et al. investigate the pharmacokinetics of baclofen in 60 patients with AUD treated with various doses of baclofen (up to 300 mg/day). The results show that baclofen has a linear pharmacokinetic profile, corresponding to a one-compartment model, with no influencing clinical or biological factor (Simon et al.). In their second article, Simon et al. review the literature investigating the baclofen dose in relation to the pharmacokinetics of the drug. Indeed, the dose–response variability in baclofen-treated patients may be related to variability in pharmacokinetics. In particular, the effects of intestinal absorption, blood–brain barrier transport, and renal elimination are highlighted (Simon et al.).

Preclinical research is reviewed by Colombo and Gessa. Baclofen suppresses many alcohol-related behaviors in laboratory animals, including locomotor activity, alcohol drinking and self-administration, binge-like drinking, relapse drinking, alcohol seeking, and AWS symptoms. These effects of baclofen in animals provide interesting elements for the understanding of its mechanism of action in AUD (Colombo and Gessa). Two clinical studies also bring new data that could help the understanding of the mechanism of action of baclofen. Morley et al., using magnetic resonance spectroscopy, show that baclofen increases the concentrations of the antioxidants glutathione and *N*-acetyl aspartate in the brain of patients with AUD, and that higher glutathione levels predict favorable outcomes at follow-up. This supports the idea that the beneficial effects of baclofen in the treatment of AUD could be, at least in part, related to neuroprotective mechanisms (Morley et al.). Durant et al. show that the effects of an acute administration of baclofen are very different in patients with AUD compared with healthy controls. The measured effects were growth hormone release and

subjective experience (for instance, feeling "drunk", "dizzy", or "stimulated"). All these responses were blunted in patients with AUD while they were very marked in healthy controls. According to the authors, these results indicate a lower sensitivity to baclofen and, by extension, a general lower GABA-B receptor sensitivity in patients with AUD (Durant et al.). Finally, the potential mechanisms of baclofen in AUD are reviewed in an article that concludes that baclofen may produce an indifference to alcohol by suppressing the Pavlovian association between alcohol cues and rewards through an action in a critical part of the dopaminergic network (the amygdala). This action of baclofen is made possible by the fact that baclofen and alcohol act on similar brain systems (in particular GABA-B systems) (de Beaurepaire).

We really hope that this special issue will contribute to improve our knowledge and enhance debates and research on the use of baclofen in the treatment of AUD, a devastating illness that is dramatically undertreated.

## AUTHOR CONTRIBUTIONS

All authors equally contributed to this work.

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# The Use of Baclofen as a Treatment for Alcohol Use Disorder: A Clinical Practice Perspective

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Alcohol use disorder (AUD) is a brain disorder associated with high rates of mortality and morbidity worldwide. Baclofen, a selective gamma-aminobutyric acid-B (GABA-B) receptor agonist, has emerged as a promising drug for AUD. The use of this drug remains controversial, in part due to uncertainty regarding dosing and efficacy, alongside concerns about safety. To date there have been 15 randomized controlled trials (RCTs) investigating the use of baclofen in AUD; three using doses over 100 mg/day. Two additional RCTs have been completed but have not yet been published. Most trials used

fixed dosing of 30–80 mg/day. The other approach involved titration until the desired clinical effect was achieved, or unwanted effects emerged. The maintenance dose varies widely from 30 to more than 300 mg/day. Baclofen may be particularly advantageous in those with liver disease, due to its limited hepatic metabolism and safe profile in this population. Patients should be informed that the use of baclofen for AUD is as an "off-label" prescription, that no optimal fixed dose has been established, and that existing clinical evidence on efficacy is inconsistent. Baclofen therapy requires careful medical monitoring due to safety considerations, particularly at higher doses and in those with comorbid physical and/or psychiatric conditions. Baclofen is mostly used in some European countries and Australia, and in particular, for patients who have not benefitted from the currently used and approved medications for AUD.

**Keywords: GABA-B, baclofen, alcohol use disorder, efficacy, safety**

## INTRODUCTION

After promising preclinical evidence [for review see Colombo and Gessa (1)], clinical studies started to investigate whether baclofen may be useful in the treatment of alcohol use disorder (AUD). However, to date, clinical studies have yielded conflicting results. Despite the lack of consistent evidence, baclofen is often used off-label in clinical practice to treat AUD, especially in some European countries and Australia (2). In this manuscript, a large group of researchers and clinicians combine their expertise in this area to provide (a) a review of the current research evidence and clinical experience of using baclofen in the treatment of AUD, (b) a description of the two different approaches used to administer baclofen in clinical practice settings ("fixed doses" or "flexible doses") to treat AUD, and (c) a brief overview of the clinical use of baclofen to treat AUD.

## REVIEW OF THE CURRENT RESEARCH EVIDENCE AND CLINICAL EXPERIENCE

### Alcohol Use Disorder and the Need for Additional Medications

AUD is a major public health problem associated with high rates of mortality and morbidity worldwide (3–7). The previous editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) described two disorders related to a pattern of maladaptive alcohol consumption, alcohol abuse and alcohol dependence [e.g., DSM-IV; (8)]. The diagnosis of dependence required the fulfillment of three (or more) criteria out of a set of seven, whereas the diagnosis of abuse required at least one out of four different criteria. These two disorders have been combined into a single disorder (AUD), where one set of criteria is now used (DSM-5; 3). In DSM-5, the AUD diagnosis requires the fulfillment of two (or more) criteria out of a set of 11, including "craving," or a strong desire or urge to use alcohol (3), instead of legal problems (included among DSM-IV alcohol abuse criteria, but excluded by DSM-5 AUD criteria). Accordingly, the previous diagnosis (DSM-IV) of alcohol dependence corresponds approximately to moderate/severe DSM-5 AUD (9).

AUD is characterized by periods of excessive alcohol consumption and a chronic relapsing, remitting course (3). According to the different AUD phases, the goal of medical treatment may be to achieve and maintain abstinence, if patients are currently drinking—or just maintain abstinence.

Even if abstinence is the best goal for AUD medical treatment, some patients prefer to reduce their alcohol consumption to low-risk drinking, instead of total abstinence. According to the US National Institute on Alcohol Abuse and Alcoholism (NIAAA), low-risk drinking corresponds to an alcohol consumption $\leq$14 (men) or 7 (women) drinks per week and $\leq$5 (men) or 4 (women) drinks on a single day (1 drink = 14 g alcohol) (10). This consumption pattern is associated with lower risks than moderate/high risk drinking, even if the safest level of drinking is none (5).

Accordingly, the recent guidelines of the American Psychiatric Association for the pharmacological treatment of AUD recommend the use of naltrexone, acamprosate, or disulfiram, based on the treatment objective (reducing alcohol consumption or achieving and maintaining abstinence), patient preference, and presence of comorbidities that may contraindicate a specific drug (11). In Europe, nalmefene has also been approved for the treatment of alcohol dependence (12). Nevertheless, only a minority of people with AUD seek and receive medical treatment (4, 13, 14) and current approved medications for AUD are of limited effectiveness (15). Therefore, identification of other medications may contribute toward increasing the number of AUD patients who benefit from pharmacological treatments with a different mechanism of action.

### Baclofen and Alcohol Use Disorder

Baclofen, a selective gamma-aminobutyric acid-B (GABA-B) receptor agonist, has emerged as a promising drug for AUD (16). It has been marketed since the early 1970s for the treatment of muscle spasticity, secondary to neurological conditions. The wide use of baclofen as a myorelaxant has provided detailed information on its safety and side effects in these patients (17). From the 1970s, research, largely in animal addiction models, suggested that baclofen may also be effective in the treatment of AUD (1).

# EVIDENCE FOR THE EFFECT OF BACLOFEN ON ALCOHOL USE

## Preclinical Studies

Animal studies showed that baclofen induced a dose-related reduction in (a) the behavioral effects caused by alcohol (18), (b) acquisition and maintenance of alcohol consumption (19–21), including binge-like drinking (22), (c) relapse-like drinking (23), (d) severity of alcohol withdrawal signs (20), (e) cue-induced reinstatement of previously extinguished alcohol seeking behavior (24), and (f) reinforcing and motivational properties of alcohol (25–30) in different validated rodent models of AUD [for a recent review, see Colombo and Gessa (1)].

## Clinical Studies

### Studies Using baclofen 30 mg/Day

Addolorato and colleagues were the first to investigate the efficacy of baclofen in reducing alcohol consumption in AUD patients (31). In this first study, 10 male AUD patients received 30 mg/day baclofen (starting from 5 mg, three times a day, and then 10 mg, three times a day) for four consecutive weeks. Patients reported their last alcohol intake in the preceding 24 h. Seven patients achieved and maintained abstinence, and another two significantly reduced their alcohol consumption. Flannery and colleagues replicated these findings in 12 AUD patients, including three women, that were active drinkers (three days abstinent before the beginning of the trial), using the same dose of baclofen for 12 weeks (32). However, conclusions that can be drawn from these results are limited by the open-label design and the absence of a (placebo) control group.

In 2002, Addolorato and colleagues conducted the first randomized controlled trial (RCT) (see **Table 1**). In this RCT, 39 AUD male participants received 30 mg/day baclofen or placebo, for 4 weeks. Participants were active drinkers (last intake in the preceding 24 h), did not suffer from any other mental disorder, were treated as outpatients, and received psychological support every week. Their mean baseline alcohol consumption was 17.6 drinks per day (1 drink = 12 g of alcohol) in the baclofen group. Compared to placebo, baclofen increased the percentage of patients who achieved and maintained abstinence (abstinent patients), as well as the number of abstinent days, and decreased the number of drinks per drinking day and anxiety levels (33).

However, a similar RCT found different results [(34); see **Table 1**]. In this RCT, 80 AUD patients, active drinkers (three days abstinent before beginning the trial), received either 30 mg/day baclofen or placebo for 12 weeks, in an outpatient setting, together with eight sessions of a comprehensive psychological intervention named BRENDA. In this study, there was no difference between baclofen and placebo in the percentage of heavy drinking days, abstinent days, time to first drink (time to lapse), or time to heavy drinking day (time to relapse).

This RCT differed from the Addolorato et al. (33) in several aspects: (a) the high number of women recruited (45% females); (b) the number of individuals who suffered from other mental disorders (e.g., 29% on antidepressants); (c) the low amount of alcohol consumed at baseline (7.3 drinks per day with 1 drink = 14 g of alcohol in baclofen group); (d) the low baseline levels of alcohol withdrawal; (f) the high placebo response; (g) the different aims of the treatment (including abstinence, occasional use, and regular but reduced use); and (h) financial compensation for attending each visit (46).

More recently, three RCTs (each with three arms) compared the efficacy of 30 mg/day (10 mg, three times a day) to another dose of baclofen and placebo in the treatment of AUD, for 12 weeks (39–41).

Regarding participants treated with 30 mg/day baclofen compared to placebo, the first RCT found that baclofen significantly reduced the number of drinks per drinking day (39), whereas the second RCT found no difference in time to relapse nor time to lapse (40). The third RCT found that baclofen treatment (both dose group composite), compared to placebo, increased (a) time to first lapse, (b) time to first relapse, and (c) percentage of days abstinent. The characteristics of these RCTs are described in detail below. Recently, another 3-arm RCT (30 mg/day, 90 mg/day and placebo) was completed, and data analysis is underway (Garbutt JC, unpublished; https://clinicaltrials.gov/, identifier NCT01980706).

Two additional RCTs tested baclofen 30 mg/day in AUD patients with liver disease. In 2007, Addolorato et al. investigated the efficacy of baclofen in AUD patients with liver cirrhosis (**Table 1**). The rationale for selecting this specific sample was that, in these patients, certain AUD pharmacological agents (e.g., disulfiram and naltrexone) are contraindicated because of their liver metabolism, whereas baclofen has lower liver metabolism and primarily renal excretion. In this RCT, 42 outpatients received 30 mg/day baclofen and 42 received placebo for 12 weeks (35). Participants were active drinkers [at least two heavy drinking days per week and an average consumption of 21/14 drinks (men/women) per week, or more, during the 4 weeks before enrollment], included 23 women (27.4% of the entire sample), did not suffer from other severe mental disorders, and were seen every week for the first month, and then every 2 weeks. At each visit, patients received an individual session of counseling support lasting 30 min. At the end of the 12-weeks study, a higher rate of participants allocated baclofen achieved and maintained abstinence and had a longer cumulative abstinence duration compared with placebo.

More recently, Hauser et al. (36) conducted a similar RCT among AUD patients with chronic hepatitis C (HCV), enrolled at four US Veteran Affairs Medical Centers (**Table 1**), and found that 30 mg/day baclofen did not increase abstinence or reduce alcohol use, craving for alcohol, or anxiety compared to placebo. In this RCT, 40 participants received 30 mg/baclofen and 40 participants placebo for 12 weeks. These patients were active drinkers (at least one heavy drinking day per week or more than 7 drinks per week, for each of the preceding 2 weeks), did not suffer from other mental disorders, and were seen every week for the first month, and then every 2 weeks. However, unlike the RCT by Addolorato et al. (35), the Hauser et al. study (36) included only three women (3.7% of the entire sample), had low baseline levels of alcohol consumption (7.1 drinks per drinking days with 1 drink = 14 g of alcohol in baclofen group), and participants received manual-guided counseling lasting 15 min at each visit.

**TABLE 1 |** Randomized double-blind placebo-controlled trials.

| References | Daily dose of baclofen; Number of participants | Mean of drinks per drinking days | Weeks of duration | Significant difference between baclofen and placebo | Effects of baclofen compared to placebo |
|---|---|---|---|---|---|
| Addolorato et al. (33) | BAC (30 mg): 20<br>PLA: 19 | BAC (30 mg): 18.0[a]<br>PLA: 10.0 | 4 | Yes | BAC (30 mg): ↓ 100.0% DD<br>PLA: ↓ 60.0% DD |
| Garbutt et al. (34) | BAC (30 mg): 40<br>PLA: 40 | BAC (30 mg): 7.3[b]<br>PLA: 6.9 | 12 | No | BAC (30 mg): 51.7% abstinent days<br>PLA: 51.6% abstinent days |
| Addolorato et al. (35) | BAC (30 mg): 42<br>PLA: 42 | BAC (30 mg): N.A.<br>PLA: N.A. | 12 | Yes | BAC (30 mg): 71.4% abstinent patients<br>PLA: 28.6% abstinent patients |
| Hauser et al. (36) | BAC (30 mg): 88<br>PLA: 92 | BAC (30 mg): 7.1[b]<br>PLA: 7.6 | 12 | No | BAC (30 mg): 32.3% abstinent days<br>PLA: 31.1% abstinent days |
| Ponizovsky et al. (37) | BAC (50 mg): 32<br>PLA: 32 | BAC (50 mg): 7.4[a]<br>PLA: 8.2 | 12 | No | BAC (50 mg): 46.1% abstinent days<br>PLA: 47.5% abstinent days |
| Krupitsky et al. (38) | BAC (50 mg): 16<br>PLA: 16 | BAC (50 mg): 0.1[a]<br>PLA: 0.3 | 12 | No | BAC (50 mg): 100% abstinent days last week<br>PLA: 100% abstinent days last week |
| Addolorato et al. (39) | BAC (30 mg): 14<br>BAC (60 mg): 14<br>PLA: 14 | BAC (30 mg): 13.9[a]<br>BAC (60 mg): 9.6<br>PLA: 12.0 | 12 | Yes | BAC (30 mg): ↓ 53% DD<br>BAC (60 mg): ↓ 68% DD<br>PLA: N.A. |
| Morley et al. (40) | BAC (30 mg): 14<br>BAC (60 mg): 14<br>PLA: 14 | BAC (30 mg): 15.5[c]<br>BAC (60 mg): 15.1<br>PLA: 14.3 | 12 | No | BAC (30 mg): 5.9 DDD<br>BAC (60 mg): 5.6 DDD<br>PLA: 2.8 DDD<br>BAC (30 mg) induced positive effects among patients with comorbid anxiety |
| Morley et al. (41) | BAC (30 mg): 36<br>BAC (75 mg): 35<br>PLA: 33 | BAC (30 mg): 17.0 [c]<br>BAC (75 mg): 13.8<br>PLA: 14.1 | 12 | Yes | BAC (30 mg): 68.5% abstinent days<br>BAC (75 mg): 64.6% abstinent days<br>PLA: 43.3% abstinent days |
| Leggio et al. (42) | BAC (80 mg): 15<br>PLA: 15 | BAC (80 mg): N.A.<br>PLA: N.A. | 12 | Yes | BAC (80 mg): 12.1% abstinent days from alcohol and tobacco<br>PLA: 3.5% abstinent days from alcohol and tobacco |
| Garbutt et al. unpublished | BAC (30 mg)<br>BAC (90 mg)<br>PLA | - | - | - | - |
| Beraha et al. (43) | BAC (30 mg): 31<br>BAC (up to 150 mg): 58<br>PLA: 62 | BAC (30 mg): 11.0 [a]<br>BAC (up to 150 mg): 12.2<br>PLA: 11.8 | 16 | No | BAC (30 mg): 41.9% abstinent patients<br>BAC (up to 150 mg): 43.1% abstinent patients<br>PLA: 46.8% abstinent patients |
| Reynaud et al. (44) | BAC (up to 180 mg): 155<br>PLA: 155 | BAC (up to 180 mg): 8.0 [a]<br>PLA: 7.8 | 26 | No | BAC (up to 180 mg): 11.9% abstinent patients<br>PLA: 10.5% abstinent patients |
| Müller et al. (45) | BAC (up to 270 mg): 28<br>PLA: 28 | BAC (up to 270 mg): 17.2 [a]<br>PLA: 16.0 | 12 | Yes | BAC (up to 270 mg): 68.2% abstinent patients<br>PLA: 23.8% abstinent patients |
| Jaury et al., unpublished | BAC (up to 300 mg)<br>PLA | - | - | - | - |

*[a] 1 drink = 12 g of alcohol; [b] 1 drink = 14 g of alcohol [c] 1 drink = 10 g of alcohol; BAC, baclofen; DD, drinking days; DDD, drinks per drinking days; N.A., not applicable; PLA, Placebo.*

### Anecdotal and Open-Label Observations With Doses of baclofen >30 mg/Day

Some case reports (47–49) suggested the potential utility of increasing the doses of baclofen to treat patients with AUD. The first of these case reports was published in 2005 by Olivier Ameisen, a physician suffering from severe AUD, who reported that he achieved abstinence from alcohol with 270 mg/day of baclofen (47). Similar observational studies started being published from 2010 (50–62). These case-series (without control groups) suggested that doses of baclofen ranging from 30 to more than 300 mg/day may be effective, with some patients achieving up to a maximum daily dose of 400 mg (55, 63). The effectiveness of baclofen was also reported in AUD patients affected by liver disease (55, 64, 65).

### RCTs Using Doses of Baclofen >30 mg/day and <100 mg/Day

Subsequently, a series of RCTs investigated the efficacy of higher doses of baclofen in the treatment of AUD compared to those administered in early studies (**Table 1**), as detailed below.

Two RCTs investigated the efficacy of 50 mg/day baclofen administered in two, instead of three, times a day [(37, 38), **Table 1**]. In both studies, participants did not suffer from other severe mental disorders, were seen every week, as outpatients, for 12 weeks, and received an individual psychosocial intervention. In one RCT, 64 AUD participants included 16 women (25% of total sample), consumed 7.4 drinks per drinking day (patients allocated to baclofen treatment; 1 drink = 12 g of alcohol), and, other than the weekly individual intervention, also received group counseling sessions, every 2 weeks (37). Participants were active drinkers (at least two heavy drinking days per week and average overall consumption >21/14 drinks per week (men/women) during the month preceding recruitment, and no more than six abstinent days per month). This study did not find differences in the percentages of heavy drinking and abstinent days between the baclofen and the placebo group. However, a high placebo effect was observed (e.g., percentage of abstinent days was 47.5% for placebo and 46.1% for baclofen).

In the second RCT, 32 AUD participants were abstinent from alcohol consumption for at least 7 days and consumed 8.5 g of pure ethanol per week at baseline (for patients allocated to baclofen treatment, equal to ∼0.1 drink per drinking day if patients drink every day, 1 drink = 12 g of alcohol) and the number of women recruited was not provided (38). The study found no differences between baclofen and placebo in alcohol consumption and time to relapse.

Two RCTs (each with three arms) compared the efficacy of 60 mg/day (20 mg three times a day) to 30 mg/day baclofen and placebo in the treatment of AUD, for 12 weeks (39, 40). The first RCT found that, compared with patients allocated to placebo, participants treated with baclofen significantly reduced the number of drinks per drinking day and this effect was greater among participants treated with 60 mg/day baclofen than those with 30 mg/day (39). Participants included 32 men (76%) and 10 women (24%) and did not suffer from other severe mental disorders. They were active drinkers (at least two heavy drinking days per week and an average overall consumption of >21/14 drinks (men/women) per week during the 4 weeks before enrollment, and ability to refrain from drinking at least 3 days before randomization day) and consumed a mean of ∼12 drinks per drinking day at baseline, with 1 drink = 12 g of alcohol). Each participant was seen as an outpatient, every week for the first month, and then every 2 weeks. At each visit, patients received an individual session of counseling support lasting 30 min.

In contrast, the second RCT found no difference between baclofen 60 mg, baclofen 30 mg, and placebo on time to relapse, nor time to lapse (40). Participants included 19 men (45%) and 23 women (55%), were active drinkers (abstinent from alcohol at least 3 days prior to randomization) and consumed high levels of alcohol at baseline [more than 15 drinks per drinking day (1 drink = 10 g of alcohol) in baclofen groups], were seen as outpatients every week for the first month, then every 2 weeks, and, at each visit, received 30-min psychosocial therapy. In addition, 41% of participants suffered with current anxiety disorders. A *post-hoc* analysis showed a beneficial effect of baclofen, compared to placebo, only among AUD patients with comorbid anxiety disorders. Namely, AUD patients with anxiety disorder treated with baclofen had the first lapse and relapse after a significantly longer period of time, compared to AUD patients with anxiety treated with placebo. However, no difference was found between 60 and 30 mg/day baclofen.

One RCT compared the efficacy of 75 mg/day (25 mg three times a day) to 30 mg/day baclofen and placebo in the treatment of 104 AUD patients (including 30 (29%) women), for 12 weeks [(41); **Table 1**]. In this study, participants were seen as outpatients every 2 weeks, and, at each visit, received adherence therapy lasting 20–60 min. People with active major mental disorders were excluded, but 55% of participants were prescribed antidepressants and 56% suffered from liver disease (with or without cirrhosis). Participants were abstinent from alcohol consumption for between three and 21 days and their baseline level of alcohol consumption was equal to 15 drinks per drinking day with 1 drink = 10 g of alcohol). The aims of treatment included both abstinence and reduction of alcohol consumption. The study found that baclofen treatment (both dose groups combined), compared to placebo, increased: (a) time to first lapse, (b) time to first relapse, and (c) percentage of days abstinent. However, there were no differences between the effects of the 75 mg/day and the 30 mg/day groups. When the results were analyzed according to the presence of liver disease, baclofen (both dose group composite) was shown to be effective in increasing the time to lapse and relapse among participants affected by liver disease, but not among those without liver disease.

One RCT investigated the efficacy of 80 mg/day (20 mg at 4 times/day) baclofen in the treatment of 30 patients affected by AUD and nicotine use disorder [(42); **Table 1**]. In this 12-weeks study, consistent with FDA recommendations, the daily dose of baclofen 80 mg/day was divided into four administrations (20 mg, four times a day). Participants included 12 females (40%), did not suffer from other severe mental disorders, were seen as outpatients every week for the first month, then every 2 weeks, and, at each visit, received an individual session of medical management. They were active smokers and drinkers at the beginning of the trial and their consumption of alcohol

at baseline was high but expressed as percent of heavy drinking days (78% for patients allocated to baclofen). Participants were looking for treatment for both AUD and smoking, but with different treatment goals (i.e., reducing or quitting both substances or quitting one and reducing the other). Regarding alcohol consumption, 48% of overall participants wanted to quit drinking. The results of the study showed that the rate of abstinent days from co-use of alcohol and tobacco was higher among participants treated with baclofen compared to those treated with placebo (42).

### RCTs Using Doses of Baclofen >100 mg/Day

A recent RCT compared the efficacy of an intended maximum dose of 150 mg/day baclofen (in three daily administrations) to 30 mg/day baclofen and placebo in 151 AUD patients [(43); **Table 1**]. The trial did not find any difference between the three groups in any outcome evaluated (time to first relapse, total alcohol consumption, and proportion of abstinent patients). However, the results showed a very high placebo effect (e.g., 66% of participants allocated to placebo remained abstinent for the full study period). This study also included patients (31% females) with comorbid depression, anxiety, and bipolar disorder. Participants were abstinent for a mean of ∼12 days (range: 4–21 days) and their baseline levels of alcohol consumption were equal to 141.8 g per day (equal to ∼12 drinks per drinking day when 1 drink = 12 g of alcohol). The RCT comprised two phases. In the first phase (lasting 6 weeks), participants gradually increased the daily dose of baclofen up to 150 mg depending on tolerance (titration phase; 10 mg every other day, up to 30 mg/week). In the second phase (lasting 10 weeks), participants received the maximum dose achieved during the previous phase. Participants in both baclofen groups started with 30 mg/day (in three daily administrations) from the first day of treatment. Participants allocated to baclofen 30 mg/day received the same dose for the whole study period (16 weeks). In this multicenter trial, the setting varied between the centers. The majority of participants were treated as inpatients for the first 4–6 weeks (79%) followed by 10–12 weeks outpatient treatment. In all centers, participants received weekly group or individual psychotherapy sessions. The results of the trial showed that among participants allocated to baclofen, up to 150 mg/day, only 16% achieved the highest dose. Overall, these patients received a mean of 93.6 mg/day baclofen.

Another multicenter RCT compared the efficacy of baclofen, up to 180 mg/day (in three daily administrations), to placebo in 310 AUD patients for 26 weeks [(44); **Table 1**]. This RCT found no difference between baclofen and placebo in the percentage of abstinent patients and in the reduction of alcohol consumption. Compared to the study of Beraha et al. (43), this RCT recruited a similar percentage of women (27%), participants were abstinent for a similar period of time prior to the start of the study medication (3–14 days) and consumed a slightly lower amount of alcohol at baseline (95.5 g of alcohol per day for patients allocated to baclofen group, equal to 7.9 drinks per drinking day when 1 drink = 12 g of alcohol). However, the two RCTs differed in the duration, mean actual baclofen dose, presence of comorbid mental disorders, setting, and frequency of psychosocial treatment. The duration of the Reynaud et al. (44) RCT was longer than in the Beraha et al. (43) study (26 vs. 16 weeks). In this RCT, a higher percentage of participants reached the maximum dose of baclofen (66 vs. 16%) and participants received a higher mean daily dose of baclofen (153.5 vs. 93.6 mg). Both RCTs excluded participants with current severe mental disorders. However, participants with bipolar disorder were excluded in Reynaud et al. (44) and included by Beraha et al. (43). In the Reynaud et al. (44) RCT, all patients were seen as outpatients, whereas in the Beraha et al. (43) study 79% of participants were treated as in patients for the first 4–6 weeks. Participants also received psychotherapy sessions less frequently (every 2 weeks vs. weekly in the other RCT) and the placebo effect was lower (e.g., 11 vs. 66%).

Only one RCT using doses of baclofen up to 270 mg/day has been published [(45); **Table 1**]. The results of a second RCT (using up to 300 mg/day) have been presented at scientific meetings but have not yet been published in full (66). Unlike the other two similar RCTs presented above (43, 44), this study found that baclofen substantially increased the percentage of abstinent patients and cumulative abstinence duration compared to placebo [(45); see **Table 1**].

In this RCT (45), patients allocated to baclofen received a mean dose of 180 mg/day (in three daily administrations) (compared to 153.5 and 93.6 mg/day in the other 2 RCTs), and 36% of these patients achieved the maximum dose (vs. 66 and 16% in the other two RCTs with doses >100 mg/day). This RCT was conducted at a single outpatient unit and recruited 56 AUD participants with high baseline levels of alcohol consumption (206.2 g per day, equal to about 17 drinks per drinking day with 1 drink = 12 g of alcohol vs. 12 and 8 drinks per drinking day in the other 2 RCTs with doses >100 mg/day). The 3 RCTs did not differ in other characteristics. This RCT included 17 women (30%) and participants did not suffer from current severe mental disorders. The study lasted 24 weeks, participants were abstinent for a mean of ∼12 days at the beginning of the trial and received supportive therapy (Medical Management).

### Meta-Analyses

To date, there have been four meta-analyses of baclofen for the treatment of AUD, based on the studies described above [(67–70); see **Table 2**]. These meta-analyses vary in the number of RCTs evaluated between five (68) and 14 (67), as well as in the outcomes investigated. The most inclusive study (67) evaluated the efficacy of baclofen pooling the outcomes chosen by each single study as the primary outcome, and in two subgroups of outcomes, one related to abstinence and one to alcohol consumption. According to the results of this meta-analysis, baclofen did not differ significantly from placebo in any of the outcomes investigated.

On the other hand, an earlier meta-analysis (68), including only baclofen studies with 30 mg/day baclofen, reported that baclofen significantly increased the rate of abstinent patients, compared to controls, at the end of treatment. A significant effect of baclofen for the same outcome was confirmed by two other recent meta-analyses in which more RCTs were included (69, 70). One of these meta-analyses also found that baclofen significantly increased the time to lapse, compared to placebo

**TABLE 2 |** Meta-analyses.

| | Lesouef et al. (68) | Bschor et al. (67) | Pierce et al. (69) | Rose and Jones (70) |
|---|---|---|---|---|
| **RCTs** | | | | |
| Addolorato et al. (33) | X | X | X | X |
| Addolorato et al. (35) | X | X | X | X |
| Beraha et al. (43) | | X | X | X |
| Garbutt et al. (34) | X | X | X | X |
| Garbutt et al. (34) | X | X | | |
| Hauser et al. (36) | | X | X | X |
| Jaury (66) | | X | X | |
| Krupitsky et al. (71) | | | | X |
| Krupitsky et al. (38) | | X | X | X |
| Leggio et al. (42) | | X | X | X |
| Mishra et al. (72) | X | | | |
| Morley et al. (40) | | X | X | X |
| Morley et al. (41) | | X | X | |
| Müller et al. (45) | | X | X | X |
| Ponizovsky et al. (37) | | X | X | X |
| Reynaud et al. (44) | | X | X | X |
| Total number of studies | 5 | 14 | 13 | 12 |
| **NUMBER OF PARTICIPANTS** | | | | |
| Baclofen | 137 | 799 | 789 | 582 |
| Placebo | 135 | 723 | 713 | 543 |
| Total participants | 272 | 1,522 | 1502 | 1,125 |
| **OUTCOMES EVALUATED** | | | | |
| **Outcome selected by each study** | - | **X** | - | - |
| SMD | - | 0.22 | - | - |
| 95% CI | - | −0.031–0.47 | - | - |
| P | - | 0.09 | - | - |
| Heterogeneity | - | $I^2 = 75.2\%$ | - | - |
| **% Abstinent participants** | **X*** | - | **X*** | **X*** |
| OR | 2.79 | - | 1.93 | 2.67 |
| 95% CI | 1.79–4.34 | - | 1.17–3.17 | 1.03–6.93 |
| P | <0.00001 | - | 0.01 | 0.04 |
| Heterogeneity | $I^2 = 0\%$ | - | $I^2 = 65\%$ | $I^2 = 76\%$ |
| **Abstinent days** | **X** | **X** | **X** | **X** |
| SMD | 3.69 | 0.20 | 0.21 | 0.03 |
| 95% CI | −0.74–8.11 | −0.08–0.49 | −0.24–0.66 | −0.10–0.15 |
| P | 0.10 | 0.16 | 0.37 | 0.67 |
| Heterogeneity | $I^2 = 99\%$ | $I^2 = 74.3\%$ | $I^2 = 83\%$ | $I^2 = 23\%$ |
| **Drinking reduction** | - | **X** | - | - |
| SMD | - | 0.28 | - | - |
| 95% CI | - | 0.00–0.56 | - | - |
| P | - | 0.05 | - | - |
| Heterogeneity | - | $I^2 = 71.9\%$ | - | - |
| **Craving** | **X** | - | - | **X** |
| SMD | −1.6 | - | - | −0.13 |
| 95% CI | −3.59–0.39 | - | - | −0.36–0.09 |
| P | 0.12 | - | - | 0.24 |
| Heterogeneity | $I^2 = 96\%$ | - | - | $I^2 = 87\%$ |
| **Time to lapse** | - | - | **X*** | - |
| SMD | - | - | 0.42 | - |
| 95% CI | - | - | 0.19–0.64 | - |
| P | - | - | 0.04 | - |
| Heterogeneity | - | - | $I^2 = 60\%$ | - |
| **Heavy drinking days** | - | - | - | **X** |
| SMD | - | - | - | −0.26 |
| 95% CI | - | - | - | −0.68–0.15 |
| P | - | - | - | 0.21 |
| Heterogeneity | - | - | - | $I^2 = 95\%$ |
| **Depression** | - | - | - | **X** |
| SMD | - | - | - | 0.06 |
| 95% CI | - | - | - | −0.22–0.34 |
| P | - | - | - | 0.67 |
| Heterogeneity | - | - | - | $I^2 = 87\%$ |
| **Anxiety** | - | - | - | **X** |
| SMD | - | - | - | −0.03 |
| 95% CI | - | - | - | −0.24–0.18 |
| P | - | - | - | 0.77 |
| Heterogeneity | - | - | - | $I^2 = 75\%$ |

*(Continued)*

**TABLE 2 |** Continued

**The meta-analysis found a significant difference between baclofen and placebo. Assessment of heterogeneity: $I^2$ > 50% = substantial level of heterogeneity. BAC, Baclofen; CI, confidence interval; OR, odd ratio; PLA, placebo; RCTs, randomized controlled trials; SMD, standardized mean difference.*

(69). However, a subgroup-analysis found a significant positive effect only across studies using 30–60 mg/day baclofen and not in the analysis of studies using higher doses of baclofen (69). Moreover, these meta-analyses did not find significant differences between baclofen and placebo on other important outcomes, such as the rate or number of abstinent days (67–70), alcohol craving (68, 70), depression (70), or anxiety (70). In one of the meta-analyses, the role of potential influencing factors was also explored (69) and found greater baclofen vs. placebo effect sizes in patients with higher baseline drinking levels.

## Human Laboratory Studies

Human laboratory studies have investigated the effects of baclofen in experimental settings (73–75). One study investigated the safety of an acute administration of baclofen, in combination with alcohol, in 18 non-treatment seeking, heavy drinkers (defined as individuals who consumed a mean ≥28 drinks per week) (73). In this study, participants received three different doses of baclofen (0, 40, and 80 mg) and 0.75 g/kg of alcohol (about 4.5 standard drinks, with 1 standard drink = 12 grams

of alcohol, in a man of 75 kg). The study found that both baclofen and alcohol impaired performance, but that few performance indicators were impaired to a greater extent when baclofen was combined with alcohol.

Another study found that 14 non-treatment seeking AUD subjects self-administered a lower amount of alcohol when they received 30 mg/day of baclofen compared to the sessions during which they received placebo. Furthermore, baclofen affected the biphasic effects of alcohol during the experimental alcohol administration session (74).

A more recent study by the same team investigated the effects induced by baclofen (30 mg/day) among a sample of 34 non-treatment seeking AUD individuals with high trait anxiety (75). They found that baclofen did not reduce the amount of alcohol consumed, but altered the subjective effects of alcohol, including an increase in the ratings of feeling high and intoxicated (75). Furthermore, in the same clinical study, they also found that baclofen may work by dissociating the link between an initial drink (priming) and subsequent alcohol consumption (self-administration) (76). Based on these results, the authors proposed that baclofen may act as a partial substitution AUD medication. A recent pharmaco-fMRI study found that baclofen specifically decreased alcohol cue-reactivity in brain areas involved in the processing of salient (appetitive and aversive) stimuli (77). However, the exact underlying biobehavioral mechanisms of baclofen in AUD individuals are still not completely understood (78–80).

## Possible Reasons For Inconsistent Results in Research to Date

The reasons for inter-study discrepancies are not fully understood. In general, it is well-established that clinical trials in AUD exhibit large variability because of a myriad of factors that affect outcome in AUD patients (46). In addition to the variability in doses (30–300 mg/day), studies varied in the following factors: age and gender; baseline severity of AUD and drinking levels; goal of the study (abstinence maintenance vs. reduced drinking); different cultures (with different drinking habits and genetic populations); addictive and psychiatric comorbidities; complications of AUD (such as cirrhosis or acquired brain injury); fixed or flexible dosing; individual adjustments; titration regimes; settings of the studies (inpatients, outpatients); completion of alcohol withdrawal and/or length of abstinence before treatment initiation; the intensity of concomitant psychological treatment and social support (leading to differences in the placebo effect); sample size; treatment duration; patient recruitment method; study endpoints; and prevalence of adverse events. In addition, it should be noted that in many studies only a minority of the patients received the intended or maximum allowed dose. Patients may require personalized doses, as some patients responded to 30 mg/day and achieved abstinence, while others required daily doses up to 300 mg/day. It has been observed that baclofen has a linear elimination in AUD patients, without saturation of baclofen clearance, over the range of doses usually administered to treat AUD [from 30 to 240 mg per day; (81, 82)]. However, wide inter-individual variability of baclofen pharmacokinetics has been observed with highly different blood concentrations achieved by patients after the administration of the same dose (81). This may account for the differences in treatment response, where some patients, but not others, benefit from baclofen treatment. This pharmacokinetic variability may also be responsible for the wide range of doses required by different patients to achieve the desired effect. Furthermore, inter-study discrepancies may also be caused by differences in GABA-B receptor sensitivity (83).

Another issue requiring further investigation is the potential for a differential response by gender to baclofen treatment in terms of side-effects, safety, and tolerability. Among the RCTs published to date (see **Table 1**), one study did not report the gender of patients (38) and the others recruited a total of 302 female patients (25.3% of the entire sample) and 893 male patients (74.7%) (33–37, 39–45). Unfortunately, the individual RCTs did not provide data analyzed by gender and none of the meta-analyses (to date) have evaluated this aspect (67–70). The lack of gender analysis has been already described for the other medications approved for the treatment of AUD (84). Interestingly, an observational open-label, non-controlled study suggests that women may require significantly lower daily doses of baclofen than men (52). These preliminary findings suggest that the male to female ratio of patients in clinical trials may be an important factor in the overall efficacy, safety, and tolerability of baclofen in AUD patients, and requires further research.

## Baclofen for Alcohol Withdrawal Syndrome (AWS)

There is some preliminary evidence that baclofen may have a role as an adjuvant treatment of AWS (16). A number of case reports (85, 86), a retrospective chart review (87), and three small controlled studies (88–90) found that its administration reduced AWS severity. However, no study has been conducted to evaluate its potential effect in protection against seizures or Delirium Tremens (DTs). Accordingly, a recent meta-analysis concluded that there is insufficient evidence for recommending baclofen as a treatment for AWS (91). In summary, GABAergic medications like baclofen, and others, might play a beneficial adjuvant role managing AWS (92), however benzodiazepines remain the gold standard-of-care in AWS treatment, given that they are the only class of drugs with proven efficacy, not only in the treatment of AWS, but also in the prevention of AWS-related complications like seizures and DTs.

# BENEFITS AND CHALLENGES OF THE TWO DIFFERENT APPROACHES USED TO ADMINISTER BACOLOFEN: FIXED DOSE VS. FLEXIBLE DOSE

In clinical practice, baclofen is usually prescribed using either "fixed" or "flexible" doses. There are contrasting opinions on these two approaches. Therefore, both the *benefits* and c*hallenges* of "fixed doses" and "flexible doses" approaches of baclofen administration to treat AUD are described.

### Fixed Dose

Most of the RCTs started baclofen treatment with a daily dose of 5 mg, three times a day, gradually increased by 5–10 mg, every 3 days, up to a fixed dose of 30–80 mg/day. In response to side effects, baclofen administration was suspended or reduced. Because of its short half-life [2–6 h; (93)], baclofen was administered in two, three, or four daily administrations.

#### Benefits

A recent meta-analysis found better results among studies using lower doses of baclofen compared to studies using higher doses [(69); see **Table 2**]. The use of lower doses is also associated with a lower risk of side-effects.

#### Challenges

Fixed maintenance doses are standard in RCTs and available evidence is driven by RCTs. However, fixed doses are rarely used in clinical practice (94). The optimal dose of baclofen varies substantially between patients, and treatment may be personalized through a slow increase of the dose. In addition, some patients may require a different distribution of daily administrations (e.g., late afternoon and early evening, instead of night time).

### Flexible Dose

This approach consists of progressively increasing the dose according to the balance of beneficial and unwanted effects. The dose required may vary widely from 30 mg/day up to more than 300 mg/day (some uncontrolled studies reported doses up to 560 mg/day), with baclofen prescribers using different titration regimes to increase the dose.

A common titration procedure is to increase the total daily dose of baclofen by one tablet of 10 mg every 3 days, or increasing each of the three daily doses by 5 mg every 3–7 days, until the treatment goal is reached. In case of significant side effects (e.g., severe sedation, dizziness, and/or confusion), the clinical advice is to stop increasing the dose or slow down the rate of increase: for example, 5 mg (half-tablet) rather than 10 mg increase every 3 days, 10 mg increase only every 4–7 days, or even less frequent dose increases.

#### Benefits

Some prescribers, in particular, those in France, claim that this titration method allows some patients to achieve a state of "indifference" toward alcohol, as initially described by Olivier Ameisen (47).

#### Challenges

There is a lack of clear evidence supporting this approach, as few studies have used it in a rigorous manner (95) and one of the meta-analyses has failed to show a significant effect of daily doses of baclofen >100 mg (69). Moreover, the use of higher doses of baclofen might be related to a higher risk of its relevant side-effects (96).

## BACLOFEN (OFF-LABEL) USE FOR THE TREATMENT OF MODERATE TO SEVERE AUD

### General Considerations

As there is still debate about the efficacy of baclofen and how best to prescribe it, baclofen has been suggested to be prescribed only when approved pharmacological treatments have failed (2). However, in some countries, experienced prescribers may use it as a first line treatment in selected patients, such as those with liver disease, for whom other drugs may be contraindicated (97).

### Treatment Initiation

Baclofen treatment should always be initiated under careful medical oversight, by a prescriber with knowledge and training in this area. Evaluation of renal function is recommended before starting baclofen administration since renal insufficiency can be a cause of rapid accumulation of circulating baclofen, and may cause acute adverse events, particularly mental confusion (98).

### Patient Information

Patients should be clearly informed about the off-label use, potential benefits, side effects, and safety issues of this treatment, and the treatment plan, including who to contact in case of concerns. They should also receive comprehensive written information about baclofen treatment, including clear dosage regimes and a side effect profile. Documented, informed consent should be obtained from all patients. Patients with AUD may have mild cognitive deficits, potentially making it difficult for them to follow instructions. In these cases, when possible and with patient consent, it may be helpful if somebody close to the patient (spouse, relative, friend, or care worker) participates in the monitoring of the treatment.

### Goals of Treatment

Goals of treatment should be discussed and agreed with the patient. The patient needs to be aware that the effective dose to achieve his/her treatment goals may vary considerably. Patients should be informed that reaching the effective dose may be challenging, and that when doses are increased, baclofen may induce adverse effects, some of them potentially severe.

### Prior Detoxification or Initiation While Still Drinking

All the RCTs conducted to investigate baclofen efficacy recruited AUD patients who were active drinkers, and had stopped drinking prior to the start of the trial from 24 h (33) to 21 days (43, 45), with a mean of 12 days. In one RCT, most participants were treated as inpatients for the first 4–6 weeks (43). Whether alcohol detoxification is necessary prior to initiation of baclofen in clinical practice remains an open question. It is well-known that alcohol and baclofen have some side effects in common, and that the sedative effects of both drugs may potentiate each other (99). Accordingly, patients should be informed of the higher risk of sedation and overdose when taking baclofen while (still) drinking alcohol or using benzodiazepines (100).

## Safety Considerations and Specific Cautions

Some physicians choose to limit the dose in view of safety concerns around higher doses of baclofen. Other physicians increase the dose as high as needed, aiming for abstinence or low-risk drinking levels for active drinkers, or maintenance of abstinence for those who have already achieved it. These different options should be discussed with the patient. During the first visit, patients need to be informed that there are broadly two types of side effects: frequently occurring non-severe ones that are mainly benign and typically disappear spontaneously (or with dose reduction), and sporadically occurring dangerous side effects. The potentially dangerous side effects are seizures, respiratory depression with sleep apnea and potentially coma (in case of intoxication), severe mood disorders (mania or depression, with the risk of suicide), and mental confusion/delirium.

Driving a car, operating heavy machinery, working on scaffolding (for building workers), or using potentially dangerous tools (e.g., power tools), should be discouraged during the first weeks of treatment until patients learn how sedation affects them, and the treatment dose is stable. It is prudent to start and increase baclofen treatment on a non-working day, so the patient can assess the degree of sedative effect.

Patients should be advised to avoid drinking when they are taking baclofen, because of the risk of excessive sedation induced by the combination of the two substances (99). Patients should also be advised of the risk of overdose, if they take doses of baclofen higher than those prescribed (100). Finally, patients should be informed that baclofen treatment should be started and ended slowly, to reduce the risk of adverse events and withdrawal symptoms. Baclofen withdrawal syndrome might be associated with confusion, agitation, seizures, and delirium, and may be confused with AWS (101).

## Patients at Risk For Baclofen Overdose

Accidental and intentional baclofen overdose presents a particular challenge and may be fatal or lead to coma and seizures requiring prolonged intensive care treatment (96, 102, 103). It is noteworthy that calls to the National Poisons Centre of France have escalated during the past decade, i.e., the period when minimally supervised baclofen use for AUD increased (99, 100, 104). For instance, a retrospective study conducted in France found a progressive increase of baclofen overdoses among AUD patients between 2008 and 2013 (104). These cases comprised of 220 suicide attempts and 74 cases of unintentional intoxication, even if, in most of the cases, the suicide attempts were not directly attributable to baclofen itself. Therefore, patients at risk of overdose—including those with history of self-harm, over-dose, current suicidal ideation, or repeated and recent suicidal attempts—should not be prescribed baclofen. This risk can particularly pertain to patients with severe personality disorders, for example with borderline personality disorders, who are more likely to use baclofen for self-poisoning (97). However, it is not possible to exclude the role of alcohol consumption in some cases of baclofen overdose.

In some settings, controlled dispensing may be available, and while no such trials have been reported, this may allow for safer use of baclofen in a vulnerable patient population. Controlled dispensing may involve attending a pharmacy daily, or perhaps twice weekly, thus limiting patient access to medication for 1–3 days. A competent family member or other care-giver may undertake a similar role. Patients prescribed sedative medications (e.g., benzodiazepines, z-drugs, and antipsychotics) should be informed about the risk of excessive sedation, and respiratory depression in case of overdose, if baclofen is added to their therapy.

## Impairment of Renal Function

As noted previously, ∼80% of baclofen is renally excreted, and thus baclofen may induce confusion, delirium, and other adverse effects in patients with renal failure (105, 106). Therefore, it is advisable to evaluate kidney function, checking for previous renal disease or current renal insufficiency, and requiring a renal function test.

## Use in Patients With Comorbid Conditions

### Comorbid Psychiatric Conditions

The role of psychiatric comorbidity in explaining different responses to baclofen treatment, in terms of alcohol drinking outcomes, is still unclear (107, 108). However, as AUD patients often suffer from other mental disorders, potential baclofen effects on psychiatric comorbidity should be considered.

#### Bipolar Affective Disorder

About one third of patients with bipolar disorder have a comorbid AUD (109). Baclofen may elevate the patient's mood, inducing manic episodes (110). This mood elevation can also occur in patients with no known history of bipolar disorder, so a careful personal and familial history should be taken prior to starting baclofen treatment. Baclofen treatment of patients with known bipolar disorder require co-management with a psychiatrist. All patients should be warned about the risk of mood changes and told to discuss them with their treating doctor.

#### Anxiety

There is some suggestion that baclofen treatment may be effective in reducing comorbid anxiety symptoms in AUD patients (33, 34, 71). In one RCT, baclofen was more effective than placebo only in AUD patients with a comorbid anxiety disorder (40). However, the results of a recent meta-analysis did not support the hypothesis that baclofen treatment will also reduce anxiety symptoms (70).

### Use of Baclofen in Patients Affected by Other Substance Use Disorders

Baclofen has also been used for the treatment of other substance use disorders (111). A few RCTs investigated its efficacy in the treatment of opioid withdrawal (112, 113), cocaine use disorder (114, 115), opioid use disorder (116), nicotine use disorder (42, 117), and methamphetamine use disorder (118). Some of these RCTs found positive results in favor of baclofen among patients with an opiate withdrawal syndrome (112, 113), and nicotine use disorders (42, 117). Notably, one of

these studies found that 80 mg/day baclofen increased the rate of abstinent days from co-use of alcohol and tobacco in AUD and heavy-smoking individuals (42). However, other RCTs found no difference between baclofen and placebo in patients affected by cocaine use disorder (114), opioid use disorder (116), or methamphetamine use disorder (118). These inconsistent findings do not allow us to draw conclusions on baclofen efficacy in the treatment of substances use disorders other than alcohol. However, baclofen may be suggested for patients affected by AUD and comorbidity with other substance use disorders for which no approved drugs are available (111).

## Comorbid Physical Conditions

### Liver Disease

The efficacy and safety of baclofen to facilitate maintenance of alcohol abstinence and prevention of relapse in AUD patients affected by liver cirrhosis (complicated or not with ascites) was first reported in an RCT by Addolorato et al. (35), in which a dose of 30 mg/day was utilized (119). These positive findings were then supported by retrospective studies (51, 55, 64, 65) and by one recent RCT (41), while another RCT in AUD patients with liver impairment did not report differences between baclofen and placebo (36), as detailed above. Baclofen treatment should be avoided in patients with liver cirrhosis complicated by encephalopathy (120) or administered at lower doses (e.g., 15 mg/day) among patients with hepatorenal syndrome (121). However, patients with these severe disorders rarely require pharmacological treatment to reduce or stop alcohol consumption given their already serious clinical condition.

### Epilepsy

Baclofen lowers the seizure threshold and may precipitate seizures in people with a history of epilepsy. Therefore, it is essential to evaluate possible vulnerability to seizures. Epilepsy is a contraindication for the use of baclofen in some countries. Baclofen treatment in people with current epilepsy requires co-management with a neurologist.

### Cardiovascular and Respiratory Diseases

Baclofen has infrequent, but well-established, effects on the cardiovascular and respiratory system, especially in overdose (104). It can slightly decrease blood pressure and heart rate, or cause hypertension, arrhythmia, and palpitations related to autonomic nervous system dysfunctions that are more likely linked with higher doses of baclofen (122). It can also potentiate the effect of antihypertensive drugs. Regarding the respiratory system, it can cause dyspnea and respiratory depression, and, most importantly, worsen obstructive sleep apnea (123). Baclofen has no substantial impact on cardiovascular and respiratory systems in healthy people, but physicians must be cautious in prescribing baclofen to patients with breathing and cardiovascular problems.

### Parkinson's Disease

Baclofen can worsen the side effects of levodopa, possibly causing hallucinations, delusions, and confusion (124). However, a recent study found promising results using a combination of baclofen and acamprosate in a preclinical model of Parkinson's disease (125).

### Urinary Incontinence

Urinary incontinence may be worsened by baclofen. Possible urinary incontinence should be investigated. Patients with this disorder may receive baclofen treatment, but the dose should be increased slowly.

### Other Physical Disorders

Some studies reported that baclofen treatment was associated with sleep disturbance among AUD patients (44, 63). These findings are supported by preclinical evidence showing that baclofen may alter normal sleep patterns in animal models (126, 127). As AUD patients often suffer from disturbed sleep [particularly during AWS; APA (3)], it is possible that baclofen treatment may increase the risk and/or severity of sleep disorders among AUD patients. On the other hand, baclofen treatment has also been found to improve sleep among AUD patients, by helping them to achieve and maintain abstinence, or reducing alcohol consumption to low risk levels (128, 129).

Sporadic cases of sexual dysfunction have been reported among patients using baclofen to treat spasticity (130) and AUD (52, 63). As excessive alcohol consumption is a known cause of sexual dysfunction, baclofen treatment may worsen these disorders among AUD patients already suffering from sexual dysfunction. However, as with sleep disorders, it is possible that baclofen treatment, by helping AUD patients to achieve and maintain abstinence from alcohol or reducing alcohol consumption to low risk levels, may improve sexual function.

