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A human laboratory pilot study with baclofen in alcoholic individuals

Lorenzo Leggio^{a,*}, William H. Zywiak^{a,b}, John E. McGeary^{a,c}, Steven Edwards^a, Samuel R. Fricchione^a, Jessica R. Shoaff^a, Giovanni Addolorato^d, Robert M. Swift^{a,c}, and George A. Kenna^a

^aCenter for Alcohol and Addiction Studies, Brown University, Providence, RI, USA

^bDecision Sciences Institute, P. I. R. E., Pawtucket, RI, USA

^cVeterans Affairs Medical Center, Providence, RI, USA

^dInstitute of Internal Medicine, Catholic University of Rome, Italy

Abstract

Preclinical and clinical studies show that the GABA_B receptor agonist baclofen may represent a pharmacotherapy for alcohol dependence (AD). However, the mechanisms by which baclofen affects drinking are not well characterized; thus this pilot study investigated possible baclofen's biobehavioral mechanisms. The design was a double-blind controlled randomized human laboratory pilot study. Fourteen non-treatment seeking alcohol-dependent heavy drinking subjects received either baclofen 10 mg t.i.d. or an active placebo (cyproheptadine 2 mg t.i.d., to control for sedation) for a 7-day period. At day 8, participants performed an alcohol cue-reactivity (CR) followed by an alcohol self-administration (ASA). Additionally, we explored possible moderators that might guide future larger studies, i.e. anxiety, family history and onset of alcoholism, and D4 dopamine receptor (DRD4) and 5-HTTLPR polymorphisms. The main results were a significant effect of baclofen for increasing stimulation ($p=.001$) and sedation ($p<.01$). Furthermore, when drinking during the ASA and the 2 days before was analyzed as a composite variable, there was a significant effect of baclofen to reduce alcohol consumption ($p<.01$). As for the exploratory analyses, baclofen's effects to increase alcohol sedation and to reduce alcohol consumption were limited to those individuals with DRD4 7 repeats (DRD4L). Yet, baclofen's effects on alcohol consumption were also moderated by 5-HTTLPR LL genotype. In conclusion, baclofen's ability to reduce alcohol drinking may be related to its effects on the biphasic effects of alcohol, but larger studies are needed to confirm these preliminary findings.

*Corresponding author at: Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, NIAAA & NIDA, NIH, 10 Center Drive (10CRC/15330) MSC 1108, Room 1-5429, Bethesda, MD 20892-1108, USA. Tel.: +1 301 435 9398; fax: +1 301 402 0445., lorenzo.leggio@nih.gov (L. Leggio).

¹Dr. Leggio's current affiliations are: Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA; and Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA.

Disclosure

All authors declare no conflict of interest.

Keywords

Baclofen; Alcoholism; Cue-reactivity; Alcohol self-administration; Biobehavioral mechanisms; Genetic polymorphisms

1. Introduction

The GABA_B-receptor(R) agonist baclofen may represent an effective pharmacotherapy for alcohol dependence (AD). Most preclinical studies show that baclofen suppresses acquisition and maintenance of alcohol-drinking behavior, oral self-administration of alcohol, and alcohol-related motivational properties (for review, Maccioni and Colombo, 2009). Similarly, open-label studies (Addolorato et al., 2000; Flannery et al., 2004; Leggio et al., 2008a, 2008b) and double-blind placebo-controlled randomized clinical trials (RCTs) (Addolorato et al., 2002, 2007) suggest that, in alcohol-dependent (AD) patients, baclofen 10 mg three times a day (t.i.d.) reduces alcohol drinking and craving and promotes abstinence. However, another RCT reported a strong overall treatment effects on alcohol consumption, but not significant differences between baclofen and placebo (Garbutt et al., 2010). Therefore, more research is needed to further understand the possible role of baclofen as a pharmacotherapy for alcoholism. In particular, the biobehavioral mechanisms by which baclofen affects drinking are not well characterized. Only one human laboratory alcohol pilot study with baclofen has been performed to date, testing a 1-day baclofen administration (0, 40, and 80 mg) in combination with intoxicating doses of alcohol in non-treatment seeking non-AD heavy drinkers; baclofen increased sedation, but not stimulant effects (Evans and Bisaga, 2009).

The present study investigated baclofen's biobehavioral mechanisms by enrolling AD individuals to receive the study medications for a period long enough to mimic its clinical use (see, Perkins et al., 2006), and using an alcohol cue-reactivity (CR) and alcohol self-administration (ASA) paradigm. Furthermore, an exploratory goal of this pilot study was to explore AD subtypes who may respond better to baclofen as inconsistencies among some RCTs suggest individual variability in baclofen response (Addolorato et al., 2002, 2007; Garbutt et al., 2010; Leggio et al., 2012). Moreover, important pre-treatment differences on drinking, withdrawal symptoms, and anxiety levels, suggest that baclofen's effect may be more pronounced in patients with more severe AD (Leggio et al., 2010). High anxiety levels, family history (FH) positive for alcoholism and early onset of alcoholism (EOA) have been correlated with the severity of alcoholism (e.g. Johnson et al., 2010; Gleeson et al., 2009; Leggio et al., 2009); therefore these factors were explored as potential moderators of baclofen's response. Additionally, we attempted to explore possible genetic moderators with the overall goal to provide very preliminary information that might guide possible fully-powered studies. Several candidate genes, including the D4 dopamine receptor (*DRD4*) and the serotonin transporter promoter region (5-HTTLPR) have been associated with risk of AD or response to pharmacotherapy (Kenna et al., 2012; McGeary, 2009). However, the role of candidate genes as moderators of baclofen's response in AD has never been investigated. The *DRD4* gene encodes a 7 transmembrane G-protein coupled receptor that responds to endogenous dopamine. A variable number of tandem repeats (VNTR)