## Special Populations

### Adolescence

No RCT has been conducted to investigate the effectiveness and safety of baclofen in adolescent patients with AUD. However, baclofen has been used in adolescents with severe spinal spasticity (17).

### Pregnancy

Pregnant women with AUD raise genuine ethical dilemmas because of the potential risks to the fetus of using medications during pregnancy. As reliable studies are lacking, drug information agencies advise against the use of baclofen during pregnancy.

### Elderly and Frail Patients

Baclofen can cause fatigue, sedation, and somnolence, which are often accompanied by decreased mobility and balance problems, especially in older people already suffering from these difficulties before starting baclofen treatment. Patients must be aware that these effects are usually tolerable, but that they

may also be intense, with a risk of falls and falling asleep abruptly.

## CONCLUSIONS

Despite controversies regarding the efficacy and justification of the "off-label" use of baclofen treatment for patients with AUD, there is consensus that baclofen is a promising medication to treat moderate to severe AUD (2). Baclofen plays an important role in the clinical treatment of AUD patients in some European countries and Australia, particularly in patients who are not responsive to the available registered medications and/or in AUD patients with significant liver disease. However, in other countries (e.g., in the US), baclofen has a very low uptake for AUD treatment (131). As for the other drugs to treat AUD, there is no clear evidence on the ideal duration of treatment. Baclofen may be suggested to help patients with AUD to maintain abstinence, if they have already achieved it, or to achieve abstinence if they are still actively drinking. However, patients need to be advised of the potential high risk of sedation due to the combination of two different sedative drugs (i.e., alcohol and baclofen). Further studies are needed to evaluate the potential efficacy and safety of baclofen in different AUD patient groups (e.g., women, adolescents, the elderly, and during pregnancy), the ideal duration of treatment, as well as to clarify risks due to the combination of alcohol and baclofen.

## AUTHOR CONTRIBUTIONS

RdB, PdL, PH, MH, PJ, and RA drafted the initial document. RdB, LL, JS, MH, and RA drafted the full-text manuscript and coordinated revisions before and after each round, up to completion of the manuscript and submission. All authors contributed to the manuscript and approved its final version.

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REVIEW
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# Baclofen for the Treatment of Alcohol Use Disorder in Patients With Liver Cirrhosis: 10 Years After the First Evidence

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Alcohol Use Disorder (AUD) is a chronic and relapsing condition characterized by harmful alcohol intake and behavioral-cognitive changes. AUD is the most common cause of liver disease in the Western world. Alcohol abstinence is the cornerstone of therapy in alcoholic patients affected with liver disease. Medical recommendations, brief motivational interventions and psychosocial approach are essential pieces of the treatment for these patients; however, their efficacy alone may not be enough to achieve total alcohol abstinence. The addition of pharmacological treatment could improve clinical outcomes in AUD patients. Moreover, pharmacological treatments for AUD are limited in patients with advanced liver disease, since impaired liver function affects drugs metabolism and could increase the risk of drugs-related hepatotoxicity. At present, only baclofen has been tested in RCTs in patients with advanced liver disease. This medication was effective to reduce alcohol intake, to promote alcohol abstinence and to prevent relapse in AUD patients affected by liver cirrhosis. In addition, the drug showed a safe profile in these patients. In this review, clinical studies about efficacy and safety of baclofen administration in patients with AUD and advanced liver disease will be reviewed. Open question about the most appropriate dose of the drug, duration of the treatment and need of additional studies will also be discussed.

**Keywords: alcohol use disorder, baclofen, alcoholic liver disease, liver cirrhosis, GABA-B receptor**

## INTRODUCTION

Alcohol Use Disorder (AUD) represents problematic patterns of alcohol consumption, leading to clinically significant impairment or distress (1). It is characterized by behavioral and cognitive changes as tolerance and craving for alcohol, and withdrawal syndrome at abrupt alcohol reduction or discontinuation.

AUD is responsible for over 2.5 million deaths every year in the world (2) and it represents the third leading risk factor for morbidity and mortality in Europe (3).

AUD represents a risk factor for alcoholic liver disease (ALD), ranging from steatosis and alcoholic hepatitis to liver cirrhosis and its complications (e.g., hepatocellular carcinoma). The

risk of developing ALD increases with the amount of alcohol intake and its duration (4). Besides alcohol's direct toxicity, hepatitis virus co-infection, overweight and host factors (i.e., gut microbiota, gender, genetic, nutritional factors and comorbidities) are additional factors, influencing the development and the progression of liver disease (5, 6).

ALD causes yearly half a million deaths worldwide, accounting for 50% of global liver disease-related mortality (7). Moreover, ALD is one of the most common indication for liver transplantation (LT) in Europe and North America (6).

Given the strong relationship between alcohol discontinuation and hepatic function improvement, regardless the stages of liver disease, total alcohol abstinence represents the main outcome in the treatment of AUD patients with liver disease (7). Medical recommendations, brief motivational interventions and/or psychosocial approach alone, although essential components for AUD treatment, may not be sufficient to induce total alcohol abstinence and prevent relapse. The addition of effective pharmacological treatment for AUD may be very useful (8). However, given the impaired hepatic function and the lack of randomized clinical trials (RCTs) investigating both efficacy and safety of approved medications for AUD (disulfiram, naltrexone, nalmefene and acamprosate) in patients with liver disease, the availability of pharmacological treatments for AUD is limited for this group of patients (9).

Baclofen is a selective GABA-B receptor agonist with primary kidney metabolism. After promising results in preclinical model of alcohol abuse and clinical studies in AUD patients without liver disease [for review see (10)], it was tested in AUD patients with advanced liver disease, including patients affected with liver cirrhosis not complicated by hepatic encephalopathy nor hepato-renal syndrome. In the present review, clinical studies investigating baclofen administration in AUD patients with liver disease were analyzed. The analysis included RTCs, observational studies and case series published in English from December 8th 2007 to May 24th 2018 (**Table S1**). The studies were searched on PubMed using the words AUD, Baclofen, anti-craving drugs, pharmacotherapy for AUD, liver cirrhosis, alcoholic liver disease and through citation chaining. Case reports were excluded from this analysis.

## BACLOFEN IN PATIENTS WITH LIVER DISEASE

Efficacy and safety of baclofen in AUD patients affected by advanced liver disease were firstly tested in a double-blind, placebo-controlled clinical trial (RCT) (11). In this study, 84 AUD patients with liver cirrhosis were randomized to baclofen treatment (10 mg t.i.d.) or to placebo. The proportion of patients with total alcohol abstinence (71% of the patients who received baclofen, 29% of the patients allocated to placebo; odds ratio 6·3 [95% CI 2·4–16·1]; $p = 0{\cdot}0001$) and cumulative abstinence duration (mean 62·8 [SE 5·4] in baclofen group vs. 30·8 [5·5] days in placebo group; $p = 0{\cdot}001$) was significantly higher in the group treated with baclofen. No differences on side effects were found between the two groups. No new-onset episode of overt hepatic encephalopathy was reported, also considering subjects with severe hepatic impairment (Child-Pugh classes B and C). The total alcohol abstinence was particularly evident in patients with more advanced liver cirrhosis, as indicated by the Child-Pugh score. The odd-ratio to maintain abstinence compared to placebo exceeded 4 in child B group and 8 in Child C group. These data suggested a possible relationship between the efficacy of the drug and the severity of AUD (11).

In a *post-hoc* analysis of this study, 24 AUD patients with hepatitis C virus infection were included. In particular, 12 were allocated baclofen 10 mg t.i.d., while 12 received placebo. A significantly higher number of patients who achieved and maintained total alcohol abstinence was found in the baclofen group with respect to the other group. Considering that their baseline characteristic differed for blood level of transaminases probably due to HCV-related damage, albumin and INR were chosen as outcome measure. A significantly higher increase in albumin values from baseline ($p = 0.0132$) and a "trend toward a significant reduction in INR levels from baseline ($p = 0.0716$)" was observed in the baclofen group. These data firstly suggested that baclofen treatment may represent an optimal and safe anti-craving medication in this typology of patients (12).

Based on observation of a possible dose-dependent effect in case series (13–15) and in a*n* RCT (16), a subsequent retrospective study investigated a tailored-dose of baclofen in 53 patients with alcoholic liver disease, comparing alcohol consumption and hospitalizations before and after baclofen treatment (17). Median highest dose administered was 60 mg/d. A trend in the decrease of hospitalizations was found in patients after baclofen treatment (on average, after baclofen initiation the patients spent 19.1 days in hospital per year, compared with 25.84 days per year before treatment initiation; $p = 0.59$) coupled with a reduction of alcohol consumption. No improvement in patients' quality of life, depression and anxiety during hospitalizations was recorded. Baclofen treatment was generally well tolerated, although a dose reduction was necessary in four patients. The strength of this study is the real-life experience, although the small sample size, the amount of missing data, the retrospective design and the absence of a control group limit its results. In this latter study, the relationship between severity of liver disease (Child score for cirrhotic patients) and maximum dose of baclofen used, although not significant, suggested that patients with high severity of liver disease might require lower doses of baclofen to suppress craving. It is conceivable that the small percentage of the drug metabolized in the liver (about 15%) is not metabolized in patients with severe liver dysfunction, increasing in these patients the blood level of medication (18). This observation could also be consistent with the higher efficacy of baclofen in patients with more severity of liver disease reported in the first RCT (11).

In a subsequent prospective cohort study (19), 219 consecutive patients with ALD (including also patients with liver cirrhosis) were treated with dose titration of baclofen up to 30 mg t.i.d according to tolerability and response to the drug. Although the lack of a control group and the observational nature represented important limits of this study, baclofen administration had a positive impact on measures of alcohol consumption and

adherence to treatment was very high. Moreover, the strength point of this study was the real-life experience in clinical practice in a joint liver and alcohol treatment clinic.

A recent prospective study conducted by Barrault et al. (20) showed a significant decrease in alcohol consumption in 100 AUD patients, 65 of them affected by liver cirrhosis, after treatment with tailored dose of baclofen (mean dosage 40 mg/d; range 30–210 mg/d). Patients were recruited over a 3-year period and they were followed for one-year in two liver and alcohol outpatient clinics. A marked improvement in liver function tests was found in patients who discontinued alcohol drinking with respect to patients who did not respond to baclofen treatment and continued alcohol consumption (20). No drug-related serious adverse events occurred, no hepatic encephalopathy, liver function and/or renal impairment were detected in treated patients. Minor side effects, such as drowsiness and vertigo were found; these symptoms decreased after tapering the dose (20). No evidence of baclofen abuse or overdose was identified. No baclofen withdrawal syndrome was observed in patients who stopped baclofen suddenly. The long-term duration of follow-up (1 year) represents a strength point of this study, although main limitation was the absence of a control group.

Two RCTs with contrasting results were recently published (21, 22). In the first one a total of 180 US veterans were enrolled (22). These patients were affected by AUD and chronic hepatitis C virus infection with ongoing alcohol consumption. Patients were randomized to baclofen treatment (30 mg/d) or placebo for 12 weeks. The primary outcome was the difference of percentage of days of abstinence. Secondary outcomes were the percentage of patients who achieved complete alcohol abstinence, the percentage of heavy drinking days, alcohol craving, anxiety, depression and post-traumatic stress disorder. No differences between the two groups of treatment in term of percentage of abstinent days was reported. No significant difference in secondary outcomes was found between baclofen and placebo group. However, it should be underlined that Veterans represent a specific group of patients as the enrolled patients were also affected by psychiatric comorbidities and use of illicit drugs. These observations prevent to draft definitive conclusions and to generalize these results on the overall AUD population, although this is the largest RCT examining baclofen efficacy and safety on liver disease patients up to date.

The second one is a very recent multi-site, double-blind, randomized placebo-controlled clinical trial named BacALD (21), which investigated the efficacy and safety of 2 fixed dose of baclofen (30 mg/d and 75 mg/d). In this study, 104 patients with AUD were enrolled. Among them, 58 patients were affected by ALD. Primary outcomes included survival time to lapse and relapse, and the composite outcome of drinks per drinking day, number of heavy drinking days and percentage abstinent days. With respect to placebo, a significant efficacy of baclofen on time to lapse ($\chi^2 = 6.44$, $P < 0.05$, Cohen's $d = 0.56$) and to relapse ($\chi^2 = 4.62$, $P < 0.05$, $d = 0.52$) was found, with no difference between the 2 doses of the drug. Moreover, a significant increase in the number of days to first lapse and relapse was found in ALD subgroup of patients. Percentage of days of alcohol abstinence was significantly higher in baclofen group with respect to placebo group, with no difference between the 2 doses of the drug (placebo 43%, baclofen 30 mg 69%, baclofen 75 mg 65%; $P < 0.05$). Although the majority of patients showed a good tolerability for the drug, patients randomized to the 75 mg dose of baclofen reported significantly more sedation and shortness of breath compared with those randomized to the 30 mg dose. In conclusion, this study supports the efficacy and safety of baclofen in the treatment of AUD patients with ALD. Moreover, no reasons to promote the use of daily doses higher than 30 mg in these patients emerged.

## BACLOFEN IN ACUTE ALCOHOLIC HEPATITIS

Alcoholic hepatitis (AH) is a severe clinical syndrome characterized by the recent onset of jaundice with or without other signs of liver decompensation in patients with ongoing alcohol abuse. Its histological features consist of steatosis, hepatocyte ballooning, and inflammatory infiltrate with polymorphonuclear neutrophils. It is associated with a high rate of morbidity and mortality (22). Corticosteroid therapy should be considered in patients with severe AH, although this treatment could not influence medium to long term survival (9). Alcohol abstinence remains the cornerstone of therapy and early management of AUD is mandatory in all patients with AH (9). However, trials investigating the use of anti-craving drugs are currently lacking in these patients. Only a single center, open, retrospective study analyzed the effects of baclofen in patients with acute alcoholic hepatitis (23). In this study 35 patients were evaluated; baclofen treatment was started when bilirubin level decreased below 10 mg/dl and after hepatic encephalopathy resolution. 10 mg t.i.d. of baclofen was used, on average, for 5.8 months; of the 35 patients treated with baclofen, 34 (97%) remained abstinent. An improvement of liver function tests and a significant decrease of severity of liver disease expressed as MELD score was observed in all treated patients. Although the retrospective design and the lack of a control group represent significant limits of the study, these observations support the safety and the usefulness of the drug in improving the clinical condition of patients with ALD. Future RCT on this special population of AUD patients are needed to confirm its efficacy and safety.

## BACLOFEN IN PATIENTS WITH ALCOHOL WITHDRAWAL SYNDROME AND LIVER DISEASE

Alcohol withdrawal syndrome (AWS) is a potentially life-threatening medical condition developing in patients who abruptly cease or reduce alcohol consumption (24). At present, the gold standard therapy is represented by benzodiazepines in the management of moderate-severe forms of AWS, given their efficacy in controlling both withdrawal symptoms and the risk of seizures and/or delirium tremens. However, some benzodiazepines own hepatic metabolism, producing active

metabolites that raise the risk of drug accumulation and excess of sedation in patients with advanced LD. Among BZDs, lorazepam or oxazepam may be preferred, given their shorter half-life and absence of active metabolites (24). Considering potential side-effects of benzodiazepines in patients with LD (25), non-benzodiazepine GABAergic drugs, might be useful in the management of AWS in patients with advanced liver disease, given their low rate of hepatic metabolism (7). Among them, Baclofen, based on its safety hepatic profile (11), seems to be a promising agent for the treatment of AWS in patients with LD, since its efficacy in the management of AWS in patients without LD has been showed (26–28). However, RCT data are required to validate the preliminary results on the use of these drugs in AWS, in particular in AUD patients with ALD.

## CONCLUSIONS

Although the role of baclofen in the treatment of AUD is still debated, the data available at moment suggest that the drug is effective and safe, in particular in some subset of patients, including those with high severity of AUD (29) and advanced liver disease (11, 21).

Additional RCTs are needed to clarify some drug aspects, in particular the most appropriate dosage and its role in AUD patients with different comorbidity.

Further trials are also required in AUD patients with ALD to compare baclofen to other anti-craving drugs, i.e., with Acamprosate, which showed a good tolerability in Child-Pugh stage A and B cirrhotic patients, although the available data are limited to a 1-day trial (30). Moreover, given the controversial results emerged about the efficacy of the drug in AUD patients affected by HCV infection (12, 31), this topic should be further investigated, considering the importance of alcohol discontinuation in HCV patients (32). Indeed, baclofen could have a potential role as bridge or concomitant treatment with antiviral therapy (12).

Finally, a further topic of interest is the potential role of baclofen in AUD patients listed for liver transplantation. At present liver transplantation represents the gold standard treatment for AUD patients affected by end-stage liver disease (33). In an era of organ shortage, it is mandatory to reduce the risk of alcohol relapse in these patients, in particular after transplantation in order to reduce the probability of graft loss and the liver damage, so total alcohol abstinence should be promoted not only before but also after LT. In view of the safety hepatic profile of baclofen, this drug could be the most appropriate medication to promote alcohol abstinence and to prevent relapse in AUD transplanted patients.

## AUTHOR CONTRIBUTIONS

CM, TD, GV, AM, CT, MA, LS, MR, AT, AG, and GA contributed equally to this work. SD helped the revision process of the paper, playing major role in answering to reviewers, table conceiving, modifying the manuscript and editing English language.

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## SUPPLEMENTARY MATERIAL

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**Table S1 |** Main features of analyzed study.

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MINI REVIEW
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# Baclofen and the Alcohol Withdrawal Syndrome-A Short Review

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The Alcohol Withdrawal Syndrome (AWS), which may occur with or without delirium, is a frequent consequence of sudden alcohol cessation in patients with moderate to severe Alcohol Dependence Syndrome (ADS). Withdrawal as a result of habituation to alcohol is part of the definition of the Alcohol Dependence Syndrome (ICD10). Since the recognition of Delirium Tremens, in the early nineteenth century, the management of the syndrome, an acute medical emergency, has proven controversial. The barbiturates, chlormethiazole, and recently the safer benzodiazepines transformed the management of these conditions. The benzodiazepines, particularly diazepam and chlordiazepoxide, are now the most used first line agents in the treatment of AWS. In addition, a number of other agents, including baclofen, a GABA-B receptor agonist, have the potential to suppress the alcohol withdrawal syndrome. In this review we review the potential use of baclofen in its role to treat AWS. We summarize initial case reports as well as more recent randomized trials of AWS treatment with baclofen. We conclude that currently there is not enough evidence to support the use of baclofen as a first line treatment for AWS. More research will be needed to determine where baclofen might have a role in second-line management of the Alcohol Withdrawal Syndrome on its own or in combination with benzodiazepines or other agents.

**Keywords: baclofen, alcohol withdrawal, alcohol dependence, alcohol history, review**

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## INTRODUCTION

The alcohol withdrawal syndrome, with and without delirium, is challenging with regards to prevention and treatment. For centuries the etiology was unclear and much disputed. In the nineteenth century it was thought that Delirium Tremens (DT) was as a result of extreme intoxication rather than discontinuation of alcohol in habitual drunkards. The patient was thought to have stopped using alcohol as a result of the confusion rather than confusion and delirium being correctly attributed to discontinuation or reduction in the level of drinking. This controversy was eventually resolved by Isbell et al. (1) in their controversial human "guinea pig" study on the etiology of DTs and "Rum Fits." Such studies also delineated the components of the alcohol withdrawal syndrome without delirium and establish the time course and range of severity of symptoms and signs of the condition. Today severity of the syndrome is measured using one of several rating scales, which also show whether response to treatment is adequate and which guide dosing of medication. One of the most commonly used scales is the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) and its revised forms (2).

In the nineteenth and early twentieth centuries it was also controversial whether alcohol treatment with or without opium was better than "conservative" management without alcohol.

Laycock (3) showed that his conservative management with water and beef tea reduced the death rate compared to alcohol and/or laudanum (a tincture of opium). The safety of treatment was again discussed in the twentieth century with the side effect rich use of barbiturates and chlormethiazole until treatment with at least equally effective benzodiazepines became routine.

Whilst benzodiazepines are the drug category of choice, research is still required to investigate other agents in situations of relative contraindication. One such candidate for consideration is baclofen. This drug may have advantages over alternatives, in particular in patients with liver disease or who risk abuse of medication (see below). In this short review we summarize the evidence gathered up to date of baclofen in relation to the management of AWS.

## ALCOHOL WITHDRAWAL SYNDROME

The severity of the alcohol dependence syndrome in patients is a strong predictor of the severity of untreated alcohol withdrawal on sudden cessation of drinking. Those most at risk describe relief drinking, drinking in the morning and throughout the day and some patients top up during the night to maintain a high blood alcohol concentration and avoid uncomfortable withdrawal symptoms. Patients with high alcohol levels but no behavioral signs of intoxication are at definite risk of AWS. The potential for the syndrome is also related to the quantity of alcohol taken daily and the length of continuous drinking. Like alcohol dependence can be mild, moderate or severe so can the withdrawal syndrome. Withdrawal may often be suppressed by a patient by the return to drinking alcohol. This relief of the discomfort of withdrawal is negative reinforcement and perpetuates the dependence syndrome. Medical intervention with safe and effective drugs to relieve this discomfort and reduce the risk of severe complications (seizures, Delirium) is the first stage in recovery from alcohol addiction in motivated patients. Elective detoxification is done at home, in outpatient clinics, day hospitals or specialist residential settings, with the intensity of supervision matching the severity of dependence and the medical risks associated with withdrawal.

However, usually treatment for the alcohol withdrawal syndrome is delivered when cessation of drinking is unplanned and where AWS is the presenting problem or arises in the context of hospitalization for a medical or surgical problem. AWS needs to be considered in all hospital admissions with appropriate screening and early treatment as indicated and dealing with AWS has been an important part of inpatient management in western countries for the last 200 years (4).

The alcohol withdrawal syndrome, with or without delirium, can be fatal if left untreated although the often quoted high rate before modern treatment of up to 35% seems an exaggeration based on either overzealous treatment with non-specific sedatives or a failure to differentiate AWS from comorbid medical conditions as the cause of death. Anticipation of the syndrome reduces the risk and allows for early intervention by pharmaceutical means and reduces withdrawal symptoms during its time-limited course [See (5) for a fuller description].

Symptoms and signs of AWS are result of a hyperexcitable central nervous syndrome. Alcohol enhances the brain's main inhibitory systems via the Gamma-Aminobutyric Acid (GABA)-A receptor for which it is an agonist like benzodiazepines (BZD). In addition, the alcohol's antagonist action on the N-Methyl-D-aspartic acid (NMDA) receptor (one of the 3 glutamate receptors) suppresses the excitatory system leading to the overall CNS depressant effect (It is a curiosity that alcohol was thought of as a "stimulant"). Chronic exposure to alcohol therefore leads to down-regulation of the GABA-A receptors and upregulation of the NMDA receptors. Thus, when alcohol is stopped the balance between GABAergic and glutaminergic systems reverses with decreased inhibition and increased CNS excitation.

The cross-tolerance between alcohol and benzodiazepines, both agonists for the GABA-A/BZD receptor, underpins the effective action of benzodiazepines in suppressing the AWS. Left untreated within a few hours, increased pulse rate, raised blood pressure, tremor, heightened anxiety, and sweating are seen as part of the AWS with autonomic hyperarousal. The risk of seizures is highest in the first 24 h and delirium can appear in up to 5% of cases after 48–72 h. Manifestations are disorientation, confusion, visual, and sometimes auditory hallucinations. Standard medical management of AWS with benzodiazepines and parenteral vitamins is well-established [see (6, 7), and the Cochrane Review on AWS: (8)].

## BACKGROUND TO BACLOFEN USE IN AWS

Baclofen is a specific agonist for the GABA-B receptor. This receptor provides a negative feedback loop for the GABA-ergic system thereby downregulating GABA-A activity and mimicking some of the effects of alcohol induced action on the GABA-A receptor [for more in depth discussion of the baclofen mechanism see (9)]. Baclofen was initially and is commonly used as a muscle relaxant but has been found to have a positive effect on alcohol craving and relapse prevention [for a review see (10)]. In the light of this, animal studies were conducted and baclofen was shown to prevent withdrawal in rats made dependent on alcohol (11, 12). Subsequently, baclofen was successfully used as an open label treatment in humans with AWS (13).

Baclofen is mainly excreted through the kidney and, unlike benzodiazepines, has minimal liver metabolism. Therefore, the risk of toxicity in the numerous patients with AWS and impaired liver function is reduced (14). In many countries there is a rising incidence of alcohol-related liver disease and many patient have undiagnosed cirrhosis and impaired synthetic liver function. However, it is vital to treat AWS at presentation in these patients and it is therefore of benefit to have non-benzodiazepine agents as an alternative to the shorter acting benzodiazepine drugs which are sometimes used in these patients (lorazepam and oxazepam).

In view of baclofen's property to prevent relapse in alcohol dependence, commencement of baclofen during or toward the end of detoxification may be more efficacious than treatment starting after a period of abstinence. The possibility that baclofen is suppressing a "post-withdrawal syndrome" and thereby

lessening the likelihood of relapse is also worth studying [For consideration of these broader aspects of baclofen see (15)].

## METHODOLOGY

We searched the up to date literature in Medline (on 26/4/18) searching for "baclofen" AND "alcohol withdrawal syndrome" AND "human" to find relevant papers. Seventy six articles were found and were reduced to 51 human clinical papers and those with primary data or an attempt to summarize the evidence were selected. This included studies using baclofen to prevent as well as studies using baclofen to treat established AWS. Our review on baclofen in the management of AWS is separated into open case studies and series, the three available randomized trials and other reviews of the literature.

## CASE STUDIES AND SERIES ON BACLOFEN USE IN ALCOHOL WITHDRAWAL

After it was shown in pre-clinical studies that baclofen prevents withdrawal symptoms in rats (11, 12), a number of open label treatment studies were conducted on in Italy including human studies of baclofen in alcohol withdrawal. In the earliest case series (13) five patients with severe AWS according to CIWA scale (score >20) received open label baclofen (10 mg 8 hourly). Rapid improvement of the CIWA score (Clinical Institute Withdrawal Assessment for Alcohol) was seen on administration of baclofen. This established the possibility of an effect of baclofen on alcohol withdrawal syndrome. An additional single case report by Addolorato et al. (16), showed the drug's efficacy in Delirium Tremens.

These studies are later reviewed in Leggio et al. (17) and in Leggio et al. (18). (See section on reviews). In a review of these studies in 2010, Leggio et al. mention an additional retrospective casenote review of 17 patients treated with baclofen for prevention of AWS. In this chart review at the St. Anthony Hospital in Oklahoma, USA from November 2004 to April 2005 patients were included if they were determined to be at risk for alcohol withdrawal (19). Baclofen was found to suppress the syndrome in 12 out of 14 of the patients (86 %) where AWS hadn't commenced. Of the 3 remaining patients where AWS had commenced there was deemed to be one treatment success and two treatment failures based on pre-determined criteria used (from the diagnostic and statistical manual of mental disorders 4th edition–DSM-IV).

In a similar vein the most recent paper (20) investigates whether prior chronic treatment with "high-dosage" baclofen (range: 60–240 mg) makes a difference during inpatient alcohol detoxification with benzodiazepines in comparison to patients who were not on prior treatment with baclofen. Their study compares 31 patients with chronic pretreatment with high dose baclofen and active alcohol dependency to 31 matched patients with similar alcohol dependence but no prior baclofen treatment. They show that there was no difference in the benzodiazepine dose over a seven day period between the two groups. Within this study there were a small number of patients with cirrhosis—3 in the baclofen group and 5 in the non-baclofen group. They report that there was less need for oxazepam in the 3 patients on baclofen but conclude that it is difficult to generalize the result given these low numbers.

## DRUG TRIALS WITH BACLOFEN IN ESTABLISHED AWS UTILIZING RANDOMIZATION

Overall, 3 independent trials, one from Italy, one from the US and one from India fulfilled the criteria of randomization, one of which was double blind, the others open label.

In a 2006 study by Addolorato et al. (21), 37 patients with established alcohol withdrawal syndrome were randomly assigned into one of two groups, the first was treated with baclofen 10 mg three times daily, and the second with diazepam calculated according to patient weight. The results showed that baclofen was comparable in efficacy and tolerability to the "gold-standard" diazepam treatment. Outcome measures were calculated using the Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-Ar) scale of alcohol withdrawal severity, which was also used to guide therapy. Scoring of the withdrawal severity was carried out by members of the research team blinded to the drug under review. All 37 patients who initially enrolled completed the study and the authors report that no rescue protocol medication was required. The median CIWA-Ar score in the baclofen group decreased from over 20 at treatment begin (day 1) to <15 on day 2 and less than 10 on day 3, a comparable decrease to the diazepam group.

The Cochrane review on baclofen in alcohol withdrawal (22) rates the evidence of this study as low quality in view of the absence of blinding participants to the treatment. However, the authors point out that with the exception of slight initial improvements in anxiety in the diazepam group, the two arms performed similarly on outcome measures.

The second study by Lyon (23) enrolled 44 patients with acute symptomatic AWS to their double-blinded trial with 19 randomized to placebo and 25 to baclofen (10 mg three times a day) and patients requiring intravenous benzodiazepines were excluded in this study. Of these 31 completed the 72 h of treatment (13 patients on placebo and 18 on baclofen). Again, in the baclofen group, the CIWA-Ar score decreased from over 12 at treatment begin (d 1) to less than 9 on day 2 to about 8 on day 3. A rescue regimen of lorazepam according to CIWA scores was provided for both groups. The authors report that significantly more rescue lorazepam was required in the placebo group, compared to the baclofen group. CIWA-scores at 8 hour intervals over a five day period show little difference between the two groups which might reflect the practice of lorazepam being given according to CIWA scores.

The Cochrane review (22) also regards this study as low quality, in particular in view of the high attrition rate and it was noted that the study period of 72 hours period was relatively short.

The Indian study by Reddy and Girish (24, 25) sought to compare baclofen with chlordiazepoxide in the context of alcohol detoxification with regards to efficacy and tolerability in uncomplicated alcohol withdrawal. In this open-label trial the authors have included patients with alcohol dependence and alcohol cessation but no established AWS but they do not give specific numbers. Matched groups of 30 participants were randomly assigned either to 30 mg baclofen daily, or 75 mg chlordiazepoxide daily. The CIWA-Ar variant of the CIWA score was used to assess outcome measures during treatment. Lorazepam was available as required for both groups to treat refractory symptoms and there were no drop-outs from this study. Both arms showed a similar reduction in symptoms of alcohol withdrawal, as measured by CIWA-Ar with a mean score of over 23 prior to treatment start (d 1) to <18 on day 2, <15 on day 3, and <10 on day 4. The authors showed that chlordiazepoxide regimen provided a quicker and more effective detoxification. They also state that lorazepam had a larger impact on CIWA-Ar scores in the baclofen group with no significant effect in the chlordiazepoxide group.

Overall, the authors feel that there is a "smoother" detoxification from alcohol with chlordiazepoxide compared to baclofen. This might well be due to the much longer half life of chlordiazepoxide especially when considering its active benzodiazepine metabolite which is in the range of days compared to the half life of baclofen which is in the range of hours (although the pharmacokinetics of these drugs is not very well studied in patients with previous regular alcohol consumption). On measures of symptom-free days and participant satisfaction, the chlordiazepoxide group was preferred.

## LITERATURE REVIEWS OF BACLOFEN IN ALCOHOL WITHDRAWAL SYNDROME

A review in 2008 (17), updated in 2010 (18) reported on open label studies by Italian teams. This included a retrospective casenote review of 17 patients treated with baclofen prophylactically for AWS in the USA. They conclude that the evidence is insufficient to recommend baclofen in AWS treatment. As reasons the open label design, low numbers, attrition bias and detection bias are mentioned but they feel that baclofen is equivalent in efficacy to other drugs and no adverse side effects were reported.

Dixit et al. (26) analyse several drug studies (benzodiazepines and non-benzodiazepines) for the treatment of alcohol withdrawal in the Intensive Care Unit. Baclofen is considered on the basis of one study (23). The small numbers and reduced statistical power but less "breakthrough" lorazepam in the baclofen group was noted.

The Cochrane group uses very strict quality criteria for inclusion in their latest review (22), and included the 3 randomized controlled trials above with 141 participants. They also conclude that insufficient and low quality evidence prevents judgment on efficacy and / or safety of baclofen in AWS.

## CONCLUSIONS AND DISCUSSION

Overall, despite weaknesses in study design some studies show that baclofen at the dose of 30 mg per day as used in all studies so far may be effective in reducing symptoms of alcohol withdrawal. With just over 140 patients treated for alcohol withdrawal syndrome with baclofen there may be a publication bias with absence of publication of less favorable studies. Also, it is not known whether there would be a benefit in using symptom triggered baclofen doses and allow higher doses. Currently routine treatment with baclofen at a dose of 30 mg per day is not recommended outside trials and benzodiazepines should be used as first line treatment. It is also unclear whether baclofen prevents severe alcohol withdrawal symptoms such as seizures and delirium tremens.

Benzodiazepine use is favored in managing both planned and unplanned AWS, using either a fixed dose or a symptom triggered regime with careful titration for the suppression of signs and symptoms of AWS. Given that tailored and significantly higher doses of baclofen are used in a number of trials in maintenance of abstinence from alcohol, it is surprising that higher (tailored) doses have not been systematically studied for AWS. Usage of higher doses might be more effective but an increased risk of adverse events and baclofen discontinuation syndrome for example on self-discharge would need to be considered (27).

The use of baclofen as a possible adjunct to benzodiazepines in AWS is worthy of further research, in particular to find out whether there are additive or synergistic effects of these two drugs. This is in particular attractive where baclofen maintenance for relapse prevention and treatment of anxiety or post withdrawal symptoms is being considered. The hypothesis that baclofen may offer neuroprotection, possibly alongside acamprosate, in some disease situations, has also been postulated on the basis of animal experiments [e.g., (28)] and it will be worth exploring this in relation to prevention of alcohol related brain damage.

Given that baclofen has a good safety profile in patients with alcohol-related liver disease including cirrhosis and these patients respond to low doses (29) it may also have a potential role in managing AWS in this patient group. It will also be important to further understand the effect of baclofen on different symptoms of the AWS.

In the light of our review we suggest several areas of further research on baclofen in the management of AWS. This includes trial of tailored (higher) baclofen doses in AWS, specific trials in patients with advanced liver disease and in patients with extreme delirium unresponsive to conventional treatment with benzodiazepines. Such studies should be of high quality and preferably multicenter trials.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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# Baclofen in the Treatment of Patients With Alcohol Use Disorder and Other Mental Health Disorders

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A limited number of medications are approved to treat Alcohol Use Disorder (AUD). Furthermore, the magnitude of their therapeutic effect is relatively modest, suggesting the potential for subtypes of patients who respond to a specific medication. The use of these medications is also limited in clinical practice by a series of contraindications such as medical comorbidities and/or concurrent use of other medications. In recent years, animal and human studies have been conducted to evaluate the efficacy of baclofen, a $GABA_B$ receptor agonist approved for clinical use as a muscle relaxant, in the treatment of AUD. However, these studies have yielded contrasting results. Despite this discrepancy, baclofen is often used off-label to treat AUD, especially in some European countries and Australia. Recently, several factors have been considered to try to shed light on the potential reasons and mechanisms underlying the inconsistent results obtained until now. The presence of a psychiatric comorbidity may be amongst the abovementioned factors playing a role in explaining different responses to baclofen treatment in terms of alcohol drinking outcomes. Therefore, the aim here was to conduct a narrative review of the scientific literature related to the use of baclofen in AUD, both in patients with and without concomitant psychiatric disorders. All clinical studies (randomized and controlled, open-label, retrospective, human laboratory studies, and case reports) were analyzed and discussed, bearing in mind other potential factors that may have influenced baclofen response, including dose administered, severity of AUD, use of other psychosocial therapies, and the presence of physical disorders. This review indicates that the most frequent psychiatric comorbidities in patients affected by AUD undergoing baclofen treatment are anxiety and mood disorders. Unfortunately, no definitive conclusions can be drawn due to the lack of specific analyses on whether baclofen efficacy is different in AUD patients with comorbid psychiatric disorders vs. those without. Therefore, it will be critical that psychiatric comorbidities are considered in the planning of future studies and in the analysis of the data, with the ultimate goal of understanding whether subtypes of AUD patients may respond best to baclofen.

**Keywords: $GABA_B$, baclofen, alcohol use disorder, mental health disorders, anxiety, mood disorders**

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# INTRODUCTION

## AUD and Need for Other Medications

Alcohol Use Disorder (AUD) is a severe and complex mental disorder mainly characterized by excessive alcohol consumption and the inability to control it (1). Despite being one of the leading causes of morbidity and mortality worldwide (2, 3), only a limited number of medications are available to help AUD patients achieve abstinence or reduce their alcohol consumption (4, 5). In most countries (e.g., Europe, North America, Australia, parts of Asia, and Africa), these medications include disulfiram, naltrexone, and/or acamprosate (6, 7). Recently, nalmefene was also approved in Europe (6). Unfortunately, only a very small number of AUD patients receive these medications. In the US, <10% of people with AUD receive any type of alcohol treatment (8) and fewer than 4% receive a medication as an intervention or treatment (9).

Possible reasons for the underutilization of medications for AUD include a lack of knowledge, by both patients and physicians, and the misperceptions that medications do not work or that AUD should not be treated with a medication (6). However, certain characteristics of AUD medications also contribute to discouraging physicians from prescribing them. Globally, the magnitude of the therapeutic effects of AUD medications is relatively modest (4), and patient response may differ to a specific drug (10, 11). AUD medications are also contraindicated in patients with some medical comorbidities (4, 5, 12, 13). For instance, naltrexone and disulfiram are contraindicated amongst patients with clinically-relevant liver diseases; on the other hand, acamprosate is contraindicated in patients with kidney failure. Furthermore, disulfiram should not be used in patients who are not capable of understanding the risks of consuming alcohol while they are taking disulfiram. In clinical practice, these conditions are frequent and contribute to a further reduction in the available treatment choices for AUD patients. Another frequent condition in clinical practice is the presence of comorbid mental disorders such as substance use disorder, mood disorder, and/or anxiety disorder, especially among patients with more severe AUD (14). The use of medications for AUD among these latter patients is even lower than among AUD patients without other comorbid mental disorders, because of the concern of medication-alcohol interactions (15). For all these reasons, the identification of new, safe, and effective medications is a critical priority in the field of AUD treatment (16–18).

## Baclofen and AUD

Baclofen is a $GABA_B$ receptor agonist approved for clinical use as a muscle relaxant. In recent years, animal and human studies conducted to evaluate the efficacy of baclofen in the treatment of AUD have yielded contrasting results (19). Despite this discrepancy, baclofen is often used to treat AUD, especially in European countries and Australia, as a consequence of the wide off-label prescription of the drug by general practitioners (20). Recently, several factors have been considered and analyzed to shed light on the potential reasons and mechanisms underlying the inconsistent treatment results obtained until now. It has been suggested that the presence of a psychiatric comorbidity may be amongst the abovementioned factors playing a role in explaining different responses to baclofen treatment, in terms of alcohol drinking outcomes. Preclinical and clinical findings clearly indicate a key role of the $GABA_B$ receptor in depression and anxiety disorders (21, 22). Some studies found that baclofen reduces anxiety levels in AUD patients (23–25). Conversely, other studies did not find significant effects of baclofen on anxiety levels in AUD patients (26), or they found that patients without comorbid mental disorders achieved better results compared to patients with comorbid mental disorders (27–29). Therefore, the aim of the present paper was to conduct a narrative review of the scientific literature related to the clinical use of baclofen in AUD to achieve abstinence or reduce alcohol consumption, both in patients with and without concomitant psychiatric disorders. All clinical studies (randomized and controlled, open-label, retrospective, test-tube lab research, and case reports) were summarized and discussed, bearing in mind other potential factors that may have influenced baclofen response, e.g., baclofen dose, severity of AUD, use of other psychosocial therapies, and the presence of medical comorbidities.

## Methodology

Data were obtained for the narrative mini-review by searching the published medical literature in Medline (PubMed) up to May 2018. There were no language restrictions; the search was limited to humans. The search terms used included alcoholism or AUD or alcohol dependence AND baclofen.

# REVIEW OF THE SCIENTIFIC LITERATURE RELATED TO THE USE OF BACLOFEN IN AUD BOTH IN PATIENTS WITH AND WITHOUT CONCOMITANT PSYCHIATRIC DISORDERS

## Case Reports

A few case reports describe the results obtained by the use of baclofen in AUD patients [see **Table 1**; (30–35)]. All these patients suffered from severe AUD, as shown by their high level of alcohol consumption at baseline, the lack of a response to other previous treatments for AUD, and the presence of one or more comorbid psychiatric disorders, such as anxiety, mood disorder, schizophrenia, and bulimia. Patients received daily doses of baclofen, ranging from 50 to 120 mg, and were followed for a timeframe ranging from 8 to 52 weeks. In all these patients, baclofen administration led to alcohol abstinence or to a marked reduction in alcohol consumption. On the other hand, possible effects of baclofen on the severity of the other mental disorders were not reported by most of the studies and, when reported, the results were contrasting.

## Retrospective Studies

A series of retrospective studies evaluated the efficacy of baclofen among large samples of AUD patients [see **Table 2**; (27–29, 36–41)]. These patients showed high baseline levels of alcohol consumption, were not responders to previous pharmacological treatments, and suffered from other mental or physical disorders.

**TABLE 1 |** Case reports.

| | Participants' characteristics | | | Baclofen treatment | | Clinical effects of baclofen treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **References** | **Gender** | **Comorbidity** | **Baseline DDD** | **Mean daily dose** | **Weeks** | **Final DDD** | **Anxiety** | **Depression** | **Schizophrenia** | **Bulimia** | **Stuttering** |
| (30) | 1 M | Schizophrenia Anxiety | ∼16 | 75 mg | 24 | 0 | ↔ | – | ↓ | – | – |
| (31) | 1 M | Anxiety | ∼20 | 120 mg | 36 | 0 | ↓ | – | – | – | – |
| (32) | 1 M | Stuttering Depression | ∼16–24 | 90 mg | >52 | 2 | - | ↓ | – | – | ↓ |
| (33) | 1 M | Anxiety Depression | ∼5–12 | 100 mg | 40 | 2–3 | ↔ | ↔ | – | – | – |
| (34) | 3 M; 1 F | Depression Bipolar disorder | ∼7–30 | 50-125 mg | 20–36 | 0 | – | – | – | – | – |
| (35) | 1 F | Anxiety Bulimia | ∼20 | 120 mg | 8 | 0 | – | – | – | ↔ | – |

*DDD, Drinks per Drinking Day (1 drink = ∼12 g of pure alcohol); F, Female; M, Male.*

**TABLE 2 |** Observational and retrospective studies.

| | Participants' characteristics | | | Baclofen Treatment | | Clinical effects of baclofen treatment | | |
|---|---|---|---|---|---|---|---|---|
| **References** | **Gender** | **Comorbidity** | **Baseline DDD** | **Mean daily dose** | **Weeks of treatment** | **Alcohol** | **Anxiety** | **Depression** |
| (27, 36) | 70 M 30 F | Other psychiatric disorders (59%)<br>Anxiety disorders (53%)<br>Depression (34%) | M = 19<br>F = 15 | M = 158 mg<br>F = 127 mg | 104 | ↓ | *After 3 months, the rate of participants who continued to drink at risk levels was higher among participants with mental disorders (70%) than without (48%)* | |
| (37) | 10 M 3 F | Anxiety (62%)<br>Depression (100%) | ∼9-33 | 30-150 mg | Up to 108 | ↓ | Some ↓ | - |
| (38) | 31 M 22 F | Liver disease (100%) | 20 | 60 mg | 104 | ↓ | ↔ | ↔ |
| (28) | 59 M 57 F | Other psychiatric disorders (92%)<br>Anxiety disorders (75%)<br>Depression (56%) | M = ∼16<br>F = ∼12 | 150 mg | 52 | ↓ | *After 12 months, the rate of participants with mental disorders was higher among non-abstinent participants (48%) than abstinent participants (12%)* | |
| (29) | 39 M 30 F | 23 patients with BPD vs. 46 patients without BPD | At least 8 | - | ∼32 | ↔ BPD<br>↓ Controls | *After a serious adverse event, the rate of treatment discontinuation was higher among participants with BPD (65%) than without BPD (6%)* | |
| (39) | 112 M 1 F | Number of patients with comorbid psychiatric illness not provided | – | – | – | ↓ | – | – |
| (40) | 348 M | No other mental disorders | ∼12.5 | 50 mg | | ↓ | – | – |
| (41) | 20 M 15 F | Patients with or without cirrhosis<br>Number of patients with comorbid psychiatric illness not provided | - | 30 mg | >23 | ↓ | – | – |

*BPD, Borderline Personality Disorder; DDD: Drinks per Drinking Day (1 drink = 12 g of pure alcohol); F: Female; M, Male. Italic indicates rates of participants suffering for the other disorder.*

The majority of these patients suffered mainly from anxiety and depression (27, 36, 37), whereas two studies were conducted in AUD patients with clinically-significant liver disease (38, 41). The daily doses of baclofen ranged from 30 to ∼150 mg. One study observed that the average dose received by female patients was lower than the one received by males (27). Three studies found that patients without comorbid mental disorders achieved better results compared to patients with comorbid mental disorders

[anxiety, depression, and/or borderline personality disorder; 27–29]]. Another study did not find a significant effect of baclofen on either anxiety or depression, which were evaluated using self-reported rating scales (38).

## Open Studies

**Table 3** shows open studies in which baclofen was administered to help AUD patients to achieve abstinence or reduce alcohol consumption [see **Table 3**; (42–47)]. Among these studies, only three provided information on comorbid mental disorders (45–47): in one study (45), five out of twelve participants suffered from mental disorders other than AUD; in the other two studies, patients with severe mental disorders, other than AUD, were excluded (46, 47). In all studies, participants received daily doses of baclofen ranging from 30 to 145 mg and were monitored from 4 to 52 weeks. All these studies reported that baclofen reduced alcohol consumption. Among the studies in which the anxiety and depression levels of participants were evaluated, baclofen administration reduced anxiety but not depression levels (45–47).

## Human Laboratory Studies

Two laboratory studies investigated the effects of baclofen in non-treatment seeking AUD participants [see **Table 4**; (26, 48)]. In both studies, participants received 30 mg/day baclofen for approximately a week. In one study, participants with recent (past 6 months) mental disorders, other than AUD, were excluded (48). In the other one, participants had high anxiety levels (see

**TABLE 3 |** Open-label studies.

| | Participants' characteristics | | | Baclofen treatment | | Clinical effects of baclofen treatment | | |
|---|---|---|---|---|---|---|---|---|
| **References** | **Gender** | **Notes and comorbidities** | **Basal DDD** | **Mean daily dose** | **Weeks** | **Alcohol** | **Anxiety** | **Depression** |
| (42) | 10 M | - | ∼8 | 30 mg | 4 | ↓ | – | – |
| (43) | 60 N/A | Article in French | - | 145 mg | 12 | ↓ | – | – |
| (44) | 75 M; 25 F | 65 participants suffered from cirrhosis | ∼7 | 40 mg | 52 | ↓ | – | – |
| (45) | 9 M; 3 F | 5 participants suffered from other psychiatric disorders<br>Anxiety levels: BAI = ∼5<br>Depression levels: BDI = ∼8 | ∼8 | 30 mg | 12 | ↓ | ↓ | ↔ |
| (46) | 80 M (vs. 75 M benfothiamine) | Participants with other psychiatric disorders were excluded<br>Anxiety levels: HAM-A = ∼20<br>Depression levels: HAM-D = 12 | - | 50 mg | 12 | ↓ | ↓ | ↔ |
| (47) | 10 M; 6 F | Participants with other psychiatric disorders were excluded<br>Anxiety levels: STAI = ∼51<br>Depression levels: ZUNG = 41 | - | 30 mg | 12 | ↓ | ↓ | ↔ |

*BAI, Beck Anxiety Inventory (cut off ≥ 10); BDI, Beck's Depression Inventory (cut off > 10); DDD, Drinks per Drinking Day (1 drink = ∼12 g of pure alcohol); F, Female; HAM-A, Hamilton Anxiety Rating Scale (cut off > 17); HAM-D, Hamilton Depression Rating Scale (cut off ≥ 8); M, Male; N/A, Not Available; STAI, Spielberger State Trait Anxiety Inventory (cut off ≥ 40); ZUNG, Self-rating depression scale (cut off ≥ 50).*

**TABLE 4 |** Human laboratory studies.

| | Participants' characteristics | | | Baclofen Treatment | | Clinical Effects of Baclofen Treatment | | |
|---|---|---|---|---|---|---|---|---|
| **References** | **Gender** | **Notes on comorbidity** | **Baseline DDD** | **Mean daily dose** | **Weeks** | **Alcohol** | **Anxiety** | **Depression** |
| (26) | 14 M; 4 F vs. 13 M; 3 F placebo | Anxiety levels: STAI = ∼47 | ∼8 | 30 mg | 1 | ↔ | ↔ | N/A |
| (48) | 10 M; 4 F | Participants with other psychiatric disorders were excluded | ∼8 | 30 mg | 1 | ↔ | Baseline anxiety levels did not modulate alcohol drinking | |

*DDD, Drinks per Drinking Day (1 drink = 12 g of pure alcohol); F, Female; M, Male;N/A, Not Available; STAI, Spielberger State Trait Anxiety Inventory (cut off ≥ 40).*

**TABLE 5 |** Randomized double-blind placebo-controlled trials.

| | Participants' characteristics | | | Baclofen treatment | | Clinical effects of baclofen treatment | | |
|---|---|---|---|---|---|---|---|---|
| **References** | **Gender** | **Notes and comorbidity** | **DDD** | **Mean daily dose** | **Weeks** | **Alcohol** | **Anxiety** | **Depression** |
| (23) | BAC: 20 M<br>PLA: 19 M | Participants with severe mental disorders were excluded<br>Anxiety levels: STAI = ∼50<br>Depression levels: ZUNG = ∼40 | ∼14 | 30 mg | 4 | ↓ | ↓ | - |
| (49) | BAC: 32 M; 10 F<br>PLA: 29 M; 13 F | Participants with severe mental disorders were excluded<br>Cirrhosis | – | 30 mg | 12 | ↓ | - | - |
| (50) | BAC: 21 M; 7 F<br>PLA: 11 M; 3 F | Participants with severe mental disorders were excluded<br>Anxiety levels: STAI = ∼50<br>Depression: ZUNG = ∼40 | ∼12 | 30 or 60 mg | 12 | ↓ | ↔ | - |
| (51) | BAC: 61 M; 28 F<br>PLA: 43 M; 19 F | Participants with severe mental disorders (other than depression, anxiety, and bipolar disorder) were excluded<br>Anxiety levels: STAI = ∼50<br>Depression levels: BDI = ∼20 | ∼12 | 30 or 94 mg | 16 | ↔ | ↔ | ↔ |
| (24) | BAC: 22 M; 18 F<br>PLA: 22 M; 18 F | Participants with severe mental disorders (except those with stable doses of antidepressants) were excluded<br>6 M + 17 F under antidepressants<br>Anxiety levels: STAI = ∼40<br>Depression levels: ZUNG = ∼36 | ∼7 | 30 mg | 12 | ↔ | ↓ | ↔ |
| (52) | BAC: 85 M; 3 F<br>PLA: 92 M | Participants with significant psychosis, mania, or elevated risk for suicide were excluded<br>Liver disease<br>Anxiety levels: BSI = 43–52<br>Depression levels: BDI = 13 | ∼9 | 30 mg | 12 | ↔ | ↔ | ↔ |
| (25) | BAC: 29 N/A<br>PLA: 23 N/A | Participants had a combination of anxiety and depression<br>Anxiety levels: STAI = ∼52<br>Depression levels: ZUNG = ∼53 | - | 37.5 mg | 3 | - | ↓ | ↓ |
| (53) | BAC: 16 N/A<br>PLA: 16 N/A | Participants with a history of severe mental disorders were excluded<br>Anxiety levels: STAI = ∼40<br>Depression levels: MADRS = ∼5.5 | - | 50 mg | 12 | ↔ | ↔ | ↔ |
| (54) | BAC: 9 M; 6 F<br>PLA: 9 M; 6 F | Participants with severe mental disorders were excluded<br>Smoking | – | 80 mg | 12 | ↓ | – | – |
| (55) | BAC: 10 M; 18 F<br>PLA: 9 M; 5 F | Participants with severe mental disorders were excluded (except those with stable doses of antidepressants)<br>Anxiety levels: STAI = ∼40<br>41% current anxiety | - 16 | 30 or 60 mg | 12 | ↔ ↓ in anxious | ↔ | – |
| (56) | BAC: 57 M; 20 F<br>PLA: 30 M; 10 F | Participants with severe mental disorders were excluded<br>Liver disease<br>57 under antidepressants<br>Anxiety levels: DASS anxiety = ∼13<br>Depression levels: DASS depression = ∼17 | - 12.5 | 30 or 75 mg | 12 | ↓ | ↔ | ↔ |
| (57) | BAC: 20 M; 8 F<br>PLA: 19 M; 9 F | Participants with severe mental disorders were excluded<br>Anxiety levels: HAM-A = ∼3<br>Depression levels: HAM-D = ∼3 | | 180 mg | 12 | ↓ | - | - |

*(Continued)*

**TABLE 5** | Continued

| | Participants' characteristics | | | Baclofen treatment | | Clinical effects of baclofen treatment | | |
|---|---|---|---|---|---|---|---|---|
| **References** | **Gender** | **Notes and comorbidity** | **DDD** | **Mean daily dose** | **Weeks** | **Alcohol** | **Anxiety** | **Depression** |
| (58) | BAC: 24 M; 8 F<br>PLA: 24 M; 8 F | Participants with severe mental disorders were excluded<br>Depression levels: BDI = ∼16 | | 50 mg | 12 | ↔ | - | ↔ |
| (59) | BAC: 118 M; 37 F<br>PLA: 107 M; 48 F | Participants with severe mental disorders were excluded<br>Anxiety levels: HAD Anxiety = ∼6<br>Depression levels: HAD Depression = ∼6 | | 153 mg | 26 | ↔ | - | - |

*BAC, Baclofen; BDI: Beck's Depression Inventory (cut off > 10); BSI, Brief Symptoms Inventory (cut off ≥ 65); DASS, Depression Anxiety Stress Scale; DASS Anxiety (cut off ≥ 8); DASS Depression cut off ≥ 10); DDD, Drinks per Drinking Day (1 drink = 12 g of absolute alcohol); F, Female; HAD, Hospital Anxiety and Depression Scale; HAD Anxiety (cut off ≥ 8); HAD Depression (cut off ≥ 8); HAM-A, Hamilton Anxiety Rating Scale (HAM-A) (cut off >17 mild anxiety); HAM-D, Hamilton Depression Scale (cut off ≥8); M, Male; MADRS, Montgomery-Asberg Depression Scale (cut off ≥ 12); N/A, Not Available; PLA, Placebo; STAI, Spielberger State Trait Anxiety Inventory (cut off ≥ 40); ZUNG (cut off ≥ 50).*

**Table 4)**, but only a few participants had a formal diagnosis, based on DSM-IV, of current anxiety disorders (5 out of 34) or current mood disorder (1 out of 34) (26). One study found that baclofen reduced alcohol self-administration but not cue-elicited craving; furthermore, baseline anxiety levels did not modulate alcohol drinking (48). The other one did not report significant effects of baclofen on either alcohol consumption, cue-elicited craving, or anxiety levels (26). In both studies, baclofen amplified the subjective effects of alcohol, which was suggested as a potential biobehavioral mechanism of how baclofen may affect alcohol drinking (26, 48).

## Randomized Double-Blind Placebo-Controlled Trials

The findings of the randomized, double-blind placebo-controlled trials of baclofen in the treatment of AUD are outlined in **Table 5** (23–25, 49–59). All the studies excluded participants with severe mental disorders other than AUD but, in some studies, participants who received stable doses of antidepressants (24, 55, 56) or participants affected by depression, anxiety, and/or bipolar disorder (51) were allowed to participate. Participants received daily doses of baclofen ranging from 30 to 180 mg for a timeframe ranging from 3 to 26 weeks. All the studies, except two (49, 54), reported the mean values of anxiety and/or depression levels. Most studies used self-reported rating scales such as STAI (Spielberger State Trait Anxiety Inventory) for anxiety and BDI (Beck's Depression Inventory) or ZUNG for depression. Only a few studies used interviewer-rated scales such as HAM-A (Hamilton Anxiety Rating Scale) for anxiety and HAM-D (Hamilton Depression Rating Scale) or MADRS (Montgomery-Asberg Depression Scale) for depression.

In two studies, participants had high baseline anxiety levels (23, 50), in two other studies high baseline depression levels (52, 58), and in three studies both high baseline anxiety and depression levels (25, 51, 56). Baclofen administration induced contrasting results regarding alcohol consumption. It reduced alcohol consumption in some studies (23, 49, 50, 54, 55, 57), but not in others (24, 51–53, 55, 58, 59). One study suggested a relationship between comorbid anxiety and treatment response to baclofen (55). In this study, baclofen administration reduced alcohol consumption in anxious patients, but did not induce significant modifications in other participants. However, this relationship was not observed in other studies. Baclofen reduced alcohol consumption in studies in which participants had high (23, 50, 56) or low (57) baseline anxiety levels. On the other hand, baclofen failed to modify alcohol consumption in other studies in which participants had high (51) or low (59) baseline anxiety levels. No study provided the results obtained specifically in participants affected by other mental disorders.

# DISCUSSION

The presence of another mental disorder, such as anxiety and depression, other than AUD represents a frequent and complex clinical phenomenon (1, 14, 60). The pharmacological treatment of AUD patients affected by comorbid mental disorders represents a significant challenge (61, 62). AUD and a second mental disorder may occur independently, or one of the two disorders may have influenced the development of the other one (1, 63). For instance, an anxious patient may develop AUD as consequence of the excessive alcohol consumption to self-medicate anxiety. On the other hand, AUD patients frequently develop temporary alcohol-induced depressive and/or anxiety symptoms during intoxication and/or withdrawal (63). Accordingly, physicians need to establish if AUD patients with a comorbid mental disorder require a pharmacological treatment for both the conditions (e.g., if both the conditions are severe and long lasting) or not (e.g., if co-occurrent symptoms are alcohol-induced and tend to resolve without treatment within 3–4 weeks) (63).

According to preclinical studies, $GABA_B$ receptors modulate anxiety and depression-related behaviors (21), and baclofen may induce better results among AUD patients affected by

anxiety and/or mood disorders through a reduction of the severity of these disorders. The present narrative mini-review was aimed at investigating the role of psychiatric comorbidity in explaining potential different responses to baclofen treatment among AUD patients. The results show that the majority of AUD patients treated with baclofen and described by the case reports, as well as the observational and retrospective studies, suffered from anxiety and/or mood disorders. This finding agrees with data of large epidemiological studies (14, 60). However, the results of the present review also show that, despite these disorders being common among AUD patients, patients with severe mental disorders (including severe anxiety and mood disorders) were excluded by the randomized, controlled, trials (RCTs) conducted to evaluate the efficacy of baclofen to treat AUD. Therefore, these results do not allow us o evaluate whether baclofen efficacy is different in AUD patients with comorbid psychiatric disorders compared to those without. One RCT found that baclofen administration reduced alcohol consumption in anxious patients, but not in patients with low levels of anxiety (55). However, in this study, baclofen administration did not significantly reduce anxiety levels. A recent meta-analysis also found no difference between baclofen and placebo in reducing both depression and anxiety levels among AUD patients (64). The results of the present review may be useful to better understand these results. Indeed, both these studies (55, 64) evaluated the efficacy of baclofen in modifying the severity of anxiety or depression among AUD patients not affected by severe mental disorders. In addition, the RCTs used different scales to measure the severity of anxiety and/or depression, such as self-reported rating scales (e.g., STAI, BDI, and ZUNG) and interviewer-rated scales (e.g., HAM-A, HAM-D, and MADRS). The exclusion of patients with severe mental disorders, and the variability in the scales adopted, prevents current meta-analyses to evaluate potential differences in baclofen efficacy in reducing the severity of the comorbid mental disorders. To reduce the variability, the interviewer-rated scales should be used rather than self-reported rating scales (65, 66). Accordingly, it is desirable that future RCTs investigate the efficacy of baclofen in AUD patients affected by other mental disorders, using interviewer-rated scales to establish the effects on the severity of anxiety and/or depression.

## CONCLUSIONS

There is a critical need to develop novel medications for AUD. In addition, the new diagnostic criteria of AUD in the DSM-5 may increase the prevalence of new cases of this mental disorder, compared to the criteria provided by the DSM-IV (67), therefore the importance of developing new effective treatments is even greater. The $GABA_B$ receptor represents a promising pharmacological target, a concept that has been supported by a plethora of animal studies. Medication development for CNS indications is challenging and, indeed, the translation of findings from animal models to humans is one of the most difficult steps in this field. The presence of both positive and negative RCTs is not uncommon in the AUD literature. The medication development field, at large, and the results of recent meta-analyses show baclofen is not exempt from this pattern (65, 68, 69). Inconsistencies across studies may be due to several factors, which may include (but are not limited to) differences at several levels, e.g., (a) medication-related differences like baclofen doses, medication adherence, interactions with other concomitant medications, or pharmacokinetics; (b) patient-related differences like gender, severity of AUD, tolerance to baclofen's effects, psychiatric comorbidities, or medical comorbidities; and (c) geographic- and site-related differences like specific patient-provider interactions, or amount and type of behavioral interventions provided in addition to the medication. These factors are likely to explain not only why RCTs have yielded different results, but also why analyses focused on one specific factor (e.g., baclofen dose, patients with anxiety comorbidity) have also generated conflicting results. Despite the lack of consistent evidence of efficacy, baclofen is frequently used off-label to treat AUD, especially in some European countries and Australia (70). It is preferable that future prospective studies and meta-analytical efforts try to look at the interactions of all these factors as they relate to the medication, patient, and site, in order to identify which are, if any, the best variables that may predict the patient's phenotype that is most likely to benefit from the treatment with baclofen. Finally, it is important to keep in mind that, while baclofen represents the prototypic agonist of the $GABA_B$ receptor, very promising rodent data suggest the $GABA_B$ positive allosteric modulators may represent a better pharmacological approach (19). Therefore, future efforts should also focus on profiling these compounds from a toxicology and safety standpoint, in order to bring them to the clinical setting and test their safety and potential efficacy in humans.

## AUTHOR CONTRIBUTIONS

RA led the literature search and drafted the manuscript. LL provided substantial contributions to the intellectual content of the manuscript. Both authors approved the final version of the manuscript.

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# Safety Challenges of Using High Dose Baclofen for Alcohol Use Disorder: A Focused Review

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Since the early 2000s, the gamma-aminobutyric acid type B (GABA-B) receptor agonist baclofen has been extensively used for treating alcohol use disorder (AUD). In some countries, like France, Australia, or Germany, baclofen has been used at patient-tailored dose regimens, which can reach 300 mgpd or even more in some patients. The GABA-B-related pharmacology of baclofen expose patients to a specific profile of neuropsychiatric adverse drug reactions (ADRs), primarily some frequent sedative symptoms whose risk of occurrence and severity are both related to the absolute baclofen dosing and the kinetics of dose variations. Other frequent neuropsychiatric ADRs can occur, i.e., tinnitus, insomnia, or dizziness. More rarely, other serious ADRs have been reported, like seizures, manic symptoms, or sleep apnea. However, real-life AUD patients are also exposed to other sedative drugs, like alcohol of course, but also benzodiazepines, other drugs of abuse, or other sedative medications. Consequently, the occurrence of neuropsychiatric safety issues in these patients is essentially the result of a complex multifactorial exposure, in which baclofen causality is rarely obvious by itself. As a result, the decision of initiating baclofen, as well as the daily dose management should be patient-tailored, according the medical history but also the immediate clinical situation of the patient. The overall safety profile of baclofen, as well as the clinical context in which baclofen is used, have many similarities with the use of opiate substitution medications for opiate use disorder. This empirical statement has many implications on how baclofen should be managed and dosing should be adjusted. Moreover, this constant patient-tailored adjustment can be difficult to adapt in the design of clinical trials, which may explain inconsistent findings in baclofen-related literature on AUD.

**Keywords: baclofen, alcohol use disorder, safety, dosing preferences, tolerability, public health**

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## INTRODUCTION

Baclofen is an agonist of the gamma aminobutyric acid type B (GABA-B) receptors. In the early 1970s, baclofen has been labeled for neurological states spasticity, which may occur in severe neurological injuries or some neurological diseases like multiple sclerosis (1). In these neurological indications, baclofen is used orally, or is directly infused within the central nervous system via

intrathecal pumps. In its oral labeled use, the maximum approved dosing is generally 80 mg per day (mgpd) for outpatients, and 120 mgpd for inpatients.

From the beginning of the 2000s, an extensive number of clinical studies have assessed the efficacy of baclofen in the treatment of alcohol use disorder (AUD). Until recently, these studies had essentially focused on low-dose baclofen, i.e., a maximum dosing of 30 mgpd or more rarely 60 mgpd. So far, the results of these efficacy studies have been relatively contrasting (2), even if recent meta-analyses have found a significant effect of baclofen in AUD, either for maintaining abstinence (3) or reducing drinking (4). In parallel, an empirical use of baclofen for AUD has also progressively spread among clinicians in several countries, for example France (5–7) or Australia (8). Due to its off-label nature, however, this use has bloomed into very heterogeneous practices, particularly with regard to the prescribing schemes and patterns of dose used (9).

Baclofen prescribing practices usually vary according to the underlying rationale of prescribers. Using baclofen in AUD has occasionally been supported by a possible action of baclofen on the dopaminergic transmission in the nucleus accumbens, which could thereby reduce craving and alcohol use in subjects with AUD (10). Another approach is that ethanol effects on the brain could in part be mediated by an action on the GABAB receptors. As baclofen can prevent the occurrence of alcohol-related withdrawal symptoms, some other authors have hypothesized that baclofen could be a form of substitution treatment for alcohol (11, 12), thus justifying that baclofen could be used in AUD similarly to how methadone or buprenorphine are used of opiate use disorder (13).

This latest rationale implies a dose-effect relationship, but also the fact that baclofen dosing should be adjusted on a patient-tailored manner (9, 14). This has been one of the arguments for using high doses in some patients. Unfortunately, the only three clinical trials that have explored the efficacy of very high doses in subjects with AUD have also yielded contradictory results with two negative trials (15, 16), and two other trials finding a significant difference compared to placebo (17, 18). This may explain why meta-analyses have not found any dose-effect relationship so far (3, 4).

In France, the empirical use of baclofen has largely spread from 2007 to 2013, when the estimated number of treated patients had reached 200,000 subjects (19). Though baclofen use has substantially decreased since 2014 in France, an important collection of safety data have been gathered, analyzed, and published, with regard to the safety profile of baclofen in the specific population of AUD patients. This French experience, mixed with other international studies, thus represent a rich amount of safety data about baclofen use in real-life patients with AUD, including at high doses, even if the prescribing habits and protocols can vary according to places and teams (9). This focused narrative review thus addresses the main pharmacoepidemiological and pharmacovigilance studies published on the off-label use of baclofen for AUD.

# ADVERSE DRUG REACTIONS WITH DEMONSTRATED CAUSALITY OF BACLOFEN

## Sedation and Related Consequences

Sedation, and the related consequences, like dizziness or confusion, are by far the most frequent ADRs related to baclofen (see **Table 1**). Moreover, the level of sedation has been found correlated with baclofen dosing and dose increases. In the three randomized clinical trials (RCTs) using high dose baclofen, sedation was reported by between 38.0 and 46.6% of the patients treated with high dose baclofen (15, 16, 18) vs. 22.6% among patients treated with low-dose baclofen (15), and between 17.7 and 25% in patients treated with placebo. Whereas no serious ADR was reported in relation to baclofen-induced sedation in the first two RCTs, only two cases of fall were reported in Reynaud et al. (16) (See **Table 1**). In the French national pharmacovigilance database, sedation/drowsiness was reported in 24.5% of all types of reported ADRs (see **Table 1**), and 32% of all cases of non-serious ADRs (20). Similarly, 17.4% of all notifications with serious ADRs reported confusion, while 11.5% of them reported sedation, and 9.6% of them reported coma (**Table 2**). Baclofen main safety concerns are thus by far the consequences of baclofen-induced sedation.

In all these data, however, the role of alcohol or other drugs was rarely studied. Even if baclofen can definitely induce sedation, patients with AUD are likely to experience other causes of sedation. In particular, it has been found that the main predictor of major sedation in AUD patients treated with baclofen is the concurrent level of alcohol use (21). Consequently, the occurrence of severe sedation or coma among AUD subjects treated with baclofen is probably the result of a complex equation which integrates baclofen dosing and recent dose increases, but also the level of alcohol use, and other drugs of abuse or sedative medications that may be more or less regularly ingested by the subject. In practice, the exact causality of baclofen in a situation of severe sedation should thus be addressed on a case-by-case basis, using an exhaustive anamnesis, and a rigorous

**TABLE 1** | Main ADRs occurring in AUD patients treated with high dose baclofen.

| | Occurrence rates in RCTs (HDB vs. placebo)[a] | Proportion of all ADRs reported in the FPVD[b] |
|---|---|---|
| Sedation/Dizziness/Fatigue | 38.0 to 46.6% vs. 17.7 to 25% | 24.5% |
| Insomnia/Sleep Disorders | 32.1 to 38.8% vs. 14.3 to 30.8% | 7% |
| Headache | 26.7% vs. 15.0% | – |
| Paraesthesia | 14.4 to 16.6% vs. 3.6 to 4.4% | – |
| Restlessness/Fasciculations | 10.8 to 14.3% vs. 3.6 to 3.8% | 3.8% |
| Headache | 24 (15.0%) 42 (26.7%) | |
| Dry mouth | 7.6 to 20.7% vs. 1.6 to 5.0% | 10% |

[a] *(15, 16, 18).*
[b] *(20).*
*ADRs, adverse drug reactions; AUD, alcohol use disorder; RCTs, randomized controlled trials; HDB, high-dose baclofen; FPVD, French Pharmacovigilance Database.*

**TABLE 2 |** Ten most frequent serious ADRs reported in the FPVD in patients treated with baclofen for AUD.

| | Proportion of all serious ADRs reported in the FPVD (%) |
|---|---|
| Confusion | 17.3 |
| Seizures | 11.5 |
| Major sedation | 11.5 |
| Agitation | 10.9 |
| Coma | 9.6 |
| Hallucinations | 7.7 |
| Falls | 7.1 |
| Behavioral disorders | 5.8 |
| Baclofen withdrawal syndrome | 5.1 |
| Space-time disorientation | 5.1 |

*Auffret et al. (20).*
*ADRs, adverse drug reactions; AUD, alcohol use disorder; FPVD, French Pharmacovigilance Database.*

pharmacovigilance approach (22). The mechanisms through which baclofen can induce or participate in inducing sedation, are probably in link with the specific pharmacology of the GABA-B receptor, which is known for regulating the activity of the GABA-A receptors (23, 24).

Similarly, the diverse toxicology studies that have addressed baclofen involvement in the severity of intoxications, including self-poisoning and resuscitation hospitalizations, have found that many pharmacological cofounders may actually contribute to the overall severity and the clinical outcomes (25–27). Consequently, baclofen should only be considered as one of the many contributing severity factors of self-poisoning and drug intoxication in AUD patients (28). Moreover, these situations of intoxications more specifically affect some subpopulations of AUD subjects, in particular those who are more likely to display self-poisoning and suicide attempts. This is particularly the case for subjects with personality disorders, including borderline personality disorder, in whom the frequency and severity of poly-substance and poly-drug intoxications have been found particularly high (29). This can also apply to AUD subjects with comorbid borderline personality disorder who are treated with baclofen (30). However, it is unclear whether these increased situations of self-harm and their consequences can be accounted directly on baclofen.

## Other Neuropsychiatric ADRs Induced by Baclofen

Other neuropsychiatric symptoms can occur in patients with baclofen, with a demonstrated causality of the drug. This is in particular the case for insomnia (20), tinnitus (20, 31), and more rarely, seizures (32, 33), hallucinations (20, 34), and manic symptoms (35). In addition, baclofen withdrawal is associated with a specific withdrawal syndrome that is addressed in section Baclofen withdrawal syndrome and non-neuropsychiatric baclofen-induced side effects. In the RCTs using high-dose baclofen, insomnia or sleep disorders affected between 32.1 and 38.8% of the patients treated with high-dose baclofen, vs. between 14.3 and 30.8% of those receiving placebo (16, 18).

The mechanisms through which baclofen can trigger these different types of neuropsychiatric symptoms are relatively unclear. Animal studies have found that baclofen could enhance the serotonin and noradrelin levels in some parts of the brain (36–38). This could contribute to baclofen anxiolytic properties (39), but also to a possible antidepressant effect that still remains to be more clearly demonstrated (40). This could also explain the risk of developing manic symptoms (40). The complex effects that baclofen may have on sleep could result from similar mechanisms. In addition, the regulation of the pineal gland is influenced by the GABAergic signaling, and it involves the GABA-B receptors (41).

Concerning the risks of both seizures and tinnitus, it is interesting to note that, depending on the situation, the level of activity of the GABA-B receptors could have both pro- or anticonvulsant consequences, (42), and pro- and anti-tinnitus effects (43). This seems to highlight that the GABA-B receptors have a complex modulatory role of other receptors involved in these symptoms, in particular the GABA-A receptors. Indeed, both the activity and the composition of the GABA-A receptors are directly regulated by GABA-B receptors (23, 24, 44, 45). Similarly, it could also explain why baclofen can cause insomnia in some patients, and sedation in other patients. Finally, baclofen was recently found to induce or increase the severity of central sleep apnea in AUD patients (46). This clinical finding is in line with previous animal studies that found that baclofen decreased the firing rate of respiratory neurons in the mesencephalon (47).

## Baclofen Withdrawal Syndrome and Non-neuropsychiatric Baclofen-Induced Side Effects

Baclofen withdrawal can induce a specific withdrawal syndrome, which consists of irritability, confusion, seizures, hallucinations, and noradrenergic peripheral symptoms. In subjects with AUD, baclofen withdrawal syndrome can easily mistaken for alcohol withdrawal syndrome. (48). Moreover, benzodiazepines could be less effective for treating baclofen withdrawal syndrome than for treating alcohol withdrawal (48), and the reintroduction of baclofen seems to be the most appropriate therapy when possible. As of now, it is unknown at what daily dosing the risk of withdrawal syndrome may occur in the treated patients, and what are the other vulnerability features for experiencing baclofen withdrawal syndrome.

Diverse non-serious gastro-enteric ADRS, such as diarrhea, gastric pain, are frequently reported by AUD patients treated with baclofen (49, 50), even if baclofen causality was never properly explored for these specific types of symptoms. By contrast, baclofen causality was demonstrated in the occurrence of ankle edema, which seem to occur in approximately 5% of the AUD patients treated with baclofen (51). The mechanism through which edema can occur is relatively

unclear, and might be related to a vasogenic effect of baclofen.

## ADVERSE DRUG REACTIONS WITH UNCLEAR BACLOFEN CAUSALITY

The sedative effects of baclofen may theoretically expose the treated patients to an increased risk of intoxication and coma. This has thus raised some logical concerns about an increased risk of death in case of baclofen intoxication. It has been previously found that beyond 150 or 200 mg of baclofen intake, the severity of intoxication may require that the treatment be carried out in intensive care units (32, 52). Moreover, anecdotal reports have suggested that baclofen could be a factor of immediate increased risk for death in case of self-poisoning (53). However, in this case report, baclofen causality was not explored and many other potential factors could actually explain the death of the patient (22). Several French toxicological reports have also raised concerns about the vital risks of using baclofen in AUD patients, especially in case of intoxication (26, 27).

In July 2017, an internal study was conducted by the French Drug Agency and the French Health Insurance using the data of the French claims database. The authors of this study found that the chronic average baclofen dose range was significantly associated with the overall risk of mortality among AUD patients (54). These findings have thus questioned the safety of a chronic prescription of high doses of baclofen among AUD patients. However, this study, which has never been peer-reviewed and never published so far, has raised a lot of criticisms in France for different reasons, including the fact that the analyses were not controlled for most of the usual cofounders, starting with the concurrent level of alcohol use, which might be an obvious cause of mortality in these patients, and is frequently associated with the concomitant use of high doses of baclofen. At this stage, there is thus no definite evidence that using baclofen in AUD patients expose them to a dose-related risk of death, independently from the associated level of alcohol use.

In 2012, a pharmacovigilance report issued by the French Drug Agency pointed out a possible risk of increased suicidal behaviors among AUD subjects (55). This safety signal was never confirmed however. Here again, peer-reviewed studies have highlighted that AUD patients have many psychiatric comorbidities that can trigger suicidal ideations and behaviors, which can thus skew the unadjusted findings that baclofen treatment is associated with an increased risk of suicidal behaviors.

## DISCUSSION

Among the different ADRs induced by baclofen in AUD patients, the most frequent types surely pertain to sedation and the associated symptoms, e.g., drowsiness, dizziness, or confusion. These ADRs are certainly those which raise the most public health concerns in baclofen use among AUD patients, including in the labeling decision. It seems now relatively demonstrated that baclofen immediate dosing is correlated with the risk of occurrence of sedation, as well as with the severity of sedation. However, the main risk factors for severe sedation are clearly the concomitant heavy use of alcohol (21). Similarly, though it has not been studied and thus demonstrated, it is very likely that the concurrent use of other sedative medications, e.g., benzodiazepines, or antipsychotics, or sedative drugs of abuse, e.g., opiates, or cannabis, may also enhance the overall level of sedation among the patients treated with baclofen. The association of baclofen with alcohol use is of course frequent in real-life AUD patients, but other associations with sedative substance or medications are also common, and no longitudinal study has assessed so far the extent to which either baclofen, or other drugs, actually contribute to the overall safety risks of patients.

This specific issue of causality is of particular importance in the case of acute intoxications. Baclofen is rarely the unique drug ingested, and the most frequent situations relate to complex drug mixes, which include potentially lethal drugs such as alcohol, benzodiazepines, or opiates. In practice, no study has ever assessed the respective causality of each molecule in the vital prognosis of the intoxicated patients. It is likely that the ingested dose of baclofen can contribute to the overall severity of acute drug intoxications, but no current evidence suggests that it is a major contributing factor, compared to other sedative drugs or sedative medications. In France, the increasing use of baclofen in AUD patients has led to an increasing number of intoxications involving baclofen (26). AUD patients are particularly exposed to suicide attempts and thus drug intoxications. At this stage, it remains unclear whether baclofen actually enhances the lethal risk related to drug intoxication.

Currently, the efficacy level of baclofen in AUD is still under debate, in particular at high doses (3). This has put the use of baclofen into question by some authors (15, 56). The same conclusion can be drawn of baclofen safety. Consequently, and despite the wide literature published on baclofen efficacy and safety in AUD patients, defining the exact benefit/risk ratio has been considered currently impossible, either by international authors (2), or by the French Alcohol Society (57). In view of these uncertainties, the French Drug Agency had issued a very supervised protocol of use of baclofen for AUD, though this measure was almost not applied on the ground (58).

It has been argued that the clinical trials that have assessed baclofen efficacy were not designed according to the common empirical use of baclofen for AUD, according to which baclofen dosing is a permanent patient-tailored equation which includes the immediate impact of craving and alcohol use on the one hand, and the overall tolerability on the other hand (13). The only study whose protocol followed this dosing scheme was "Bacloville," a French study that has been announced as positive on efficacy (17), but which is currently still unpublished more than 4 years after the end of the trial. All put together, the scientific evidence on baclofen is confused and unclear. Baclofen efficacy, in particular at high doses, lacks clear evidence. Similarly, baclofen tolerability has been questioned by some pharmacovigilance signals, but no well-designed unbiased study has ever demonstrated that

baclofen could be clearly harmful for AUD patients. In this context, a labeling is being examined by the French Drug Agency, and their decision is clearly difficult to guess at this stage.

## AUTHOR CONTRIBUTIONS

BR, NS, and NF conducted the literature search and wrote the manuscript.

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# Baclofen Response in Alcohol Dependent Patients Concurrently Receiving Antidepressants: Secondary Analysis From the BacALD Study

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**Background and Aims:** There is little information with regards to the efficacy of baclofen among alcohol patients concurrently receiving antidepressants (AD). The present study aimed to conduct a secondary analysis of the moderating role of antidepressants in the BacALD trial which evaluated the efficacy of baclofen to reduce alcohol consumption in alcohol dependent patients.

**Methods:** Alcohol dependent patients ($N = 104$) were treated for 12 weeks with 30 mg/day of baclofen (21 = AD and 15 = no AD), 75 mg baclofen (19 = AD and 16 = no AD) or placebo (17 = AD and 16 = no AD). Patients were included in the trial if they were concurrently receiving anti-depressants upon enrolment but were excluded if they commenced antidepressants 2 months prior to enrolment. Patients were also excluded in the case of concurrent psychotropic medications, active major mental disorder such as bipolar disorder, psychosis, or history of suicide attempt. Predefined primary outcomes included time to lapse (any drinking), relapse (>5 drinks per day in men and >4 in women). Other outcomes included drinks per drinking day, number of heavy drinking days, and percentage days abstinent and frequency of adverse events.

**Results:** For the number of days to first lapse, there was a trend of significance for the interaction baclofen × AD (Log Rank: $\chi^2 = 2.98$, $P = 0.08$, OR: 0.41, 95%CI: 0.15–1.12). For the number of days to relapse, there was a trend of significance for the interaction of baclofen × AD (Log Rank: $\chi^2 = 3.72$, $P = 0.05$, OR: 3.40, 95%CI: 1.01–11.46). Placing significant baseline variables into the models as covariates (tobacco, ALD) weakened these interactions ($P$'s $> 0.15$). There were no significant effects of ADs on the frequency of adverse events reported ($P$'s $> 0.19$).

**Conclusion:** Concurrent receipt of ADs commenced more than 2 months prior to baclofen treatment did not negatively impact on drinking outcomes. Future research examining the interaction between commencing ADs during baclofen treatment on alcohol dependent patients is required.

**Trial Registration:** ClinicalTrials.gov, NCT01711125, https://clinicaltrials.gov/ct2/show/NCT01711125

**Keywords: baclofen, alcohol dependence, antidepressants, depression, anxiety, comorbidity, treatment**

## INTRODUCTION

World-wide, harmful use of alcohol is responsible for 5.9% of all deaths and is a causal factor in a larger number of disease and injury conditions (1). Alcohol dependence is a common disorder characterized most often by chronic relapses to heavy alcohol consumption (2). Comorbidity of alcohol use disorders (AUDs) and mental illness such as major depression are highly prevalent in treatment settings (3, 4) and these individuals present with greater symptom complexity and poorer outcomes (3, 5).

Pharmacological treatment options for these complex patients are limited and little is known about the effectiveness of current pharmacological approaches for alcohol problems. Many of the randomized controlled trials exclude patients that are concurrently receiving antidepressants and/or with comorbid major depression despite the fact that a substantial percentage of treatment-seeking AUD patients fall into these categories. In our previous clinical trials, up to 50% of alcohol dependent patients were receiving anti-depressants prior to treatment seeking for alcohol problems (6–9).

Baclofen, a selective $GABA_B$ receptor agonist, has emerged as a potential treatment for alcohol dependence (10). There has been expanded utilization including increased use in primary care (11). Nonetheless, there has been several reports of adverse events in AUD patients with psychiatric comorbidity including mood disorders (12) and also a higher rate of self-poising in those with concomitant borderline personality disorder and AUD (13). Moreover, a recent report from the Australian Poisons Information Centre (PIC) observed that antidepressants represented 17% of co-ingestants associated with baclofen toxicity (14). Thus, although treatment with baclofen appears to be popular in the community, there remain several important clinical issues in need of exploration. Improvement in the ability to predict baclofen response particularly among those with common comorbid mood conditions or concurrent receipt of antidepressants would be of clinical importance. No clinical trials have examined the role of antidepressants during treatment of alcohol dependence with baclofen.

The current study thus aimed to retrospectively examine the moderating role of concurrent antidepressant use on baclofen treatment response. We conducted a secondary analysis of the Baclofen in the treatment of Alcohol Liver Disease (BacALD) randomized controlled trial (15) which demonstrated a beneficial effect of baclofen on treatment outcomes (6).

## METHODS

### Design

The main study rationale, design, and methods have been previously detailed (15) and the primary outcomes reported (6). In brief, after baseline assessment, eligible alcohol-dependent individuals were randomized to placebo, baclofen 30 mg (10 t.i.d.) and baclofen 75 mg (25 t.i.d.) for 12 weeks. Of the 104 individuals randomized in the main trial, 57 individuals were receiving concurrent antidepressants (AD) prior to randomization (**Figure 1**). The list of antidepressants prescribed is depicted in **Table 1**. No individuals commenced AD while on the trial. The study was approved by the Human Ethics Review Committee of the Sydney Local Health District, Northern Sydney Local Health District and South Western Sydney Local Health District (X11-0154 & X07-0041 & X01-0262) and the main trial was registered in the Clinical Trials Registry (NCT01711125). The study involved off-label use of a registered medication in Australia and approval was given under the Clinical Trial Notification (CTN) scheme of the Therapeutics Goods Administration (TGA) (2013/0060).

### Participants and Procedure

Participants were Australian Caucasian men and women who had attended an inpatient detoxification program, outpatient treatment or follow-up or who had responded to advertising. All participants signed informed consents.

Inclusion criteria: (i) Alcohol dependence according to the ICD-10 criteria; (ii) Age 18–75; (iii) Adequate cognition and English language skills to give valid consent and complete research interviews; (iv) Willingness to give written informed consent; (v) Abstinence from alcohol for between 3 and 21 days; (vi) Resolution of any clinically evident alcohol withdrawal (CIWA-AR); (vii) Not $<$48 h after ceasing any diazepam required for withdrawal management. For stratification, alcoholic liver disease (ALD) was defined as the presence of symptoms and/or signs referable to liver disease or its complications with or without cirrhosis. Alcohol use was considered to play a major etiological role and exceeded an average of 60 g/day in women and 80 g/day in men for $>$10 years. If other co-factors such as chronic hepatitis C were present, a significant contribution of alcohol to liver disease was considered present if a period of supervised abstinence (e.g., in hospital) led to a $\geq$50% improvement in liver enzymes. Exclusion criteria: (i) Active major mental disorder associated with psychosis or significant

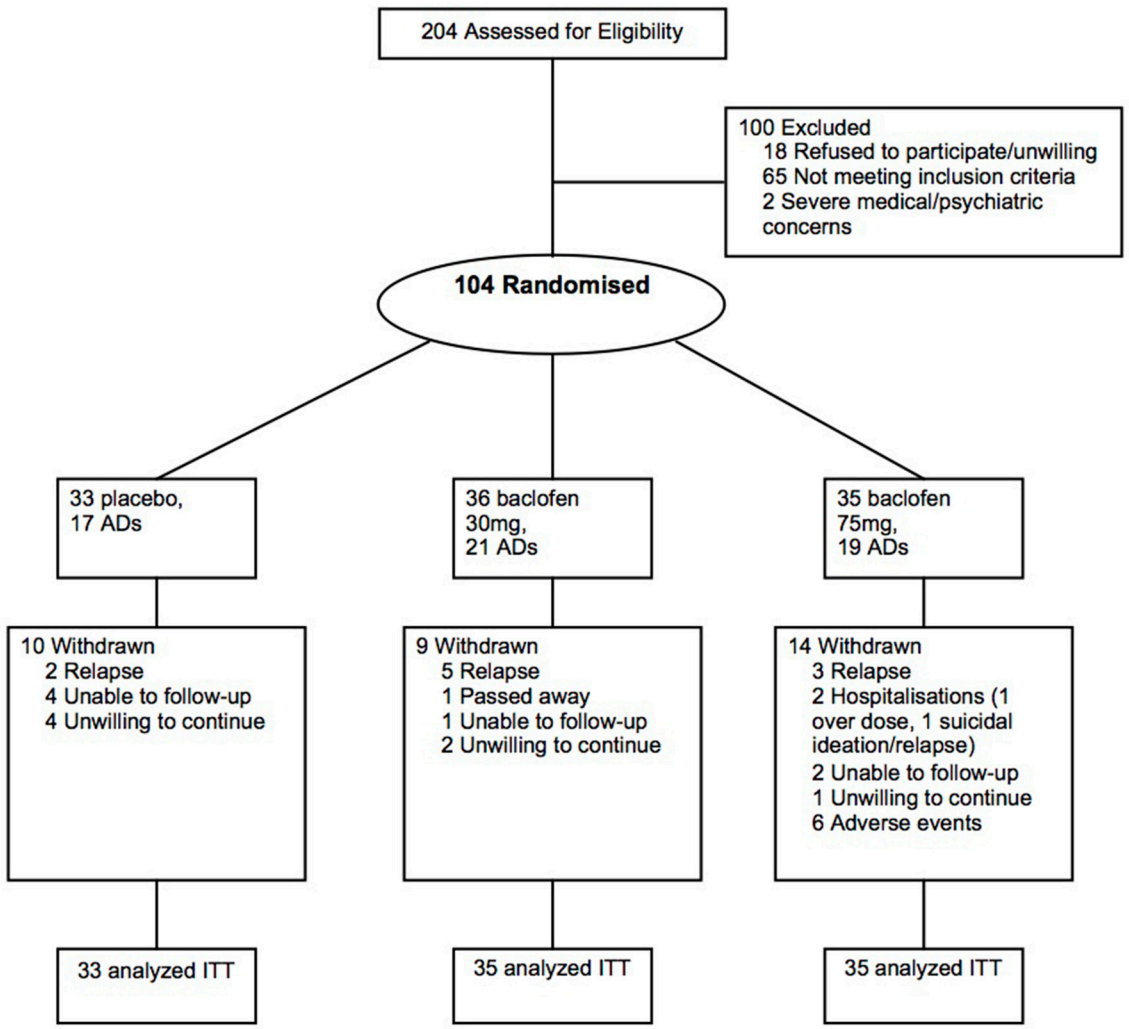


**FIGURE 1 |** Flow of participants through the randomized controlled 12-week trial of placebo, baclofen 30, and baclofen 75 in the treatment of alcohol dependence, including receipt of concurrent antidepressants (AD) at least two months prior to trial commencement.

suicide risk, (ii) Pregnancy or lactation, (iii) Concurrent use of any psychotropic medication other than antidepressants (provided these are taken at stable doses for at least 2 months); (iv) Unstable substance use; (v) Clinical evidence of persisting hepatic encephalopathy (drowsiness, sleep inversion or asterixis); (vi) Pending incarceration; (vii) Lack of stable housing, (viii) Peptic ulcer; (ix) Unstable diabetes mellitus.

## Assessments

A detailed list of assessments has been outlined previously (15). Briefly, the outcomes for this study were derived from drinking measures in the Time Line Follow Back [TLFB] (16) obtained from structured interviews at baseline and during the 12-week trial period (weeks 1, 3, 6, 9, 12). Depression as measured by the Depression Anxiety Stress Scale (DASS (17). In addition, trained interviewers conducted a structured psychiatric diagnostic interview using the Mini International Neuropsychiatric Interview (M.I.N.I.) (18). Compliance was assessed by self-report, pill count of the returned medication package, the daily monitoring diary and urinary analysis of baclofen levels in a randomly selected 50% of participants. Researchers, clinicians, and participants were blinded from treatment allocation.

## Interventions

Participants were allocated 1:1:1 as per a computer-generated randomization sequence provided to the hospital clinical trials pharmacist. Participants in the baclofen 30 mg/day or 75 mg group took a capsule of 10 or 25 mg, respectively, 1 × day for the first 2 days, 2 × day on days 3–4, 3 × day on days 5–80, 2 × day on days 81–82 and finally 1 × day for the last 2 days. The placebo pills, which were identical in appearance, were also titrated upward and downward to maintain the double blind. All participants received medical care typically available at hospital based drug and alcohol treatment services in Sydney, Australia. All participants received 1 medical assessment and 5

**TABLE 1 |** List of antidepressants participants were receiving at least two months prior to trial commencement.

| Compound | Antidepressant class |
|---|---|
| Allegron (nortriptyline) | TCA |
| Arapax (paroxetine) | SSRI |
| Brintellix (vortioxetine) | SSRI |
| Cipramil (citalopram) | SSRI |
| Effexor (venlafaxine) | SNRI |
| Elavil (amitrptyline) | TCA |
| Lexapro (escitalopram) | SSRI |
| Pristiq (desvenlafaxine) | SNRI |
| Prozac (fluoxetine) | SSRI |
| Remeron (mirtazapine) | TCA |
| Zoloft (sertraline) | SSRI |

*TCA, Tricyclic antidepressant; SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin and norepinephrine reuptake inhibitor.*

follow-up medical reviews over the 12 week treatment period, held at weeks 1, 3, 6, 9, 12. Participants were medically monitored for adverse events and prescribed the study medication at each appointment. Participants who experienced moderate side effects had their dose reduced according to physician judgment. All participants received brief compliance therapy, a 4–6 session intervention lasting 20–60 min focused on enhancing medication compliance (such as targeting ambivalence and misperceptions about medication). Participants were encouraged to defer concurrent psychotherapy until at least week 6 of the trial.

## Outcomes Measures

As per the main study published results, the primary outcomes include time to first lapse (1 drink); time to relapse (>4 drinks for women, >5 drinks for men); average drinks per drinking day (at wk 12 follow-up) and number of heavy drinking days (at wk 12 follow-up); percentage days abstinent (over the wk 12 trial).

## Statistical Analysis

Analyses were performed on an intention-to-treat basis including all participants who took at least one dose of medication. As previously outlined and published in the main trial results (6, 15), the analyses of primary outcomes included placebo vs. baclofen (composite of the two doses). Analysis of variance (ANOVA) for continuous characteristics and $\chi^2$-tests for categorical variables were conducted to determine differences between groups at baseline. Cox regression, which allows for the analysis of the effect of several risk factors on survival, was conducted to examine the effect of baclofen (PL vs. BAC) × AD on length of time to relapse and length of time to lapse (calculated from day 1 to day 84 on the trial). Participants were censored if they did not experience the outcome (relapse or lapse) on or before day 84 of the trial. The primary outcome alcohol consumption variables were entered together into a MANOVA using Pillai's trace for small samples. These were the percentage of days abstinent, number of heavy drinking days, average drinks per drinking day at week 12. The role of AD status and baclofen (BAC vs. PL) was investigated with "AD," "baclofen," and the interaction term "AD × baclofen" in a full factorial model. We placed covariates in the above models that were significantly different following individual ANOVA tests to control for group baseline differences. Due to collinearity between baseline depression and AD use we did not include this baseline characteristic in the model. Frequency of common adverse events associated with baclofen (sedation, skin rash, dizziness) were examined between the non-AD group vs. the AD group among those participants randomized to baclofen using $\chi^2$-tests.

All analyses were 2-tailed, with significance level at $P < 0.05$. Data were analyzed using SPSS 23 for Mac OSX.

# RESULTS

## Patient Baseline Characteristics and Study Variables

Socio demographic and drinking characteristics of this study sample are depicted in **Table 2** per treatment group and by AD. ANOVA revealed that baseline demographic and drinking characteristics were not significantly different across baclofen × AD groups ($P > 0.16$) except for DASS anxiety and depression scores ($F = 3.12$, $P = 0.03$; $F = 3.38$, $P = 0.02$, respectively). There were no significant differences between groups on categorical characteristics ($\chi^2 < 6.95$, $P$'s $> 0.07$) except for tobacco ($\chi^2 < 9.69$, $P < 0.02$), depression ($\chi^2 < 10.55$, $P = 0.01$) and ALD ($\chi^2 < 9.69$, $P = 0.05$). There were no significant differences in the frequency of dose (25 vs. 75 mg) between AD groups suggesting that the dose of baclofen was distributed evenly among AD groups. There were no significant AD × treatment group differences in study completion rates ($P$'s $> 0.72$).

## Main Drinking Outcomes

At week 12, drinking data for relapse and lapse was available for 89% of subjects. **Table 3** depicts the main outcome measures. Cox regression survival analyses revealed that, for the number of days to first lapse, there was a main effect of baclofen (Log Rank: $\chi^2 = 7.47$, $P < 0.05$, OR: 2.55, 95%CI: 1.30–4.50) but not for AD (Log Rank: $\chi^2 = 0.12$, $P = 0.73$, OR: 1.10, 95%CI: 0.62–1.97) and a trend for significance occurred for the baclofen × AD interaction (Log Rank: $\chi^2 = 2.98$, $P = 0.08$, OR: 0.41, 95%CI: 0.15–1.12). Similarly, for the number of days to relapse, there was a main effect of baclofen (Log Rank: $\chi^2 = 7.76$, $P < 0.01$, OR: 2.59, 95%CI: 1.33–5.06) but not for AD (Log Rank: $\chi^2 = 0.35$, $P = 0.55$, OR: 2.00, 95%CI: 0.66–2.17) and a trend for significance occurred for the baclofen × AD interaction (Log Rank: $\chi^2 = 3.72$, $P = 0.05$, OR: 3.40, 95%CI: 1.01–11.46). MANOVA revealed a significant overall treatment effect attributed to alcohol consumption [Wilks multivariate test of significance; $F_{(3, 62)} = 3.14$, $P < 0.05$] but not for AD [Wilks multivariate test of significance; $F_{(3, 62)} = 2.10$, $P = 0.11$] and a trend for significance occurred for the baclofen × AD interaction [Wilks multivariate test of significance; $F_{(3, 62)} = 2.51$, $P = 0.07$]. Placing significant baseline variables into the models (tobacco, ALD) reduced both the Cox regression and MANOVA AD × baclofen interaction trends ($P$'s $> 0.15$).

**TABLE 2 |** Intention to treat: Baseline characteristics of patients according to concurrent antidepressant use.

| Characteristic | Placebo | | Baclofen 30–75 mg | |
|---|---|---|---|---|
| | AD (*n* = 17) | Non-AD (*n* =16) | AD (*n* = 40) | Non-AD (*n* =31) |
| Age, y | 47.12 ± 10.59 | 49.00 ± 9.27 | 48.85 ± 8.99 | 48.00 ± 11.51 |
| Gender, % F | 41 | 21 | 32 | 21 |
| Education, y | 14.63 ± 2.55 | 14.25 ± 3.24 | 12.66 ± 3.68 | 13.10 ± 2.86 |
| Unemployed, % | 23 | 50 | 60 | 42 |
| Drinks per drinking day[a] | 13.81 ± 6.89 | 14.37 ± 7.23 | 17.82 ± 12.72 | 14.74 ± 7.31 |
| Abstinence days before enrolment | 2.29 ± 2.23 | 4.71 ± 7.23 | 6.27 ± 7.49 | 3.96 ± 5.52 |
| Years since alcohol-related problems began | 13.75 ± 10.48 | 20.92 ± 12.01 | 19.18 ± 10.86 | 16.39 ± 12.25 |
| Cigarette smokers, %* | 64 | 64 | 84 | 50 |
| Lifetime Major Depression, %+* | 66 | 57 | 81 | 42 |
| Lifetime Anxiety Disorder, %+ | 88 | 70 | 64 | 57 |
| ALD, %* | 29 | 79 | 58 | 57 |
| ADS | 17.94 ± 9.18 | 17.57 ± 9.41 | 21.63 ± 10.89 | 17.56 ± 7.96 |
| PACS craving | 18.31 ± 6.54 | 17.36 ± 6.54 | 17.10 ± 7.95 | 14.74 ± 7.31 |
| DASS Depression* | 20.00 ± 13.83 | 20.29 ± 10.64 | 18.10 ± 12.15 | 11.48 ± 7.56 |

*Data represent mean + SD of raw data unless otherwise noted. There were no significant differences between the groups for continuous variables (P = 0.16) except for DASS Depression (P's < 0.05). There were no differences between groups on categorical variables except for tobacco, ALD and past depression (P's < 0.05). *P < 0.05.*

[a]*During the 30 days preceding the first day of the study, based on the Time-Line Follow-Back method.*

*AD, antidepressant; ADS, Alcohol Dependence Severity Scale; PACS, Penn Alcohol Craving Scale; DASS, Depression Anxiety Stress Scale; + as measured by the MINI Neuropsychiatric Diagnostic Interview.*

**TABLE 3 |** Intention to treat: drinking outcome measures at week 12 of participants treated with either baclofen (30–75 mg) or placebo according to concurrent antidepressant use.

| Outcome | Placebo | | Baclofen | |
|---|---|---|---|---|
| | AD (*n* = 17) | Non-AD (*n* = 16) | AD (*n* = 40) | Non-AD (*n* = 31) |
| **Alcohol consumption measures** | | | | |
| Time to first lapse (days)± SEM | 2.07 ± 0.55 | 23.08 ± 9.43 | 29.50 ± 6.13 | 25.08 ± 6.51 |
| Time to first relapse (days) ± SEM | 5.00 ± 2.32 | 30.23 ± 10.18 | 35.59 ± 6.37 | 30.35 ± 6.93 |
| Percentage days abstinent | 28.37 ± 28.29 | 68.10 ± 36.14 | 68.00 ± 35.26 | 66.34 ± 28.46 |
| Average drinks per drinking day[+] | 7.29 ± 4.49 | 7.37 ± 9.38 | 5.46 ± 5.63 | 5.78 ± 6.91 |
| Number of heavy drinking days[#++] | 2.83 ± 2.52 | 1.00 ± 2.21 | 1.83 ± 2.63 | 2.18 ± 2.74 |

*Data represent raw means ± SD unless otherwise noted. Drinks is equal to standard drink (10 g ethanol). [#]Defined as >4 drinks for women and >5 drinks for men, +at week 12 follow-up, [++] per week at week 12 follow-up. AD, antidepressant; SEM, standard error of the mean. There were trends for AD × baclofen interaction effects (P's < 0.08) for time to first lapse (P = 0.08), relapse (P = 0.05) and the combined alcohol consumption variables (P = 0.07: borne out in percentage days abstinent, P = 0.02) although these diminished when controlling for pre-existing baseline differences (ALD, tobacco) (P's > 0.15).*

## Adverse Events

We explored the role of the AD on response to baclofen by comparing the frequency of adverse events between AD among those participants randomized to baclofen (see **Table 4**). There were no differences between groups for any adverse event (*P*'s > 0.19).

# DISCUSSION

The main aim of the current study was to examine the role of concurrent antidepressant use in baclofen treatment response in a randomized, placebo-controlled double blind study. We demonstrated a significant baclofen vs. placebo effect as per previously described (6). We also demonstrated that ADs did not have a significant moderating effect on treatment outcomes at follow-up. We demonstrated a trend for a significant interaction effect of AD (AD vs. non-AD) × baclofen (BAC vs. PL) on days to relapse, days to lapse and alcohol consumption outcomes. Further analysis revealed that this effect is observed in the AD group whereby allocation to placebo resulted in poor outcomes such as shorter time to relapse and lapse. Nonetheless, these trends were diminished when controlling for significantly different baseline characteristics. It is likely that any potential interaction effect is not due to the action of baclofen and ADs

**TABLE 4 |** Side effect profile of subjects treated with either baclofen (30–75 mg) or placebo and concurrent antidepressant use.

| Clinical event | Baclofen 30–75 mg | |
|---|---|---|
| | AD ($n = 40$) *n* (%) | Non-AD ($n = 31$) *n* (%) |
| Sedation or drowsiness | 13 (32.50) | 10 (32.26) |
| Dizziness | 4 (10.00) | 4 (12.90) |
| Skin rash/itching | 5 (12.50) | 1 (3.23) |
| Constipation | 3 (7.50) | 3 (9.68) |
| Shortness of breath | 2 (5.00) | 2 (6.45) |
| Dry mouth | 2 (5.00) | 1 (3.23) |
| Urination problems | 1 (2.50) | 0 (0.00) |
| Serious adverse events* | 4 (10.00) | 0 (0.00) |

*$P < 0.05$, significant difference between AD and non-AD groups randomized to baclofen. AD, antidepressant. In the 75 mg group, 9% (3) of patients reduced the dose due to intolerability (1 patient = 25 mg/day and 2 patients = 50 mg/day). Serious adverse events included one death (not baclofen related), one overdose and two hospitalizations due to intoxication and suicidal ideation.

*per se* but pre-existing comorbidity in those participants already receiving ADs which lead to shorter relapse in the absence of active treatment.

One retrospective analysis of a clinical trial exploring the relationship between antidepressant use and the alcohol pharmacotherapy naltrexone observed that, for those receiving antidepressants, there was a naltrexone vs. placebo effect on drinking outcomes but this effect was absent for those not receiving antidepressants (19). These results are similar to the trends found in our current results with baclofen (without controlling for pre-exisiting factors) whereby for those receiving anti-depressants, the placebo group displayed shorter times to lapse and relapse that were not seen in those randomized to baclofen. One interpretation is that in these studies patients receiving antidepressants, and presumably with comorbid depression, respond poorly in the absence of active treatment.

We also observed that there were no significant differences on frequency of specific commonly reported adverse events across the AD × baclofen groups. These results should be interpreted with caution given the small sample size, limitations with measuring frequency rather than severity and that the adverse events examined were only those commonly reported across the entire sample. Neuropsychiatric adverse drug reactions such as mania were not systematically examined in this analysis. It is imperative to note that this data was derived from a structured monitored clinical trial with low doses of baclofen whereby patients with an active major mental disorder including bipolar, psychosis or unstable mood, history of suicide attempt or recent commencement of ADs were excluded from the trial. Indeed, there have been case reports of baclofen-induced manic symptoms in the literature yet these have generally occurred at higher doses of baclofen during the dose-increase phase (e.g., up to 180 mg/d) but mainly in patients with a history of bipolar disorder (20).

There are several limitations of the current study. Given the trend for significance of interaction effects it is possible that we had limited power to detect a significant effect. In addition, the study is a retrospective analysis and was not designed to examine ADs and baclofen such that baseline characteristics were not balanced. However, we did control for these in our analyses which suggested that the trends for interaction effects were due to pre-existing factors. Longitudinal modeling of symptoms of depression comparing AD and non-AD groups during baclofen treatment would further elucidate this relationship. Further, it would be important to determine any interaction effect of the two medications including mood and side effects in participants that commence ADs in conjunction or within a similar time frame to baclofen. Indeed, participants receiving ADs in the current study were required to be stable and to have commenced more than 2 months prior to baclofen. Participants in the current study were provided a thorough assessment of mood stability before enrolment and monitored for safety throughout as part of the clinical trial schedule. It is possible that this level of monitoring may not be provided in the wider community which may limit the generalizability of these results. Finally, while we have some diagnostic information regarding mood and anxiety disorders in this sample, we do not have direct evidence regarding the clinical indication for why the antidepressants were initially prescribed.

## CONCLUSION

This is the first study to investigate the moderating role of antidepressant use on response to baclofen. Our results suggest that the concurrent receipt of antidepressants commenced more than 2 months prior to baclofen treatment in less complex alcohol dependent patients (with no history of bipolar or suicide attempt) does not negatively impact on drinking outcomes. Trends for an interaction effect between antidepressants and baclofen that were observed for all drinking outcomes may be due to pre-existing factors in the antidepressant group which lead to poor outcomes in the absence of active treatment (i.e., placebo allocation). Well-controlled prospective clinical research examining the effect of commencing antidepressants on neuropsychiatric adverse events during baclofen treatment is required.

## AUTHOR CONTRIBUTIONS

KM supervised the study, analysis of data, and writing of the manuscript. SH wrote the manuscript and completed data presentation and analysis. NJ assisted in writing of the manuscript and interpretation. AB assisted supervision of the study, interpretation and writing of the manuscript. EL completed the psychological assessments and assisted writing the manuscript. NP and GD were site physicians. PH supervised the overall conduct of the study and was the lead physician.

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# How to Manage Self-Poisoning With Baclofen in Alcohol Use Disorder? Current Updates

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Specialists in addiction medicine continue to debate whether baclofen is still indicated to treat alcohol use disorders in view of conflicting results as to its efficacy. This review summarizes current knowledge on self-poisoning with baclofen focusing of alcohol-use disorder in order to provide an overview of the reliable scientific knowledge on management of such an intoxication. Moreover, as alcohol-dependent patients experience many psychiatric co-morbidities, the risk in suicide attempt using baclofen seems real. Numerous studies have suggested that patients given daily-doses of baclofen higher than 80 mg/day are more likely to attempt suicides than others. Following an ingestion of a large amount of baclofen, central nervous system depression is usually observed. Seizures require the patient to be admitted in intensive care unit and should be treated like other toxicological seizures. Cardiac complications include prolonged QTc interval, degree heart block, premature atrial contractions, and supraventricular tachycardia, hypotension and bradycardia. In cases of intoxication, the elimination half-life of baclofen may last between 12 and 36 h post-overdose and renal failure is known to delay its clearance. Rarely measured in clinical practice, the toxic level of baclofen blood level ranges from 1.1 to 3.5 mg/l, and coma or fatal intoxication are observed from 6 to 9.6 mg/l. Baclofen withdrawal has been observed but making the diagnosis of withdrawal in case of suspected self-poisoning is difficult as baclofen intoxication and baclofen withdrawal share many clinical signs. Admission to hospital to manage of suicide attempt with baclofen is mandatory and should not be limited to baclofen alone. It needs to include other aspects of the overall care of patients with alcohol disorders (psychological and psychosocial interventions, management of comorbid mental conditions and physical complications).

**Keywords: baclofen, intoxication/pharmacology, comorbid conditions, seizures, psychiatry**

## INTRODUCTION

Baclofen has been commonly used to treat spasticity in neurological diseases because of its muscle relaxant effects. As it acts on gamma-aminobutyric acid (GABA)-B receptors in the spinal cord, it is used to treat muscle spasm associated with spinal cord diseases and injury. Since 2002, many medical teams have studied the use of baclofen in the management of alcohol-dependent patients. Conflicting results were observed in double-blind randomized clinical trials (RCTs) conducted to assess the efficacy of baclofen at both low doses, i.e., between 30 and 50 mg/d (1–3) and at higher doses, up to 400 mg/d (4). Nonetheless, recent RCTs failed to show that baclofen is superior in terms of long-term follow-up with such high doses (5–7). Baclofen was found to be safe and well-tolerated in alcohol-dependent patients including those suffering from liver cirrhosis (2). Nonetheless, guidelines or evidence are still lacking about how to prescribe baclofen in this indication. Meanwhile, baclofen is increasingly prescribed at both low and high doses, especially in European countries. The increasing number of prescriptions has been followed by an increasing number of cases of self-poisoning with baclofen. In France, since 2008, the use of high-dose baclofen (HDB), that is, up to 300 mg/day and sometimes more, has rapidly spread among general practitioners and alcohol addiction specialists. This has led to discussions between specialists, particularly with regard to increased risk of suicide attempts.

The increasingly widespread use of baclofen leads to greater likelihood of intentional and unintentional exposures. Evidence in the literature suggests that the effects of baclofen overdose are usually severe and require admission to intensive care. Seizures, cardiac arrest and fatal outcomes have been reported. In view of this conflicting information, we performed a systematic review of the literature on baclofen overdose, focusing on patients with alcohol use disorder (AUD). We aimed to present an overview of the manifestations of acute baclofen overdose, to determine whether serum concentrations are predictive of poisoning severity, and to describe the effectiveness of the therapeutic interventions used to manage an overdose.

## BACKGROUND: BRIEF OVERVIEW OF THE SENSITIVE CONTEXT OF BACLOFEN PRESCRIPTION

Specialists in addiction medicine continue to debate whether baclofen is still indicated to treat AUD in view of conflicting results as to its efficacy. In many countries, baclofen is prescribed off-label. In France, baclofen may be prescribed under temporary recommendation for use (TRU). In July 2017, the French National Agency for the Safety of Medicines and Health Products (ANSM) revised the TRU asking physicians not to give baclofen to alcohol-dependent patients at a daily dose higher than 80 mg/d. The optimal daily dose of baclofen for AUD has not yet been approved, but it may be prescribed to alcohol-dependent patients whose goal is not to reach abstinence but to reduce consumption and when approved drugs have failed (8).

In the literature, the daily dose given to patients varied depending on the objectives of the study. Some authors prescribed low to moderate doses, while others used high doses. As chronic baclofen consumption is considered to induce tolerance, it is important to bear this in mind.

## OVERVIEW OF SELF-POISONING WITH BACLOFEN REPORTED BY NUMEROUS ANTIPOISON CENTERS

Intoxication with baclofen has been described for decades. Since the growing interest in its use to treat AUD, numerous studies have focused on self-poisoning in alcohol-dependent patients (9–14). In 2006, Leung et al. (9) showed that self-poisoning with baclofen was responsible for severe symptoms when the supposed ingested dose (SID) was higher than 200 mg. However, the authors gave no details on comorbid AUD or current treatment with baclofen at the time of intoxication.

Studies performed by poison centers showed that the SID at the time of self-poisoning was 400 mg (15) and 480.7 mg (10), higher than the dose believed to cause severe intoxication.

A recent study performed by the French National Safety Agency for Medicines and Health Products (Agence Nationale de Sécurité des Médicaments et des produits de santé, ANSM) assumed that among all causes of death in baclofen-treated patients ($n = 385$), 97 were believed to be the result of a suicide attempt. The number of suicides with baclofen differed according to the daily dose taken: 9 suicides occurred in patients receiving a dose lower than 30 mg/day, 10 in patients receiving 30 to 75 mg/day, 6 in patients receiving 75 to 180 mg/day, and 2 in patients receiving doses higher than 180 mg/day. Such an observation in this study is of paramount importance, as it might be thought that patients given high doses of baclofen were more likely to attempt suicide than those given lower doses under 80 mg/day. Baclofen at a high dose is believed to reduce anxiety (16) and increase sedation (17), which may induce disinhibition at the time of peak drug effect, triggering suicide attempt in alcohol-dependent patients over-represented among suicide victims. Conversely, suicide attempt because of behavioral disinhibition related to hypomanic episodes induced by baclofen given at high dose (18) have been described (19, 20). Nonetheless, constructive conclusions cannot be reached without taking a holistic view of the patient (21).

## CLINICAL PRESENTATION

Clinical features described in self-poisoning with baclofen are summarized in **Table 1**. Following acute ingestion of a large amount of baclofen, central nervous system depression ranging from drowsiness to coma is usually observed. The threshold leading to CNS depression has been arbitrarily defined by Leung et al. (9) as a dose higher than 200 mg. However, the mg/kg dose or the patient's weight were not given.

Seizures are usually reported in baclofen overdose, requiring the patient's admission to an intensive care unit (6, 7, 12, 14–16). The pathophysiological mechanisms of these seizures are

**TABLE 1 |** Clinical features described in self-poisoning with baclofen.

| | Clinical features | References |
|---|---|---|
| Central nervous system findings | Decreased level of consciousness (drowsiness to coma) | (9, 26) |
| | Seizures | (10, 12, 14, 15) |
| | Burst suppression | (23, 24) |
| Laboratory findings | Acidosis | (24) |
| | Rhabdomyolysis | (25) |
| Cardiovascular findings | Prolonged QTc interval | (25) |
| | First-degree heart block | (26) |
| | Premature atrial contractions | (13) |
| | Supraventricular tachycardia | (12, 27) |
| | Bradycardia | (13, 14) |
| Pulmonary findings | Respiratory depression | (14, 27) |
| | Aspiration pneumonia | (10, 15) |

still poorly understood. Baclofen is known to be a proconvulsant drug, mediated by complex GABA-B regulation of both the GABAergic and glutamatergic systems. Experimental data suggest that activation of GABA-B receptors could accentuate neural excitation contrast in some parts of the brain (22).

As baclofen is usually co-ingested with alcohol and other medications, the seizure threshold is decreased and the patient should be closely monitored. Baclofen-induced seizures should be treated like other toxicological seizures. Benzodiazepines are the first-line treatment but should be associated with propofol and barbiturates if needed. Seizure activity is evidenced by continuous electroencephalogram monitoring.

Baclofen overdose is also responsible for encephalopathy, with a clinical presentation typical for brain-death (23). Marked electroencephalographic abnormalities combine slowing down of the background activity with paroxysmal activity. In severe overdose, burst-suppression has been observed (24), and electroencephalogram should be continuously recorded until the abnormal features disappear.

Metabolic acidosis although not a common finding, has also been reported. It should be seen as complications of decreased consciousness or coma, co-ingested drugs or rhabdomyolysis.

The cardiac complications include prolonged QTc interval (25), first-degree heart block (26), premature atrial contractions (13) and supraventricular tachycardia (12, 27), which are related to autonomic nervous system disturbances. In view of the similarities of baclofen to GABA, it may decrease the sympathetic outflow leading to hypotension and bradycardia. Autonomic nervous system disturbances may also result in respiratory depression, although in baclofen overdose a central respiratory effect cannot be ruled out.

## THE PHARMACOKINETICS OF INTOXICATION

Many studies have focused on changes in the half-life of baclofen, as this may influence the management of intoxication. At a therapeutic dose, its half-life is about 2–6 h with a reported average of 3.5 h. However, in alcohol-dependent patients in particular, wide individual variations have been observed, showing linear pharmacokinetics with a proportional relationship only with doses between 30 and 240 mg per day (28).

In cases of intoxication, the elimination half-life of baclofen may be as long as 12 to 36 h post-overdose (29). Patients need to be closely monitored because of prolonged sedation and coma and the increased risk of seizures.

## RENAL REPLACEMENT THERAPY, INTOXICATION WITH BACLOFEN AND RENAL FUNCTION

Renal failure is known to delay clearance of baclofen and an accumulation phenomenon can occur (30), exposing patients to complications. In patients with impaired renal function, the drug is almost completely eliminated from the body by renal filtration and tubular secretion, whereas only a minor pathway involves liver metabolism (31). The value of hemodialysis after overdose is still under debate. When the patient is severely intoxicated, some authors recommend a renal replacement therapy, in particular continuous veno-venous hemofiltration to increase baclofen elimination, even if renal function is normal (32). They argue that renal replacement therapy is indicated as baclofen is moderately lipophilic and is moderately bound to protein, with a limited volume of distribution ($\sim$1 L/kg). Conversely, other authors have underlined the fact that in patients whose renal function is normal, extracorporeal treatments including hemodialysis and hemofiltration do not enhance the elimination of baclofen (33). Other authors reported a case of a 29-year-old woman who took 3500 mg of baclofen (31). Hemodialysis sessions were guided according to baclofen plasma concentrations. A delayed rebound in baclofen plasma concentration was associated with recurrence of toxicity after each hemodialysis session. The authors stated that the cause was either sustained retention of baclofen in tissue or red cells or was due to continuing absorption from a pharmacobezoar. Although pharmacobezoar is a rare event, Cleophax et al. observed the resolution of intoxication after the late introduction of charcoal and poly-ethylene-glycol, following the repeated failure of hemodialysis. They concluded that baclofen elimination was not enhanced by hemodialysis in this patient with normal renal function and that gastro-intestinal decontamination should be performed if delay rebound in plasma baclofen concentration is observed (31).

## PLASMA BACLOFEN CONCENTRATION

Blood baclofen levels are rarely measured in clinical practice, unless intoxication is considered as severe (10, 15, 25, 31) or if the patient has renal impairment. The toxic level ranges from 1.1 to 3.5 mg/l and coma or fatal intoxication are observed from 6 to 9.6 mg/l (34). Conversely, the therapeutic level is $<$0.6 mg/l. Nonetheless, whatever the plasma concentration, baclofen

penetrates the blood-brain barrier. Although its concentration in the brain is lower than in serum, it is eliminated more slowly from the central nervous system than from serum. This observation is of paramount importance as CNS depression may persist even after plasma baclofen levels return to normal (29).

## BACLOFEN WITHDRAWAL

Baclofen withdrawal has been observed after abrupt discontinuation of the drug (35). When a patient with suspected self-poisoning with baclofen is admitted to an emergency department, withdrawal is difficult to diagnose as baclofen intoxication and withdrawal share many clinical signs: worsening spasticity, muscle spasms, status epilepticus, hallucinations, pruritus, hyperthermia, rhabdomyolysis and multisystem organ failure, in some cases leading to death.

## DISCUSSION

The most frequent cause of severe intoxication with baclofen is self-poisoning. Accidental exposures have been described, with less severe clinical features (10). Acute recreational intoxication with baclofen has occurred leading to coma (26). Focusing on AUD, because alcohol-dependent patients experience psychiatric comorbidity there is a real risk of self-poisoning. In many patients, early symptoms were followed by delayed worsening of their condition which required rapid admission to an emergency department or intensive care unit. When baclofen self-poisoning occurs at home, because of its potential severity transportation by emergency medical services, with close monitoring of clinical status and vital signs, should be considered. The rapidity of the deterioration may be difficult to assess, especially in the pre-hospital setting, firstly because the onset of symptoms may be abrupt depending on the co-intoxicants (10), and secondly because the interval between the poisoning and the emergency call is usually not known, particularly if the patient is unconscious.

Because suicidal ideation and suicide attempts are more prevalent in people with substance use disorders than in the general population, admission to hospital is mandatory particularly after a suicide attempt. The patient must be seen by a psychiatrist after being detoxified (36).

The risk of coma should be stressed. CNS depression is a well-recognized symptom associated with baclofen intoxication and is increased by concomitant ethanol consumption. It should be kept in mind that baclofen may be taken at the same time as alcohol by patients for whom total abstinence is not the goal (8, 37). Sedation, dizziness and confusion are by far the most frequent symptoms related to self-poisoning with baclofen. Baclofen-induced seizures should be treated like other toxicological seizures. Benzodiazepines are the first-line treatment, and propofol and barbiturates should be used for refractory seizures. Monitoring the blood level of baclofen at the same time as continuous electroencephalogram monitoring may be indicated. Nonetheless, the blood level of baclofen does not correlate with coma duration as the drug penetrates the blood-brain barrier and is eliminated more slowly from the central nervous system (CNS) than from serum. This leads to prolonged CNS depression even after plasma baclofen levels return to normal (29). The efficacy of gastric decontamination in baclofen overdose patients has not been proven. In one case of massive intoxication with baclofen (SID 3500 mg), the attending physician administered polyethylene glycol and activated charcoal on day 9 after the self-poisoning, which resulted in decreased plasma baclofen concentration (31).

Patients who experience bradycardia after baclofen overdose should be given an atropine bolus to reverse central vagal stimulation induced by baclofen (13).

Patients should be monitored for significant morbidity (e.g., aspiration). In patients with severe intoxication and/or elevated creatinine kinase level as a complication of coma or hypotension, renal function should be monitored by serum measurement of urea nitrogen and creatinine. Intravenous hydration may be required to prevent renal failure. Serial monitoring of serum creatinine kinase activity may help in gauging the efficacy of treatment interventions and help the physician start renal replacement therapy.

No antidote exists. Empirical administration of flumazenil to reverse coma is not advisable. Because polydrug intoxication including alcohol with baclofen is commonplace, flumazenil may trigger seizure although this complication is rare.

From the literature, it appears that 200 mg is the ingested dose at which moderate to severe symptoms can be expected to occur (9). However, the authors give no details on any current treatment with baclofen, which limits the interpretation of these results. Moreover, the absorption of higher doses, particularly in suicide attempts, has since been described by poison centers.

An important point that needs further investigation, and which may explain the high doses of baclofen taken with the purpose of self-harm, is the development of tolerance during prolonged treatment. This underlines the need to assess the daily dose taken by the patient (21, 38) at the time of the suicide attempt. Tolerance may lead to variability in the clinical features of intoxication and even decrease its severity. Although development of tolerance to baclofen attenuates baclofen-induced encephalopathy in rats (24), further investigations are warranted. Tolerance to baclofen may affect patient management by differentiating between acutely intoxicated patients with no previous treatment by baclofen and baclofen-treated patients ("acute-on-chronic poisoning").

Patients with acute-on-chronic poisoning require particular attention as they are at risk of baclofen withdrawal. The treating physicians should not neglect to reintroduce baclofen, although the dose that should be given is still debated. Titrated doses should be the rule.

Management should not be limited to baclofen alone. It needs to include other aspects of the overall care of patients with alcohol disorders (psychological and psychosocial interventions,

management of comorbid mental conditions and physical complications) (38).

## AUTHOR CONTRIBUTIONS

NF and FP conceived the paper and performed literature search. NF, FP, BR, and NS wrote the paper. All authors critically reviewed the manuscript and agreed on its final version.

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# Neurometabolite Levels in Alcohol Use Disorder Patients During Baclofen Treatment and Prediction of Relapse to Heavy Drinking

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**Background and Aims:** Baclofen, a $GABA_B$ agonist, is used as a treatment for alcohol dependence. We aimed to examine brain metabolites following administration of baclofen or placebo in alcohol dependent individuals enrolled in a randomized placebo-controlled trial.

**Methods:** Participants included 31 alcohol dependent individuals (recent drinking: $N = 16$; and abstinent: $N = 15$) who had received daily baclofen (BAC 30–75 mg = 20) or placebo (PL = 11) for at least 2 weeks (average 17 days). Using *in vivo* proton magnetic resonance spectroscopy ($^1$H-MRS), spectra from the right parietal lobe were analyzed to obtain measures of GABA, Glutamate (Glu), Glutathione (GSH) and N-Acetyl Apartate (NAA) 120 min following administration of PL or BAC.

**Results:** When weighting alcohol dependent participants according to recent alcohol consumption (within 24 h), there were significant differences between BAC and PL on parietal concentrations of GSH ($p < 0.01$) and NAA ($p < 0.05$). Multiple linear regression revealed a significant predictive effect of GSH on heavy drinking days at 12 weeks follow-up (Model: $F = 14.28$, $R^2 = 0.85$; GSH: $B = -1.22$, $p = 0.01$) and also percentage days abstinent at 12 weeks follow-up (Model: $F = 6.50$, $R^2 = 0.72$; GSH: $B = 0.99$, $p = 0.06$).

**Conclusion:** Our data provide preliminary evidence that the effect of baclofen may be mediated by increased parietal concentrations of the antioxidant GSH and NAA in recently drinking alcohol dependent patients. GSH/Cr levels were also predictive of improved drinking outcomes in the trial and suggests a role for neural oxidative stress in alcohol use disorder.

**Keywords: GABA, glutamate, GSH, NAA, baclofen, alcohol dependence**

## INTRODUCTION

Alcohol dependence is a common disorder characterized most often by chronic relapses to heavy alcohol consumption (1). Although alcohol use disorders are leading causes of preventable death treatment options are still limited. Heavy chronic alcohol use can result in a down-regulation of ɣ-aminobutyric (GABA) receptor activity, dysregulation of glutamatergic neurotransmission and disinhibition of the reward pathway. Baclofen, a selective $GABA_B$ receptor agonist, has emerged as a potential treatment for alcohol dependence and is thought to counterbalance these processes given that presynaptic $GABA_B$ receptors regulate neuronal excitability and neurotransmitter release in many different neuronal pathways including the mesolimbic system (2, 3).

While there has been expanded utilization of baclofen in the treatment of alcohol dependence (4), there remains controversy in the field with mixed results from clinical trials [for example see (5–11)]. We have recently demonstrated that baclofen is effective in increasing abstinence in patients with and without alcoholic liver disease (12). There is significant variation in treatment response and not all individuals with alcohol dependence respond favorably to baclofen. Alcohol dependence is a complex and heterogeneous disorder involving disruption of multiple neurobiological mechanisms whereby advances in the understanding of this heterogeneity and associated variations in response to pharmacotherapies will have clinical appeal for treatment.

Proton magnetic resonance spectroscopy ($^1$H-MRS) enables the *in vivo* detection of neurometabolites whose levels may be reflective of neurobiological dysregulation associated with chronic alcohol use disorders in humans (13). Correspondingly, $^1$H-MRS enables the investigation of the effects of pharmacological treatment such as baclofen on these abnormalities. There are some inconsistencies in the literature with regards to the levels of metabolite concentrations in patients with alcohol use disorder yet a substantial proportion of this variation can be explained by differences in recent alcohol consumption. $^1$H-MRS studies have generally demonstrated brain Glu levels in alcohol patients relative to healthy non-drinking controls to be significantly lower during intoxication (14), higher during initial withdrawal (15) and low again at least 7 days from last alcohol consumption (16). Glutathione (GSH) is a key antioxidant synthesized in cells and has been found to be reduced in the hippocampus in heavy drinkers (17). Reduced levels of N-acetylaspartate (NAA), a marker of neuronal integrity, have also been reported in frontal lobes (18) and these have been found to negatively correlate with recent heavy alcohol consumption (13). There have been a paucity of $^1$H-MRS studies examining GABA concentrations in patients with alcohol use disorder with some research reporting decreased GABA (19) while other studies have not been able to replicate these findings (16).

Many of these neurochemical aberrations reported above at least partially normalize following prolonged abstinence (between 14 and 35 days) (15, 16). This early time period of recovery is particularly challenging for many patients. $^1$H-MRS investigations of the effects of alcohol pharmacotherapies on metabolite concentrations have revealed significant amelioration of these abnormalities following treatment relative to placebo. For example, two studies have reported that acamprosate reduced glutamate concentrations in the anterior cingulate cortex (20, 21). To date, there have been no $^1$H-MRS studies examining neurometabolite concentrations following baclofen administration in alcohol patients or other clinical populations.

The present study therefore sought to investigate (i) neurometabolite levels following administration of baclofen (BAC) or placebo (PL); and (ii) the relationship between neurometabolite ratios (glutamate/Cr, GSH/Cr, NAA/Cr) and $GABA^+$, and future drinking outcomes previously defined (as heavy drinking days, percentage abstinent days and drinks per drinking days) from a randomized controlled trial of BAC vs. PL (12).

## METHODS

The study was approved by the Human Ethics Review Committee of the Sydney Local Health District (X11-0154). The study involved off-label use of a registered medication in Australia and approval was given under the Clinical Trial Notification (CTN) scheme of the Therapeutics Goods Administration (TGA) (2013/0060) as part of a clinical trial (ClinicalTrials.gov, NCT01711125, https://clinicaltrials.gov/ct2/show/NCT01711125). All participants included in this MRS substudy provided written informed consent after commencement of randomization for the main trial.

### Participants

Participants were recruited from a larger clinical trial investigating baclofen in the treatment of alcohol dependence. The main study rationale, design, and methods for the clinical trial with which these patients were recruited have been previously detailed (22) and the results reported (12). Eligibility included: (i) alcohol dependence according to the ICD-10 criteria; (ii) age 18–75; (iii) adequate cognition and English language skills to give valid consent and complete research interviews; (iv) willingness to give written informed consent; (v) abstinence from alcohol for between 3 and 21 days leading up to randomization; (vi) resolution of any clinically evident alcohol withdrawal (CIWA-AR); (vii) <48 h after ceasing any diazepam required for withdrawal management.

Exclusion criteria: (i) active major mental disorder associated with psychosis or significant suicide risk, (ii) pregnancy or lactation, (iii) concurrent use of any psychotropic medication other than antidepressants (provided these are taken at stable doses for at least 2 months); (iv) unstable substance use; (v) clinical evidence of persisting hepatic encephalopathy (drowsiness, sleep inversion or asterixis); (vi) pending incarceration; (vii) lack of stable housing, (viii) peptic ulcer; (ix) unstable diabetes mellitus.

### Procedure

For the main trial, participants received upward and downward titrations of medication for the 84 days of treatment and were

randomized 1:1:1 to baclofen took a capsule of 10 or 25 mg: 1 × day for the first 2 days, 2 × day on days 3–4, 3 × day on days 5–80, 2 × day on days 81–82 and finally 1 × day for the last 2 days. The PL pills, which were identical in appearance, were also titrated upward and downward to maintain the double blind. All subjects received one medical and research assessment and five follow-up reviews over the 12-weeks treatment period. Participants underwent $^{1}$H-MRS scanning at week 2 (on average 17 days following enrolment), approximately 120 min post-administration of either 10, 25 mg BAC or PL. Breath alcohol concentration was obtained and only participants with a reading of 0.00 were permitted to proceed with the scan. Participants were informed to abstain from caffeine for 4 h prior to scan session.

## Assessments

A detail list of assessments has been outlined in detail previously (22). At baseline, structured diagnostic information regarding alcohol dependence and demographic variables were gathered. Alcohol consumption in the previous 30 days was determined using the timeline follow back (TLFB) alcohol consumption form (23) and a daily monitoring diary utilized in our previous alcohol treatment studies (8, 24, 25). Severity of alcohol dependence was assessed using the Alcohol Dependence Scale (ADS) (26), craving was measured by the Penn Alcohol Craving Scale [PACS; (27)]. In addition, trained interviewers conducted a structured psychiatric diagnostic interview using the Mini International Neuropsychiatric Interview (M.I.N.I.) (28). The treatment outcomes for this study were derived from drinking measures [TLFB] obtained during each visit.

## $^{1}$H-MRS

$^{1}$H-MRS spectra were acquired on a 3 Tesla GE Discovery MR750 scanner using an 8-channel phased array headcoil. The protocol comprised a three-dimensional sagittal whole-brain scout for orientation and positioning of all subsequent scans (TR = 50 ms; TE = 4 ms; 256 matrix; no averaging, $z$ = 5 mm thickness). To aid in the anatomical localization of the sampled voxels as well as gray–white-CSF segmentation, the T1-weighted structural image acquired at the beginning of the scan session was used (MPRAGE sequence: TR = 7.2 ms; TE = 2.8 ms; flip angle = 10°; matrix 256 × 256; 0.9 mm isotropic voxels, 196 slices). Next, a single voxel PRESS acquisition with two chemical shift-selective imaging pulses for water suppression (TR = 2,000 ms; TE = 35 ms; 128 averages) was acquired for GSH, Glu, NAA and Cr. Single voxel MEGA-PRESS (29) was acquired for GABA$^{+}$ determination [TR = 1,800 ms; TE = 68 ms; NEX (phase cycling) = 8; number of acquisitions = 256; number of points = 4,096; spectral width = 5,000]. Anatomical localization of the voxel placement in the right parietal lobe (voxel size = 3 × 3 × 3 cm$^{3}$) was based on the Talairach and Tournoux brain atlas and positioning was guided by the T1-weighted image (see **Figure 1**). Unsuppressed water scans (acquired from the same voxel) were collected prior to acquisition of the metabolite scans. All spectra were shimmed to achieve line widths (FWHM) of <15 Hz. Prior to any post-processing all spectra were visually inspected separately by two independent raters, to ensure the consistency of the data. Poorly fitted metabolite peaks, as reflected by large Cramer–Rao Lower Bounds (CRLB) (i.e., >20%) were excluded from further analysis.

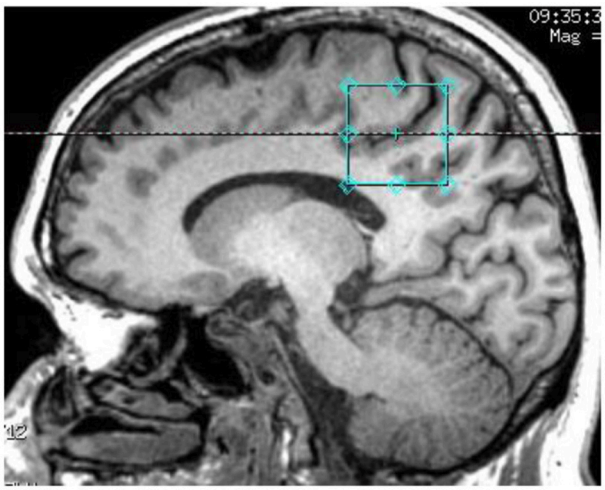


**FIGURE 1 |** T1-weighted structural image showing the anatomical localization of 3 × 3 × 3 acquisition voxel.

Following $^{1}$H-MRS acquisition, data were transferred offline for post-processing. GABA data were processed using the Gannet software toolkit (30). In brief, the data were first processed using the GannetLoad module which parses variables from the data headers and applies a line broadening of 3 Hz. Next, individual spectra were frequency and phase corrected using Spectral Registration. The data were then processed by the GannetFit module, which employs a single Gaussian model to fit the edited GABA$^{+}$ signal and evaluates GABA concentration in institutional units relative to water. The quality of the data were determined by the overall "Fit Error" index of each subject. This index represents the standard deviation of the fitting residual divided by the amplitude of the fitted peaks, and thus a measure of the signal-to-noise ratio. Only spectra with a relative Fit Error of GABA$^{+}$ below 10% were used for the subsequent statistical analyses. Next, the LCModel software package (31) was used to estimate GSH, Glu, NAA, and Cr (see **Figure 2**). The radiographers and the neuroimaging expert who read the spectroscopy data were blinded to group allocation.

## Statistical Analysis

Although participants were randomized to medication allocation, only consenting individuals participated in the neuroimaging arm of the study. Thus, baseline variables were examined for differences between groups to examine differences between the groups on continuous baseline demographic and clinical characteristics (ANOVA) and $\chi^{2}$ tests were performed for categorical variables.

As previously outlined in the original protocol paper (22) and the main effects analysis from the trial (12), planned analyses were conducted including PL (placebo) vs. BAC (baclofen: composite of the two doses). One way ANCOVA were used to examine medication differences for the

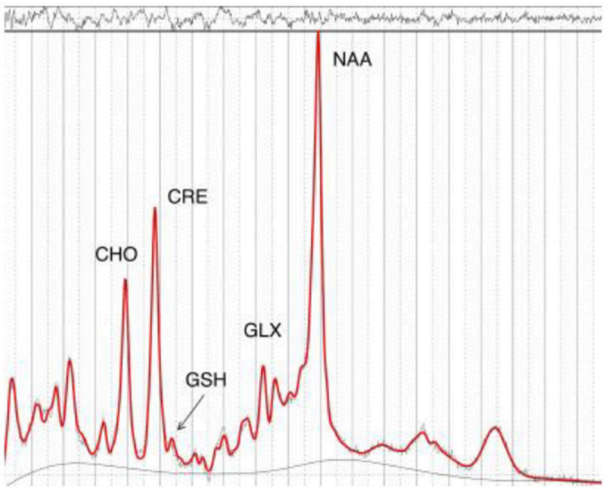


**FIGURE 2 |** Example MR-spectrum from the right parietal cortex.

**TABLE 1 |** Demographic and clinical characteristics of participants.

| Characteristic | Placebo ($n = 11$) | Baclofen 30–75 mg ($n = 20$) |
|---|---|---|
| Age, y | 51.73 ± 12.06 | 48.65 ± 9.24 |
| Gender, % *F* | 46 | 25 |
| Education, y | 14.36 ± 2.63 | 14.45 ± 2.38 |
| Unemployed, % | 18 | 40 |
| Drinks per drinking day[a] | 12.12 ± 4.34 | 9.92 ± 5.90 |
| Years since alcohol-related problems began | 14.15 ± 9.59 | 16.23 ± 11.24 |
| Alcohol dependence severity | 13.73 ± 6.18 | 16.95 ± 8.29 |
| PACS craving | 17.91 ± 5.11 | 15.60 ± 5.62 |
| Alcoholic liver disease, % | 27 | 20 |
| Cigarette smokers, % | 73 | 75 |
| Antidepressant use, % | 82 | 60 |

*Data represent mean ± SD unless otherwise noted. [a]During the 30 days preceding the first day of the study, based on the Time-Line Follow-Back method. ADS, Alcohol Dependence Severity Scale; PACS, Penn Alcohol Craving Scale. There were no significant differences between groups on baseline variables.*

**TABLE 2 |** $^1$H-MRS neurometabolite concentrations of participants treated with either baclofen (30–75 mg dose) or placebo.

| Metabolites | Placebo | Baclofen 30–75 mg |
|---|---|---|
| Full sample, *n* | 11 | 20 |
| $GABA^+$ | 0.55 ± 0.04 | 0.53 ± 0.09 |
| Glu/Cr | 1.50 ± 0.07 | 1.47 ± 0.09 |
| GSH/Cr* | 0.43 ± 0.03 | 0.45 ± 0.03 |
| NAA/Cr* | 1.40 ± 0.13 | 1.47 ± 0.11 |
| NAAG/Cr | 0.14 ± 0.05 | 0.13 ± 0.07 |
| Recent alcohol consumption^, *n* (%) | 5 (46) | 4 (20) |
| $GABA^+$ | 0.53 ± 0.04 | 0.59 ± 0.05 |
| Glu/Cr | 1.47 ± 0.06 | 1.55 ± 0.08 |
| GSH/Cr* | 0.42 ± 0.02 | 0.47 ± 0.01 |
| NAA/Cr* | 1.38 ± 0.09 | 1.54 ± 0.05 |
| NAAG/Cr | 0.12 ± 0.03 | 0.09 ± 0.05 |

*Data represent raw means ± SD. ^ in previous 24 h before scanning, Y/N. *$p < 0.05$, comparing baclofen (30–75 mg) vs. placebo. Patients were previously treated with either BAC or PL for an average of 17 days and were scanned approximately 120 min following administration of BAC or PL.*

neurometabolites (Glu/Cr, GSH/Cr, $GABA^+$, NAA/Cr) between BAC and PL with recent drinking (24 h) placed as covariates. For neurometabolites that showed significant differences, we then performed exploratory analyses across all three treatment group (separating the doses) followed by *post-hoc* tests between each of the two doses (30 vs. 75 mg) and PL. We also explored the role of time on treatment with BAC (days) on metabolite correlations with bivariate correlations. We also used bivariate correlations to examine the association of metabolite concentrations following BAC vs. PL administration and later drinking outcomes on the trial. We then placed relevant metabolites into a linear regression weighting for recent alcohol consumption (previous 24 h). Drinking outcomes, as outlined in the main trial (12) and previous protocol (22), included percentage days abstinent and heavy drinking days (although both variables were calculated from the day after the scan until the end of the trial).

All analyses were two-tailed, with significance level at $P < 0.05$. Data were analyzed using SPSS 23 for Mac OSX.

# RESULTS

## Sample Characteristics

Of the 31 patients recruited for the neuroimaging study, 9 were randomized to receive placebo, 11 to receive baclofen 30 mg and 11 to receive baclofen 75 mg. As per our main results paper groups were analyzed as placebo vs. baclofen (composite doses). Baseline characteristics are displayed in **Table 1**. There were no significant differences between treatment groups with regards to sociodemographic or clinical characteristics (*F*s $< 1.99$, *p*'s $> 0.17$ for continuous and $\chi^2$'s $< 0.22$, *p*'s $> 0.26$ for categorical).

## Metabolite Concentrations Following Acute Administration of BAC vs. PL

Means for each of the metabolites following administration with BAC or PL (as per alcohol consumed within the previous 24 h) are presented in **Table 2**. There were no significant differences between groups (PL vs. BL) for any of the metabolite concentrations ($GABA^+$: $F = 0.35$, $p = 0.56$; Glu/Cr: $F = 0.50$, $p = 0.49$; GSH/Cr: $F = 2.46$, $p = 0.13$; NAA/Cr: $F = 2.34$, $p = 0.14$). However, when weighting alcohol dependent participants according to recent drinking (24 h) there were significant differences between BAC and PL on GSH/Cr ($F = 20.88$, $p < 0.01$) and NAA/Cr ($F = 10.63$, $p < 0.05$; see **Figure 3**). There were no significant differences between BAC and PL for the other metabolite concentrations ($GABA^+$: $F = 3.70$, $p = 0.10$; Glu/Cr: $F = 2.81$, $p = 0.14$).

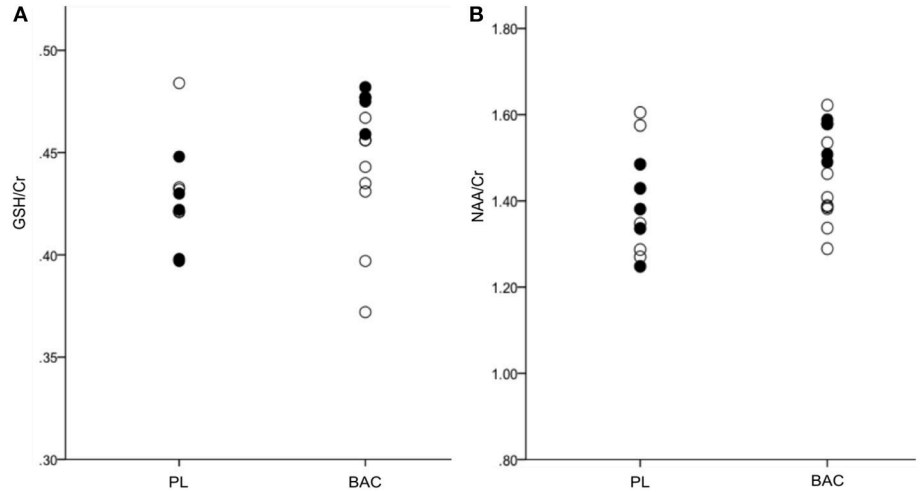


**FIGURE 3 | (A)** GSH/Cr and **(B)** NAA/Cr in the right parietal cortex for PL (placebo) and BAC (baclofen: 30–75 mg) treated alcohol dependent patients (•, recent alcohol consumption <24 h; ○, no recent alcohol consumption <24 h).

## Association of Metabolite Concentrations With Previous Treatment Days With BAC

There were significant correlations between previous treatment days with BAC and GSH/Cr ($r = 0.44$, $p = 0.03$) and NAA/Cr ($r = 0.43$, $p = 0.04$). When examining these associations in only the BAC-treated patients there was a trend for significance for GSH/Cr ($r = 0.48$, $p = 0.10$) and the association between NAA/Cr and days treated with BAC remained significant ($r = 0.54$, $p = 0.05$). There were no significant correlations between other metabolite concentrations and previous treatment days with BAC (entire sample: $p$'s $> 0.52$; only BAC-treated patients: $p >$'s 0.14).

## Association of Metabolite Concentrations With Drinking Outcomes at Follow-Up

There was a significant negative correlation between Heavy Drinking Days (at follow-up) and GSH/Cr ($r = -0.47$, $p = 0.04$). There were no significant correlations between metabolite concentrations and other drinking outcomes ($p$'s $> 0.10$). The results of the multiple linear regression are presented in **Table 3**. We entered relevant neurometabolites (significant in the acute administration study and bivariate associations: GSH, NAA) into a multiple regression (Model 1) and then weighted for recent alcohol consumption (Model 2). For heavy drinking days, there was no significant effect of the model ($F = 2.61$, $R^2 = 0.24$, $p = 0.10$). When examining only patients that reported recent alcohol consumption (within the last 24 h) the model was significant ($F = 14.28$, $R^2 = 0.85$** $R^2$ change $= 0.61$, $p = 0.01$) with a significant predicting effect of GSH ($B = -1.22$, $p = 0.01$). For percentage days abstinent, there was no significant effect of the model ($F = 0.49$, $R^2 = 0.10$, $p = 0.62$). When examining only patients that reported recent alcohol consumption (within the last 24 h) the model was significant ($F = 6.50$, $R^2 = 0.72$** $R^2$ change $= 0.62$, $p = 0.04$) with a near significant effect of the predictor GSH ($B = 0.99$, $p = 0.06$).

**TABLE 3 |** Neurometabolite predictors of heavy drinking days$^{+}$ and percentage days abstinent$^{+}$ throughout the trial by linear regression analysis, and weighted effects with recent alcohol consumption (24 h).

| **Heavy drinking days** | $R^2$ | $F$ | $B$ | $p$ |
|---|---|---|---|---|
| Model 1 | 0.24 | 2.61 | | 0.10 |
| GSH/Cr | | | −0.37 | 0.18 |
| NAA/Cr | | | −0.17 | 0.53 |
| Model 2**, weighted by recent alcohol consumption, $R^2$ change = 0.61 | 0.85 | 14.28 | | 0.01 |
| GSH/Cr* | | | −1.22 | 0.01 |
| NAA/Cr | | | 0.41 | 0.23 |
| **Percentage days abstinent** | | | | |
| Model 1 | 0.10 | 0.49 | | 0.62 |
| GSH/Cr | | | 0.06 | 0.83 |
| NAA/Cr | | | 0.19 | 0.52 |
| Model 2*, weighted by recent alcohol consumption, $R^2$ change = 0.62 | 0.72 | 6.50 | | 0.04 |
| GSH/Cr | | | 0.99 | 0.06 |
| NAA/Cr | | | −0.18 | 0.68 |

*$^{+}$Calculated from the time of scanning (on average 17 days) to the end of treatment (week 12). *Significant at $p < 0.05$, **Significant at $p < 0.01$, independent of treatment status. For both treatment outcomes, when considering just the patients that consumed alcohol within the last 24 h, the model yielded the highest $R^2$ whereby GSH was a significant and a trend for significant predictor for heavy drinking days and percentage days abstinent, respectively.*

# DISCUSSION

This is the first $^{1}$H-MRS study of the effects of baclofen on neurometabolite concentrations in alcohol dependent individuals. There were significant differences between baclofen and placebo on parietal concentrations of GSH when controlling for recent drinking, with baclofen treated

participants demonstrating significantly higher levels of GSH/Cr ratio relative to placebo. That is, baclofen significantly increased depleted GSH relative to placebo for those participants that drank alcohol in the previous 24 h (although these participants were not intoxicated, reading 0.00 BAC). GSH deficiency is associated with early abstinence in alcohol dependent patients (32) and is a pathophysiological characteristic of alcohol-related hepatotoxicity (33). We also observed that decreased GSH/Cr predicted greater heavy drinking days throughout the trial following the scan and increased GSH/Cr predicted greater percentage days abstinent throughout the trial. These results support a growing number of preclinical studies and one clinical study suggesting that replenishing intracellular levels of GSH may play a role in reducing alcohol withdrawal (34), alcohol consumption (35) and relapse (36). These results are also consistent with our previous published data demonstrating accurate low levels of GSH with an $R^2 = 0.98$ using short TE PRESS sequence based on the cysteine moiety i.e., ($7CH_2$) at 2.97 ppm (37), despite suggestion in the literature that a short TE PRESS sequence is not capable of accurately resolving low concentrations of GSH (38).

$GABA_B$ mediated signaling has previously been suggested to play a role in oxidative stress. For example, baclofen has been found to attenuate oxidative damage and neuroinflammation that is induced by MPTP in rats (39), reduce stress-induced brain $NO_x^-$ levels in rats (40) and has also been found to be neuroprotective by reversing oxidative stress and free radical damage *in vitro* (41). Moreover, administration of GABA has been reported to reduce the level of oxidative stress markers in the rat brain following streptozocin-induced (STZ) oxidative stress (42). One study observed a $GABA_B$ antagonist but not high dose baclofen reversed reduced GSH following STZ (43). Thus, there may be some $GABA_B$ mediation of oxidative stress yet the exact nature of this relationship remains to be determined. The deficit in GABAergic signaling that may occur in alcohol dependence has been implicated in the up-regulation of glutamatergic excitotoxic neuronal damage which may also lead to oxidative stress (44). Low dose agonism following baclofen may enhance GABA release which in turn regulates excitotoxic signals and subsequently reduces oxidative stress. Further, preclinical studies have demonstrated that baclofen administration decreases glutamate release (45) and a direct relationship has been observed to occur between microglial glutamate uptake and GSH synthesis (46). However, in this study we did not observe any corresponding significant increase in parietal Glu/Cr or $GABA^+$ concentrations, although this could be due to a regional disparity or limited technological sensitivity with the obtained sample size.

In the current study, we also observed significantly higher parietal levels of NAA/Cr concentrations following BAC administration relative to PL. Generally speaking, levels of NAA in various parts of the brain correlate with neuronal health or integrity, whereby decreased levels of NAA have been interpreted to indicate neuronal/axonal loss, or compromised neuronal metabolism (47). Heavy alcohol consumption has been suggested to have a disrupting influence on neuronal metabolism (13). Previous studies in alcohol dependent individuals have reported a significant negative correlation between concentrations of cortical and subcortical NAA with recent and lifetime heavy drinking levels (13, 18). Our results suggest that treatment with BAC improved compromised neuronal metabolism caused by recent drinking. It is possible that this reflects an indirect treatment effect related to increased previous abstinence due to the chronic efficacy of BAC to reduce alcohol consumption via various mechanisms. To further investigate the potential role of chronic efficacy of BAC, we examined the relationship between days on BAC and metabolite concentration. We observed a significant positive association between time on BAC treatment and NAA levels which may suggest either an indirect of beneficial treatment efficacy to reduce drinking or a cumulative effect of extended $GABA_B$ mediated effects on NAA levels. Given that the BAC vs. PL acute effect on NAA and GSH was only significant in participants that recently consumed alcohol while there was no effect in patients that were abstinent, it is likely that BAC directly and acutely elevates these markers in the case of alcohol-induced deficits that occur in very early abstinence.

To this degree, it is important to note that $^1$H-MRS investigations in the literature have also revealed results that varied in relation to drinking and withdrawal status (48–50). Indeed, in the current study, the effects of baclofen on GSH/Cr and NAA levels and the predictive associations of GSH/Cr concentrations with follow-up drinking were only evident when controlling for recent alcohol consumption. Thus, our data support the hypothesis that recent alcohol consumption may account for differences in neurometabolites that may be observed in alcohol dependent patients.

There are several limitations in our study including the modest sample size, albeit not uncommon in $^1$H-MRS studies. Increased power would allow for analysis of interactions between PL vs. BAC, abstinence vs. recent drinking and the relationship between treatment outcome. Indeed, this was a secondary substudy of a larger trial and although we controlled for recent alcohol consumption and there were no differences between groups on baseline characteristics, interpretation would be improved if scanned participants were specifically randomized and all participants reported the same window of alcohol consumption. To this degree, the before vs. after treatment design with two scans scheduled at baseline and follow-up in the trial is optimal. Strengths include the inclusion of follow-up drinking outcomes in a randomized controlled trial and that this is the first examination of neurometabolites following baclofen administration in patients with alcohol dependence.

## CONCLUSION

This is the first $^1$H-MRS study of baclofen administration on neurometabolites in alcohol dependent individuals. Baclofen, relative to placebo, significantly increased levels of the antioxidant, GSH, and NAA a marker of neuronal integrity, in the parietal lobe of recently drinking alcohol dependent patients. In these patients, higher GSH levels predicted beneficial treatment outcomes at follow-up suggesting a role for oxidative

stress in AUD. MRS is a valuable technique to study neurobiology of human AUD *in vivo* and to identify the impact of treatment.

## AUTHOR CONTRIBUTIONS

KM contributed to MRS study conception and design, supervision of the MRS study and main trial, data analysis and writing of the manuscript. JL contributed to the design of the MRS protocol and analysis. KC contributed to the MRS analysis. WL contributed to patient recruitment, conducting neuroimaging sessions and data maintenance. WL also contributed to data analysis and the presentation of the manuscript. PH and AB contributed to conception of the main trial, design and supervision. PH contributed as site investigator and physician. All authors have approved the final manuscript.

## ACKNOWLEDGMENTS

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# Tailored-Dose Baclofen in the Management of Alcoholism: A Retrospective Study of 144 Outpatients Followed for 3 Years in a French General Practice

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**Background:** More information is needed about the efficacy and safety of long-term baclofen in the treatment of alcohol use disorders. The objective of this study was to assess the effect of treatment with tailored-dose baclofen on alcohol consumption in patients with alcohol use disorders followed for 3 years after first initiating baclofen treatment.

**Methods:** This retrospective descriptive cohort included outpatients followed in a French general practice clinic for 3 years and treated with tailored-dose baclofen to reduce or eliminate alcohol consumption. At 3 years, treatment was considered successful if alcohol consumption was at or below levels defined as low-risk by the WHO ($\leq$ 40 g/d in men and $\leq$ 20 g/d in women).

**Results:** The study population included 144 patients (88 men and 56 women). The participants' mean age was 46 $\pm$ 11 years and mean daily alcohol intake before treatment was 167 $\pm$ 77 grams. At the end of the study, treatment was successful for 91 (63.2%) patients. Participants' mean dose of baclofen at the end of study period was 100 $\pm$ 101 mg/d. We identified 75 (52.1%) patients for whom treatment was successful at each annual follow-up appointment: at 1, 2, and 3 years. The mean maximum dose of baclofen over follow-up of the 144 patients was 211 $\pm$ 99 mg/d (dose range: 40 mg/d to 520 mg/d).

**Conclusion:** In this study, tailored-dose baclofen appears to be an effective treatment in patients with alcohol use disorders, with sustainable effect over time (3 years). There are many adverse effects but they are consistent with those already described in the literature.

**Keywords: alcoholism, baclofen, retrospective study, primary care, long-term treatment**

# INTRODUCTION

Baclofen, a gamma-aminobutyric acid B-receptor agonist, has been prescribed for more than 40 years for treating spasticity caused by diseases of the central nervous system, at recommended doses between 30 and 80 mg/day. It appears to be a promising candidate for treating patients with alcohol use disorders (1), by reducing or even suppressing their craving.

The first randomized placebo-controlled double-blind trial to assess the benefits of baclofen at 30 mg/day to treat alcohol dependence was published in 2002 (2). Subsequent randomized placebo-controlled studies of doses up to 60 mg/day reported contradictory results (2–8). Four of these 7 studies reported positive findings for the primary outcome.

At the same time, several case reports (9–12) and retrospective observational studies (13–15) indicated that high-dose baclofen (up to 400 mg/d) could be effective for treating alcohol dependence. One randomized placebo-controlled double-blinded trial (Baclad) assessing high-dose baclofen (up to 270 mg/day) over 6 months for treating alcohol dependence reported a significantly higher proportion of abstinence with baclofen vs. placebo (42.9% vs. 14.3%, $P = 0.037$) (16). Another randomized placebo-controlled double-blind trial of doses up to 150 mg/day over 4 months in alcohol-withdrawn patients did not find a difference in the groups from the first initiating treatment to the first relapse (17). Two randomized placebo-controlled double-blind trials of high-dose baclofen were conducted in France (18, 19). The Alpadir study did not demonstrate the efficacy of baclofen at the target dose of 180 mg/day in maintaining abstinence over 6 months (19). The Bacloville study reported a significantly higher proportion of patients with a low risk alcohol consumption (WHO) or abstinent in baclofen group (doses up to 300 mg/day) vs. placebo group after 1 year (18).

The maximal duration of the follow-up in these randomized placebo-controlled double-blind trials was 1 year and the longest retrospective study was for 2 years. Hence, we need information on long-term baclofen treatment. Indeed, studies are needed on whether patients who became abstinent or managed to control their alcohol consumption with baclofen could stop or reduce the treatment while remaining abstinent or controlling their consumption.

Here we present the retrospective clinical experience of a general practitioner (PJ) who has prescribed tailored-dose baclofen since 2008 for patients at high risk for alcoholism as defined by the World Health Organization (WHO; >40 g/day for women and >60 g/day for men). The primary objective of this study was to assess effectiveness of tailored-dose baclofen for alcohol consumption in patients with alcohol use disorders who were followed over 3 years after first initiating baclofen. Secondary objectives were to analyse the dose of baclofen prescribed during the 3 years of follow-up and tolerance of the treatment and to explore patient characteristics associated with low-risk alcohol consumption.

# METHODS

## Study Design

This was a retrospective study among patients of a French general practitioner (PJ) trained in addictology. Patients were eligible for the study if they (1) were at least 18 years old, (2) drank at a high-risk level according to the WHO (20), (3) first began taking baclofen before December 31, 2011, and (4) were willing to be followed up for more than 3 months to assure stability of patient care.

Eligible patients were identified from an exhaustive list of patients who received a baclofen prescription that the general practitioner (PJ) maintained. For each patient, data were collected retrospectively from their medical file by one independent investigator (JP). If necessary, data collection was completed by asking the patient questions during a consultation with the general practitioner or by telephone with the investigator.

## General Practitioner Follow-Up and Prescription

Patients did not necessarily stop drinking alcohol before beginning baclofen treatment. They could drink alcohol with the treatment. Baclofen was prescribed at progressively increasing doses according to the standard of care at the time. This practice was later published in prescription guidelines (21) without any pre-set limit up to the dose that allowed patients to control their alcohol consumption or even become indifferent to it. The objective for this treatment was harm reduction (as proposed by European Medicines Agency, 2010, and confirmed by recommendations from the US Food and Drug Administration, 2015, and UK Chief Medical Officers' Low Risk Drinking Guidelines, 2016) (22). Each patient received comprehensive care according to NICE guidelines (23), with or without the additional prescription of psychotropic drugs. Each patient received written and oral information about the treatment (modality of prescription, follow-up, main side effects, potential risks of combining higher doses of baclofen and high volumes of alcohol importance of stopping treatment progressively).

## Data Collection

The following data were collected:

- social and demographic data: age, sex, marital status, work status
- history of treatment for management of alcoholism: episodes of detoxification, participation in discussion groups, drug treatment (e.g., acamprosate, naltrexone, or disulfiram)
- psychiatric disorders: depression, bipolar, anxiety, or borderline personality disorders
- history of use of other toxic substances: tobacco, cannabis, heroin, cocaine
- history of eating disorders
- history of insomnia
- at treatment initiation and at 1, 2, and 3 years follow-up visits: reported alcohol consumption (in grams per day), daily baclofen dose (in milligrams), consumption of other toxic substances (tobacco, cannabis, heroin, cocaine), a list and dose

of psychotropic drugs (anxiolytics, hypnotics, antidepressants, antipsychotics, and mood stabilizers), a list and dose of psychotropic drugs used as substitutes for opiates
- maximum dose of baclofen taken during follow-up.
- tolerability of baclofen (reported by the patient at each consultation). We focused on the sides effects reported by patients during the first year of follow-up given that it corresponds to the phase of baclofen initiation and titration. After titration, we only reported serious adverse effects (hospitalizations and deaths).

## Outcome

Treatment was considered successful if patients were either abstinent or drinking at a low-risk level as defined by the WHO ($\leq$40 g/day for men and $\leq$20 g/day for women) at 3 years after beginning the treatment even if no longer taking baclofen.

## Data Analyses

We analyzed data for patients who were eligible for the study and for whom data on alcohol consumption was provided during the 3 years follow-up. Descriptive analyses were used for alcohol consumption defined according to the WHO risk categories and baclofen dosage during follow-up. Pearson's correlation analysis was used to determine correlation between the maximum baclofen dose used for efficacy and patient characteristics as well as daily alcohol intake before starting baclofen. We attempted to identify factors associated with treatment success (baseline characteristics of patients associated with successful treatment at 3 years in univariate with $p < 0.20$ were considered in multivariate logistic regression). We described any adverse effects and compared patients lost to follow-up before 3 years to those who completed follow-up. Chi-square or Fisher's exact test was used as appropriate to analyze categorical variables and Student *t*-test for quantitative variables. Statistical analyses involved use of STATA v12.0 and R 3.2.5. $P < 0.05$ was considered statistically significant.

## Ethical Aspects

All patients included were informed of the study objective and provided informed consent during a consultation with the general practitioner or by telephone with the investigator. This study was not reviewed by a research ethics committee because as a retrospective study, it was not at this time within the scope of the French statutes regulating biomedical research.

# RESULTS

## Descriptive Characteristics

We identified 219 eligible patients who initiated baclofen treatment before December 31, 2011: 75 were lost to follow-up, including 6 who died, resulting in a final cohort of 144 (65.8%) for analysis.

The mean (SD) age at inclusion was 46 (11) years and 88 (61.1%) were men (**Table 1**). The mean (SD) quantity of alcohol consumed daily at baclofen initiation was 167 (77) g. Overall, 103 patients (71.5%) previously received treatment for alcohol use disorder (drugs or detoxication or discussion groups).

**TABLE 1 |** Baseline characteristics of patients who completed and did not complete follow-up at 3 years (lost to follow-up or died).

| | Completed follow-up (*N* = 144) | Did not complete follow-up (*N* = 75) | *p* |
|---|---|---|---|
| Male | 88 (61.1) | 46 (61.3) | 0.974 |
| Age (years), mean (SD) | 46.43 (11.00) | 46.51 (11.16) | 0.962 |
| Living with a partner | 83 (57.8) | 41 (55.4) | 0.742 |
| Employed | 85 (59.4) | 44 (59.5) | 0.998 |
| Had tried a drug approved for relapse prevention | 91 (63.2) | 46 (61.3) | 0.787 |
| - acamprosate | 71 (49.3) | 27 (36.0) | 0.060 |
| - naltrexone | 62 (43.1) | 28 (37.3) | 0.414 |
| - disulfiram | 21 (14.6) | 11 (14.7) | 0.987 |
| Had undergone detoxification | 47 (32.6) | 29 (38.7) | 0.374 |
| Had participated in discussion groups | 38 (26.4) | 14 (18.9) | 0.220 |
| Previously treated for alcoholism (drugs or detoxications or discussion groups) | 103 (71.5) | 54 (72.0) | 0.941 |
| Quantity of alcohol consumed daily at inclusion (g), mean (SD) | 167 (77) | 159 (119) | 0.582 |
| Psychiatric disorders (clinician assessment) | 120 (83.3) | 57 (76.0) | 0.191 |
| - anxiety | 96 (66.7) | 44 (58.7) | 0.242 |
| - depression | 90 (62.5) | 44 (58.7) | 0.581 |
| - borderline personality | 23 (16.0) | 5 (6.7) | 0.056 |
| - psychosis | 5 (3.5) | 3 (4.0) | 1.00 |
| - bipolar disorders | 7 (4.9) | 4 (5.3) | 1.00 |
| Other addictions: | | | |
| - smoking | 109 (75.7) | 44 (58.7) | **0.009** |
| - cannabis | 29 (20.1) | 13 (17.3) | 0.617 |
| - heroin | 1 (0.7) | 0 (0) | 1.00 |
| - cocaine | 6 (4.2) | 2 (2.7) | 0.718 |
| History of eating disorders | 7 (4.9) | 3 (4.1) | 1.00 |
| Treatment at baseline: psychotropic drugs | 100 (69.4) | 40 (53.3) | **0.018** |
| - anxiolytics and hypnotics | 84 (58.3) | 35 (46.7) | 0.133 |
| - antidepressants | 60 (41.7) | 17 (22.7) | **0.005** |
| - antipsychotics | 13 (9.0) | 6 (8.0) | 0.798 |
| - mood stabilizers | 5 (3.5) | 2 (2.7) | 1.000 |
| Treatment at baseline: opiate substitutes (buprenorphine and methadone) | 19 (13.2) | 3 (4.0) | **0.034** |

*Data are n (%) unless indicated. Bold values correspond to values where p < 0.05.*

At baclofen initiation, 120 patients (83.3%) had a psychiatric disorder [Diagnostic and Statistical Manual of Mental Disorders, 4th [DSM-IV] criteria]. Before beginning baclofen treatment, 69.4% were taking at least one psychotropic drug.

## Alcohol Consumption and Baclofen Dose

At 3-year follow-up, treatment was successful for 91 patients (63.2%): 61 abstinent (42.4%) and 30 low-risk drinkers (20.8%) according to the WHO classification. Had all the patients lost to follow-up analyzed and classified as failures, the success rate at 3 years would have been 41.6%.

For 75 patients (52.1%), treatment was successful at each annual follow-up visit, at 1, 2, and 3 years (**Figure 1**).

At 3 years, the mean (SD) daily dose of baclofen was higher for patients with than without successful treatment (100 [101] vs. 58 [102] mg/day, $P = 0.017$). In all, 29 patients with successful treatment were no longer taking baclofen at 3 years (i.e., 20.1% of all patients and 31.9% with successful treatment).

The mean (SD) maximum dose of baclofen during follow-up was 211 (99) mg/day (range: 40–520) and the median was 210 mg/day (first quartile: 120, third quartile: 300) (**Figure 2**). The mean (SD) maximum dose prescribed did not differ significantly between patients with and without successful treatment (219 [98] vs. 194 [100] mg/day, $P = 0.137$).

We found a significant but low correlation between alcohol consumption at inclusion and maximum baclofen dose ($r = 0.2607$, $P = 0.0017$).

At 3 years, in univariate and multivariate analysis the two outcome groups did not differ significantly in any baseline characteristics (social and demographic characteristics, alcohol intake, previous treatment for alcoholism, other addictions, psychiatric disorders, or psychotropic medication).

For the 75 patients with successful treatment at each annual follow-up visit, the mean (SD) maximum dose of baclofen during follow-up was 220 (100) mg/day (range: 60–520) (**Table 2**) and the median was 240 mg/day (first quartile: 150, third quartile: 300); 22 could stop baclofen and the other 53 could reduce the maximum baclofen dose by an average of 35%.

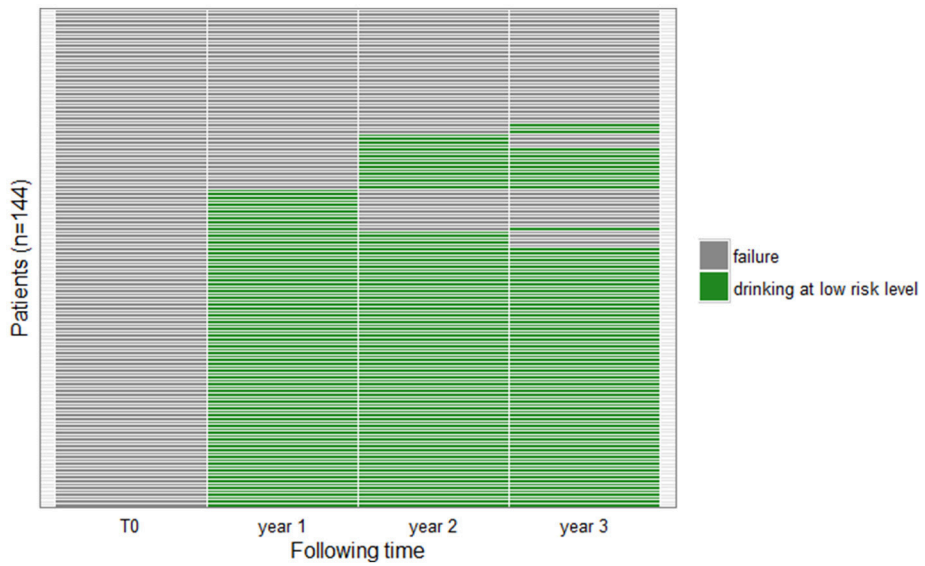


**FIGURE 1 |** Patient outcomes during follow-up. Each row corresponds to one patient. The colors correspond to drinking levels for patients at 3 follow-up visits (year 1, year 2, year 3): green: abstinent or low-risk drinkers; gray: failure.

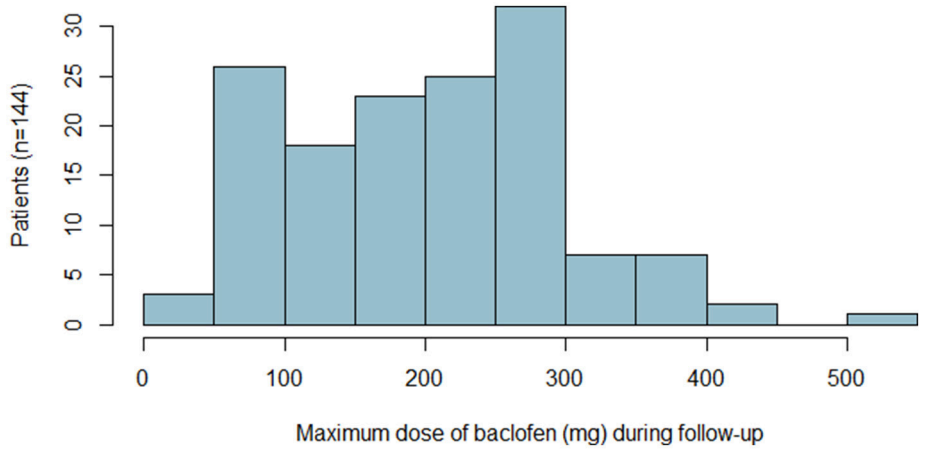


**FIGURE 2 |** Maximum dose of baclofen taken by patients with the number of patients.

**TABLE 2 |** Baclofen dose during follow-up for patients with successful treatment at each yearly follow-up visit ($n = 75$).

| | 1 year | 2 years | 3 years |
|---|---|---|---|
| Patients no longer taking baclofen—n (%) | 13 (17.3%) | 18 (24.0%) | 22 (29.3%) |
| Patients taking baclofen—*n* (%) | 62 (82.7%) | 57 (76.0%) | 53 (70.7%) |
| Current baclofen dose (mg/d), mean (SD) | 172 (100) | 142 (95) | 143 (91) |

## Adverse Effects

During the first year of follow-up (including the phase of baclofen initiation and titration) 16 patients (11.2%) reported no adverse effects. The most frequently adverse effects, reported by 128 (88.8%) patients during year 1, included drowsiness (48.6%), asthenia (37.5%), insomnia (28.5%), vertigo (20.8%), nausea (18.8%), headaches (16.7%), sudden fatigue (12.5%), concentration disorders (11.8%), sweating (11.8%), hypomania (11.8%), and memory disorders (10.4%).

During follow-up, ten serious adverse effects occurred: four patients were hospitalized and six died.

Three patients were hospitalized for confusion: one patient had a baclofen overdose and two patients did not follow the general practitioner's prescriptions and recommendations (they specifically stopped baclofen abruptly and then resumed it at a high-dose without titration; moreover, one of the two patients also consumed a high dose of alcohol at the same time). One patient was hospitalized for encephalopathy: this patient abruptly stopped and then resumed a high dose of baclofen without titration. These hospitalizations led to the discontinuation of baclofen for all four patients. One of these patients was classified as a success at each annual follow-up visit at 1, 2, and 3 years. For two patients, outcome was successful only at 1 year. And the fourth patient was lost to follow-up before 1 year.

Concerning the six patient who died during follow-up, the general practitioner considered that they were not related to baclofen. Three patients with long-standing psychiatric disorders committed suicide (two had not taken baclofen for more than 6 months), two overdosed with heroin (one had not taken baclofen for 3 months), and one patient died during an alcohol coma.

## Comparison of Patients Completing and Not Completing Follow-Up (Lost to Follow-Up or Died)

Patients completing follow-up were more frequently current smokers (75.7 vs. 58.7%, $P = 0.009$) and taking antidepressants (41.7 vs. 22.7%, $P = 0.005$) or opiate replacements (13.2 vs. 4.0%, $P = 0.034$). The two groups were comparable in all other characteristics (**Table 1**).

# DISCUSSION

This study aimed to assess the efficacy of tailored-dose baclofen for alcohol consumption in 144 patients with alcohol use disorder who were followed over 3 years after first initiating baclofen. At the end of the follow-up, treatment was successful for 63.2% of patients—they were abstinent or drinking at a low-risk level—and their mean (SD) dose of baclofen was 100 (101) mg/day. Our study is the first with a follow-up of 3 years and thus could assess the efficacy and the safety of the treatment over a longer term than previous studies.

We did not find any association between patient characteristics at inclusion and their alcohol consumption reported in the WHO risk categories at 3 years. Nor did we identify any particular patient profile or characteristics associated with a good response to baclofen.

Moreover, we found a significant but low correlation between the maximum dose of baclofen and alcohol consumption at inclusion, as previously reported by de Beaurepaire (14) and Shukla et al. (24). This result suggests that the higher the initial alcohol intake, the higher the baclofen dose needed to control it.

One limitation is that our study was a single-center with a single prescriber retrospective cohort, so the generalizability of our findings may be limited, and our results are prone to biases inherent of this type of design. The alcohol use disorder requires a long-term care, this is the reason why patients (125) with a follow-up of <3 months were excluded because alcohol use disorder requires a long-term care. Among this group, some (46) were seen only once and probably never began the baclofen treatment. Others were seen for a short period for an opinion or to begin the treatment before being followed up by a doctor closer to their home. The other patients excluded were probably not sufficiently motivated to undergo treatment for their drinking problem. For those patients with insufficient motivation to undergo treatment, it is important to develop specific alcohol care packages.

At 3 years, 32.4% of the patients had been lost to follow-up. The investigator (JP) sought to contact the 116 patients no longer seen by the general practitioner at 3 years; data were completed for 47 patients. Among the patients lost to follow-up, some had changed their telephone number ($n = 21$, 30.4%), some did not want to respond to questions on the telephone ($n = 9$, 13.0%), and others never responded to calls ($n = 39$, 56.5%). Some patients had requested a prescription for high-dose baclofen before the doctor suggested it. These patients had a positive view of the treatment in advance, which might have accentuated the placebo effect. Another limitation is linked to the retrospective design of the study. We were unable to corroborate the alcohol consumption reported by patients by biomarker testing or questioning family or friends. Therefore, the effect of baclofen on alcohol consumption we found may be overestimated. Some of the observed effect may be associated with the intervention by the physician (motivational interview and psychological support) or family and friends. All patients were offered the same follow-up and treatment. Nonetheless, the management of alcoholism is complex and cannot be summarized by the simple prescription of a medication.

One of the main strengths of the study is the large number of patients and the duration of follow-up: 144 patients at 3 years. The other observational studies of baclofen prescription in alcoholism analyzed fewer patients for shorter periods. Moreover, our study had a follow-up at 1 and 2 years. Thus, 52.1% of patients

had successful outcomes at each of the 1, 2, and 3 years visits. The effect of baclofen on alcohol consumption appears to be sustainable.

In our study, the baclofen prescription dose was progressively increased, without any pre-set limit: it ranged from 40 to 520 mg/day. The mean (SD) maximum dose prescribed was 211 (99) mg/day, which was higher in our study than the mean (SD) dose prescribed in the studies by Rigal et al. and de Beaurepaire: 145 (75) mg/day (range: 30–400), 159 (87) mg/day (range: 30–400), and 147 mg/day (range: 20–330) (13–15). In two randomized placebo-controlled double-blind trials examining the highest doses of baclofen before our study, the baclofen doses prescribed ranged from 30 to 270 mg/day for one (mean [SD] maximum baclofen dose was 180 [87] mg/day) (16) and from 15 to 300 mg/day for the second (18). Hence, the higher mean baclofen doses in our study as compared with the literature provides further information about the tolerability and safety of high-dose baclofen prescription. The adverse events we observed in our study suggest that future prescribing physicians need to be carefully informed and trained about potential severe events.

One of the original aspects of this study [as for Rigal et al. (13, 15)] is that it included patients who were not necessarily alcohol-dependent according to DSM-IV criteria. All patients had alcohol use disorders and wanted medical assistance.

Baclofen prescription was pragmatic. Patients with psychiatric disorders or using psychotropic medication or illegal drugs were included and maintained their usual treatments. Psychiatric disorders and the use of psychotropic medication were often exclusion criteria for previous randomized double-blind placebo-controlled studies of baclofen used to treat alcohol dependence (3–5, 8, 16). Some exceptions were Beraha et al. including patients with depression, anxiety or bipolar disorder (17); the Alpadir study including patients using an antidepressant at a stable dose for 2 months or anxiolytics such as diazepam or oxazepam and excluding only patients with severe psychiatric disease (19); and the Bacloville study excluding only patients with severe psychiatric disorders that could compromise their participation in the study (18).

## CONCLUSION

Tailored-dose baclofen seems an effective treatment for patients with alcohol use disorders, with sustainable effect over time (3 years). We found many adverse effects, but they are consistent with those described in the literature.

## AUTHOR CONTRIBUTIONS

All patients were from the general practitioner's practice (PJ). JP and LR participated in the conception and design of the study. JP collected the data. JP and SS performed the statistical analysis. All authors interpreted the results. JP drafted the manuscript and all authors revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

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OPINION
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# Use of Baclofen for Alcohol Use Disorders in the United States

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**Keywords: Baclofen, alcohol use disorders, United States, clinical use, cirrhosis**

The management of alcohol use disorders (AUDs) has been undergoing transformation since the discoveries of the effectiveness of naltrexone in the United States and acamprosate in Europe in the 1990's. These discoveries indicated that medications that target neurobiological processes can indeed have therapeutic value in AUDs. Prior to this there was only one effective medication for AUDs—disulfiram—with a mechanism of action targeted to the metabolism of acetaldehyde. The realization that medications that affect neurobiological processes can treat AUDs was truly a revolutionary finding and one that generated great hope that the treatment of AUDs would be based, at least in part, on a rational, scientific framework with, accordingly, improved effectiveness. Unfortunately, the intervening 20 years since these nodal discoveries has not seen a marked shift in the treatment of AUDs in the United States. Medications for AUDs are woefully under prescribed in the United States with estimates of only 5–10% of individuals with an AUD being offered an FDA approved medication on a backdrop of only 20% of AUD patients ever receiving any treatment (1). The reasons for this low rate of medication use are complex but appear to involve a lack of knowledge on the part of both clinicians and patients on the potential value of these medications coupled with concerns about tolerability and efficacy (2). Additionally, in the United States, the pharmaceutical industry is essentially not marketing any medication for AUDs that greatly reduces both clinician and patient awareness of medications for AUDs within the United States health care system.

The scientific community has approached the challenge of medication development for AUDs in two principal ways: (1) searching for new molecular targets connected with the underlying pathophysiology of AUDs with a goal of finding medications that may have efficacy for certain components of AUDs, e.g., protracted withdrawal, preoccupation, craving, with associated improvement in drinking behavior; (2) attempting to identify individual predictors of response to specific medications to enhance efficacy and move the field toward personalized medicine.

Baclofen represents a somewhat mature effort to target the $GABA_B$ receptor—a novel target not addressed by other agents in the United States. The clinical evidence for efficacy and tolerability with baclofen for AUDs has grown considerably in the past 5 years but remains mixed with one meta-analysis showing evidence for efficacy for enhancing complete abstinence (3) and another (4) not finding clear evidence for an effect and a third showing evidence for reduction in drinking (5). This plays out in recent clinical trials where some show clear positive results and others no positive results using baclofen doses ranging in the 30–300 mg/d range. Furthermore, concerns with tolerability to baclofen, especially with sedation/drowsiness at higher doses (6), may deter clinicians and patients. Additionally, there is no effort on the part of the pharmaceutical industry to seek FDA approval for a baclofen formulation for AUDs in the United States. Thus, the use of baclofen in the U.S. is off-label. The upshot of all of this is that baclofen has a very low profile for the treatment of AUDs in the United States and there is minimal evidence of its use except by limited numbers of specialists. Accurate data on the use of baclofen for AUDs in the U.S. is lacking however, which makes it difficult to know with any precision how many clinicians have prescribed baclofen for AUDs.

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One area that has attracted attention is the use of baclofen in patients with liver disease and an active AUD. The initial positive report of Addolorato et al. (7) that baclofen can increase rates of abstinence in patients with cirrhosis and improve liver profiles was noteworthy as it was the first evidence that a medication for AUD could be safe and effective in patients with liver disease. However, there has been limited clinical trial data to confirm this finding though a recent report by Morley et al. (8) is supportive. Because alcohol-induced liver disease is a significant cause of morbidity and mortality world-wide with nearly 500,000 yearly deaths (9), the further study of baclofen and other $GABA_B$ receptor agonists for the treatment of AUDs in patients with liver disease is of obvious importance. However, to date, even within this population in the United States there appears to be limited use of baclofen.

From this writer's perspective, the use of baclofen for the treatment of AUDs in the United States faces two major impediments. First, the use of any medication to treat AUDs in the United States is very low. Second, the clinical trial data for baclofen is mixed which sends a complicated signal to clinicians. As additional baclofen trials are published it is hoped that evidence of efficacy becomes clearer and that some sense of who is the baclofen-responsive patient emerges along with guidance on dose and safety. Until this happens, it is unlikely that baclofen use for AUDs in the United States will expand. If new formulations of baclofen, such as R-baclofen or allosteric modulators of the $GABA_B$ receptor, are shown to be effective for AUDs and are pursued by the pharmaceutical industry for FDA approval that would represent a significant positive step toward the use of $GABA_B$ receptor agonists in the treatment of AUDs in the United States.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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# A Review of the Potential Mechanisms of Action of Baclofen in Alcohol Use Disorder

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Baclofen, a GABA-B receptor agonist, is a promising treatment for alcohol use disorder (AUD). Its mechanism of action in this condition is unknown. GABA-B receptors interact with many biological systems potentially involved in AUD, including transduction pathways and neurotransmitter systems. Preclinical studies have shown that GABA-B receptors are involved in memory storage and retrieval, reward, motivation, mood and anxiety; neuroimaging studies in humans show that baclofen produces region-specific alterations in cerebral activity; GABA-B receptor activation may have neuroprotective effects; baclofen also has anti-inflammatory properties that may be of interest in the context of addiction. However, none of these biological effects fully explain the mechanism of action of baclofen in AUD. Data from clinical studies have provided a certain number of elements which may be useful for the comprehension of its mechanism of action: baclofen typically induces a state of indifference toward alcohol; the effective dose of baclofen in AUD is extremely variable from one patient to another; higher treatment doses correlate with the severity of the addiction; many of the side effects of baclofen resemble those of alcohol, raising the possibility that baclofen acts as a substitution drug; usually, however, there is no tolerance to the effects of baclofen during long-term AUD treatment. In the present article, the biological effects of baclofen are reviewed in the light of its clinical effects in AUD, assuming that, in many instances, clinical effects can be reliable indicators of underlying biological processes. In conclusion, it is proposed that baclofen may suppress the Pavlovian association between cues and rewards through an action in a critical part of the dopaminergic network (the amygdala), thereby normalizing the functional connectivity in the reward network. It is also proposed that this action of baclofen is made possible by the fact that baclofen and alcohol act on similar brain systems in certain regions of the brain.

**Keywords: GABA receptor b, reward network, amygdala, Pavlovian associations, substitution (morphine, methadone, buprenorphin)**

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## INTRODUCTION

Baclofen is a gamma-aminobutyric acid (GABA) analog that activates the GABA-B receptor subtype, and is used worldwide in neurology for the treatment of spasticity due to its myorelaxant properties (1). Many preclinical [see (2), for review] and clinical studies have demonstrated the efficacy of baclofen in the treatment of several addictive disorders, including

alcohol use disorder (AUD) (3–10), even though negative results have also been published (11, 12). While it is clearly established that the myorelaxant properties of baclofen are related to a dampening of the spinal motor reflex (13), its potential mechanism of action in AUD remains elusive. Central GABA-B receptors are involved in the regulation of a large number of systems and functions, including several neurotransmitter systems (dopamine, serotonin, norepinephrine, glutamate), transduction pathways, memory, and other cognitive functions, as well as inflammation. All these systems and functions are possibly involved in the anti-addictive effects of baclofen. In the present paper, the biological effects of baclofen are reviewed in the light of its clinical effects, assuming that, in many instances, clinical effects can be reliable indicators of underlying biological processes.

The effects of baclofen in the treatment of alcohol dependence have been thoroughly described by a physician suffering from AUD, Olivier Ameisen, who reported the cure of his alcohol dependence with a high dose of baclofen, first in an article published in 2005, then later in a book published in 2008 (3, 14). He reported that, in his case, the dose of 270 mg/day produced a state of "complete indifference" toward alcohol. Indifference is not an operational concept in addictology. It is nevertheless a concept that should be taken into consideration. It is characterized by an effortless suppression of craving, but goes beyond it. In people indifferent to alcohol, the experience of drinking or seeing alcohol cues has changed completely, as if alcohol had no meaning to them anymore. Those who are indifferent to alcohol can drink a glass of an alcoholic beverage, they do not finish the glass, they do not want to continue drinking, they feel nothing, while they remain unchanged for other aspects of their life, which they enjoy normally. The state of indifference is not transitory when the effective dose of baclofen is maintained: on the contrary, it is very long lasting, and people completely indifferent to alcohol can generally stop baclofen after one or a few years of treatment, and they most often do not relapse (as if all memories associated with alcohol had vanished). This differs from those who have been cured by using other methods, for whom abstinence most generally requires a lot of effort, and for whom craving for alcohol often returns when they resume some alcohol drinking or see alcohol cues. However, all AUD patients treated with baclofen do not reach such a state of complete indifference. My experience (more than a thousand patients treated with a high-dose of baclofen over the last 10 years) is that about one third of the patients reach this state of complete indifference; while another third experiences a clear decrease in craving, but not its complete suppression (these patients drink very significantly less, but still have moments of desire for alcohol); in the last third of patients baclofen treatment is ineffective despite often reaching very high doses. In these latter patients, the dose increase may have been limited by adverse effects, but it happens that some patients reach very high doses (superior to 400 mg/day) without achieving a state of indifference. In any event, a state of indifference can be reached in a substantial number of patients, and one of the aims of the present article is to try to address the concept of indifference in biological terms.

AUD is a chronic relapsing disorder characterized by an increased motivation to seek alcohol and drink compulsively, with an increasing loss of control over drinking, progressing from impulsivity to compulsivity (15). In clinical research, the concept of compulsion is generally not used: the word compulsion is absent from the DSM-5 AUD section, where the term *craving*, defined as "a strong desire or urge to use alcohol" (16), seems to encompass the compulsion to drink. According to the DSM-5, AUD is commonly associated with anxiety, depression, psychotic disorders, cognitive disorders and sleep disorders. Impulsivity is cited as a vulnerability factor for AUD. Regarding biological research, addiction models use the concept of craving (associated with those of preoccupation/anticipation), and add the concepts of positive and negative reinforcement to those of impulsivity and compulsivity. In positive reinforcement, cues and contexts associated with drinking acquire incentive salience after repeated association with drinking, and increasing strength of salience progressively leads to compulsive alcohol seeking and drinking. In negative reinforcement, craving is induced by the motivational value of the negative states of alcohol withdrawal. This leads to a state of preoccupation/anticipation where craving is intensified by the anticipation of access to alcohol resulting in compulsive alcohol seeking and drinking. A challenge in alcohol research is to explain how specific cues or contexts are paired with states of craving, while explaining which mechanisms of brain encoding are involved in these associations. It is hypothesized that the understanding of how specific neuronal ensembles encode and mediate the recall of learned associations among the cues, contexts, and behaviors during alcohol seeking and drinking will be helpful for the comprehension of how baclofen works in the treatment of AUD (17).

As mentioned above, baclofen is a selective GABA-B receptor agonist. GABA-B receptors are heterodimeric metabotropic receptors consisting of one GABA-B receptor-1 subunit (GABBR1) and one GABA-B receptor-2 subunit (GABBR2). GABA-B receptors are coupled via G-proteins to potassium and calcium channels, and to adenylate-cyclase (18). Studies have shown that GABA-B receptors are highly expressed all throughout the brain, some regions having a very high density of receptors, other regions a low or a very low density, and some regions insignificant densities. The variable densities of GABA-B receptors may have important implications regarding the use of baclofen in the treatment of AUD, given that, when a patient takes baclofen activation of regions with high densities should have clearer and more immediate physiological and behavioral consequences than the activation of regions with low densities. Binding and expression of GABA-B receptors have been studied in rodents. The Chu et al. binding study (using baclofen) showed highest densities of GABA-B receptors in the medial habenula, thalamus, cerebellum, cortex and colliculus; while ventral tegmental area and mesolimbic dopaminergic projections were among the structures with the lowest binding (19). Bowery et al. reported highest densities of GABA-B binding in the cerebellum, interpeduncular nucleus, frontal cortex, and thalamus (20), and highest GABBR1 mRNA transcripts in the hippocampus, thalamus, and cerebellum (21). Billington et al. (22), using immunohistochemistry targeting GABBR1 and GABBR2, found

receptor colocalization in the cerebellum, hippocampus, cortex, thalamus, and basal ganglia; the raphe nucleus was strongly stained for GABBR1 and weakly for GABBR2; there was no significant staining in the VTA and mesolimbic dopamine projections. Lu et al. reported strong expression of GABBR1 in the medial habenula, hippocampus, hypothalamus (supraoptic and suprachiasmatic nuclei), and cerebellum; intermediate expression in thalamus and brainstem nuclei containing monoaminergic neurons; and low expression in globus pallidus, ventral pallidum, and substantia nigra pars reticulata (23). Li et al. (24) reported strong expression of both GABBR1 and GABBR2 in medial habenula, cingulate and piriform cortex, cerebellum, and hippocampus; moderate expression in thalamic nuclei, amygdala, and other parts of the cortex; low expression in the basal ganglia and hypothalamus; insignificant expression in the ventral mesencephalon, where the VTA is located (24). Conversely, a study using immunohistochemistry and focusing selectively on midbrain monoaminergic nuclei showed that GABA-B receptors are present in neurons of the VTA and raphe nuclei (no comparison in terms of density of receptors was made with other parts of the brain) (25). Besides, acute treatment with baclofen in rats produces an activation of a number of brain nuclei, mostly in the hypothalamus, the amygdala, and the brainstem, and has no detectable effect in reward-relevant regions such as the nucleus accumbens, striatum, or ventral tegmental area (26). In conclusion, despite some discrepancies between these studies and despite the fact that it is not known to what extent observations made in rodents are relevant to humans, it is likely that, when given to patients, baclofen action is much stronger in brain structures that contain high or very high densities of GABA-B receptors, such as the cerebellum, medial habenula, hippocampus, some nuclei of the hypothalamus and thalamus, and certain parts of the cortex, than in dopaminergic structures.

Adverse effects generally occur before anticraving effects during baclofen treatment of AUD, especially when baclofen is used in order to make patients reach a state of complete indifference, for which high or very high doses are most often necessary. Many adverse effects may in large part be explained by an early occurring activation of brain areas containing high densities of GABA-B receptors. For example, the most common and early occurring baclofen adverse effects include fatigue, diurnal somnolence and nocturnal insomnia. Theses symptoms may be explained by an action of baclofen on GABA-B receptors in the brainstem and hypothalamus, which are among the structures most strongly activated by baclofen, and which control basic states of vigilance (in particular through the suprachiasmatic nucleus). Frequently occurring adverse sensory effects (tinnitus, paresthaesias, blurred vision, etc.) may be explained by the high density of receptors in the thalamus, and memory problems by the high density of receptors in the hippocampus. Baclofen can also frequently promote anxiolysis; this could possibly be explained by an early occurring effect of baclofen on serotonin neurons and on the amygdala. Hyperactivity of serotonin raphe neurons or hyperactivity of the amygdala are mechanisms known to produce anxiety; baclofen acutely inhibits serotonin neurons and serotonin release (27, 28) while short-term baclofen treatment inhibits amygdala reactivity to incentive cues (29). Most importantly, it has recently been shown that alcohol addiction is associated with impaired GABA clearance in the amygdala, with an increase in GABA tone associated with higher anxiety-like behavior (30). Baclofen could possibly improve anxiety through a rapid normalizing effect on amygdala GABA tone. Clinical studies have shown that baclofen has anxiolytic effects in patients with AUD (31) and it has been hypothesized that the anticraving effects of baclofen could be related to an anxiolytic effect (5, 6, 32). A study by Morley et al. showed no anticraving effect in AUD patients, but a secondary analysis showed that baclofen was effective in the group of anxious patients included in the study (33). Given that craving for alcohol is closely related to states of stress (34, 35), the stress-relieving effects of baclofen may contribute to reduce craving in AUD patients. In addition, activation of GABA-B receptors could normalize the abnormal GABA tone in the amygdala and have significant therapeutic effects (36). However, adverse and anxiolytic effects generally occur during the first days or weeks of treatment, while a state of complete indifference most often occurs much later, after one or several months of treatment (depending on the dose needed and the protocol of dose increase). This could imply that complete indifference to alcohol does not result from an immediate or short-term effect of baclofen on GABA-B receptors, but is rather the result of long-term plastic remodeling of certain brain systems.

Preclinical studies have highlighted such plastic effects of baclofen or other GABA-B agonists on brain systems after chronic treatment. Keegan et al. have shown that rats treated chronically with baclofen have significant decreases in G-protein-dependent signal transduction (measured by GTP-gamma-S binding) in the frontal cortex, septum, amygdala, and parabrachial nucleus (37). Such decreases demonstrate a general desensitization of G-protein-dependent systems. But chronically treated rats also show signaling alterations via kinase cascades, including increases in activation of focal adhesion kinase (FAK) and of activated glycogen synthase kinase 3 (GSK3ß), and elevations in phosphorylated dopamine- and cAMP-regulated phosphoprotein-32 (DARPP-32), in several brain structures, which could indicate an absence of desensitization in these structures (i.e., no tolerance). According to Keegan et al. neuroadaptation mediated by G-proteins correlates with tolerance, while signaling alterations via kinase cascades shows cross-talk between GABA-B receptors and alternative mechanisms that are resistant to desensitization. Regarding brain areas, chronic baclofen treatment produced a sustained increase in auto-phosphorylation of FAK in the caudate, an increase in phosphorylations of GSK3ß in the caudate and putamen, and an increase of DARPP-32 in the nucleus accumbens. These actions demonstrate that chronic baclofen can induce significant plastic effects in dopaminergic structures, and that the effects of baclofen in these dopaminergic structures are associated with an absence of tolerance. The Keegan et al. study shows that chronic baclofen treatment also produces a sustained increase in kinase cascades activity in other regions, namely the cortex, thalamus, and hippocampus for FAK; the cortex, thalamus and septum for GSK3ß; and the

cortex, thalamus, hippocampus and amygdala for DARPP-32. These regions are not primarily dopaminergic, but nevertheless receive dopaminergic projections, and, for many of them, they are part of the reward network (38). In summary, chronic baclofen produces G-protein desensitization in a certain number of structures, and alterations in signaling via kinase cascades, with resistance to desensitization, in a set of structures that are closely related to the dopamine network. It may be hypothesized that structures showing desensitization could be involved in the adverse effects of baclofen, which all tend to vanish over time, while structures showing no desensitization are involved in the therapeutic effect on baclofen in AUD—these last structures being possibly involved in the indifference toward alcohol. Indeed, when baclofen produces a complete indifference toward alcohol, there is no tolerance to this effect [no requirement for "markedly increased dose [. . . ] to achieve the desired effect," as tolerance is defined in the DSM-5 (16)]; on the contrary baclofen can be progressively decreased over time in patients indifferent to alcohol, until, for many patients, a possible discontinuation of the treatment after a more or less lengthy period of time.

## THE ANTI-DOPAMINERGIC HYPOTHESIS

All addictive substances alter dopaminergic signaling in the mesocorticolimbic system, and models of addiction posit positive and negative reinforcement as closely linked to dopaminergic reward systems (39). In positive reinforcement, an increase in drinking is associated with increases in the release of dopamine in the brain, producing a feeling of pleasure. Whereas in negative reinforcement, alcohol is taken to alleviate a negative emotional state, and is associated with decreased dopamine in the striatum. And it is widely accepted that, in patients with chronic AUD, reward thresholds are increased and dopamine function is decreased, leading to a general "dopamine-impoverished" brain (40). The enduring reduction of dopaminergic systems activity in patients' brains logically implies that drugs used in the treatment of AUD should enhance dopamine function to restore brain circuits disrupted by alcohol use. The idea of a strict hypo-dopaminergic state in the brain of AUD patients remains controversial (41). However, dopamine antagonists have never shown effectiveness in the treatment of AUD (42). Furthermore, preclinical studies have shown that baclofen inhibits dopamine transmission (43–48). Such dopamine antagonist properties do not *a priori* posit baclofen as a good candidate for the treatment of subjects who have a dopamine-impoverished brain. However, some studies have shown that baclofen could have dose-dependent effects on dopamine systems, with low doses increasing dopamine transmission and high doses inhibiting it. This has been demonstrated in animals (49), in *in vitro* cell preparations (50), and in humans (51).

Studies investigating the effect of baclofen in animal models of addiction show that systemic administration of baclofen reduces the acquisition and maintenance of alcohol consumption (52–55), motivation to drink (56), binge-like drinking (57), relapse-like drinking (58), severity of alcohol withdrawal signs (53), cue-induced reinstatement of previously extinguished alcohol-seeking behavior (59), and the reinforcing and motivational properties of alcohol (60–65) in different validated rodent models of AUD [for review, see (2)]. That baclofen reduces alcohol consumption in animal models has been further strengthened by the demonstration that R(+)-baclofen, and not S(-)-baclofen selectively reduces self-administration of alcohol in rats (66). Regarding the mechanism of action of baclofen in these models, it is generally hypothesized that baclofen reduces alcohol consumption through an anti-dopaminergic effect. The hypothesis is based on two major points. The first is the fact that baclofen has clear anti-rewarding effects. These effects have been shown not only for alcohol consumption, but also for the consumption of cocaine (67), amphetamine (68), and even of non-drug reinforcers such as sucrose, saccharin, or regular food pellets, suggesting that baclofen produces a generalized suppression of reward-motivated behaviors (2). The second is that microinjection of baclofen directly into the VTA blocks the behavioral response to cues and the cue-evoked firing of subpopulations of NAc neurons that respond to predictive cues (69). Baclofen and other GABA-B agonists microinjected into the VTA suppress alcohol-seeking behavior (70), alcohol consumption (71), and alcohol-induced conditioned place preference (72). Microinjection of baclofen in the nucleus accumbens also decreases binge-like alcohol drinking (73). Given that the microinjection of baclofen in the VTA dampens the activity of dopaminergic neurons, it has been hypothesized that baclofen may exert its anti-addictive properties by means of its ability to reduce the activity of dopaminergic neurons (74).

From a clinical standpoint, this hypothesis is not entirely satisfying because the clinical effects of baclofen in AUD patients are not really those of an antidopaminergic effect. Indeed, acute administration of baclofen may produce sedation, and sedation could be related to an inhibition of dopaminergic systems, but baclofen often produces a behavioral disinhibition, and quite frequently an evident hypomania (approximately 15% of patients). Disinhibition could be possibly linked to a dose-related effect of baclofen on dopaminergic neurons, where a low dose of baclofen activates VTA neurons and a high dose inhibits them (50, 51). However, the experience of baclofen treatment in patients with AUD shows that most often the stimulant effect is not dose-dependent; it appears at any dose, and sometimes at high doses. And when a disinhibitory effect occurs at a low dose, it is almost never followed by a state of inhibition when doses are increased, as should be the case if baclofen had a dose-dependent biphasic effect. In baclofen-treated patients, a disinhibitory effect is generally accompanied by a sensation of well-being, or euphoria, or even by a hypomanic state; and it is well established that these feelings or symptoms are associated with an increase in striatal dopamine activity (75–77). On the other hand, inhibition of dopaminergic systems has been consistently related to apathy, anhedonia and depression (78). Baclofen's ability of to produce major depression during treatment of AUD is a subject of discussion [see (79)]; if this were the case, it is certainly very rare. However, baclofen makes patients sometimes feel dull, apathetic, and joyless (approximately 15% of patients),

suggesting, rather, a state of atypical depression that does not meet the criteria of a major depressive episode. This state is possibly related to a hypo-dopaminergic state. Thus, baclofen can produce states of disinhibition/hypomania or of apathy, in about 30% of patients. The large majority of patients never experience these symptoms. This shows that baclofen can have an effect on dopaminergic systems during treatment of AUD patients, but this effect can be that of a hyper- or a hypo-dopaminergic effect, and that it occurs in a minority of patients. More importantly, the clinical experience shows that the states of sedation, apathy, disinhibition, or hypomania have no relation to the therapeutic effect of baclofen; they occur independently of an anti-craving effect, and these symptoms are commonly considered as side-effects of baclofen. As a whole, these elements are not compatible with a general hypothesis that would posit an inhibition of dopaminergic systems as a central mechanism for the anti-addictive action of baclofen (**Table 1**).

Another reason why the therapeutic effect of baclofen in AUD is likely not to be related to a global anti-dopaminergic effect is that it is not compatible with the phenomenology of the state of indifference toward alcohol. Patients indifferent to alcohol are no longer interested in alcohol, but they experience normal enjoyment for the other aspects of their life. People who enjoy life normally necessarily have intact reward systems. The state of indifference is always reached after treatment has lasted for a certain amount of time, which is likely a period of remodeling brain circuits. It cannot be excluded that that an initial blockage of the dopaminergic systems participates in the remodeling of brain circuits. The above-mentioned study by Keegan et al. shows that chronic baclofen treatment induces plastic changes in a number of structures and systems, most of which are part of, or are closely linked with, the brain's reward network.

## LONG-TERM NETWORK ALTERATIONS

The concept of indifference is not a scientific concept, while those of craving and compulsive drinking are such concepts. Craving/compulsive consumption of alcohol occurs after repeated consumption of alcohol, likely in relation with complex adaptations in brain circuits. The challenge is to explain how a chronic treatment with a GABA-B agonist is able to overcome these numerous and complex brain adaptations, and to lead to a state of indifference toward alcohol. The different components of the progressive set-up of the compulsive drinking behavior involve neural substrates that belong to the dopaminergic reward network. Schematically, the reward network has three major components (38): a VTA-ventral striatum/nucleus accumbens system (VTA-NAc) that encodes stimuli valence; a VTA-amygdala/hippocampus system (which in the amygdala includes the basolateral and central nuclei) that forms associative related memories; And a VTA-medial prefrontal cortex system (VTA-mPFC) that regulates executive control. Studies have shown that craving occurring in response to alcohol cues is associated with the activation of structures, which, for the most part, belong the reward system. These structures are the nucleus accumbens/ventral striatum; the anterior, posterior and dorsal cingulate cortex; the orbitofrontal cortex; the dorso-medial prefrontal cortex; the amygdala, the hippocampus and para-hippocampus; and the cerebellum (93–95). These different structures are interconnected through complex networks. Preclinical models have demonstrated that a direct inactivation of some of these structures can suppress craving or the reinstatement of drinking. For instance, it has been shown that inactivation of the prelimbic cortex inhibits ethanol self-administration (80); that the inactivation of the baso-lateral amygdala attenuates context-induced alcohol-seeking (81); or that the inactivation of the ventral subiculum decreases context-induced relapse to alcohol seeking (82). Therefore, inactivation of localized parts of the reward network may globally inhibit craving or compulsive drinking. Studies in AUD patients have shown the same kind of results. Transcranial Magnetic Stimulation (TMS) targeted to the dorsal anterior cingulate cortex (dACC) has been shown to reliably suppress craving (83, 96); a similar effect has been found with Deep Brain Stimulation (DBS) targeted in the nucleus accumbens (84). It is well established that TMS and DBS efficacy are related to their ability to change network connectivity (97).

Many studies have shown that AUD is associated with abnormal brain connectivity. It seems, in a simplified way, that in AUD patients connectivity is increased in regions that are involved in appetitive drive and reduced in regions that mediate executive control, while in long-term abstinent patients activity is decreased in reward circuitry and increased in executive control regions (98–102). This is however a simplified view of the question, which is certainly far more complex (103–108). But the important point in the context of the present article is to highlight that there are dysfunctional networks in the brains of AUD patients, and to try to understand how effective pharmacological treatments used in AUD can normalize these dysfunctional networks. The literature dealing with the effects of pharmacological treatments for AUD on brain connectivity is scarce. A study by Morris et al. (85) showed that AUD patients have heightened local efficiency of neural networks, indicating disturbances of information processing—more isolation and clustering of functionally related regions, stronger processing in certain regions, with less cross-talk between distinct functional processes—, and that naltrexone, a commonly used treatment of AUD, can normalize these abnormalities. Gamma-hydroxybutyrate (GHB), a medication used in the treatment of AUD that activates GABA-B receptors, has been shown to markedly alter functional connectivity in healthy volunteers (109). Generally speaking, it is very likely that all effective AUD treatments, whether pharmacological, psychological, or using local stimulation, do so by normalizing functional connectivity, possibly leading to a decrease in the strength of appetitive networks and to an increase of that of executive control regions, with a recovery of balanced cross-talk between the different local functions.

It is therefore hypothesized that chronic baclofen treatment produces a state of indifference through a normalization of brain network connectivity. Chronic baclofen produces many

**TABLE 1 |** Correspondence between potential mechanisms, symptoms and neurobiological substrates.

| Mechanism | Symptom | Neurobiological substrate | Method | References |
|---|---|---|---|---|
| Dopamine | Anticraving effect | ↘ dopamine in VTA-NAc | Intra-VTA B inject | (2) (review) |
| | Sedation/apathy | ↘ dopamine in VTA-NAc | Peripheral B inject | (44) |
| | Hypomania/mania | ↗ dopamine in striatum | Brain imaging | (75) |
| | Indifference | Long-term remodeling of dopamine circuits? | | |
| Connectivity | Inhibits reinstatement | Inactivation of infralimbic cortex in rats (similar to anterior cingulate in humans) | Gaba inhibition | (80) |
| | Eth seeking decrease | Inactivation of baso-lateral amygdala | Gaba inhibition | (81) |
| | Eth relapse | Inactivation of ventral subiculum | Gaba inhibition | (82) |
| | Anticraving effect | Stimulation of dorsal anterior cingulate | TMS | (83) |
| | Anticraving effect | Stimulation of the nucleus accumbens | DBS | (84) (review) |
| | AUD treatment | Multiple networks | Naltrexone | (85) |
| | Indifference | Gaba tone in the amygdala? | Baclofen | |
| Substitution | Similar effects of Eth and GABA-B activation | Multiple brain structures | Eth and GABA-B agonists studies | (86); (87) |
| | General symptoms | | | (16); (88) |
| | Anxiolysis | | | (89); (90) |
| | Withdrawal | | | (16); (91) |
| | GHB deficiency hypothesis | Brain GHB receptors | GHB studies | (92) |

*B, baclofen; Eth, ethanol; VTA-NAc, Ventral Tegmental Area-Nucleus Accumbens; Gaba inhibition, local injection of baclofen+muscimol; TMS, Transcranial Magnetic Stimulation; DBS, Deep Brain Stimulation. References, only the first author is cited; Two references on the substitution line, the first refers to alcohol, the second to baclofen or other GABA-B agonists.*

changes in the brain that could impact connectivity. We have previously mentioned that chronic baclofen produces plastic changes in regions of the reward system, including desensitization in G-protein-dependent systems and alterations in signaling of several kinase cascades (FAK, GSK3ß, DARPP-32) that are resistant to desensitization (37). In addition, AUD is associated with marked brain neuro-immune alterations (110); and studies have shown that baclofen has anti-inflammatory and neuroprotective effects on the brain. Baclofen attenuates neuro-inflammation (111) and inflammatory signaling (112); inhibits the release of pro-inflammatory cytokines from microglia (113) and from astrocytes (114); and decreases oxidative stress (111); interestingly, baclofen is an allosteric modulator of CXCR4, a receptor for the chemokine CXCL12, which has been causally involved in several neurological disorders, including stroke, brain tumors, HIV encephalopathy and multiple sclerosis (115). GABA-B-receptor activation alters also the activity of dopamine, serotonin, norepinephrine, GABA and glutamate, which are prominent neurotransmitters implicated in alcohol dependence and are involved in the modulation of brain networks. It is not known whether these effects of baclofen on neurotransmitter or neuroimmune factors can alter functional connectivity in AUD, but it has been shown that neuroimmune/neurotransmitter dysregulation in other psychiatric disorders, such as bipolar disorder, disrupt local brain network connectivity and have deleterious effects on the brain, and that these effects can be treated with appropriate pharmacological treatments (116). Abnormal glutamate release and function have been found in the brains of AUD patients and glutamate and/or GABA neurotransmission may underlie resting-state functional deficits in drug addiction (117). Therefore, the effects of baclofen on neuroimmune/neurotransmitter systems may participate in a normalization of functional connectivity in patients with AUD.

Indifference to alcohol is a special phenomenon. The case of Olivier Ameisen is very illustrative (3, 14). Ameisen progressively increased the dose of baclofen up to 270 mg/day, and became completely indifferent to alcohol at that dose. At the dose of 260 mg/day, he was not indifferent at all. It is the addition of 10 mg that abruptly and completely changed his attitude toward alcohol. The long experience of baclofen prescription in AUD shows that this abrupt occurrence of a state of indifference at a given dose is common. Patients call it "my threshold." The threshold of indifference is unique to each patient. Some reach it at moderate doses, some at high or very high doses. The passage from a state of extreme vulnerability to compulsive drinking to a state of indifference is however not always as abrupt as in the case of Olivier Ameisen. Instead, it is often preceded by a period of a slow decrease of craving; but almost all patients who reach a state of indifference say that at a certain dose they felt a complete change in their attitude toward alcohol. For the majority of patients, baclofen treatment is a quest to reach the threshold of indifference. In a recently published guidance for baclofen treatment of AUD, primarily written by expert patients, the quest for the threshold of indifference was clearly described (79). In this guidance article, the authors present what they call the "Ameisen test:" "One of the best ways to confirm that the effective treatment dose has been reached is to ask the patient to go to the shop where s/he used to buy alcohol. If the desire to drink alcohol is ignited by the sight of wine and spirits, the baclofen dose should continue to be increased progressively. If the sight of alcohol has no more effect than looking at nappies or washing powder, the effective dose of baclofen has been reached." Patients indifferent to alcohol are no longer concerned or stressed by the sight of alcohol. Alcohol has become devoid of meaning. It is well established that craving and the subsequent sequence of compulsive drinking are triggered by feelings of stress that can themselves be triggered by the exposition to alcohol cues (118). The analysis of the mechanisms potentially involved in the dose-dependent, and often abrupt, passage from a state of extreme vulnerability to compulsive drinking to a state

of complete indifference is critical in addressing the question of the mechanism of action of baclofen in the treatment of AUD.

From a clinical/phenomenological standpoint, craving and compulsive drinking can be assimilated to a Pavlovian reaction where stress or the activation of an alcohol-related cue or mental imagery is associated with the memory of a reward, and triggers an irrepressible drinking behavioral sequence. The learning of cue-reward associations is a slow process causing long-lasting synaptic plasticity changes in cortico-limbic-striatal circuitry, via multiple gene and protein expression. It is well established that there is a very important relation between stress and alcohol use (34, 35). The biological bases of craving and drinking in response to stress or alcohol cues have been extensively studied in preclinical models of alcohol addiction and in AUD patients themselves. Interestingly, endogenous substances like dopamine and corticotropin-releasing factor and exogenous acute and chronic ethanol act in brain regions that regulate stress and anxiety-related behaviors (119), the most important region being the amygdala. The amygdala is a critical part of the reward network, involved in the way cues associated with rewards gain access to regions attributing incentive salience (120). The way stress and cues associated with rewards are processed in the amygdala may therefore determine subsequent behaviors such as compulsive drinking. Baclofen can interfere with these processes. Baclofen affects memory processes in rodent addiction models, impairing consolidation of memory (121), facilitating extinction learning (122), and interfering with fear extinction (123). Amygdala CREB is known to be involved in the modulation of fear memory (124); and baclofen suppresses stimulant-induced increases in pCREB levels in the amygdala (125). Progressive increase in the reinforcing effects of drug cues is associated with the increases in BDNF and extracellular signal regulated kinase (ERK) activity in the central nucleus of the amygdala (126–128); and GABA-B receptors are involved in the regulation of BDNF release (129), and of the ERK pathway (130). Baclofen also has important neuromodulatory effects in the amygdala, through its inhibitory action on neurotransmitters and complex effects on second-messenger signaling (37). It reduces the strength of excitatory (glutamate) and inhibitory (GABA) transmission in the amygdala by a presynaptic mechanism (131). Furthermore, as mentioned previously, alcohol addiction is associated with impaired GABA clearance and increased GABA tone in the amygdala, associated, in turn, with higher anxiety-like behavior (30). GABA-B receptor stimulation, which inhibits GABA transmission, should therefore be useful in the treatment of alcohol dependence and associated anxiety (**Table 1**).

Chronic neuromodulatory effects of baclofen in the amygdala may change the processing of stress and cues, and ultimately alter the functional connectivity within the reward network, in such a way that cues associated with rewards lose their meaning. The dose of baclofen needed to achieve this effect could be very variable from one subject to another in relation to each individual's variable strength of the Pavlovian association between the cue and the reward. In other words, the dose of baclofen would be that which is necessary to overcome the strength of a long-lasting associative learning "carved" in the limbic memory. This could be in accordance with studies that show that higher doses of baclofen are correlated with a higher severity of addiction (8, 132). Clinical experience also shows that when the effective dose is reached—the threshold dose producing a state of indifference—the treatment has to be continued for several months at the same dose before it can be reduced. It is proposed that this delay is necessary to completely suppress the Pavlovian association between the cue and the reward. It has been highlighted that, in patients indifferent to alcohol, those who remain completely free of alcohol for many months are those who will be able to stop taking baclofen, while those who continue to drink, even at moderate levels and without any real desire for alcohol but who do so out of habit or on certain social occasions, will have greater difficulty in stopping baclofen (79). Indeed, in terms of connectivity and synaptic strength, it is likely that the continuation of regular drinking reactivates the Pavlovian association between the cue and the reward every time, making it impossible to suppress, and paving the way for relapse if baclofen is stopped.

## THE SUBSTITUTION HYPOTHESIS

Alcohol and baclofen produce many similar symptoms or behavioral effects in patients. Both can produce unsteady gait, dizziness, feelings of drunkenness, mood alterations, sensory alterations, confusion, impairment in attention and memory, and sleep disorders, among others (16, 88). Both can also reduce anxiety (89, 90). Patients taking baclofen often spontaneously notice these similarities. Abrupt withdrawal from alcohol and high-dose baclofen may also produce similar symptoms, including confusion, hallucinations, delirium, and seizures (16, 91) (**Table 1**). The main difference between alcohol and baclofen is that alcohol progressively produces a state of dependence, while this is not the case with baclofen (although a few cases have been reported (133)—likely because these are exceptional). Besides, chronic alcohol consumption induces tolerance, whereas tolerance with baclofen is equivocal: as previously mentioned, there is no tolerance to the clinical effectiveness of baclofen in AUD, but there is tolerance to most of its adverse effects (e.g., its effects on locomotor activity) (134).

These clinical similarities raise the possibility that baclofen and alcohol act on the same brain systems, and that baclofen could be a substitution treatment for alcohol dependence. In addictology, a substitution substance is a substance that acts on the same receptors as the targeted substance of abuse. The two substances share many similar effects, but the substitution substance is less prone than the substance of abuse to induce dependence, or not prone at all to do so. Substitution treatments appeared in addictology about 50 years ago for the treatment of opiate addiction. Buprenorphine and other substitution substances used in the treatment of opiate addiction indeed act directly as full agonists, or as agonist/antagonists, on opiate receptors. The problem with baclofen and alcohol is that they do not act on the same receptors. Baclofen is a selective

GABA-B agonist, and alcohol has no direct action on GABA-B receptors. However, it is very likely that the two substances indirectly act on the same systems, especially the glutamatergic and GABAergic systems. Even though alcohol does not directly act on GABA-B, it increases GABA(B1) and GABA(B2) receptor expression in different parts of the brain, while baclofen partially reverses these effects (87). Besides, it has been shown that stimulation of presynaptic GABA-B receptors decreases the GABAergic effects of alcohol (86), demonstrating that GABA-B activation can moderate the behavioral sensitivity to alcohol. This has led Clapp et al. (135) to propose that treatment with a GABA-B agonist could substitute for the anxiolytic effect of ethanol, leading to its reduced consumption. Similarly, GABA-B stimulation may substitute the GABA transporter GAT-3 deficiency in the brains of alcoholics, leading to a normalized GABA function in the amygdala (30). More generally, chronic alcohol consumption alters many brain substances, receptors, and pathways (136), including several that interact with GABA-B receptors, such as, among others, the PKA and PKC pathways (137), the Akt pathway (138), the mTORC-1 pathway (139), the ERK1/2 pathway (130), BDNF release (129), or CREB (125): in all these systems, GABA-B stimulation could, in some ways, substitute for the effects of alcohol. The definition of substitution, limited to the notion that substitution should strictly involve substances that act on the same receptors, has been questioned. For instance, Chick and Nutt proposed much more broad and unspecific criteria to define substitution (140). It remains that chronic alcohol consumption impacts many brain systems and that GABA-B may interfere with some of these effects with potential clinical advantages, assimilated to substitution or not.

Another approach to the substitution hypothesis has been proposed by Ameisen (92, 141), who hypothesized that there is a deficit of GHB in the brain of AUD patients. He highlighted the similar behavioral effects of alcohol, baclofen and GHB. Baclofen and GHB share several common neurobiological effects, including GABA-B activation; among alcohol, baclofen and GHB, only GHB occurs naturally in the brain and has brain specific receptors. According to Ameisen, a deficit in brain GHB could cause dysphoria, itself promoting alcohol misuse. Baclofen could be able to compensate the deficit in GHB, thereby suppressing dysphoria and possible dependence (**Table 1**). Furthermore, GHB itself is used as a treatment of AUD, and it is possible that the effectiveness of GHB is related to its ethanol-mimicking action, making it behave as a substitute for alcohol in the brain (142). Although these are only hypotheses, they exemplify the many ways by which a substance could work as a substitution. However, there are no solid theoretical bases supporting the hypothesis that baclofen is a substitution treatment in AUD.

## CONCLUSION

This review on the mode of action of baclofen from a clinical standpoint and with a biological perspective highlighted three potential modes of action of baclofen; namely on dopamine, functional connectivity, and as a substitution drug. It is tempting to hypothesize that these approaches are complementary, and that they could be synthesized in the proposition that baclofen may suppress the Pavlovian association between cues and rewards through an action in a critical part of the dopaminergic network (the amygdala), thereby normalizing the functional connectivity in the reward network. It is also proposed that this action is made possible by the fact that baclofen and alcohol act on similar brain systems in certain regions of the brain.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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# Full-Profile Pharmacokinetic Study of High Dose Baclofen in Subjects With Alcohol Use Disorder

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Baclofen a gamma amino-butyric acid type B (GABA-B) receptor agonist, which has raised some interest for the treatment of alcohol use disorder (AUD), occasionally at dose up to 300 mg/d. We conducted the first full-profile pharmacokinetic study on baclofen in AUD subjects, up to the oral daily dose of 300 mg. Sixty subjects treated for AUD with marketed baclofen were enrolled in a prospective phase-1 study. Participants were divided into four dose groups (1: <60 mg/d; 2: 60–120 mg/d; 3: >120 mg/d-180 mg/d; and 4: >180 mg/d), and they underwent a full-profile pharmacokinetic analysis of baclofen, using a nonlinear mixed effects modeling. The influence of different clinical and biological covariates was assessed in an upward modeling. Fifty-seven participants completed the study (522 observed concentrations collected). Racemic baclofen showed a linear pharmacokinetic profile, corresponding to a one-compartment model, with no influencing clinical or biological factor. The pharmacokinetic parameters of baclofen were (bootstrap 95% confidence intervals): absorption constant (Ka) 1.64 1/h (1.34–2), clearance (Cl/F) 11.6 L/h (10.8–12.3) and volume of distribution (Vd/F) 72.8 L (66.5–80.4) leading to a half-life of 4.4 h. The interindividual variability (IIV) was 44% (19–65), 21% (16–27), and 22% (11–36) for Ka, Cl/F, and Vd/F, respectively. The residual variability was 24% (21–26). No serious adverse event was reported.

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## INTRODUCTION

Baclofen is a gamma amino-butyric acid type B (GABA-B) receptor agonist, which has been used for treating spasticity since the 1970s (1). In this neurological indication, the oral form of baclofen is usually approved for outpatients at the maximum dose of 80 mg/d. In adult, only a few studies have explored the pharmacokinetic profile of oral baclofen in neurological population or healthy volunteers (2–6). Overall, these studies have found a linear elimination of baclofen. For

example, Wuis et al. after an oral administration of 40 mg baclofen among healthy volunteers, found a half-life of 6.8 (standard deviation: 0.68) hours (2). The same author team investigated the pharmacokinetics (PK) of baclofen among subjects treated for multiple sclerosis at daily doses between 30 and 80 mg/d, and they confirmed the linear elimination of baclofen at this dose range (3). Moreover, the last study found an important interindividual variability (IIV) of baclofen concentrations among the treated patients.

Since the beginning of the 2000s, an increasing interest has been shown on the therapeutic action of baclofen for alcohol use disorder (AUD). Several randomized clinical trials have investigated the efficacy of a dose of 30 mg/d or 50 mg/d baclofen on different AUD outcomes, with contradictory findings (7–12). Marketed baclofen consists of a racemic mixture, which could impact the efficacy results of these clinical trials. In addition, a few observational studies have suggested that baclofen could have a dose-effect relationship in AUD (13–16). The use of high doses, namely up to 300 mg/day in some patients, has been reported in clinical practice for a few years (13–16). In France, an important prescribing practice of high dose baclofen has been observed since 2008 (17), and has been framed by an official temporary regulatory measure issued by the French drug agency up to the dose of 300 mg/d (18). Two recent randomized clinical trials found no efficacy of baclofen up to the maximum doses of 150 mg/d and 180 mg/d, respectively, on abstinence maintenance (19, 20). However, another trial has found that baclofen, at the maximum dose 270 mg/d, was associated with significantly increased abstinence rates at 12 weeks, compared to placebo (21). Altogether, these findings suggest that, should baclofen be efficacious for drinking reduction and abstinence maintenance, the efficacious dose ranges could occasionally exceed 180 mg/d, which was also suggested by a recent observational study (13). However, the spreading use of high dose baclofen has also been associated with some safety concerns, insofar as baclofen exerts a dose-related sedative action that has may potentiate that of alcohol (21, 22). Overall, this situation warrants exploring the pharmacokinetic features of baclofen in AUD, in particular at high dose ranges, to confirm the linear elimination of baclofen up to the dose of 300 mg/d.

So far, the pharmacokinetics and pharmacodynamics of baclofen have been poorly studied in patients treated for AUD. A recent exploratory study has suggested that baclofen exhibits a linear PK profile in AUD subjects, including at high doses (23). However this study was based on sparse data, and only 3 patients received a dose higher than 120 mg/d. A loss of linearity at high dose could thereby not be excluded, in particular in case of a saturation of elimination or a decrease of absorption. In the first situation, the patient is exposed to a toxicity process, whereas the second consists of a lower than expected exposure. A saturation of renal elimination is theoretically not expected, because glomerular filtration seems to be the dominant mechanism of baclofen elimination (2). However, little is known regarding the absorption process of baclofen, and the use of a possible active transport. Moreover, in a 1992 pilot study that was conducted in 11 neurology patients treated with high dose baclofen, an increased half-life was found, thus suggesting a loss in the linear elimination of baclofen at high doses (4). Studies in healthy volunteers described an absolute bioavailabity of 80% (5, 6), but only with doses of 10 or 20 mg.

Furthermore the article by Marsot and collaborators found an important IIV, which was not explained by individual features such as body weight, gender or biological parameters, i.e., creatinine clearance (23). Secondarily, it has been suggested that two sub-groups of patients could be distinguished, with different speeds of clinical response (24). Such IIV could be explained by differences in drug exposure, meaning that patients receiving a similar dose exhibit different blood and/or concentrations and a variability of the drug efficacy is then expected (23). Otherwise, it can be suggested that the IIV is more likely explained by pharmacodynamic factors. Consequently, a clinical PK study in AUD patients, using appropriate dose ranges, was required to distinguish between these two modalities of variability features.

Xylka® is a new oral formulation of 20 mg baclofen tablets which has been developed with the aim to be labeled for AUD (20). A phase 1 study explored the PK of different dose regimens of this new formulation among subjects who were treated by off-label baclofen for AUD in France. The aims of the study were: (1) to confirm the linear PK of baclofen at high dose ranges; (2) to screen for individual features that may affect baclofen exposure; and (3) to assess the safety of this formulation and the safety of switching from the currently approved forms of oral baclofen into the new one and vice versa.

# MATERIALS AND METHODS

## Study Design

This was a Phase I, open-label, steady state study among 60 patients with alcohol use disorder, namely 15 patients in each of the following oral dose ranges: (1) <60 mg/d; (2) 60–120 mg/d; (3) >120–180 mg/d; and (4) >180 mg/d. The total study duration was a maximum of 16 days, including the screening period. Baclofen dispensing and PK sampling were undertaken in a center for clinical investigation (CIC), among three different French university hospitals (Lille, Rennes, and Grenoble).
The different visits were as follows:

- Inclusion Visit: patients were recruited by the investigators within 14 days prior to the PK sampling day (D1).
- Dispensing visit (CIC): 4–7 days prior to D1. Three days before D1, patients had to switch from their marketed baclofen product to the new formulation according to their usual dosing regimen.
- PK sampling visit (D1): patients were admitted to the CIC at least 1 h before the first dose of baclofen and stayed until at least 2 h after the second dose.
- Ending visit (D2): patient were met at the CIC for the last PK sample and collection of patient diaries, and then switched back to the previous marketed baclofen treatment.

## Participants

Sixty subjects were planned to be included in the study. Inclusion criteria were as follows: (1) men and women aged 18 years or more; (2) meeting the DSM-5 criteria for alcohol use disorder; (3)

being treated with marketed baclofen for supporting abstinence maintenance or drinking reduction; (4) on a stable dose of baclofen for a least 1 week prior to the drug switch (see below); (5) displaying normal hepatic function or liver cirrhosis with Child Pugh A or B stage; (6) being able to remain abstinent during housing; (7) being affiliated to the French health insurance system; and (8) if females of childbearing potential, being on an efficient birth control method for at least 14 days prior to the first administration of baclofen.

A patient with at least one of the following exclusion criteria was not eligible for enrolment: (1) hypersensitivity to baclofen or to one of the excipients of the new formulation; (2) pregnancy or breast-feeding; (3) liver cirrhosis with Child Pugh C stage, recent hepatic encephalopathy, or current ascites; (4) severely impaired renal function (defined as a creatinine clearance <30 mL/min according to Cockcroft and Gault formula), or severely impaired cardiac or pulmonary function; (5) uncontrolled epilepsy or any history of seizure in non-abstinent patients; (6) infection by Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV) or Hepatitis C virus (HCV).

## Selection and Timing of Dose for Each Patient

Patients took the tested formulation according to their usual dosing regimen regarding, unit and daily oral doses as well as frequency of administration from 3 days before the day of PK sampling. Since baclofen has a $t_{1/2}$ of ∼5 h, 3 full days of treatment prior to the start of PK sampling ensured a complete washout from the marketed baclofen product. The number of administrations of baclofen over 24 h depended on the patients' needs. However, the daily schedule must have been fairly established to avoid significant variations from a day to another. Every attempt should be made to include patients having at least 4 h between 2 consecutive intakes in the daytime in order to comply with the PK sampling schedule.

## Drug Concentration Measurements

Patients were admitted to the Phase I unit (CIC) for PK sampling for a period estimated between 7 and 18 h, depending on the dosing schedule. No food was provided during the hour preceding and following baclofen intakes (N = primary intake and n = secondary intake).

Blood was collected on D1 over 2 consecutive baclofen intakes (N and n). The blood-sampling schedule followed a sparse sampling design given that the results were treated through a population PK analysis. The timing for blood sampling was not absolutely defined, but they were spread over defined time windows for the different patients. The actual blood sampling times were accurately recorded for each patient.

For each patient, the blood sampling occurred during the following time windows:

- Just prior each of the two baclofen doses (preN and pren).
- After the primary administration of baclofen (N): one blood sample during each of the following time windows: 0–1, 1–2, 2–3 h. At least one blood sample was taken between 3 h and the next administration of baclofen (two samples were taken if sufficient time).
- Following the secondary administration of baclofen (n = N+1 or N-1) one blood sample between 0–1 h and another between 1–2 h.

A last blood sample was taken on D2 before one dose (N or n) of baclofen to determine intra- individual variability on residual drug levels.

A total of 9–10 samples were to be taken from each patient.

**Figure 1** shows the two PK sampling schemes used, depending on the daily baclofen intakes.

Baclofen plasma concentrations were determined with a validated method using LC/MS-MS. The method was linear within a calibration range of 5.00–500 ng/mL. Sample reanalysis was conducted on ∼10% of the assayed samples to demonstrate reproducibility of the analytical method. The concentration levels from this reanalysis were not used for the pharmacokinetic and statistical evaluations. Standard and quality control samples were distributed through each batch of the study sample assayed. Samples with drug concentrations greater than the upper limit of quantification (ULOQ) of the assay range were diluted with the appropriate drug-free biological fluid and reassayed; those that were below the lower limit of quantification (BLQ) were reported as such by the lab.

## Other Data Collected

At the inclusion visit, the following data were collected: (1) age; (2) gender; (3) ethnic group; (4) surgical, medical history and concomitant diseases according to the MedDRA; (5) current tobacco smoking (yes/no) and, if yes, number of daily cigarettes; (6) indication of baclofen (abstinence maintenance or controlled drinking); (7) duration of marketed baclofen treatment (in months); and (8) current average weekly use of alcohol.

At the dispensing visit, the total daily dose (mg), daily number of intakes, and mean dose per intake (mg), of baclofen were noted. Concomitant medications were described according to their anatomical therapeutic chemical code (ATC text level 3) and PT (WHO Drug Dictionary, version of March 2013).

All adverse events (AEs) were collected and described according to their system organ class (SOC), as defined in the Medical Dictionary for Regulatory Activities (MedDRA). AEs were defined as "serious" according to the definition of the Food and Drugs Administration (https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.html).

## Population Pharmacokinetic Analysis

The racemic baclofen mixture was analyzed using a non-linear mixed effects modeling as implemented in NONMEM version 7.3.0 (25). The concepts of this approach known as population pharmacokinetic modeling has been extensively described in the literature (26–28) The First-Order Conditional Estimation (FOCE) with interaction estimation methods was used throughout the modeling. The first step of the base model development was to fit base structural models to the data. Input and output processes was tested as zero,

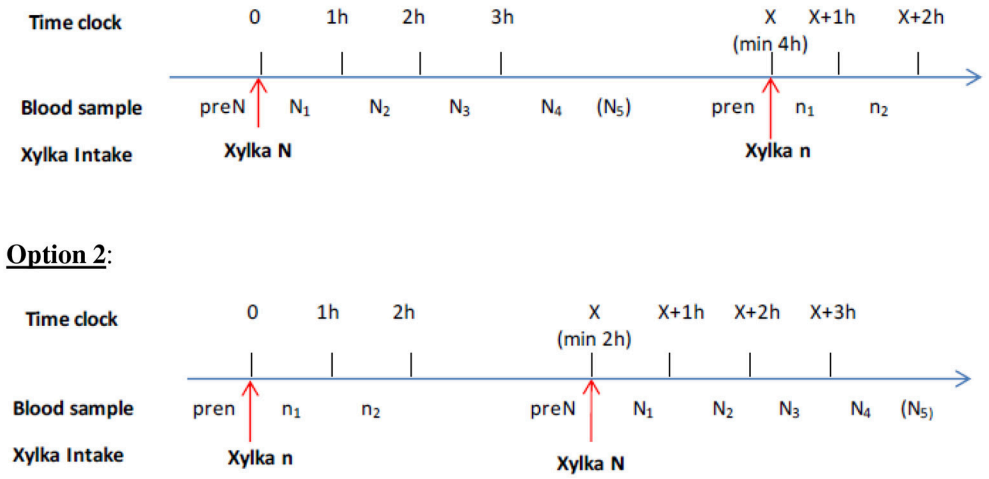


**FIGURE 1 |** Types of PK sampling strategy, depending on the daily baclofen intake.

first order or using a Michaelis-Menten equation. Between-subject variability (BSV) of the different pharmacokinetic parameters was estimated with an exponential error model. Several error models (additive, proportional, or both) were investigated to describe residual unexplained variability (RUV). The performance of the models was judged by both statistical and graphic methods (29, 30). Relative standard errors were calculated by use of the COVARIANCE option of NONMEM. The diagnostic plots were the following: observed concentrations (depending variable, DV) vs. population predictions (CPRED) or vs. individual predictions (IPRED) and Normalized predictive distribution error (NPDE) vs. CPRED or vs. TIME. According to these performances, the model that best described the each set of data was defined as "Base Model."

Once the base model was defined, the influence of different parameters (or covariates), on the pharmacokinetic parameters was explored via an upward model building. These covariates include:

- dose schedule and physiological pieces of information which could impact PK: the daily amount of baclofen (mg) and the inclusion group (GP) but also number of intake by day, sex (1 male, 2 female), body weight (WT in kg), age (yr), body mass index (BMI), lean body mass (LBM).
- and markers of renal and hepatic function: creatinine clearance (CRCL), serum creatinine (CREA), prothrombin time (PT in %), bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

For categorical covariates, if a particular subgroup represents <10% of the overall population, the categories were pooled, as appropriate, to obtain groups with sufficient size for analysis.

The influence of continuous covariates was modeled according to the following equation, using CL for example,

$$CL = TVCL^{*}\{age/median(age)\}^{\theta age}$$

where TVCL is the typical value of CL for a patient with the median covariate value and θ age is the estimated influential factor for age (it can be a positive or a negative effect).

The influence of categorical covariates was modeled according to the following equation, using sex effect for example,

$$CL = TVCL^{*}\ \theta\_sex\ ^{**}(SEX)$$

where TVCL is the typical value of CL, θ_sex is the estimated influential factor for sex effect and SEX = 0 if male, SEX = 1 otherwise.

When more than 2 categories exit (i.e., the dose "group" covariate has 4 levels), different values of the tested PK parameters was evaluated for each level.

The diagnostic plots described above, the change in objective function, and the change in parameter variability was noted to select those which improved the model prediction. A decrease in the objective function value (OFV) of at least 3.84 (chi-squared distribution with one degree of freedom for $P < 0.05$) relative to the base pharmacokinetic model was required for the addition of a single parameter in the model. Covariates selected during the screening step, was included in a so called "full model." This was evaluated by a backward elimination procedure in which each covariate was removed in turn from the "full model" and the difference in OFV between the full and each reduced model was examined. An increase in OFV >10.8 ($P < 0.001$) was required to retain the covariate in the final model (the threshold became 16.3 for 3 ddl).

The performance of the model was judged by both statistical and graphic methods. Bootstrap procedures were performed using Wings for NONMEM (www.wfn.sourceforge.net) to evaluate confidence intervals non-parametrically. The final model was used to simulate new data (500 replicates) from the original dataset using the SIMULATION feature in NONMEM

**TABLE 1 |** Sociodemographics, smoking, and drinking habits, and baclofen dosing features, regarding the subjects included in the study.

| | | Dose range | | | | |
|---|---|---|---|---|---|---|
| | | **<60 mg/d** ***N* = 10** | **60–120 mg/d** ***N* = 15** | **>120–180 mg/d** ***N* = 16** | **>180 mg/d** ***N* = 16** | **Total** ***N* = 57** |
| Age (years) | Mean ± SD | 56.75 ± 9.83 | 44.80 ± 13.21 | 45.16 ± 11.29 | 43.97 ± 9.16 | 46.76 ± 11.73 |
| | Min; Max | 42.2; 75.0 | 23.4; 66.1 | 25.6; 68.7 | 33.8; 59.4 | 23.4; 75.0 |
| Sex | N females (%) | 5 (50.0%) | 3 (20.0%) | 5 (31.3%) | 6 (37.5%) | 19 (33.3%) |
| Smokers | N (%) | 4 (40.0%) | 11 (73.3%) | 13 (81.3%) | 14 (87.5%) | 42 (73.7%) |
| If smoker, N cig/d | Mean ± SD | 22.50 ± 8.66 | 14.64 ± 5.87 | 21.92 ± 8.05 | 16.64 ± 8.39 | 18.31 ± 8.10 |
| **INDICATION FOR BACLOFEN PRESCRIPTION** | | | | | | |
| Abstinence maintenance | N (%) | 8 (80.0%) | 8 (53.3%) | 8 (50.0%) | 9 (56.3%) | 33 (57.9%) |
| Drinking reduction | N (%) | 2 (20.0%) | 7 (46.7%) | 8 (50.0%) | 7 (43.8%) | 24 (42.1%) |
| Duration of marketed baclofen treatment (months) | Mean ± SD | 11.03 ± 10.31 | 11.54 ± 11.31 | 10.80 ± 5.73 | 16.10 ± 11.97 | 12.72 ± 10.19 |
| | Min; Max | 0.2; 26.4 | 0.3; 35.4 | 4.2; 20.8 | 1.7; 39.6 | 0.2; 39.6 |
| Current alcohol abstinence | N (%) | 6 (60.0%) | 10 (66.7%) | 7 (43.8%) | 5 (31.3%) | 28 (49.1%) |
| If no, average weekly alcohol consumption (g alcohol/week) | Mean ± SD | 130.8 ± 235.4 | 82.0 ± 54.0 | 137.8 ± 175.8 | 216.8 ± 255.9 | 158.1 ± 202.9 |
| | Min; Max | 0 ; 49.0 | 0 ; 15.0 | 0 ; 60.0 | 0 ; 84 | 0 ; 84 |
| Baclofen total daily dose (mg) | Mean ± SD | 37.00 ± 9.49 | 93.33 ± 21.93 | 163.13 ± 17.78 | 250.63 ± 39.41 | 147.19 ± 81.91 |
| | Min; Max | 30.0; 50.0 | 60.0; 120.0 | 130.0; 180.0 | 190.0; 300.0 | 30.0; 300.0 |
| Baclofen mean number of daily intakes | Mean ± SD | 2.80 ± 0.63 | 3.40 ± 0.74 | 3.44 ± 1.15 | 3.94 ± 1.48 | 3.46 ± 1.13 |
| | Min; Max | 2.0; 4.0 | 2.0; 5.0 | 2.0; 7.0 | 2.0; 8.0 | 2.0; 8.0 |
| Baclofen mean dose per intake (mg) | Mean ± SD | 13.92 ± 5.24 | 28.49 ± 9.11 | 50.47 ± 11.48 | 70.16 ± 23.19 | 43.80 ± 25.26 |
| | Min; Max | 10.0; 25.0 | 20.0; 50.0 | 25.7; 75.0 | 37.5; 125.0 | 10.0; 125.0 |

*N, number;*
*SD, standard deviation;*
*cig, cigarette.*

(Monte Carlo simulation). These simulated concentrations were then used to construct prediction intervals and were compared with observed data (prediction-corrected Visual Predictive Check).

## Ethics Procedure

The study protocol was submitted to and approved by a national ethics committee before the first inclusions (Avis Comité de Protection des Personnes - Amiens 2013/47). In addition, the protocol was declared on an international protocol register prior to the study start (EudraCT Number 2013-003412-46). Written informed consent was obtained from all patients.

# RESULTS

Among the 60 included patients, 3 of them (5%) prematurely discontinued the study and did not receive any dose of baclofen. Thus, the final study sample consisted of 57 patients. The sociodemographic, smoking and drinking patterns, and baclofen intake features of the included subjects are displayed in the **Table 1**. Only 3 patients were cirrhotic and had a Child-Pugh A score. Two of them were in the dose range >180 mg per day and one in the dose range <60 mg per day.

**TABLE 2 |** Population pharmacokinetic parameters of baclofen.

| **Parameters** | **Estimation** | **Rse (%)** | **Bootstrap 95% CI** |
|---|---|---|---|
| CL/F (L/h) | 11.6 | 3 | 10.8–12.3 |
| Vd/F (L) | 72.8 | 5 | 66.5–80.4 |
| Ka (1/h) | 1.64 | 10 | 1.34–2.00 |
| **BETWEEN SUBJECT VARIABILITY** | | | |
| ω(CL/F) | 0.21 | 14 | 0.16–0.27 |
| ω(Vd/F) | 0.22 | 31 | 0.11–0.36 |
| ω(Ka) | 0.44 | 24 | 0.19–0.65 |
| **RESIDUAL VARIABILITY** | | | |
| σ exponential | 0.24 | 5 | 0.21–0.26 |

*Rse, relative standard error; CL/F, clearance; Vd/F, volume of distribution; Ka, absorption constant; CI, confidence interval.*

No outlier was visually identified, and the modeling was thus performed on all available concentrations (i.e., 522 observations, 57 patients).

The dataset was best described using a one-compartment model, with first order absorption and elimination (ADVAN2, TRANS2 subroutine). The PK model was parameterized in term of clearance (CL/F), volume of distribution (Vd/F), and absorption rate constant (Ka). Between subject variability (BSV)

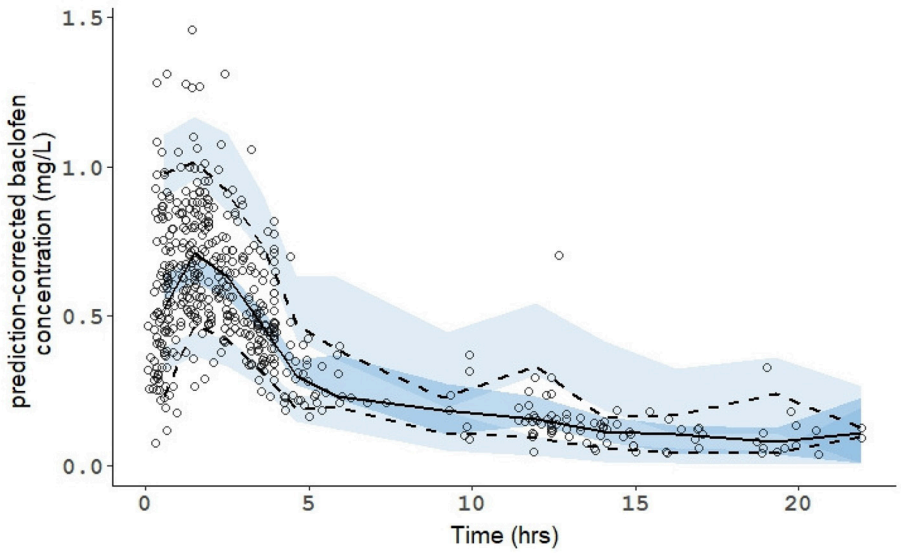


**FIGURE 2 |** Prediction-Corrected Visual Predictive Check (pcVPC) of the population pharmacokinetic model for the racemic mixture of baclofen. The line and the dashed lines are the observed percentiles (50, 5, and 95th percentiles). The shaded fields represent a simulation-based 95% confidence interval for the 5, 50, and 95th percentiles. The observed plasma concentration (prediction corrected) are presented by circles.

of the different PK parameters and residual unexplained variability (RUV) were estimated with an exponential model. The estimates of the shrinkage for CL/F, Vd/F, and Ka were 0.05, 0.22, and 0.37, respectively for baclofen, suggesting that individual estimates for CL/F and Vd/F were robust but less reliable for Ka. None of the covariates tested were able to improve the fit, to decrease the intra-individual variability (IIV) or to decrease significantly the objective function of the model. Thus, the model without any covariate (i.e., basic model) was considered as the final model.

The performance of the model was judged satisfactory as depicted by the diagnostic plots (see **Figure 3**). The plots describing population (CPRED) or individual (IPRED) predicted concentrations vs. observed concentrations showed a good correlation. The normalized predictive distribution error (NPDE) vs. time or CPRED did not show any trend of a bias (**Figure 3**). The values were mostly between −4 and +4 and were evenly distributed around "0." The estimation of the PK parameters is shown in **Table 2**.

The robustness of the estimation was confirmed by the bootstrap method. All estimated parameters were within the 95% confidence interval which demonstrated the stability of the final models. Consistently, the prediction-corrected Visual Predictive Checks confirmed that simulated data are consistent with observed data (**Figure 2**).

Safety features were also assessed during the study. 21 patients (36.8%) presented at least one AE; 37 AEs occurred in total. The System Organ Class (SOC) details of the observed AEs are reported in **Table 3**. No serious AE was observed during the study. No significant changes were observed for vital signs between the dispensing visit and the assessment visit or between the assessment visit and the end of study visit when relevant. No significant values or differences between dose ranges were observed in the clinical laboratory data.

## DISCUSSION

The objectives of the study were: (1) to confirm the linear PK of baclofen with a new formulation; (2) to screen for individual features that may affect baclofen exposure; and (3) to assess the safety of a new oral formulation and the safety of switching from currently approved forms of oral baclofen into the new oral formulation and vice versa.

The concentrations were appropriately described by a linear one-compartment model with first order input, clearance, and a volume of distribution. More complex models did not improve the fit. The final model displayed no formal bias as shown in both the diagnostic plots (see **Figure 1**) and the prediction-corrected Visual Predictive Checks (see **Figure 2**). There was no saturation effect in the absorption, distribution, metabolism, or elimination processes. Consequently, the final model demonstrates the linear kinetics of baclofen over the tested range. This main finding is consistent with what was suggested in previous studies (23, 24). However, before the present study, this was never investigated using richer data, in a full-profile pharmacokinetic study.

As part of the second objective, we explored the covariates that could influence the PK characteristics of baclofen. However, none of the covariate tested were able to explain the IIV or improve the fit of the initial model. Consequently, the final model did not include any covariate. In particular, the clearance was not influenced by the dose used (see **Figure 3**). This result means that no change in metabolism/elimination

**TABLE 3 |** Most frequent adverse events displayed according to System Organ Class and Preferred Term.

| | | Dose range | | | | |
|---|---|---|---|---|---|---|
| **System organ class** | **Preferred term** | **<60 mg/d** ***N* = 10** | **60–120 mg/d** ***N* = 15** | **>120–180 mg/d** ***N* = 16** | **>180 mg/d** ***N* = 16** | **Total** ***N* = 57** |
| **At least one AE** | | 4 (40.0%) | 4 (26.7%) | 7 (43.8%) | 6 (37.5%) | 21 (36.8%) |
| **Nervous system disorders** | | 2 (20.0%) | 1 (6.7%) | 1 (6.3%) | 4 (25.0%) | 8 (14.0%) |
| | Headache | 1 (10.0%) | – | 1 (6.3%) | 2 (12.5%) | 4 (7.0%) |
| | Dizziness | 1 (10.0%) | – | – | 1 (6.3%) | 2 (3.5%) |
| | Paresthesia | – | 1 (6.7%) | – | 1 (6.3%) | 2 (3.5%) |
| **Gastrointestinal disorders** | | – | 1 (6.7%) | 1 (6.3%) | 3 (18.8%) | 5 (8.8%) |
| | Nausea | – | – | – | 3 (18.8%) | 3 (5.3%) |
| | Vomiting | – | 1 (6.7%) | 1 (6.3%) | – | 2 (3.5%) |
| **Psychiatric disorders** | | 1 (10.0%) | 1 (6.7%) | 2 (12.5%) | – | 4 (7.0%) |
| | Anxiety | 1 (10.0%) | 1 (6.7%) | | | 2 (3.5%) |
| | Sleep disorder | | | 2 (12.5%) | | 2 (3.5%) |

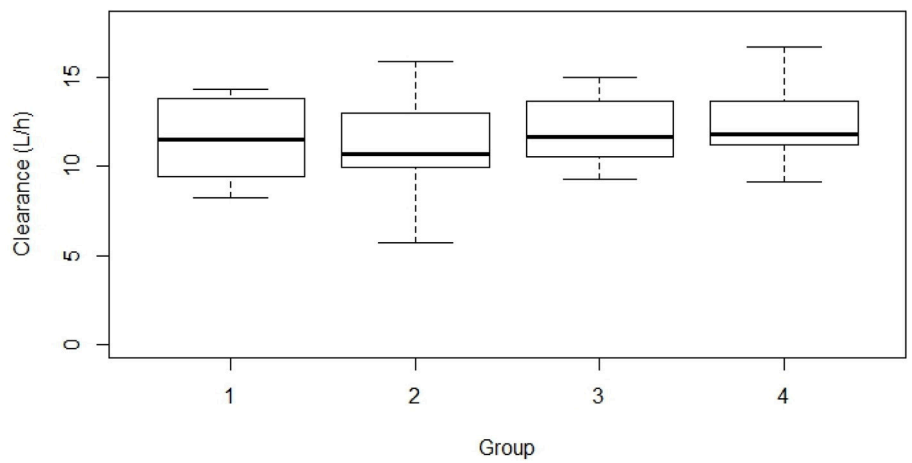


**FIGURE 3 |** Clearance of baclofen according to the group. (1) <60 mgpd; (2) 60–120 mgpd; (3) >120–180 mgpd; and (4) >180 mgpd.

was observed for baclofen up to 300 mg/day. Furthermore, the IIV were 21, 22, and 44% for CL/F, Vd/F, and Ka, respectively. These values are in accordance with previous results which did not find a wide inter-individual variability of the exposure (23). The blood concentrations of baclofen exhibited a linear PK corresponding to a one-compartment model without any influencing covariate. For the doses used in this study (30–300 mg/day), no accumulation after once daily dosing was noted, and no adjustment was required whatever be the gender, body weight, or creatinine clearance.

This set of findings has some clinical and therapeutic implications. The efficacy of high dose baclofen is still under debate, based on the most recent published clinical trials (19, 20, 31). However, the results of some observational studies have suggested that the effectiveness of baclofen was very variable among individuals (13–17), which could be related to a variability of blood exposure. Our study confirms the IIV of baclofen PK parameters (21% for CL/F and 22% for Vd/F), but this variability cannot fully explain the variability of baclofen effectiveness. Other mechanisms should thus be explored to address this variability, including the mechanisms involved in the crossing of the blood-brain barrier, or pharmacodynamics features that may affect the action of baclofen on the GABA-B receptors. This statement is also applicable to some baclofen-induced AEs, for example sedation, whose occurrence is dose-related but also highly variable according to individuals (23). In the light of the present results, such clinical variability cannot be explained by PK features.

The third and last objective of the study was to assess the tolerability of a new oral formulation, as well as the safety of switching from currently approved forms of oral baclofen into a new one and reciprocally. Overall, baclofen was well tolerated, with no serious AEs occurring during the study. The types of non-serious AEs reported with the new formulation were

similar those reported with the off-label use of marketed forms of baclofen for alcohol dependence (22). The switching stages from marketed forms of baclofen to the tested formulation, and reciprocally, were associated with few and mild TEAEs. However, the collecting of safety data in this protocol only consisted of assessing whether safety issues occurred during the study. We did not intend to paint an exhaustive picture of baclofen safety, which has been addressed elsewhere (32). Moreover, other PK studies on baclofen have reported that safety issues could occur in case of impaired renal function (33), and no such patient was recruited in our study. In addition, concerns about suicidal ideations have been raised with the use of high dose (34–36), even if no clear baclofen causality has been found so far (37). However, no suicidal ideation was reported during our study.

In total, this study confirmed that the racemic mixture of baclofen showed a linear PK profile, corresponding to a one-compartment model with no significant influencing covariate. Overall, baclofen was well tolerated, and switching from marketed forms of oral baclofen into the new one, or the opposite, did not induce substantial safety issues.

## AUTHOR CONTRIBUTIONS

NS, BR, and DD, wrote the study design. BR, RM, and MD, recruited the subjects. NS performed the statistical analyses. NS and BR wrote the first draft of the manuscript. NS, BR, DD, RB, RM, and MD contributed to and have approved the final version of the manuscript.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Using Baclofen to Explore GABA-B Receptor Function in Alcohol Dependence: Insights From Pharmacokinetic and Pharmacodynamic Measures

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**Background:** The role of GABA-B neurotransmission in addiction has recently received increased attention, with clinical trials indicating that baclofen, a GABA-B receptor agonist, may reduce alcohol consumption, craving and promote abstinence. However, the optimal dose to treat alcohol dependence is unclear with patients requesting and tolerating much higher doses of baclofen, compared with other clinical uses. We assessed the pharmacokinetics and pharmacodynamics (PK/PD) of baclofen to provide insight into GABA-B sensitivity in this patient group, relative to controls.

**Methods:** Male healthy volunteers (controls, $n = 12$) and abstinent alcohol dependent individuals (AD, $n = 8$) received single oral doses of baclofen or placebo in a 3-way crossover design. Controls received placebo/10 mg/60 mg baclofen in a randomized, double-blind design, AD received placebo/60 mg/90 mg baclofen in a single-blind design. PK/PD measures were recorded at baseline and multiple time-points up to 6 h post-dosing, including plasma baclofen, plasma growth hormone (GH), Subjective High Assessment Scale (SHAS) and biphasic alcohol effects scale (BAES). Repeated measures ANOVA analysis explored "change from baseline" dose, time, group, and interaction effects, *t*-tests compared peak effects.

**Results:** Dose-dependent effects of baclofen on PK and PD measures were observed in both control and AD groups. Whilst there were no significant group differences in any baclofen PK parameters ($t_{1/2}$, $t_{max}$, $C_{max}$, *AUC*), marked differences in PD effects were clearly evident. In controls, 60 mg baclofen significantly increased total SHAS and BAES scores, and significantly increased plasma GH levels compared with placebo, with peak effects at 60–120 min, in line with its PK profile. In AD, 60 mg baclofen had limited effects on these parameters; SHAS scores, BAES scores and plasma GH levels were significantly blunted compared with controls (significant group*time interactions $P = 0.0014$, 0.0015 and $P < 0.0001$, respectively).

**Conclusions:** Our study shows blunted sensitivity to baclofen in AD relative to controls, with no difference in PK suggesting a lower GABA-B receptor sensitivity. This may explain why higher baclofen doses are requested and tolerated in the treatment of alcohol dependence. Our data has implications for choice of dose in future clinical trials in AD and possibly other substances of dependence.

**Keywords: baclofen (PubChem CID: 2284), addiction, pharmacodynamic (PD), pharmacokinetic (PK), alcohol use disorder (AUD), GABA-B receptor, EEG, growth hormone**

## INTRODUCTION

The GABA-B receptor plays a central role in the control of neurotransmitter release and there is good evidence from preclinical studies that modulation of this receptor modifies the brain's reward process and mesolimbic dopamine release (1–3). Preclinical animal studies have shown that GABA-B agonists (e.g., baclofen) attenuate many of the positive reinforcing effects of reward, especially to drugs and alcohol (4–8).

Baclofen is the only selective GABA-B agonist available for use in man. Based on the promising preclinical evidence, its potential to treat alcohol/drug dependence has been investigated. Baclofen is currently licensed for the treatment of spasticity in neurological conditions. However, there is widespread off-label use in the treatment of alcohol dependence, particularly in relapse prevention (9–11). Open-label studies and clinical trials have shown that oral baclofen at doses of 30–80 mg/d can increase rates of abstinence (12, 13), reduce alcohol craving (13–15) and anxiety (14–16), with good tolerance and few side effects (17). Such studies have resulted in increasing off-label use of baclofen in many parts of the world for the treatment of alcohol dependence, particularly for those with higher severity and anxiety levels (9–11, 18). Its widespread use in France led to "Temporary Recommendations for Use" in alcohol dependence in 2014. Marketing Authorization Approval was recently granted by the French National Agency for the Safety of Medicines and Health Products (ANSM) for doses up to 80 mg daily. More recent studies however, have failed to demonstrate a superior clinical outcome of baclofen to maintain abstinence at similar doses (30–60 mg/d), compared with placebo. This may have been due to an increased proportion of participants with milder levels of dependence (19–21). Of note, one study showed a beneficial effect only in those with higher levels of comorbid anxiety (19).

The foremost and critical debate concerning the use of baclofen to treat alcohol dependence has centered on what is the appropriate dose. In the first clinical studies, 10 mg three times a day (30 mg/d) was chosen "based on the minimum therapeutic dosage at the fractioning modality recommended by the drug manufacturer to avoid side effects" (22). Thus the dose of baclofen used in these early clinical studies was determined by its license for, and experience in, treating of muscle spasticity in neurological conditions. However, a case report described using 270 mg/d of baclofen to successfully treat alcohol dependence and to suppress craving and anxiety. The chosen dose was based on neurologists' use of baclofen up to 300 mg/d and the translation of preclinical doses to the clinic (23). Following this report, much higher doses of baclofen began to be requested and prescribed (up to 300 mg/d).

Accordingly, more recent trials included doses of up to 270 mg/d, although the mean dose achieved was generally much lower (24–26). Of these, only one study reported that baclofen was superior to placebo in maintaining abstinence, though no dose-response effects or benefit in craving or anxiety were observed (24). The effective comprehensive psychosocial programme in another of the studies likely reduced the potential for any additional effect of baclofen (25). In the French trial, it was speculated that public debate about taking baclofen whilst drinking impacted on abstinence rates though a "tendency toward a reduction in alcohol consumption and a significantly decreased craving" (26). Whilst trials of higher doses of baclofen generally reported good tolerability and safety, concerns have been expressed about adverse effects at such high doses, particularly when taken with alcohol (27–29).

In the absence of a robust biomarker to assess the efficacy and optimal dose of baclofen to treat alcohol dependence, it is therefore important to understand if the pharmacokinetics of baclofen and/or the sensitivity of the GABA-B system itself is altered in alcohol dependence. In healthy individuals, a linear plasma concentration-dose relationship has been reported after 10–40 mg of baclofen (30–33). However baclofen plasma levels have been reported to be highly variable in alcohol dependent individuals at a range of doses [30–240 mg; (34)]. Concerning the pharmacodynamic effects of baclofen, changes in sedation, impulsivity, EEG markers and psychomotor performance have been assessed in healthy controls at low, i.e., 10–30 mg, doses (32, 35–39). Studies in abstinent alcohol dependent individuals reported blunted baclofen induced growth hormone (GH) release compared with healthy controls (40–44). This blunted release was evident at low doses of baclofen (10–20 mg) but there are no similar studies using higher doses, nor were plasma levels measured.

Despite interest in the clinical use of baclofen in alcohol dependence, and debate around optimal dose, there is a paucity of human laboratory studies characterizing its combined pharmacokinetic (PK) and pharmacodynamic (PD) effects. We therefore explored these measures further by comparing the effects of a single dose of baclofen (10, 60, or 90 mg) with placebo on a range of objective and subjective measures, whilst measuring plasma levels in healthy volunteers (controls) and abstinent alcohol dependent (AD) individuals.

# METHODS

This was a randomized, placebo controlled, three-way crossover study, in which control and abstinent AD participants received a single oral dose of 10, 60, or 90 mg baclofen or placebo (ascorbic acid 100 mg). Study days were separated by at least 1 week and were conducted at the National Institute of Health Research Clinical Research Facility (NIHR CRF) at Imperial College Healthcare NHS Trust, Hammersmith Hospital. Studies were approved by UK National Ethics (NRES) Committees (London-Chelsea, REC number; 11/LO/1973 and West London & GTAC, REC number; 15/LO/1000, for control and AD studies, respectively), and were carried out in accordance with Good Clinical Practice Guidelines and the principles outlined in the Declaration of Helsinki.

## Participants

Healthy male participants (controls, $n = 12$), and male abstinent alcohol dependent (AD, $n = 8$) participants were recruited via advertising, volunteer databases, or through local NHS addiction services and other partner organizations. Dependent individuals met DSM-5 criteria (45) for severe alcohol use disorder, were abstinent for at least 4 weeks prior to study sessions and had never met dependence criteria for other substances (excluding nicotine). Healthy controls were recruited who had no history of drug or alcohol dependence (except nicotine). Exclusion criteria included current use of psychoactive medication (including benzodiazepines, antidepressants and relapse prevention medication), current primary axis I diagnosis, past history of psychosis, past history of enduring severe mental illness. The higher doses of baclofen (60 and 90 mg) used in this study were predicted to produce substantial subjective effects, some of which are similar to those of alcohol. For this reason, we deliberately recruited healthy subjects who were regularly drinking between 8 and 160 g (1–20 UK units, i.e., within recommended safe limits from UK Chief Medical Offer guidelines at the time of testing) of alcohol per week (**Table 1**), and thus were familiar with such central effects. Two of these control participants scored 8–9 on the Alcohol Use Disorders Identification Test (AUDIT) and one participant scored 20 (though stated he had recently reduced his alcohol intake). Careful screening by a psychiatrist with addiction expertise, found no evidence of current or previous alcohol use disorder in these participants. There were two separate cohorts of controls recruited. Cohort one was recruited first ($n = 9$) in order to establish the PK-PD protocol, and consisted of young male volunteers (average age 24.7 years). Cohort two ($n = 3$, average age 52.0 years) was recruited alongside the AD cohort (average age 53.1 years), in order to provide a better age match, and to allow higher doses of baclofen to be explored. There were no PK or PD differences in response to baclofen between young and old controls, and no correlation between age and PD variables, so control data were collapsed across cohorts, unless otherwise stated.

Following informed consent, subjects attended a screening visit which included taking medical, psychiatric and alcohol use history, a physical examination, routine blood hematology/biochemistry and electrocardiogram. Participants also completed the Fagerstrom test for nicotine dependence (46), Spielberger Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI (47) and Locus of Control Scale (48). A time-line follow-back was completed to calculate lifetime alcohol exposure in the AD cohort. High-risk alcohol exposure was calculated as lifetime cumulative weeks with greater than 60 g average daily alcohol consumption, converted into years [according to WHO guidelines, (49)].

**TABLE 1** | Demographic variables.

| | Healthy control, $n = 12$ | Alcohol dependent, $n = 8$ |
|---|---|---|
| Age (range) | 31.5 ± 13.2 (21-56) | 53.1 ± 8.9* (39-63) |
| BMI | 23.8 ± 5.1 | 31.3 ± 4.9* |
| Current smokers (n) | 0 | 4 |
| Cig/day | – | 11.3 ± 14.4 |
| Fagerstrom | – | 7.0 ± 2.3 |
| AUDIT (range) | 7.8 ± 5.6 (2-20) | – |
| Alcohol intake (g/week) | 67.2 ± 42.4 | – |
| Months abstinent (range) | – | 34.9 ±27.0 (8-72) |
| Lifetime 'high risk' alcohol exposure (years) | – | 21.1 ± 11.8 |
| Beck Depression Inventory | 3.2 ± 4.7 | 4.1 ± 3.9 |
| STAI (trait anxiety) | 32.2 ± 9.2 | 36.1 ± 8.6 |
| Locus of Control Scale | 6.3 ± 2.0 | 6.4 ± 2.9 |

*Values are mean ± S.D. unless otherwise stated.*
**P < 0.05 unpaired t-test.*

## Procedures

On each study day, eligibility was checked, including a negative urine drug screen and alcohol breath test. Caffeine intake was permitted but was matched across study days. All participants had breakfast and were provided with a similar lunch. An intravenous cannula was inserted for blood sampling (for baclofen and GH levels) and electrodes were applied for EEG monitoring. Objective and subjective measurements were variously undertaken at baseline (prior to baclofen dosing) and at 30, 60, 120, 180, 240, and 360 min after dosing, including measures of vital signs, rating scales, psychomotor performance and adverse events. Due to the time to complete certain measures (e.g., EEG), the subjective questionnaires were performed 15–20 min later than the times indicated. Participants were allowed to smoke *ad-libitum*, to reflect their typical cigarette use, so were not in overt withdrawal during behavioral or EEG measurements. Smoking breaks were taken at the same time across sessions, wherever possible.

Following completion of baseline measures, controls were dosed with either oral placebo, 10 or 60 mg baclofen in a randomized, double-blind cross-over manner. In the first control cohort, 9 participants received placebo, 8 received 10 mg baclofen and 9 received 60 mg baclofen. In the second control cohort, 3 received placebo, 3 received 60 mg and 1 received 90 mg baclofen. The 90 mg baclofen dose was administered in a single-blind

manner, but the effects were not well tolerated, so this test dose was abandoned in further control participants.

The AD group were dosed with placebo, 60 or 90 mg baclofen in a randomized, single-blind cross-over manner. In this case a pseudo-randomization was adopted in order to ensure that participants could tolerate the 60 mg dose of baclofen, prior to receiving the higher 90 mg dose. Researchers were aware of the pseudo-randomization but participants were not, so remained fully blinded. In hindsight, because of the greatly increased tolerance to baclofen in this group, the need for pseudo-randomization was unwarranted. In the AD cohort, 8 received placebo and 60 mg baclofen, and 6 received 90 mg.

## Drugs

Drugs were supplied by Hammersmith Hospital Pharmacy and comprised of baclofen (10 mg, white scored tablets, or ascorbic acid (vitamin C, 100 mg, white scored tablets). Drugs were stored within the NIHR CRF and prescribed by the study doctor according to the randomization on the day of testing. To maintain blinding, drugs were administered by a study nurse who had no further part in the study. All participants were blindfolded and took their tablets with plenty of water. In controls, 6 tablets were administered (6x vitamin C, 6x baclofen 10 mg, or 1x baclofen 10 mg with 5x vitamin C. The AD group took 9 tablets (9x vitamin C, 9x 10 mg baclofen or 3x vitamin C with 6x 10 mg baclofen).

## Blood Sampling and Assays

Blood samples were taken from the venous cannula at $t = 0$ (prior to baclofen dose), then at +30, 60, 120, 180, 240, and 360 min time points post baclofen dose and stored on ice. Plasma was separated by cold centrifugation and stored at −30°C for later analysis.

### Growth Hormone Assay

Plasma GH levels were measured (μg/L) using a standard IMMULITE®2000XPi solid-phase, two-site chemiluminescent immunometric assay system with a sensitivity of 0.05 μg/L. Analyses were carried out by the Clinical Biochemistry Department, Imperial College Healthcare NHS Trust, Charing Cross Hospital, London, UK.

### Baclofen Assay

Plasma concentrations of baclofen were measured using the liquid chromatograph mass-spectrometry (LC-MS) method as previously described (50), at the Toxicology Unit, Imperial College London.

## Pharmacokinetics

Pharmacokinetic parameters were calculated by modeling the data as follows: plasma concentrations ($C_P$) of baclofen at time $t$ were fitted using a non-linear least squares algorithm to a first-order absorption-elimination model (absorption constant; $k_a$, elimination constant; $k_e$, mass of drug administered x fraction of drug absorbed; $X_a$) to calculate the following parameters: peak plasma concentration ($C_{max}$) and time to reach $C_{max}$ ($t_{max}$) (both solved graphically), half-life ($t_{1/2}$) (ln 2/$k_e$ and area under the curve ($AUC$) for the duration of the recording, according to the formula:

$$C_P(t) = \frac{X_a \cdot k_a}{k_a - k_e}(e^{-k_e(t)} - e^{-k_a(t)}) \quad (1)$$

Further, the relationship between plasma levels of baclofen and the EEG response were estimated using a simple two-compartment (or one-tissue-compartment) model, which is incomplete but practical and suited to the data available. If the EEG response is assumed to be directly coupled to the mass of baclofen in the brain, then the brain is treated as a single compartment and only uptake ($K_1$) and washout ($k_2$) rates are needed to describe the change in EEG power ($P_{EEG}$) (see Equation 2).

$$\frac{dP_{EEG}(t)}{dt} = K_1 C_P(t) - k_2 P_{EEG}(t) \quad (2)$$

Solving this equation, we fit $P_{EEG}$ over time using a convolution integral of the plasma model with a monoexponential curve (Equation 3), using a non-linear least squares optimizer.

$$P_{EEG}(t) = C_P(t) \otimes K_1 e^{-k_2 t} \quad (3)$$

## Objective Measures

Heart rate and blood pressure observations were made using a Phillips SureSigns VM4 monitor. The "Zig-Zag" pencil and paper maze test of motor coordination and sedation was administered at all time-points except 30 min post dosing [Zig-Zag Tracking task; (51)].

EEG was acquired using the Neuroscan (Compumedics) system, with a sampling rate of 1,000 Hz. A total of 24 electrodes were placed according to standard 10–20 criteria, and EEG was recorded for 5 min with eyes open and 5 with eyes shut at each time point, using Cz as the common reference. During recording, subjects were seated upright in a reclining chair and were asked to try and stay awake. If they fell asleep during eyes closed they were allowed to doze but were woken if the EEG showed sleep during the eyes open period. In the control group, for the placebo and 60 mg conditions $n = 7$ recordings were available for analysis (3 data sets were lost due to interference & technical issues). For the 10 mg condition a further data set was lost (due to drop-out), resulting in $n = 6$ overall. In the AD group, $n = 6$ recordings were collected, however, these were not further analyzed after visual inspection (see below results).

Offline analysis was performed visually and automatically for each recording. We first carried out visual scoring of all recordings using a scale for daytime sleepiness previously used by our group (52), which uses the presence of eye movements, muscle activity, alpha and theta activity to assign a score to each 15 s' activity. Data were examined visually for gross artifacts (e.g., head movements) and sections containing these were removed. Because data from periods with eyes open included copious eye movement and muscle artifacts, we excluded the electrodes Fp1, Fp2, F8, F7, A1, A2 from the analysis, leaving 15 recording electrodes. The data were then globally re-referenced (excluding electrodes outlined above, Cz and any channels

identified as poor) and segmented into epochs of 2 s in length. Using the FieldTrip toolbox, a low pass filter was applied (35 Hz) and any bad channels interpolated using the spline method. Frequency analysis was conducted using Hanning windowed fast Fourier transforms between 1 and 50 Hz at 0.5 Hz frequency steps. For statistical analysis, theta (4–8 Hz) band activity was extracted from individual spectra (53, 54). We did not investigate the delta spectra as we were unable to accurately remove all eye movements which contaminated this band. Pre-dose baseline recordings were subtracted from each time-point to give change from baseline, and then paired contrasts were performed between placebo and 60 mg baclofen using permutation testing of t statistics (54). False discovery rate (FDR) across multiple channels with each comparison was controlled using resampling, with 50,000 permutations for each map.

## Subjective Measures

Participants completed the following rating scales at all time points: Subjective High Assessment Questionnaire [SHAS, (55)], Drinking Expectancy Questionnaire [DEQ, (56)], Biphasic Alcohol Effects Scale [BAES; (57)], and verbal visual analog scales (VAS) using a visual prompt (0–100) for Sleepy, Relaxed, Tense and Alert.

## Data Analysis

All statistical analyses were carried out using Graphpad Prism, version 7.00 or IBM SPSS (version 24). For graphical representation and statistical analyses, raw data were converted to change from baseline (CB) with the exception of plasma baclofen levels. In a small number of missing value cases, data were interpolated using the average of time points either side of the missing data. Repeated measures ANOVAs were used to explore effects of dose, time and interaction for within-subjects comparisons in those participants who were able to complete *all* measures for that variable, with Tukey's multiple comparison *post-hoc* test to determine significant dose effects at each time-point. Mixed ANOVAs were used to explore effects of group, time and interaction across all subjects, as appropriate, with Sidak's multiple comparison *post-hoc* test to determine significant group effects at each time-point. Paired and unpaired *t*-tests were conducted to determine dose and group differences, respectively, at peak baclofen concentrations ($t = 120$ min time-point). Correlations were based on Spearman's rho or Pearson correlation coefficients. For GH data, all non-determinable values (i.e., those that fell below the limit of detection of 0.05 μg/l) were replaced with 0.05/2 (i.e., 0.025) to avoid data skew.

# RESULTS

## Demographics

Control participants were significantly younger than AD patients, with lower body mass index, and there were fewer current smokers in this group (**Table 1**). There were no significant group differences between depression, anxiety and locus of control scores.

## Pharmacokinetics

Plasma levels increased in a dose-dependent manner following oral administration with baclofen in both controls and AD (**Figure 1**). No baclofen was detected in plasma samples after placebo. Good separation was observed between 10 and 60 mg baclofen doses in controls, and between 60 and 90 mg doses in AD, although there was considerably more variability at the higher doses in both groups. Significant increases in $C_{max}$ values were observed with increasing dose (**Table 2**). Modeled data revealed that there was a significant increase in $C_{max}$ with increasing dose in both groups as expected. An increase in $t_{max}$ was evident between 10 and 60 mg baclofen in controls, where $t_{max}$ occurred approximately 30 min later (62 and 88 min for 10 and 60 mg, respectively). $t_{max}$ was similarly increased following 90 mg compared with 60 mg in AD (135 and 102 min, respectively). There were no significant differences in any PK parameters between controls and AD following the 60 mg baclofen dose (**Table 2**). Terminal half-life ($t_{1/2}$) was consistently around 3 h, independent of dose or group (**Table 2**).

## Pharmacodynamics-Objective Measures

### Growth Hormone

In controls, baclofen dose-dependently increased GH levels at 10 and 60 mg doses (**Figure 2A**), with peak effects measured at 120 min. Peak plasma GH levels were over 2-fold higher following 60 mg (observed $C_{max}$: 10.8 ± 6.0 μg/ml) compared with 10 mg baclofen (observed $C_{max}$: 4.1 ± 4.9 μg/ml). Both returned to baseline levels within 240 min. GH was unchanged after placebo. In AD, there was no significant effect of baclofen dose on GH (**Figure 2B**). An effect of time was observed [$F_{(6,30)} = 3.223$, $P = 0.015$], driven by a small but significant increase in GH after 90 mg baclofen at the 120 min time-point only, where plasma levels reached 3.0 ± 4.8 μg/ml.

This marked differential effect of baclofen on GH release between groups at the 60 mg dose is depicted in **Figure 2C**), in which it can be observed that baclofen-induced increases in GH are absent in the AD group relative to controls. There was no significant difference between younger ($n = 9$) and older ($n = 3$) cohorts of healthy controls in their GH response to 60 mg baclofen, and there was no association between age and GH response in our control sample ($R^2 = 0.0671$) so the absence of a response in AD group is not age-related.

### Zig-Zag Tracking Task

Optimal performance on this task is achieved through a trade-off between speed and accuracy, and is typically subject to practice effects. It can be observed that in controls under placebo, the error rate improves over the first three attempts at the task then subsequently plateaus, whilst the time to complete the task continues to shorten over the course of the whole testing period (**Figures 3A,B**). Under 60 mg baclofen, the relative improvement on error rate did not occur with time. Although there were no overall significant effects of dose on zig-zag task performance across the whole testing period, there was a trend for an effect of dose on error rate [$F_{(2,16)} = 2.94$, $P = 0.08$], such that

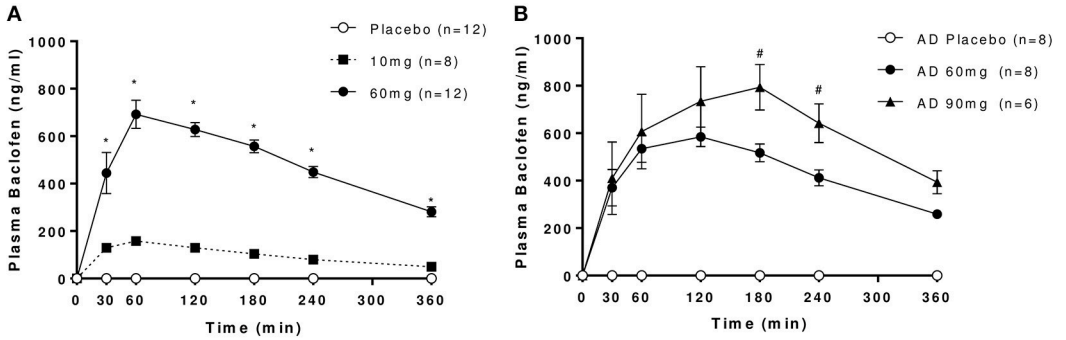


**FIGURE 1 |** Plasma levels of baclofen following oral administration of 10, 60, or 90 mg baclofen or placebo in **(A)** controls and **(B)** AD. Data are mean ± S.E.M. Repeated measures ANOVA revealed significant effects of time, dose and dose by time interaction in controls ($n = 8$): Time: $F_{(6, 42)} = 58.1$, $P < 0.0001$, Dose: $F_{(2, 14)} = 227.7$, $P < 0.0001$, Dose × Time: $F_{(12, 84)} = 43$, ($P < 0.0001$) and in AD ($n = 6$): Time: $F_{(6, 30)} = 9.5$, $P < 0.0001$, Dose: $F_{(2, 10)} = 122.6$, $P < 0.0001$, Dose × Time: $F_{(12, 60)} = 5.7$, ($P < 0.0001$). *60 mg > 10 mg, #90 mg > 60 mg ($P < 0.05$, Tukey's multiple comparison test).

**TABLE 2 |** Pharmacokinetic parameters with 95% confidence intervals for model fit.

| | Healthy controls | | Abstinent AD | |
|---|---|---|---|---|
| | **10 mg ($n = 8$)** | **60 mg ($n = 12$)** | **60 mg ($n = 8$)** | **90 mg ($n = 6$)** |
| $C_{max}$ (ng/ml) | 154.4 | 681.9 | 593.7 | 786.4 |
| 95% C.I. | (134.4–174.1) | (390.9–998.5) | (547.0–641.7) | (0–5,763) |
| $T_{max}$ (min) | 62 | 88 | 102 | 135 |
| 95% C.I. | (57–67) | (82–111) | (101–104) | (0–360) |
| $t_{1/2}$ (h) | 2.7 | 3.0 | 2.8 | 2.7 |
| 95% C.I. | (2.4–3.1) | (2.3–5.4) | (2.7–3.0) | (0–5,000) |
| *AUC* (min*ng/ml) | 35,734 | 174,944 | 155,824 | 215,680 |
| 95% C.I. | 30,604–41,555 | 101,060–282,511 | 142,744–169,777 | 0–1,875,126 |

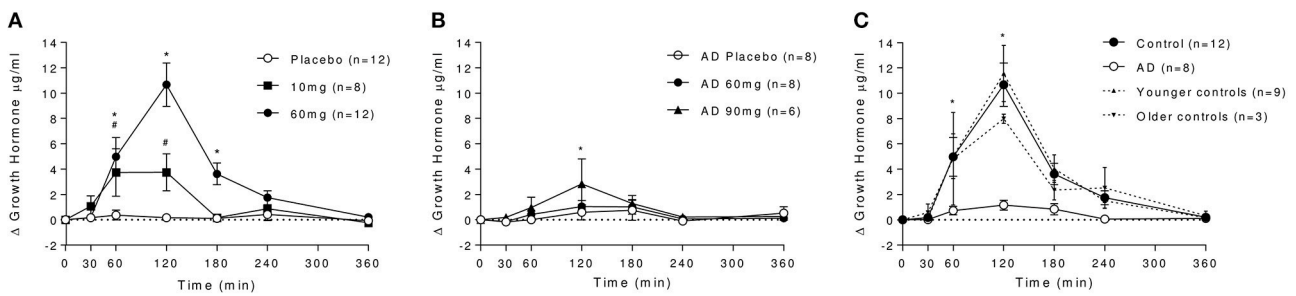


**FIGURE 2 |** Effect of baclofen on plasma GH levels in controls and AD. Data are mean ± S.E.M. **(A)** Effect of placebo, 10 and 60 mg baclofen on GH levels in controls. A significant effect of time, dose and a dose by time interaction was observed [$n = 8$, Time: $F_{(6, 48)} = 10.44$, $P < 0.0001$, Dose: $F_{(2, 16)} = 11.34$, $P = 0.0009$, Dose × Time: $F_{(12, 96)} = 10.16$, $P < 0.0001$]. *60 mg > placebo, #10 mg > placebo ($P < 0.05$, Tukey's multiple comparison test). **(B)** Effect of placebo, 60 and 90 mg baclofen on GH levels in AD. *90 mg > placebo ($P < 0.05$, Tukey's multiple comparison test). **(C)** Differential effect of baclofen on plasma GH levels in controls and AD. A significant effect of group [$F_{(1, 18)} = 15.36$, $P = 0.001$], time [$F_{(6, 108)} = 16.35$, $P > 0.0001$] and a dose × time interaction [$F_{(6, 108)} = 10.31$, $P < 0.0001$] were observed. *Control > AD ($P < 0.05$, Sidak's multiple comparison test). Differential effects on GH in younger controls (cohort 1, $n = 9$, dashed line) and older controls (cohort 2, $n = 3$, dotted line) are also depicted in **(C)**. There was no significant difference between GH levels following baclofen in younger and older control cohorts at any time point, and the significant differences between AD and both young and old controls remained (mixed ANOVA with Sidak's multiple comparison test). The average age of the younger cohort was 24.7 ± 4.7 years, compared with the older cohort (average age 52.0 ± 6.1) and the AD group (53.1 ± 8.9 years).

significant increases in errors were observed at 60 and 180 min post 60 mg dose relative to placebo. A significant reduction in time taken to complete the task over time was observed, independent of dose [$F_{(6, 48)} = 4.14$, $P = 0.002$], reflecting an overall improvement in task performance with practice in controls.

In the AD group, under placebo there were no apparent improvements in error rate with practice (**Figure 3C**). Indeed,

an increase in the number of errors made under placebo relative to baclofen was observed at earlier time points, which coincided with reductions in time taken to complete the task (**Figure 3D**). There was no significant effect of time on task performance and no significant dose or interaction effects. After 90 mg, there was a significant slowing in speed of completion at 60 and 120 min post dose relative to placebo (**Figure 3D**), with a corresponding reduction in the number of errors made (**Figure 3D**). There were no significant effects of 60 mg baclofen in AD relative to placebo.

Direct comparisons between the effects of 60 mg baclofen across groups revealed no significant differences in performance ($n$ = 12 and 8, data not shown), but all participants showed

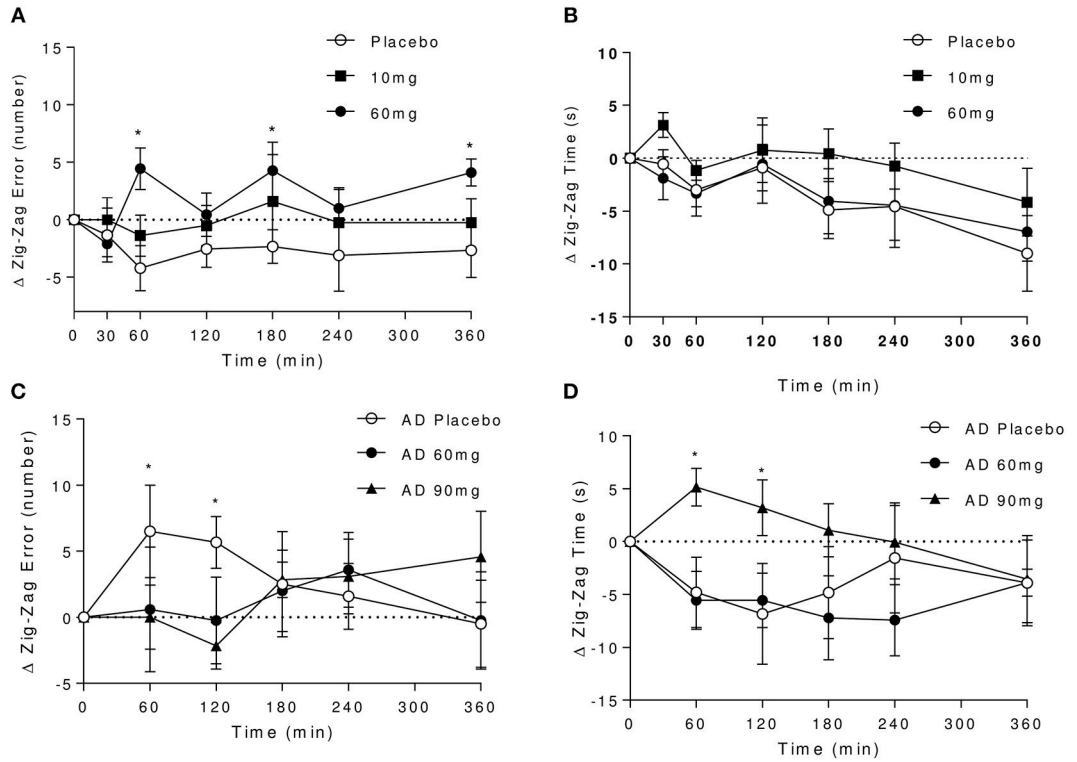


**FIGURE 3 |** Effect of baclofen on Zig-Zag tracking task performance in controls and AD. Data are mean ± S.E.M. **(A)** number of errors following administration with placebo, 10 and 60 mg baclofen in controls. No significant time or interaction effects, trend for an effect of dose [Repeated measures ANOVA, $n = 9$; effect of dose: $F_{(2, 16)} = 2.94$, $P = 0.08$], *60 mg > placebo ($P < 0.05$, Tukey's multiple comparison test). **(B)** Time to completion after placebo, 10 and 60 mg baclofen in controls. Significant effect of time [$F_{(6, 48)} = 4.14$, $P = 0.002$], no effect of dose or interaction. **(C,D)** Number of errors and time to completion after placebo, 60 and 90 mg baclofen in AD. No overall significant dose, time or interaction effects were observed ($n = 6$), but significant effects of 90 mg dose were observed at 60 and 120 min ($P < 0.05$), **(C)** *90 mg < placebo, **(D)** *placebo > 90 mg.

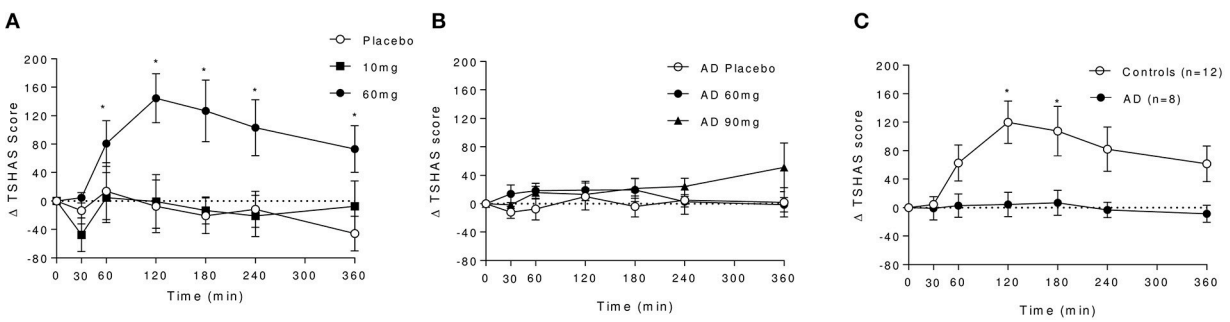


**FIGURE 4 |** Effect of baclofen on Total SHAS (TSHAS) scores in controls and AD following placebo, 10, 60, or 90 mg baclofen. Data are mean ± S.E.M., expressed as change from baseline. **(A)** Effect of placebo, 10 and 60 mg baclofen on TSHAS in controls. Repeated measures ANOVA; Dose × Time Interaction: $F_{(12, 96)} = 3.20$, $P = 0.0007$. *60 mg > placebo ($P < 0.05$, Tukey's multiple comparison test). **(B)** Effect of placebo, 60 and 90 mg baclofen on TSHAS in AD. Repeated measures ANOVA; no significant effect of dose or time, significant dose by time interaction [$F_{(12, 60)} = 2.37$, $P = 0.014$], *90 mg > placebo ($P < 0.05$, Tukey's multiple comparison test). **(C)** Comparison of the effect of 60 mg baclofen on TSHAS in controls and AD. Mixed ANOVA; significant group effect: $F_{(1, 18)} = 6.0$, $P = 0.025$). *60 mg > placebo ($P < 0.05$, Sidak's multiple comparison test).

significantly reduced completion times with practice at this dose [effect of time; $F_{(5,90)} = 3.77$, $P = 0.004$].

Overall this suggests differential effects of baclofen on tracking performance. The data suggest there may be an effect of 60 mg baclofen (but not 10 mg) to impair performance without sedative effects in controls, and an effect of 90 mg (but not 60 mg) to produce a slowing of performance in AD, possibly reflecting sedative component.

### Vital Signs

In controls, there were no significant effects of baclofen on blood pressure or heart rate overall, although a significant reduction in HR in response to 10 mg baclofen was evident at high plasma baclofen concentrations (60 and 120 min). There was a significant decrease in diastolic blood pressure over time [$F_{(6,48)} = 8.13$, $P < 0.0001$] independent of dose, and time-dependent alterations in systolic blood pressure were also observed which were in keeping with task-related activity and time of day effects [$F_{(6,48)} = 2.45$, $P = 0.038$].

In AD ($n = 6$), there was a marginally significant dose by time interaction effect of baclofen on diastolic BP [$F_{(12,60)} = 1.97$, $P = 0.044$]. In addition, systolic and diastolic BP were transiently increased by 60 mg baclofen at 120, 180, and 240 min relative to placebo. As was observed in controls, a significant effect of time on systolic BP [$F_{(6,30)} = 6.75$, $P = 0.0001$] was observed.

In group comparisons between controls and AD after 60 mg baclofen ($n = 12$ and 8), a significant group by time interaction effect on HR was observed [$F_{(6,108)} = 3.04$, $P = 0.0087$], such that HR tended to increase in controls and decrease in the alcohol group with time relative to baseline. No significant peak effects were observed in any measure.

None of the effects observed were deemed to be clinically significant.

## Pharmacodynamics-Subjective Measures

### SHAS

A robust increase in total SHAS scores was observed in controls following baclofen [Dose × Time Interaction: $F_{(12,96)} = 3.20$, $P = 0.0007$, **Figure 4A**], with significant effects of 60 mg compared with placebo at all time-points except 30 min. Peak effects were observed at $t = 120$ min which diminished with time but remained significant at 6 h post dose. Subscore analyses revealed that increases at $t = 120$ min in response to baclofen relative to placebo were driven primarily by items related to sensations similar to the effects of alcohol such as feeling "drunk," "effects of alcohol," "dizzy," and "float" (**Figure 5A**), all of which were significantly increased by 60 mg baclofen. In repeated measures ANOVA analyses, these subscales also demonstrated overall significant dose and dose by time interaction effects (data not shown). **Figure 5A** shows the outcome of paired *t*-tests comparing the TSHAS raw scores at $t = 120$ min between placebo and 60 mg baclofen, uncorrected. A trend for a reduction in the "uncomfortable" item was observed in controls following the 10 mg dose [Dose by Time interaction: $F_{(12,96)} = 1.83$, $P = 0.053$], which was significant at all time-points relative to placebo except 360 min.

In the AD group, no significant effect of baclofen at the 60 mg dose was observed on total TSHAS scores. A significant Dose by Time interaction was apparent [$F_{(12,30)} = 2.37$, $P = 0.014$] which was driven by a significant effect of 90 mg relative to placebo at the 360 min time-point only. There were no significant differences in subscore items between placebo and 60 mg at peak baclofen concentrations (**Figure 5B**). The only subscore item which displayed significant dose effects in this group was "sleepy" [Dose by Time interaction: $F_{(12,60)} = 2.18$, $P = 0.024$], in which there was an increase following 90 mg at the 360 min time-point (thus mirroring the overall interaction effect in total TSAS score).

Comparison of TSHAS scores ($n = 12$ and 8) revealed substantial differences between the control and AD group to 60 mg baclofen (**Figure 4C**). TSHAS scores were markedly lower in AD relative to controls for the duration of the study day [group effect: $F_{(1,18)} = 6.0$, $P = 0.025$], with peak effects at 120 and 180 min. TSHAS subscore analyses revealed significant blunting of the effect of baclofen in the AD group in "drunk" and "effect of alcohol" items (significant group effects) relative to controls. Significant blunting at peak baclofen concentrations was observed in the following TSHAS items; "drunk," "dizzy" "effect of alcohol," "muddled," and "difficulty concentrating" (unpaired *t*-tests, uncorrected).

### BAES

Significant increases in total BAES scores were observed in controls following 60 mg baclofen [Dose: $F_{(2,16)} = 3.85$, $P = 0.043$, Interaction: $F_{(12,96)} = 3.06$, $P = 0.0011$], with significant increases at 60, 120, and 180 min post dose relative to placebo (**Figure 6Ai**). This effect was driven primarily by increases in the "sedation" subscale (significantly increased at 120 and 180 min) and to a lesser extent by increases in "stimulation"'subscale (significantly increased at 60 and 180 min) after 60 mg baclofen (**Figures 6Bii,iii**). There were no significant difference in BAES scores after 10 mg baclofen.

In AD, there was a trend for an effect of baclofen to increase total BAES scores (**Figure 6B**, dose by time interaction: $F_{(12,60)} = 1.90$, $P = 0.053$) which was driven primarily by a significant attenuation by 90 mg baclofen of time-dependent reductions in the stimulation component score following placebo at 60, 120, 180, and 240 min post dose (**Figure 6Biii**). There were also small but significant increases in sedation score in response to 60 mg baclofen at 30 and 60 min (**Figure 6Bii**).

In a direct group comparison ($n = 12$ and 8), the effect of baclofen to significantly increase total BAES scores in controls following 60 mg can be seen to be significantly blunted in AD [group effect: $F_{(1,18)} = 4.23$, $P = 0.05$, group by time interaction: $F_{(6,108)} = 3.89$, $P = 0.0015$, **Figure 6C**]. This group effect was driven by the difference in sedation, and not the stimulation component [group by time interactions: $F_{(6,108)} = 3.61$ and 0.97, $P = 0.0027$ and 0.45, respectively].

### VAS

In controls ($n = 9$), there was no overall effect of baclofen on VAS scores. However, a significant effect of time for both

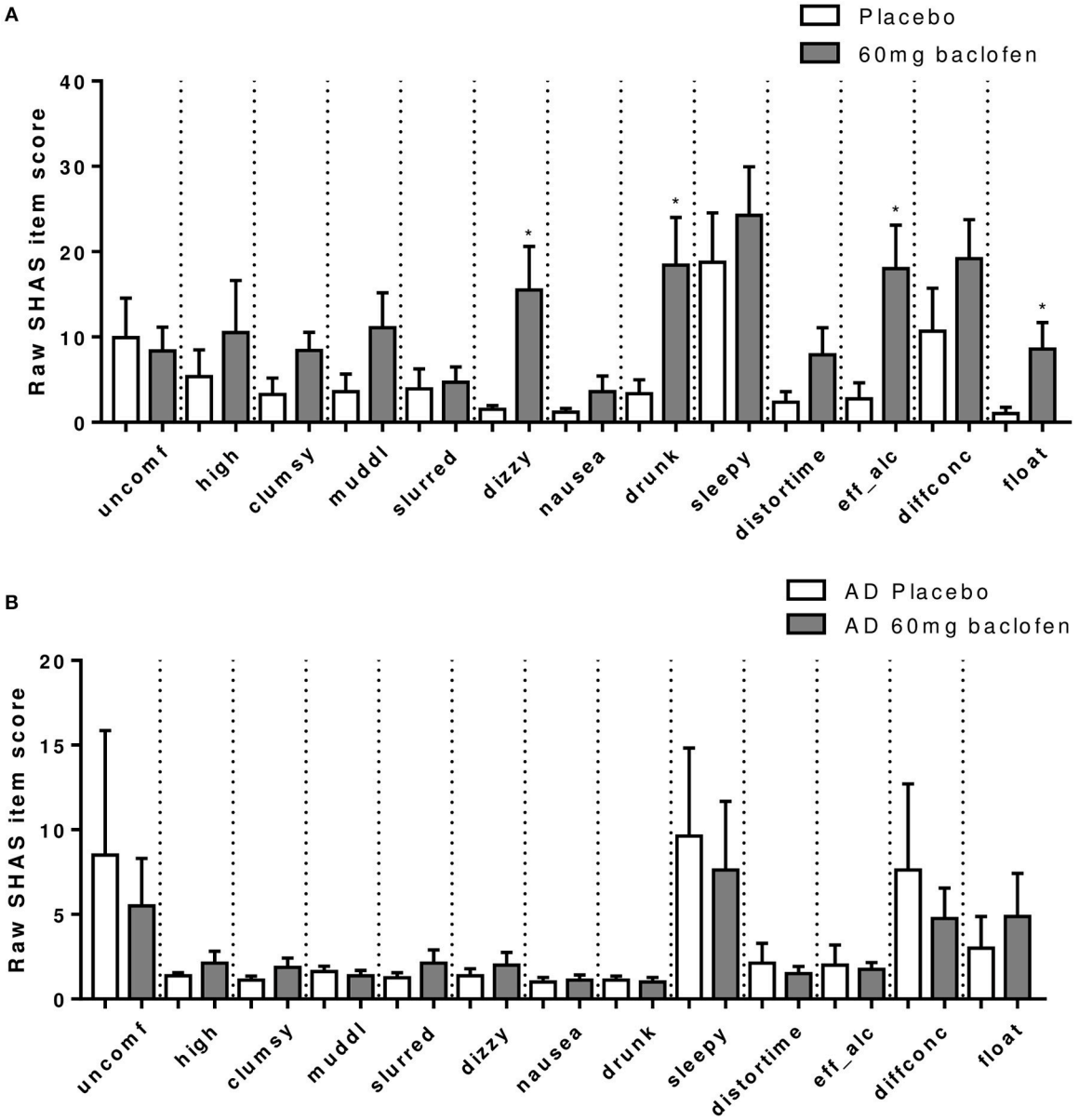


**FIGURE 5 |** Effect of baclofen on SHAS subscores in **(A)** controls ($n = 12$) and **(B)** AD ($n = 8$) after 60 mg baclofen. Data are mean ± S.E.M. and represent the raw scores which are a breakdown of total SHAS items at 120 min post administration of 60 mg baclofen. The SHAS consists of 13 items scored 0–100. These items are "uncomfortable," "high," "clumsy," "muddled," "slurred speech," "dizzy," "nauseated," "drunk," "sleepy," "distorted sense of time," "effects of alcohol," "difficulty concentrating," and "feeling of floating". *60 mg > placebo ($P < 0.05$).

"sleepy" and "alert" factors was observed [$F_{(6,48)} = 4.67$ and 5.66, respectively, $P < 0.001$]. Increases in subjective sleepiness as the day progressed were evident across all three doses, with corresponding reductions in alertness. In terms of peak effects, a significant reduction in alertness was observed following 10 mg baclofen at 60 min, and following 60 mg at 60, 120, and 180 min post administration, relative to placebo ($P < 0.05$, Tukey's multiple comparison test). There were no changes in VAS scores for "relaxed" or "tense."

In AD ($n = 6$), there were no significant overall effects of time or baclofen dose on VAS measures. A dose by time interaction was observed in the "relaxed" measure [$F_{(12,60)} = 2.33$, $P = 0.016$], primarily driven by attenuation of reductions in relaxation observed under placebo by baclofen, at peak effects: a significant increase in response to 60 mg baclofen was observed at 60, 120, 180, 240, 360 min, and in response to 90 mg at 60 and 120 min relative to placebo ($P < 0.05$, Tukey's multiple comparison test).

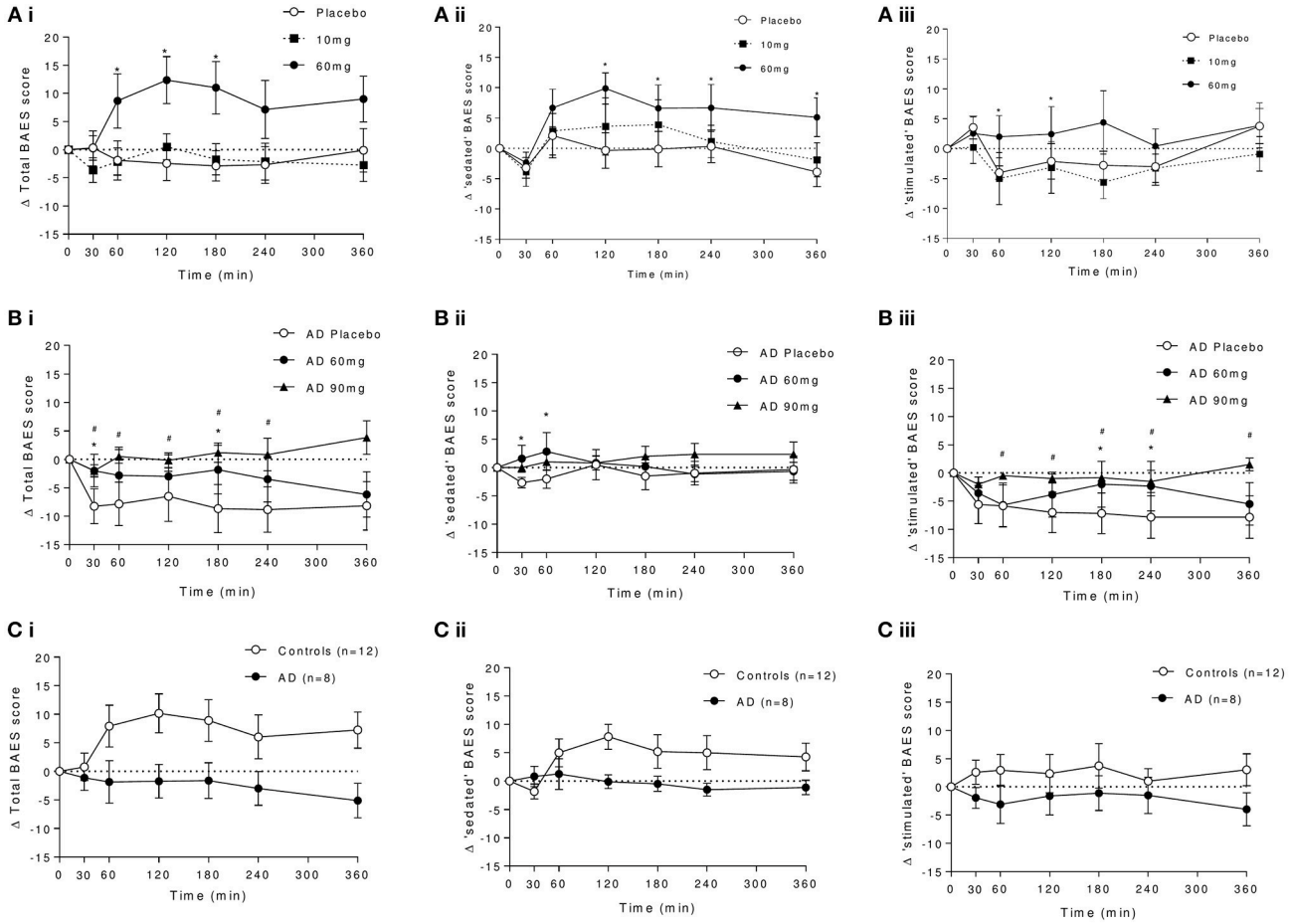


**FIGURE 6 |** Effect of baclofen on **(i)** total, **(ii)** sedating, and **(iii)** stimulating components of the biphasic alcohol effects scale (BAES) in controls and AD. **(A)** Shows the dose response to placebo, 10 and 60 mg baclofen in controls. **(B)** Shows the dose response to placebo, 60 and 90 mg in AD. **(C)** Shows the group comparison at 60 mg baclofen ($n = 12$ controls and $n = 8$ AD) of **(i)** total, **(ii)** sedation, and **(iii)** stimulation components of the BAES. Data are mean ± S.E.M., *60 mg baclofen > placebo, #90 mg baclofen > placebo, ($P < 0.05$). Scale-items contributing to the sedation effects include "difficulty in concentrating," "down," "heavy head," "inactive," "sedated," "slow thoughts," and "sluggish." Scale-items contributing to the stimulation effects include "elated," "energized," "excited" "stimulated" "talkative," "up" and "vigorous." Items are scored between 0 and 8.

There were no group differences in response to 60 mg baclofen, and no other significant effects apart from an effect of baclofen to increase "sleepy" factor with time [$F_{(6, 108)} = 2.61$, $P = 0.02$], which was primarily driven by the control rather than AD group.

## DEQ

Exploratory analyses of responses to the drinking expectancy questionnaire (DEQ) at peak baclofen effects (60, 120, and 180 min) in the older control cohort ($n = 3$) relative to AD ($n = 8$) revealed no significant group differences following 60 mg baclofen [$F_{(6, 12)} = 10.43$, $P = 0.084$]. However, the "feel some effect" factor was significantly higher than placebo at 120 min post-dose (60 mg > placebo, $P < 0.05$), Tukey's multiple comparison test, with no changes in "high," "like," "dislike," or "want more" factors. Conversely in AD, there was a tendency to "dislike" the effects of 60 mg baclofen at 60 min post dose, with a non-significant increase in "feel some effect" factor at 120 min, instead reporting significant increases in "high" and "I would like more" at this time point.

## Guess Analysis

Subjects were asked to guess which doses they had received at each visit. In controls, 8 of 9 (89%) receiving the 60 mg dose guessed correctly that they had received baclofen. Fewer correctly guessed the 10 mg dose; 5 of 8 (63%) receiving 10 mg baclofen correctly guessed they had received baclofen. 5 of 9 (56%) receiving placebo correctly guessed that they had received placebo, with only one confusing this with the high (60 mg) baclofen dose. These data suggest that the effects of the lower dose were more subtle.

In AD, 5 of 8 (63%) correctly guessed baclofen when they had received 60 mg (i.e., the same proportion to controls receiving 10 mg), whereas the vast majority (5 of 6, 83%) were able to correctly discriminate 90 mg, pointing to greater drug effects at this dose. 4 of 8 (50%) guessed correctly on the placebo day.

## Pharmacodynamics-EEG Measures

In controls, increased theta power was observed as the study day progressed in all three conditions (**Figure 7**), but was more pronounced following the 60 mg baclofen dose, particularly posteriorly and this change was reliably and consistently observed across participants. In a subsequent comparison between 60 mg baclofen and placebo, significant increases in theta were evident at 4 and 6 h post administration in both eyes open and eyes closed conditions (**Figure 8**). There were no significant differences between 10 mg and placebo. Changes in theta power from baseline were well fitted by compartmental modeling over the time course of the experiment, using the baclofen plasma data as the input function (**Figure 9**). The time-course of the effect was different to that of plasma baclofen levels and subjective effects of baclofen. Baclofen concentration-effect plots demonstrate that while plasma baclofen and subjective or GH effects follow a similar time course (**Figures 1**, **4**), theta activity appears delayed, and continues to rise long after plasma baclofen $C_{max}$, with highest values at the final time point (360 min). No later recordings were made.

In AD, large variations in theta activity (and other bands) were observed between participants, both at baseline and on placebo days, possibly due to age. We were unable to reliably model the data, and therefore group level analyses did not reveal consistent findings across any frequency bands (data not shown).

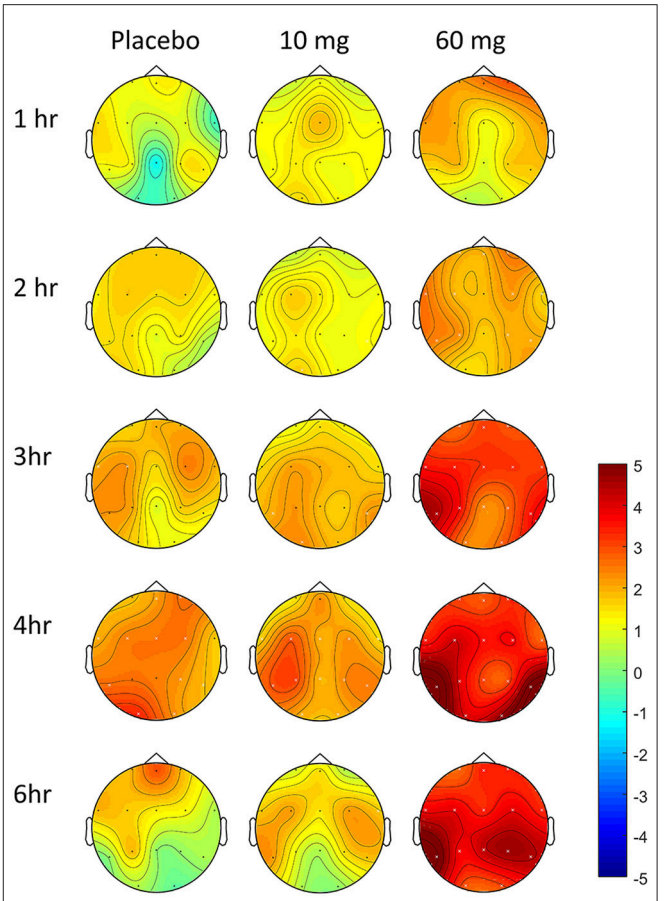


**FIGURE 7 |** Effect of baclofen on change in theta power over time in controls, relative to baseline. Data are theta power (4–8 Hz EEG activity), change from baseline comparisons after placebo ($n = 7$), 10 mg baclofen ($n = 5$) and 60 mg baclofen ($n = 7$) at five time points following dosing (eyes shut). Pre-intervention baseline spectra were subtracted from spectra at each post-intervention time-point (1, 2, 3, 4, and 6 h post baclofen) to provide statistical maps (paired *t* statistics). Red indicates relatively more power following baclofen, and blue indicates relatively less power. Black dots represent location of electrodes. Differences relative to baseline were tested using permutation testing; white crosses represent channels with significant differences relative to baseline (FDR corrected).

## DISCUSSION

We have shown here in this unique pharmacokinetic-pharmacodynamic study, that baclofen induced objective and subjective effects are substantially blunted in the AD group compared with healthy controls, in the absence of any significant differences in pharmacokinetics. Our data therefore suggest that lower GABA-B receptor sensitivity is present in alcohol dependence.

The pharmacokinetic profile of baclofen in our healthy control and alcohol dependent cohorts is broadly consistent with that reported previously, with peak plasma levels evident at about 1hr after dosing, and a half-life of approximately 3 h (30–32, 58). There is some variation in pharmacokinetic indices between studies which may be due to dose, age and gender of participants, different tablets, absorption, blood sampling times and methods of analysis of baclofen plasma levels. The overall lack of clinically significant changes in blood pressure and heart rate suggests that baclofen is safe, from a cardiovascular perspective, at these doses.

We found that the pharmacokinetic profile of 60 mg of baclofen was similar in healthy controls and abstinent alcohol dependence. Indeed, there were no significant differences in any PK parameter between groups. Two previous studies have similarly reported that the PK does not differ markedly between alcohol dependence and healthy controls (34, 59). These studies reported the baclofen PK effects following treatment with 15–250 mg daily, in divided doses. In both, a linear relationship was found, even at higher (>120 mg) doses, but substantial inter-individual variability was evident, which could not be attributed to age, gender, weight, smoking status, renal or liver function. It was suggested the variability might be responsible for differences in clinical response. Consistent with these studies, we observed greater variability in plasma baclofen levels in our alcohol dependent group at 90 mg compared with 60 mg. One likely and important difference between these clinical studies and our lab-based study is that our participants had been abstinent from alcohol for a considerable number of months, from 8 to 72, whilst the drinking status was not clear in the clinical samples.

Our AD participants were older than the healthy controls. However, we found no relationship between age and peak plasma levels of baclofen, and no difference in PK parameters between the younger and older control cohorts. Additionally, others have reported no difference in $T_{max}$ or total plasma baclofen levels in older (69–81 years) adults compared with younger controls (23–53 years), although elimination times of baclofen were slower

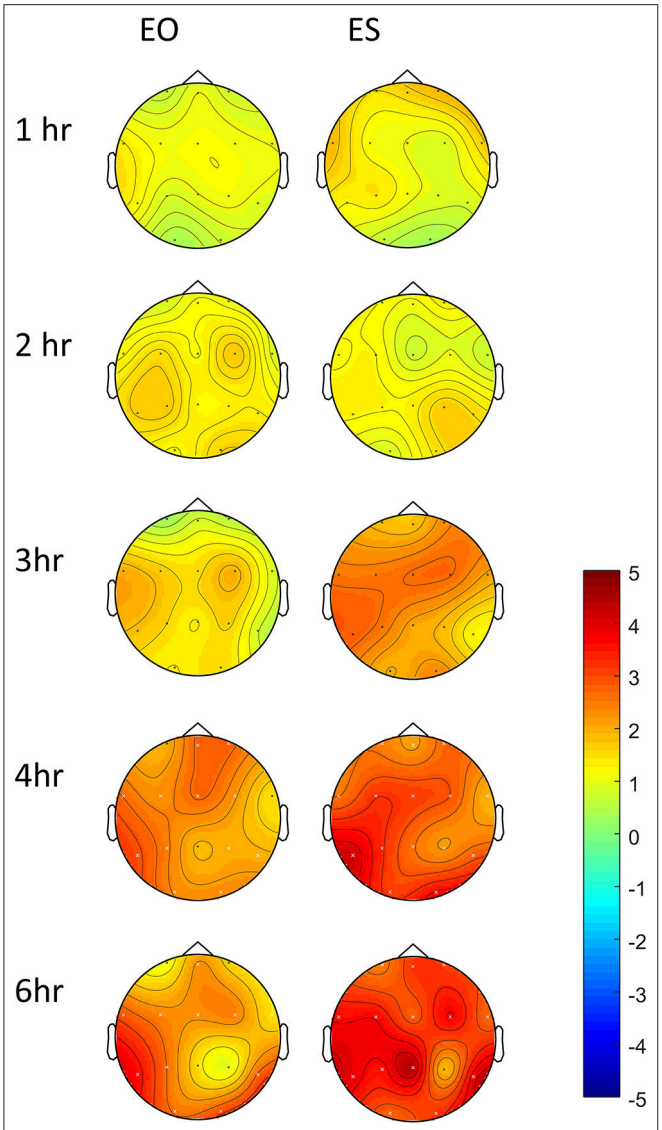


**FIGURE 8 |** Differences in change-from-baseline theta power between placebo and 60 mg baclofen, shown with both eyes open (EO) and eyes shut (ES) at 5 time points in controls ($n = 7$). Contrasts were performed between placebo and baclofen (t statistics of difference between the difference at baseline) to create one image per time point. This represents a subtraction of column 1 (placebo) from column 3 (60 mg baclofen) as depicted in **Figure 7**. Red indicates relatively more power following baclofen relative to placebo. Electrodes with significant differences between placebo and baclofen are shown with a white cross, corresponding to $p < 0.05$, FDR corrected.

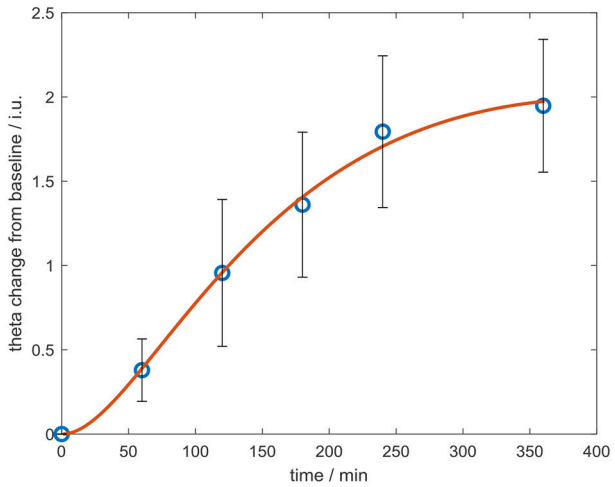


**FIGURE 9 |** Change in whole-brain theta power from baseline over the course of the experiment, after the 60 mg dose of baclofen, with eyes shut. Data are mean ± S.E.M. The data were fitted using a compartmental model (red line).

in the older participants which was likely due to impaired renal function (58). Our alcohol dependent participants were all healthy with normal renal and hepatic function.

We were only able to compare the effects of 60 mg baclofen between the two groups since the limited effects of the 10 mg dose in healthy controls meant that we did not investigate this dose in the AD group, and the pronounced sedation induced by 90 mg in our first healthy control precluded further analysis or comparisons at this dose.

The subjective effects of 60 mg of baclofen in our healthy controls were as expected, with marked increases seen in both the SHAS and BAES scales, and these effects were dose-dependent. 10 mg of baclofen resulted in more limited subjective effects, whereas 90 mg resulted in profound sedation such that the participant could not complete the protocol. The time-course of these observations are consistent with other studies using similar doses of oral baclofen (36). Following 60 mg baclofen, controls reported a number of subjective effects which are primarily sedative in nature, including a selective increase in sedation scores on the BAES and also drunkenness, dizziness, floating and other effects similar to those of alcohol in the SHAS.

Conversely, in alcohol dependent participants the 60 mg dose did not result in significant changes in any subjective measures. At 90 mg, there was a suggestion of mild increases in sleepiness as measured by the SHAS, and attenuation of the stimulation component of the BAES but no direct evidence of significant increases in subjective sedation. These data are consistent with the vast majority of control, but not AD, participants being able to correctly identify when they had received 60 mg baclofen relative to placebo in the guess analysis. The AD group could only reliably guess they had received baclofen at the higher 90 mg dose. Interestingly, in clinical trials of baclofen in alcohol dependence, dizziness is one of the most common side-effects experienced from a range of doses but was not reported here, after a single 60 or 90 mg dose of baclofen.

Sedation is a commonly cited side-effect and limits tolerability in some patients, whereas others welcome it and find some sedation acceptable (17, 29). In controls, subjective sedation was demonstrably higher following 60 mg baclofen, with the increases observed in the BAES primarily related to increases in the sedation rather than stimulation subscale. It is therefore notable that limited sedation was seen in our abstinent alcohol dependent individuals, even after 90 mg. In previous studies, baclofen has been reported to increase sedation in a lab-based

study in heavy drinkers [40 mg, 80 g; (36)], but baclofen (30 mg/d) alone did not increase sedation in a study of alcohol dependent individuals (60). It therefore appears that alcohol dependent individuals are less sensitive to the sedative effects of baclofen alone. This is consistent with clinical experience where those who do not experience sedation are able to tolerate "higher" doses of baclofen.

Performance on the zig-zag task, which we chose as an objective measure of sedative effects of drugs, was interestingly not significantly different overall between healthy controls and abstinent alcohol dependent participants after 60 mg of baclofen. However, there was some evidence of reduced accuracy following 60 mg in controls, but not in AD. There was also evidence of slowing in AD following 90 mg baclofen, pointing to a possible psychomotor retardation effect at this dose. The slowing in speed of completion was accompanied by a reduction in error rate suggesting that participants were engaging in a compensatory trade-off, such that the reduced speed permitted fewer errors. This could be important, as although participants were not overtly sedated, and higher doses were better tolerated, there may still be risks associated with altered motor responses in alcohol dependence e.g., driving. The pattern of performance in healthy controls was also different since their performance consistently improved with practice. They appeared to adjust their speed to achieve higher levels of accuracy if their previous performance was poor, an adaption which was not clearly observed in abstinent alcohol dependent participants.

The finding of increased EEG theta activity in controls is supported by previous clinical studies of sleep and EEG effects after baclofen administration (35, 37). Badr et al showed increased theta activity during wakefulness following 2 days of baclofen (30 mg, bid), whereas Vienne et al showed increased theta activity during a daytime nap following acute baclofen. Increased theta was also apparent during the subsequent night time sleep period, alongside increases in first-episode slow-wave sleep, total sleep time and decreases in sleep onset latency, at baclofen doses equivalent to approximately 30 mg (37). A study combining EEG and transcranial magnetic stimulation (TMS) also indicates effects of baclofen at the level of the cortex (61). Previous preclinical studies have similarly shown hypersomnia following baclofen administration in rats (62). Interestingly, this effect was not attributed to a GABA-B specific mechanism, since GABA-B1 and GABA-B2 knock out animals also displayed similar effects.

Given the concerns raised about potential abuse liability of baclofen it is interesting that, unlike the controls, our abstinent alcohol dependent participants did not report significant "alcohol-like" or "drunk" effects on the SHAS following 60 or 90 mg of baclofen. However on the drug expectancy questionnaire, although there were no overall significant effects, there was a suggestion of increased "high" and "liking" effects after the 90 mg dose. Anecdotally, several participants stated that they enjoyed the effects, and likened them to those of opiates or benzodiazepines. This has potential implications for abuse liability, particularly at higher doses, and requires further study. A study in heavy social drinkers similarly showed that unlike alcohol, baclofen (0, 40, 80 mg) did not significantly increase "high," "drug-liking," or "stimulation", though at the highest dose "good drug effect" and "elevated mood" were reported (36).

Together with our data, this suggests that baclofen is not experienced as "alcohol-like," and therefore may not be substituting for alcohol, as previously suggested as a potential mechanism underlying its efficacy in alcohol dependence (63). It should be noted however that some of the evidence supporting a substitution model comes from studies where alcohol and baclofen are combined, rather than the effects of baclofen alone. In that situation baclofen appeared to enhance "intoxication" ratings and "feeling high" from alcohol, though no reduction in alcohol consumption was observed (60).

Concerning objective effects, baclofen resulted in dose-dependent increases in GH levels which were notably absent in our abstinent alcohol dependent participants. Others have previously shown similar blunting (40–44). However, our study shows that such blunting is still present even after a high (90 mg) dose of baclofen. It also coincides with an absence of subjective effects, and PK is demonstrably no different between groups. Further it is clear from our data, and from others, that such blunting persists in to longer-term abstinence (42). It is of considerable interest that blunted baclofen-induced GH release has also been reported in opiate dependent individuals who were abstinent for a few days, and also 2 months later (64). Together this suggests that lower sensitivity to baclofen, and by extension GABA-B receptor sensitivity, might be a trait marker of addiction and play a fundamental role in the addiction process. It is not clear whether chronic alcohol or drug exposure results in this lower sensitivity. Therefore it would be interesting to assess whether baclofen induced GH levels is altered in those at high risk of addiction, such as individuals with a positive family history. It is also worth noting that GH responses to noradrenaline challenge are also blunted in alcohol dependence (65), both during withdrawal and in abstinence. These findings suggest that deficits in neurotransmitter receptor mediated endocrine responses, including those mediated by GABA-B receptors, are a feature of alcohol dependence and may persist for some time.

Our results suggest there may be a delayed component to the baclofen response; we observed short delays in the subjective response to baclofen relative to the PK profile (TSHAS and BAES effects peaked at approximately 2–3 h after dosing whilst $T_{max}$ occurred at approx. 90 min), but the time-course of the EEG effects was much longer; theta activity remained elevated at the final 6 h time point, with no sign of dissipation. Preclinical studies indicate delayed central effects of baclofen including toxicity response (66), anti-nociception (67) and EEG (62, 68). There are a number of possible explanations for delayed effects including slow drug accumulation in CNS, slow equilibrium kinetics, and/or involvement of non-GABA-B dependent or downstream receptor mechanisms.

Our data showing blunted objective and subjective responses to baclofen in abstinent alcohol dependent individuals strongly suggests altered GABA-B sensitivity, but the underlying mechanism(s) cannot easily be characterized in the absence of tools such a PET ligand or GABA-B antagonist for use in man. Our findings could result from a range of different mechanism(s)

such as a reduction in GABA-B receptor function. This could be brought about by a reduction in receptor number, reduced G-protein coupling or altered internalization or trafficking mechanisms (69–71). Preclinical studies have shown that chronic ethanol exposure produces neuroadaptations in GABA-B receptor function, for example by reducing the sensitivity of GABA IPSPs in the central amygdala (72), or reducing presynaptic modulation of GABA release in hippocampus (73). Alternatively, dysregulation of one of the "downstream" neurotransmitter systems that GABA-B receptors modulate could be involved. For instance, it is well known that alcohol impacts on a wide range of neurotransmitter receptor systems that GABA-B modulates including GABA-A, dopamine, noradrenaline and glutamate (9, 74). It is possible that genetic factors may contribute to the variability in PK and PD effects of baclofen. For example a polymorphism in the ABC transporter gene A*BCC9* is associated with greater clearance of baclofen (75), and the *GABBRI* polymorphism, rs29220, has been reported to modulate response to baclofen, with CC carriers deriving greater benefit with fewer side-effects compared with G-carriers (76, 77). Unfortunately we did not genotype our participants.

There are several study limitations that are worth noting. The groups were not well matched for age. This was partially mitigated by the addition of the second older control cohort ($n = 3$) which were found not to differ from the younger control cohort on any PK or PD measure. In addition, there was no association between age and any PK or PD measure in the control sample. There is also no evidence of a relationship between age and baclofen response in the clinical AUD or spasticity literature. Although circulating basal GH levels are known to decline with age, we found that increased GH release following baclofen challenge did not change significantly with age in our control sample. We studied longer-term abstinent alcohol dependent individuals who were able to complete our protocol safely in the community. We acknowledge that this population does not necessarily reflect those currently in treatment services. In clinical practice, baclofen is started soon after alcohol detoxification, or even whilst still drinking. Nevertheless our participants were still at risk of relapse, and indeed some did subsequently relapse (though not related to the study). The fact that lower baclofen sensitivity was seen even after a considerable period of abstinence requires further investigation as to its implications. Our sample size is small, but commensurate with other PK-PD and similar challenge studies where effect sizes are often large (as observed here). Whilst we observed no relationship between age or months abstinent and any PK or PD measure, the sample was too small to adequately explore such relationships, or to assess, for example, whether alcohol exposure was related to baclofen sensitivity. Despite the small sample, the effect size of the group differences observed in subjective and GH response to baclofen were substantial. For example Cohen's d was 2.19 for peak GH levels following 60 mg baclofen at 120 min post-dose. This makes it unlikely that smaller contributions made by age, or other factors, would change the study outcome.

In summary we have shown blunted sensitivity to baclofen in abstinent alcohol dependent individuals compared with healthy controls. This adds to the growing evidence about dysregulated GABA-B system in addiction, though the underlying mechanism is not well characterized. This lower sensitivity likely contributes to the fact that "high" doses of baclofen are tolerated in alcohol dependence, and are proposed as necessary for the effective treatment of alcohol dependence. This study also has important implications with regard to the choice of baclofen dose in future studies in addiction. It may also serve those investigating the potential of other GABA-B agonists or positive allosteric modulators in meeting the immense unmet need in treating addiction.

## AUTHOR CONTRIBUTIONS

CD and LP contributed equally to this manuscript. CD, SW, DN, and AL-H contributed to conception and design of the study. LP, CD, ST, AV, IM, and TJ were involved in data collection and collation. SP, LN, and RC performed the baclofen plasma analysis. JM performed data modeling. CD, SW, JM, and SM performed the EEG analyses. CD and LP performed all other data analyses. LP wrote the first draft of the manuscript, AL-H wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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# Pharmacokinetic Studies of Baclofen Are Not Sufficient to Establish an Optimized Dosage for Management of Alcohol Disorder

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Several clinical randomized trials have evaluated the interest of baclofen in patients with alcohol use disorder. Depending on the study design and the inclusion criteria, the results vary from enthusiastic to pessimistic. However, all researchers and practitioners agree that they observe a wide variability in the therapeutic responses. If some patients exhibit a clinical response at low doses, ∼40 mg daily, others require doses higher than 300 mg. Before multiplying new other clinical trials, it is required to better understand the reason of this variability. Several mechanisms may be responsible for providing different effects with an identical daily dose. Especially, each pharmacokinetic step, absorption, distribution, metabolism, and elimination may lead to a different exposure after an identical dose. Absorption may imply a saturation process limiting the bioavailability (F) of baclofen in some patients. In such a situation, food, or drug-drug interaction can change the absorption rate of the drug modifying the maximum concentration (Cmax) and area under the curve (AUC). Distribution and brain penetration across the blood-brain barrier may depend of a specific transporter. These transporters are subject to genetic polymorphism and drug-drug interaction. Finally, elimination may be increased by a specific secretion pathway. This review describes all available pharmacokinetic data on these different pharmacokinetics steps aiming to identify the source of variability of baclofen in patients with alcohol use disorder.

**Keywords: clinical pharmacokinetics, baclofen, alcohol use disorder, modeling, GABA**

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## INTRODUCTION

Baclofen is a racemic drug with GABA-B receptor agonist properties. It is widely prescribed as a spasmolytic agent to treat spasticity caused by central nervous system lesions or dysfunction (1). For several years baclofen has been prescribed off-label in Alcohol Use Disorder (AUD) patients to prevent relapse or to reduce drinking (2). This new indication is even authorized in France as "temporary recommendation for use." Unfortunately, the use of this compound is made difficult by the lack of knowledge on prescription guidelines, dosage and characteristics of patients with the highest probability of a clinical response (2, 3). In clinical practice, a wide inter-individual variability of dose required to obtain an effect is often described from 30 up to 300 mg per day (2). Curiously, randomized clinical trials have been performed before full evaluation

of pharmacokinetic properties and even a clear pharmacodynamic proof of concept. This lack of a standard clinical drug development in this new indication may explain the discrepancy between clinical trials (4–7). Thus, the aim of this review is to recapitulate the pharmacokinetic properties already reported and to identify the studies required to optimize its evaluation in this new indication.

## ABSORPTION

Only oral formulation with an immediate release is currently available. In healthy volunteers the time to reach the peak concentration in plasma after administration (Tmax) varied between 1 h (8) and 2.79 h (9). Other pharmacokinetic studies in healthy volunteers found similar results: 1.13 h (10), 1.2 h (11), or 2 h (12, 13). The pharmacokinetic studies performed in AUD patients have been realized in real life conditions. Such studies used sparse sampling instead of full profiles, which did not allow a direct observation of Tmax. Meanwhile a formula (Equation 1) can be used for computing Tmax from the constant of absorption (Ka) and the constant of elimination (Ke). The calculated Tmax obtained from two population pharmacokinetics studies are 1.23 h (14) and 1.74 h (3).

$$Tmax = log(Ka/Ke)/(Ka - Ke) \quad (1)$$

The baclofen's Tmax indicates a rapid absorption of the compound from the intestinal tract to the bloodstream and should not be confused with the time required to observe an effect. Indeed, some effects may change over time in parallel with plasma concentrations, but this has never been described for baclofen. Unless a direct relationship is described between plasma concentration and a baclofen effect, the Tmax indicates nothing more than a laboratory value. This rapid absorption can be explained by the site of penetration into the digestive tract wall. The upper small intestine completely absorbs baclofen with almost no contribution of the colon (15). This characteristic suggests that baclofen absorption could be modified when prescribed in patients who have undergone a bariatric surgery. Unfortunately, no pharmacokinetic data are currently available in such situation and any prescription to these patients should be made with caution.

Several mechanisms are suggested to explain the ability of a compound to pass through the digestive barrier and to enter into the bloodstream. Depending on its chemical and physical properties, a compound will be absorbed by a passive process, a transporter or both of them. *In vitro* and *in vivo* studies have been performed in different species to understand the mechanism of baclofen absorption. Even if more studies are required to fully understand the compound behavior in the digestive wall, some convincing results described that baclofen used more than one intestinal carrier system (16). At least baclofen shares a saturable transport mechanism with essential branched-chain aminoacid (BCAA) such as leucine (17, 18). Since aminoacids are a normal component of food, a competitive inhibition could arise. However, a study performed with healthy volunteers under fasting condition vs. a standard meal did not find a significantly influence of food neither on the rate nor on the extent of baclofen absorption (19).

The absolute oral bioavailability has not been evaluated in AUD patients, but in healthy volunteers it was ∼74% for 10 mg (8) and 108, 85.8, and 81.2% for 10, 15, and 20 mg, respectively (10). To summarize, following an oral administration the absorption did not seem to be a limiting step for baclofen.

## DISTRIBUTION

Baclofen is 30% protein bound into the plasma which suggests that protein-binding changes will not be clinically relevant for routine practice (20). In special circumstances such as a baclofen intoxication, where a hemodialysis could be proposed, the protein binding may have an influence.

The mechanism of baclofen in AUD is suggested to be related with its ability to bind to the GABA-B receptor. So, the concern about baclofen distribution in AUD patients is the rate and extent of penetration into the CNS. With a logD of −0.96 the lipophilicity of baclofen is insufficient to allow a brain penetration by passive diffusion (21). The baclofen brain entry across the blood-brain-barrier is due to an interaction with the large neutral aminoacid transporter (22, 23). However, the resulting influx clearance is counterbalanced by an efficient efflux from the brain through a probenecid-sensitive organic anion transporter 3, OAT3 (SLC22A8) (24, 25). The overall restricted distribution of baclofen in the brain is then the result of an asymmetric transport at the blood-brain-barrier with an efflux transport rate 40-fold higher than the influx transport rate (25). The fact that baclofen is a substrate of OAT3 remains to be confirmed but recent results corroborate its low apparent permeability coefficient (Caco-2 $P_{app}$: $0.9 \pm 0.7\ 10^{-6}$ cm/s) and its unbound brain/blood ratio (26).

In patients with spastic paresis, a study was designed to elucidate whether the therapeutic responses and the side effects were related to plasma concentrations and CSF levels (27). Four hours after the administration, the authors found CSF levels nine to ten times lower than the plasma concentrations. However, optimal therapeutic responses were obtained at very different levels of plasma and CSF baclofen concentrations and without a clear relationship. The analytical method used for CSF estimation was a limitation resulting in numerous samples below the quantification limit and wasn't able to fully describe the interindividual variation. A recent study used a more efficient quantification analysis to describe the baclofen concentrations in CSF (1). The population wasn't AUD patients but patients with various etiology of severe spasticity. Meanwhile interesting information can be extrapolated to baclofen used in AUD. Before the intra-thecal administration, ten patients were treated with a repeated oral dose of baclofen ranging from 30 to 125 mg per day. The resulting individual trough CSF concentrations were available but not showed in the original article. However, the authors kindly agreed to communicate them allowing the description of the relationship between oral doses and CSF trough concentrations (**Figure 1**). This figure shows

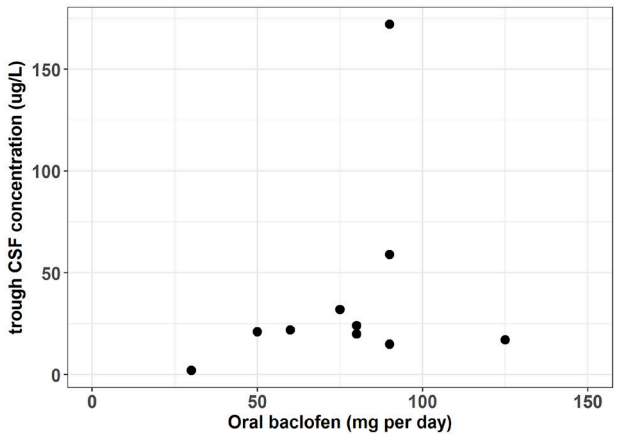


**FIGURE 1 |** Oral dose vs. trough CSF baclofen concentration in patient with severe spasticity. [From data published by Heetla et al. (1) and individuals CSF trough concentration values kindly communicated by the authors].

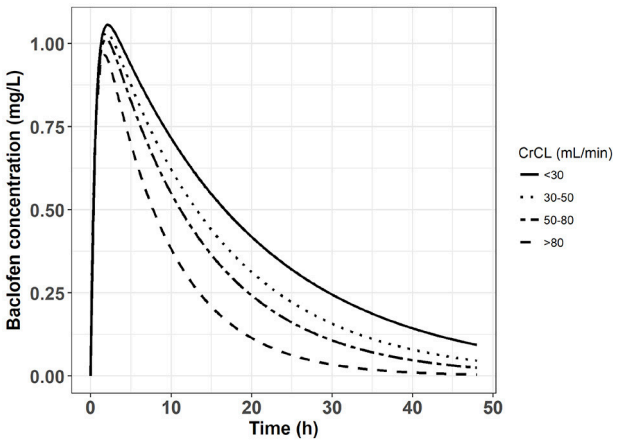


**FIGURE 2 |** Simulated concentration vs. time profile following an oral dose of 80 mg of baclofen in four groups of patients with different chronic kidney disease stages.

that between a dose of 30–125 mg per day the corresponding CSF concentrations seem to vary slightly around 25 μg/L. This result suggests that plasma concentration is probably not a good biomarker of baclofen brain exposure. Interestingly, the patients included in this study were recruited on the basis of a severe spasticity which could not be treated sufficiently with an oral therapy. However, following the intrathecal administration, all these patients achieved an adequate spasmolytic effect. The pharmacokinetic/pharmacodynamic (PK/PD) model of spasticity estimated a CSF concentration at 50% of the maximum effect (EC50) of 194 ug/L (95% CI 112, 350), which is higher than the 25 ug/L obtained with the oral administration. A PK/PD model of baclofen in AUD remains to be identified but the results in patients with spasticity suggest that baclofen brain penetration could be a limiting factor for its efficacy and may explain a large inter-individual variability.

## METABOLISM AND ELIMINATION

A stereoselective metabolic difference between R- and S-baclofen has been recently described (28). In this study no metabolites were observed following an oral administration of the single R-enantiomer. However, the administration of the mixture R- and S- allowed the identification of an oxidative deamination metabolite. This stereoselective metabolism of only the S-enantiomer of baclofen is then followed by a glucuronide conjugation. Meanwhile the overall contribution of metabolism is low with 85% of the dose excreted as unchanged (29). This result may explain that in another study the gamma-hydroxymetabolite was not detected (12).

Baclofen is mainly cleared through kidneys with a fraction of the dose unchanged in the urine ranging from 65% (13) to 80.9% (11). In healthy volunteers a high correlation between the apparent renal clearance of baclofen and the creatinine clearance was described (12). This has been confirmed by a study including four groups of patients with different kidney disease stages (30). The authors found the following significant linear relationship ($R^2 = 0.67$, $p < 0.0001$) between baclofen clearance (CL/F) and creatinine clearance (CrCL):

$$CL/F(L/h) = 2.25 + 0.05 \times CrCL(ml/min) \quad (2)$$

This result suggests that, if baclofen has to be prescribed in patients with chronic kidney disease, a dose reduction should be applied. Using Equation 2 and a one-compartment model of baclofen described by Imbert et al. (3), it was possible to simulate concentration vs. time profiles with different values of baclofen clearance (CL/F) depending on the creatinine clearance. The **Figure 2** depicts these baclofen simulated concentrations following an oral dose of 80 mg in patients according to different values of creatinine clearance. Meanwhile none of the pharmacokinetic studies performed in AUD patients identified a significant influence of creatinine clearance on baclofen clearance (3, 14, 31). This surprising result can be explained by the homogeneity of patients included in these studies regarding the renal function.

The baclofen half-life (T1/2) in alcohol-dependent patients with the current immediate release formulation ranged from 3.8 h (14) to 6.4 h (3). These values were obtained for doses up to 180 mg per day (3). It's noticeable that during a baclofen overdose an increase of T1/2 is not always observed (32). In such situation, which may lead to comatose, severe respiratory depression and neurotoxicity, hemodialysis has been effective in reversing baclofen toxicity if the patient had a renal insufficiency (33). A gastro-intestinal decontamination with activated charcoal can also be proposed to avoid a persistent intestinal absorption related to a reduced gastro-intestinal mobility or a pharmacobezoar (34).

To conclude on these pharmacokinetic steps, baclofen exhibited no saturation of elimination with clinical doses used and thus no accumulation. However, in patient with chronic kidney disease a decrease of clearance is expected, and the baclofen dosage should be adjusted accordingly. The guidelines for drug dosing regimens in chronic kidney disease deserve further studies.

## DISCUSSION

Baclofen, as are all drugs, needs to reach its site of action to produce an effect. Because its mechanism of action seems to be related to a binding on the GABA-B receptor in the CNS, the concentrations in plasma are only an indirect marker. It would be more interesting to describe the relationship between an oral dose and CSF concentration, but this kind of study required a catheter located at a spinal level. Other studies such as positron emission tomography imaging could evaluate the baclofen binding to the cerebral GABA-B receptors. For example, we can suggest an imaging study aiming to determine whether patients requiring higher doses and/or patients with poor response correspond to subjects with a lower cerebral binding of baclofen. However, the lack of suitable radiotracers for imaging GABA-B receptors is a current limitation.

Meanwhile a variability in plasma exposure following an oral administration must be evaluated because it is an essential step before the brain penetration. The aim of pharmacokinetic studies is to identify the main source of inter-individual variability such as age, body weight, food, drug-drug interaction, tobacco, renal and hepatic function, genetic polymorphism. However, because the time course of plasma concentration did not necessary follow the time course of an effect, pharmacokinetic studies are not sufficient to establish an optimized dosage. Usually, the increase of plasma concentrations following an administration did not follow the effect onset and likewise the decrease of plasma concentrations presents a different rate than the decrease of the effect. When prescribing baclofen, it's important not to misinterpret Tmax and T1/2: they are not describing the time to effect and the effect disappearance, they are only describing the plasma concentration. Considering the suggested effect of baclofen on craving in AUD, the time to the maximum effect as well as the duration of this effect is still to be described.

Currently only three population pharmacokinetic studies of baclofen have been performed in AUD patients (3, 14, 31). Two studies were based on the same cohort with different objective and population size (3, 31). The population were AUD patients, mainly male (43 males, 24 females) from 29 to 68-year-old, with a body weight ranging from 42 to 128 kg, normal renal function and a daily baclofen dose up to 180 mg (3). The second evaluated population present identical demographic and laboratory characteristics (14). These population pharmacokinetic analysis identified a one-compartment model with first-order input and output to describe the time course of plasma concentrations. However, none of these studies were able to identify factors explaining inter-individual variability.

The pharmacokinetic parameters were not clearly correlated with age, body weight, sex, smoking status, height, aspartate, aminotransferase, alanine aminotransferase, total bilirubine, gamma-glutamyltransferase, and alkaline phosphatases. Both studies found an influence of creatinine clearance on the baclofen clearance, but this relationship never reached a statistical significance (14, 31). Interestingly these studies described a proportional relationship between the oral dose of baclofen and concentrations which did not suggest an accumulation at least up to a daily dose of 180 mg per day.

Concerning putative pharmacokinetic drug-drug interaction, a recent review did not find any of them described in the literature (35). Because baclofen is mainly excreted unchanged in urine, it's unlikely that an inhibition or an induction of its metabolism may have a clinically relevant impact. However, the impact of efflux transporter (OAT3) inhibition in renal tubules and/or in the blood brain barrier deserves an investigation [for a review on OAT family, (36, 37)]. Several compounds such as probenecid and proton pump inhibitors have been described to inhibit OAT3 transport which increases plasma and brain concentrations (38, 39). It could be of interest to combine baclofen with an OAT3 inhibitor to investigate if brain and plasma concentrations are increased and if it is associated with an improvement of the clinical effect.

## CONCLUSION

Although pharmacokinetic studies already performed in AUD patients described a linear relationship between dose and plasma concentrations, they did not adequately explain the major source(s) of inter-individual variability. Meanwhile caution should be taken if baclofen must be prescribed in patients with chronic kidney disease. A study performed in patients with severe spasticity found no relation between baclofen oral doses and CSF concentrations. This result could partly explain the inter-individual variability of the dose required to reach a clinical effect. Indeed, a concern remains on the ability of baclofen to reach the brain with an appropriate rate and extent and new studies are required to investigate this question.

## AUTHOR CONTRIBUTIONS

NS wrote the first draft of the manuscript. NS, BR, and NF contributed to and have approved the final version of the manuscript.

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# Suppressing Effect of Baclofen on Multiple Alcohol-Related Behaviors in Laboratory Animals

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This paper summarizes the several lines of experimental evidence demonstrating the ability of the prototypic $GABA_B$ receptor agonist, baclofen, to suppress multiple alcohol-related behaviors in laboratory rodents and non-human primates exposed to validated experimental models of alcohol use disorder (AUD). Specifically, treatment with baclofen has repeatedly been reported to suppress alcohol-induced locomotor stimulation, alcohol drinking (including binge- and relapse-like drinking), operant oral alcohol self-administration, alcohol seeking, and reinstatement of alcohol seeking in rats and mice. Treatment with baclofen also reduced operant oral alcohol self-administration in baboons. Several of these effects appear to be mediated by $GABA_B$ receptors located in the ventral tegmental area. The often observed co-occurrence of "desired" pharmacological effects and "unwanted" sedative effects represents the major drawback of the preclinical, *anti*-alcohol profile of baclofen. Collectively, these data underline the role of the $GABA_B$ receptor in the mediation of several alcohol-related behaviors. These data possess remarkable translational value, as most of the above effects of baclofen have ultimately been reproduced in AUD patients.

**Keywords: baclofen, $GABA_B$ receptor, alcohol drinking and seeking, reinstatement of alcohol seeking, animal models of alcohol use disorder**

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## BACLOFEN EFFECT ON ALCOHOL-INDUCED STIMULATION OF LOCOMOTOR ACTIVITY

Historically, the first study investigating the effect of the $GABA_B$ receptor orthosteric agonist, baclofen, on an alcohol-induced response *in vivo* was conducted in Sweden more than 40 years ago (1); it included, amongst the authors, the Nobel laureate Arvid Carlsson. This study found that acute pretreatment with 5 mg/kg baclofen (i.p.) completely abolished alcohol-stimulated locomotor activity in mice. Besides being the "foundation stone" in the alcohol-baclofen research field, this study was of relevance for the translational value of its data: drug-induced hyperlocomotion in rodents and euphoria in humans are indeed homologous phenomena, as they are mediated by common neural systems [see (2)]; accordingly, in their paper Carlsson and his colleagues wrote that their finding "may be of heuristic value in the treatment of chronic alcoholism,", hypothesizing the translation of the ability of baclofen to suppress alcohol-stimulated locomotor activity in mice to alcohol stimulating and euphorigenic effects in humans.

These initial results have been confirmed by a series of subsequent studies reporting the suppressing effect of acutely administered baclofen on alcohol-stimulated locomotor activity in alcohol-preferring "University of Chile bibulous" (UChB) rats (3) and mice belonging to different strains and lines (4–9). Baclofen-induced suppression of alcohol-stimulated locomotor activity has also been recorded in preweanling (12-day-old) Sprague-Dawley rats (10), suggesting the involvement of the $GABA_B$ receptor system in the mediation of the stimulating effects of alcohol already in this developmental period.

## BACLOFEN EFFECT ON ALCOHOL DRINKING

### Homecage Alcohol Drinking

Human alcohol drinking is conventionally modeled in rodents by exposing rats and mice—usually singly housed in their homecage—to the choice between a water bottle and a bottle containing an alcohol solution. Under this simple procedure, animals can freely choose when and how much alcohol they drink. Under specific experimental conditions, this regimen results in voluntary intakes of psychopharmacologically relevant amounts of alcohol, mimicking excessive alcohol drinking (*too much, too often*) in humans and providing a reliable tool for pharmacological tests [see (11)].

Several studies have used the 2-bottle "alcohol vs. water" choice regimen to investigate baclofen effect on alcohol drinking. In most studies, acute or repeated systemic administration of baclofen produced substantial reductions in alcohol intake [(3, 12–16); see however (17)] in alcohol-experienced rats and mice. "Alcohol-experienced" means that, in these animals, consumption of high doses of alcohol was already consolidated before the start of treatment with baclofen; these animals are thought to model the "maintenance" or "active drinking" phase of human alcohol use disorder (AUD). Repeated i.p. treatment with 2.5 and 5 mg/kg racemic baclofen or the corresponding doses of R(+)-baclofen (the active enantioner) markedly reduced daily alcohol intake in selectively bred Sardinian alcohol-preferring (sP) (13) and alcohol-preferring UChB (3) rats; fully compensatory increases in daily water intake and lack of effect on spontaneous locomotor activity indicated that the reducing effect of baclofen on alcohol intake was not attributable to any baclofen-induced motor-incapacitating or sedative effect (that would otherwise disrupt the normal rates of drinking) (3, 13).

Although generally consistent in reporting a reducing effect of treatment with baclofen on alcohol drinking, studies conducted to date have reported considerable differences in baclofen efficacy. These differences are likely due to diversities in drinking history (resulting or not in the development of an addiction-like state) and genetic background of rats and mice used in those studies. An additional explanation of the differential efficacy of baclofen in reducing alcohol drinking has been proposed to reside in the at times reported opposite effect of R(+)- and S(-)-baclofen enantiomers on some alcohol-related behaviors [(18); see however (19)].

The suppressing effect of 5 mg/kg baclofen (i.p.) on alcohol intake in rats was fully prevented by pretreatment with the $GABA_B$ receptor antagonists, phaclofen and CGP36742 (20). These results provide strong evidence that baclofen effect on alcohol drinking is secondary to activation of the $GABA_B$ receptor.

Repeated treatment with baclofen (1–3 mg/kg, i.p.) over the initial phase of exposure to alcohol prevented acquisition of alcohol drinking in sP rats (21). These data suggest that activation of the $GABA_B$ receptor blocked detection of the psychopharmacological effects of alcohol underlying alcohol drinking. Rats acquired alcohol drinking behavior only once treatment with baclofen had been ceased (21). The translational value of these results may reside in pharmacologically delaying the onset of excessive alcohol drinking during adolescence and early adulthood, with the intent of potentially reducing the risk of developing AUD later in life.

### Binge-Like Drinking

Baclofen has also been tested in two validated mouse models of binge drinking, named "drinking-in-the-dark" (DID) and "scheduled high alcohol consumption" (SHAC), respectively. The DID procedure is based on exposure of mice to alcohol in brief (2–4 h) daily drinking sessions occurring at fixed times during the early period of the dark phase of the daily light/dark cycle [(22); for review, see (23)]. In the SHAC procedure, water-deprived mice are given daily periods of fluid access varying between 4 and 10 h; every third day, an alcohol bottle is presented over the initial 30 min of the drinking session (24). Both procedures result in excessive alcohol drinking and intoxicating blood alcohol levels at the end of the drinking session, reproducing the "*too much, too fast*" condition of human binge drinking.

In the "DID" studies, systemic administration of doses of R(+)-baclofen in the 5–10 mg/kg range markedly reduced alcohol intake in C57BL/6J mice (18, 25), selectively bred High Alcohol Preferring 1 (HAP1) mice (18), and High DID (HDID) mice (selectively bred for high alcohol drinking under the DID regimen) (26). When tested in the SHAC procedure, baclofen (2.5 and 5 mg/kg, i.p.) dose-dependently reduced—up to complete suppression—alcohol intake in Withdrawal Seizure Control mice (27).

### Relapse-Like Drinking

Relapse drinking is modeled in rodents by the so-called "alcohol deprivation effect" (ADE), that is the transient increase in voluntary alcohol intake occurring after a relatively long period of forced abstinence from alcohol [see (28)]. The effect of baclofen on ADE has been investigated in alcohol-preferring sP rats (29, 30) and alcohol-addicted Wistar rats (31).

In the two studies employing sP rats (29, 30), animals were initially exposed to a period of continuous alcohol drinking under the 2- or 4-bottle "alcohol vs. water" choice regimen (in the latter case, multiple alcohol concentrations were concurrently available), during which rats developed high and steady daily intakes of alcohol. Rats were then deprived of alcohol for 7–14 consecutive days. Re-exposure to alcohol resulted in a substantial

increase in alcohol intake over the first hour of re-access as well as in a shift in preference for the highest concentrated alcohol solution. Acute treatment with baclofen (1–3 mg/kg, i.p.), administered immediately before re-exposure to alcohol, produced a complete blockade of both ADE-associated events (increase in alcohol intake and shift in alcohol preference). The lack of baclofen effect on food and water intake and spontaneous locomotor activity conferred specificity for alcohol intake to the reducing effect of baclofen (29, 30).

In the study employing Wistar rats (31), animals were exposed to long periods of alcohol drinking interposed with periods of alcohol abstinence, resulting—after ∼1 year—in the development of addiction-like behaviors. Baclofen (1 and 3 mg/kg, i.p.) was injected repeatedly over the last drinking and deprivation phases. Treatment with 3, but not 1, mg/kg baclofen (i.p.) significantly reduced the post-abstinence, extra-intake of alcohol; specificity was not complete, as the reducing effect of baclofen on alcohol drinking was accompanied by a reduction in spontaneous locomotor activity, suggestive of a sedative effect. Again, drinking history and genetic background of rats may explain the differences observed in the ADE studies on baclofen.

## BACLOFEN EFFECT ON OPERANT ALCOHOL SELF-ADMINISTRATION

A major step forward in the assessment of the preclinical, *anti*-alcohol profile of baclofen has been represented by the several studies using operant procedures of oral alcohol self-administration, in which alcohol is made available once the animal has activated an *operandum* (usually a lever or a nose-poke). Operant procedures allow measurement not only of the mere consumption of alcohol but also of the amount of "work" that the animal is willing to perform to access alcohol; when a high workload is required, operant procedures well model the human condition of excessive amounts of time spent in obtaining and using alcohol [a fundamental criterion for diagnosis of AUD (32)].

Rodent studies on baclofen have focused mainly on the use of two different procedures of oral alcohol self-administration: (i) fixed ratio (FR) schedule of reinforcement and (ii) progressive ratio (PR) schedule of reinforcement. Under the FR schedule, response requirement (RR; i.e., the "cost" of each alcohol presentation in terms of responses on the *operandum*) is predetermined and maintained throughout the session; this schedule provides a measure of alcohol consumption and reinforcing properties of alcohol [see (33)]. Under the PR schedule, RR is progressively increased after the delivery of each reinforcer; the lowest ratio not completed (breakpoint) provides a measure of motivational properties of alcohol [see (33)].

Rat studies have almost unequivocally reported the ability of systemic baclofen [0.5–5.6 mg/kg (i.p.) or corresponding doses of R(+)-baclofen] to markedly reduce alcohol self-administration under the FR schedule of reinforcement (with FR varying from FR1 to FR4); this effect was observed both in selectively bred alcohol-preferring rats (19, 34–36) and unselected Wistar and Long Evans rats (37–42). A mouse study reported similar results: treatment with baclofen (1–17 mg/kg, i.p.) reduced lever-responding for alcohol (43).

Interesting results, with possible translational value, have been yielded by "FR" studies testing baclofen in rats with high levels of responding for alcohol and large amounts of self-administered alcohol. Specifically, treatment with baclofen resulted to be particularly effective in Indiana alcohol-preferring (P) rats (36) and Wistar rats made physically dependent on alcohol by exposure to alcohol vapors (40). These data apparently mirror the results of clinical studies suggesting a greater efficacy of baclofen in patients affected by severe AUD [see (44)].

The relatively few studies using the PR schedule of reinforcement generated results similar to those of the "FR" studies: treatment with baclofen (1–3 mg/kg, i.p.) effectively reduced lever-responding and breakpoint for alcohol in different lines of selectively bred alcohol-preferring rats (36, 45) as well as in alcohol-dependent and –non-dependent Wistar rats (40).

The selectivity of the reducing effect of baclofen on alcohol self-administration was limited; treatment with baclofen reduced indeed self-administration of alternative, non-drug reinforcers—such as sucrose or saccharin solutions or regular food pellets—with potency and efficacy often comparable to those observed in "alcohol" experiments (34, 36, 38, 39, 45). Some studies also reported partial overlap between baclofen doses reducing alcohol self-administration and those inducing hypolocomotion (43), suggesting a possible confounding impact of baclofen-induced motor-incoordination on lever-responding for alcohol.

Operant procedures also allow the investigation of alcohol seeking, separated from any alcohol drinking. This may be done with animals trained to respond for alcohol and then exposed to test sessions during which responding are never reinforced: the only measurable outcome is extinction responding (ER). ER is taken as measure of the appetitive and motivational properties of alcohol [see (33)]. An alternative experimental procedure (commonly named "sipper") – that provides a clear separation between the appetitive and consummatory phases of alcohol self-administration within a single session—is based on animals trained to complete a single RR (usually, 16–30 lever-responses) to gain access to alcohol for a substantial period of time (usually, 20 min) [see (46)]. In an "ER" study (47), treatment with 1–3 mg/kg baclofen (i.p.) completely suppressed ER for alcohol in alcohol-preferring sP rats; although not influenced by any motor-incoordinating effect, the suppressing effect of baclofen on ER was not selective for alcohol, as baclofen treatment also suppressed ER for a sucrose solution. A subsequent "ER" study using Long Evans rats reported a comparable reduction of ER for alcohol and sucrose after treatment with 3 mg/kg baclofen (i.p.) (48). When tested under the "sipper" procedure, systemic administration of baclofen reduced lever-responding to access alcohol in Long Evans rats (48) and C576BL/6 mice (27); in both studies, treatment with baclofen also affected lever-responding for sucrose, limiting the selectivity of baclofen effect.

Two recent studies (49, 50) investigated the effect of baclofen on alcohol self-administration in non-human primates. In both studies, adult male baboons were exposed to a chained schedule of reinforcement with three linked components; sequential completion of RR of each component made alcohol available. Baclofen was injected intramuscularly at doses varying between 0.1 and 2.4 mg/kg. Treatment with baclofen decreased lever-responding for alcohol, number of alcohol drinks, and amount of self-administered alcohol. Treatment with baclofen was effective when initiated during ongoing alcohol access, but not when initiated during an alcohol-abstinence period preceding alcohol access (50). These data are in agreement with the results of human studies indicating a greater efficacy of baclofen when treatment was initiated during active drinking [e.g., (51)] rather than after abstinence had been achieved [e.g., (52)]. An additional experiment found that baclofen treatment facilitated ER for alcohol (49). As in the majority of rodent studies of alcohol self-administration, in these two monkey studies selectivity of baclofen effect was modest, as baclofen also reduced self-administration of a non-drug reinforcer (orange-flavored beverage). Sedation and transient side-effects were also observed.

## BACLOFEN EFFECT ON REINSTATEMENT OF ALCOHOL SEEKING

Two rodent studies investigated the effect of baclofen on reinstatement of alcohol-seeking behavior. In this procedure, largely used in the alcohol and drug addiction field, previously extinguished unreinforced lever-responding or nose-poking for alcohol is reinstated by (i) environmental stimuli previously associated to alcohol availability, (ii) limited availability of alcohol, (iii) exposure to stressors, or (iv) administration of specific drugs (e.g., nicotine and cannabinoids). Reinstatement of alcohol-seeking behavior models loss of control over alcohol and relapse episodes in AUD patients [see (28)], resulting to be complementary to ADE.

In the first study (53), alcohol-preferring sP rats—trained to lever-respond for alcohol under the FR4 schedule of reinforcement—were exposed to a single session made of an initial phase of ER followed, once lever-responding for alcohol was virtually completely extinguished, by a reinstatement phase; the latter was preceded by an alcohol-associated stimulus complex, that effectively reinstated lever-responding (still unreinforced). Acute treatment with baclofen (3 mg/kg, i.p.), given after extinction of lever-responding and 30 min before presentation of the alcohol-associated stimulus complex, resulted in a marked reduction of an otherwise robust reinstatement of lever-responding. These data complement well with those reporting the ability of 1–3 mg/kg baclofen in suppressing relapse-like drinking in sP rats exposed to the ADE procedure (29, 30).

In the second study (31), Wistar rats—trained to nose-poke for alcohol under the FR3 schedule of reinforcement—were first exposed to a series of ER sessions and then to reinstatement sessions in which unreinforced nose-poking was reinstated by the presentation of alcohol-associated stimuli. Treatment with baclofen (1 and 3 mg/kg, i.p.) fully abolished, in a dose-related manner, reinstatement of nose-poking.

## MECHANISM OF ACTION OF BACLOFEN EFFECTS ON ALCOHOL-RELATED BEHAVIORS

Several lines of experimental evidence converge to support the hypothesis that the suppressing effect of baclofen on multiple alcohol-related behaviors are mediated by the activation of $GABA_B$ receptors located in the ventral tegmental area (VTA), a key area of the mesolimbic dopamine system [i.e., the neuronal system mediating the rewarding, reinforcing, motivational, and stimulating properties of natural stimuli and drugs of abuse [see (54)], including alcohol [see (55)]. Indeed, baclofen microinjection into the VTA of rats and mice suppressed several alcohol-motivated behaviors and *in vivo* actions of alcohol, including (a) alcohol drinking (56), (b) alcohol self-administration (57), (c) alcohol seeking (58), (d) alcohol-stimulated locomotor activity (8, 59), (e) alcohol-induced sensitization of locomotor activity (59), and (f) alcohol-induced conditioned place preference (60). More specifically, intra-VTA microinjection of 0.03–0.3 μg baclofen dose-dependently suppressed lever-responding for alcohol in sP rats (57); suppression of lever-responding for alcohol was particularly evident over the first minutes of the test session, suggestive of the ability of intra-VTA baclofen to suppress rat motivation to start seeking and consuming alcohol. The effect of intra-VTA baclofen on alcohol self-administration was site-specific and devoid of any motor-incoordinating effect (57).

In close agreement with the above data, and as further confirmation of the hypothesis relating to the hyperpolarization of mesolimbic dopamine neurons as the mechanism of action through which baclofen suppresses alcohol-related behaviors, intra-VTA microinjection of baclofen suppressed dopamine release—stimulated by cues anticipating alcohol reinforcement—in the rat nucleus accumbens (NAc; the target brain area of mesolimbic dopamine neurons) (58, 61, 62).

Brain regions other than VTA likely contribute to mediation of the suppressing effects of baclofen on alcohol-related behaviors. Accordingly, recent experimental data highlighted a role for the ventral pallidum (VP), a brain area to which GABAergic neurons located in the NAc project their axons; indeed, baclofen microinjection into the VP reduced alcohol intake in selectively bred alcohol-preferring Alko Alcohol (AA) rats (63). More recent data pointed to involvement of the amygdala: due to reduced levels of the GABA transporter GAT3, high concentrations of extracellular GABA have been found in the amygdala of alcohol-dependent rats (64). It has been proposed that baclofen-induced activation of amygdalar presynaptic $GABA_B$ receptor would lower extracellular GABA, possibly normalizing the enhanced tonic inhibition of amygdala and, subsequently, reducing excessive alcohol drinking (65).

## BACLOFEN EFFECT ON ALCOHOL WITHDRAWAL SYNDROME

An additional series of *in vivo* studies tested the ability of baclofen to ameliorate signs of alcohol withdrawal syndrome (AWS) in rats. AWS is experimentally induced by the abrupt termination of alcohol administration to rats made physically dependent on alcohol by the forced, prolonged exposure to intoxicating amounts of alcohol [e.g., (66)]. The resulting signs closely resemble those observed in AUD patients (67, 68).

Treatment with baclofen (1.25–25 mg/kg, i.p.) suppressed several AWS signs, including increase in alcohol self-administration, anxiety-related behaviors, tremors, and seizures in alcohol-dependent Wistar, Sprague-Dawley, and Lister rats (13, 40, 69, 70). The ability of baclofen to effectively suppress AWS signs in rats has since been effectively translated to AUD patients [e.g., (71)]. A $GABA_B$ receptor-mediated counterbalance of the AWS-associated, enhanced function of glutamate excitatory neurotransmission has been proposed as the mechanism by means of which baclofen exerts its suppressing effects on AWS signs (13, 40).

## CONCLUSIONS

Treatment with the prototypic, orthosteric agonist of the $GABA_B$ receptor, baclofen, suppressed several different alcohol-related behaviors in laboratory rodents and non-human primates. These results are of relevance as they suggest a critical role for the $GABA_B$ receptor in the neural substrate underlying alcohol seeking and drinking. Additionally, these data possess remarkable translational value, as most of the effects of baclofen observed in animals have subsequently been reproduced in AUD patients: most of the clinical surveys conducted to date indeed reported substantial reductions in alcohol drinking and craving for alcohol after treatment with baclofen [see (62, 72)], making baclofen a promising pharmacotherapy for AUD.

The limited separation between baclofen-induced "desired" pharmacological effects and "unwanted" sedative effects appears to be the most relevant drawback of the *anti*-alcohol profile of baclofen. A major step forward in this field is likely represented by the positive allosteric modulators (PAMs) of the $GABA_B$ receptor; notably, rodent data collected to date on this new class of $GABA_B$ receptor ligands suggest indeed that $GABA_B$ PAMs reproduce all the *anti*-addictive properties of baclofen at doses largely lower than those inducing motor-incoordination and sedation [see (62, 73–75)]. Since the first $GABA_B$ PAMs are now approaching clinical testing, it will soon be possible to assess whether they retain baclofen effects, while possessing higher therapeutic index and more favorable side-effect profile, also in humans.

## AUTHOR CONTRIBUTIONS

GC and GG contributed equally to literature search and manuscript writing. Both authors approved the final draft of the manuscript.

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**Conflict of Interest Statement:** GC and GG are inventors of a European patent on "The use of baclofen in the treatment of alcoholism". GC is partner of Cagliari Pharmacological Research (Cagliari, Italy), owner of the above patent.

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