polymorphism in exon 3 impacts the length of the protein in the receptor's third cytoplasmic loop, altering receptor sensitivity and there is evidence of a robust relationship between urge for alcohol and the *DRD4* polymorphisms, i.e. the presence vs. absence of the *DRD4* allele 7-repeat (McGeary, 2009). GABA_B-R agonists exert direct and indirect inhibitory actions on the dopamine neurons in the ventral tegmental area (VTA) (Yoshida et al., 1994). This pathway may explain how baclofen suppresses alcohol-stimulated dopamine release and, in turn, dopamine-mediated, alcohol-reinforced behaviors. Functional control of the 5-HT system may be regulated by genetic differences in the 5-HT transporter (5-HTT) SLC6A4 gene, mediating 5-HT neurotransmission function by controlling its strength and duration. The 5-HTTLPR polymorphism is a common insertion/deletion of two 22-bp repeats in a region of the promoter with multiple 22- to 23-bp repeats in the 5-HTT "promoter" region (for review, Kenna et al., 2012). The short (S) variation has 2 fewer repeats than the long (L). The major types of allele combinations are the homozygous L/L, S/S, and heterozygous S/L. The L/L allele combination results in higher 5-HT transporter mRNA transcription, than the SS/SL, and is hypothesized to be one mechanism by which some individuals are at greater risk of AD than others; thus the L/L genotype may be associated with an increased risk of AD (Kenna et al., 2012). Baclofen is a selective GABA_B-R agonist and interestingly, a dual action of baclofen on serotonergic function has been hypothesized, including an indirect (disinhibitory) effect mediated through GABA_B pre-synaptic autoreceptors located on GABAergic terminals projecting to serotonergic neurons, and a direct (inhibitory) effect mediated through postsynaptic GABA_B receptors located on 5-HT neurons in the dorsal raphe (Serrats et al., 2003).

2. Patients and methods

2.1. Study design and setting

The design was a between-subject double-blind controlled randomized human laboratory study performed at the Brown University Center for Alcohol and Addiction Studies, Providence (RI). The study [ClinicalTrials.gov: NCT01076283] was approved by the Brown Institutional Review Board (IRB) and reviewed by the Food and Drug Administration (FDA) (IND#106609) and considered exempt from IND requirements.

2.2. Study population

Participants were non-treatment seeking AD men and women screened according to the inclusion criteria, e.g. 21 and 65 year-old; DSM-IV diagnosis of AD; and heavy drinking, defined as averaging 4 drinks/day for women and 5 drinks/day for men. Exclusion criteria included DSM-IV diagnosis of current substance dependence (other than alcohol and nicotine; a urine drug screen was also performed); recent (past 6 months) DSM-IV diagnosis of Major Depressive Disorder or Anxiety Disorder; lifetime DSM-IV diagnosis of schizophrenia, bipolar disorder, or other psychoses; and lifetime history of attempted suicide. DSM diagnoses were based on the Structured Clinical Interview for DSM-IV (SCID; First et al., 1994) administered by trained research clinical staff supervised by a clinician.

Individuals with clinically significant medical problems were excluded, as assessed by medical history, physical exam, ECG, and blood/urine tests. Additional exclusion criteria were contraindications to take baclofen (or cyproheptadine); reasonable expectation of being institutionalized during the study; significant alcohol withdrawal symptoms; and history of seizures or epilepsy. Potentially fertile women were admitted to the study only if practicing an effective method of birth control (a urine pregnancy test was also performed at each visit).

2.3. Study medication and “active” placebo

After a 3-day half-dose titration, baclofen was increased to 10 mg t.i.d. until day 8 (the CR/ASA day). After the CR/ASA, a 3-day downtitration was used. Sedation is an occasional side-effect of baclofen therefore, as previously validated (Hutchison et al., 2003), we used cyproheptadine as an “active” placebo to control for sedation. After a 3-day titration, cyproheptadine dose was 2 mg t.i.d. until day 8 (followed by a 3-day downtitration). Baclofen or cyproheptadine was administered as opaque capsules containing drug and 25 mg riboflavin (used as a compliance measure; Del Boca et al., 1996) placed into blister packs.

2.4. Study overview

Potential participants recruited via mass media were phone screened. Passing participants came for an in-person visit, during which they received information on the study, including study procedures, study medications and their possible side-effects; after signing an informed consent form, participants received a comprehensive screening (Visit 1). At Visit 2 (day 1), participants were randomized to either baclofen or active placebo by using a 3-urn variable procedure (Stout et al., 1994), i.e. gender, FH of alcoholism and baseline drinks per drinking day. Participants performed the CR/ASA session at Visit 3 (day 8) and a brief follow-up (Visit 4) a week after Visit 3. A breath alcohol concentration (BrAC) 0.00 was required at each visit. Compensation in the form of cash was provided.

2.5. CR/ASA session

The CR/ASA session was conducted individually in a private bar-like atmosphere. Participants were asked to fast at least 4 hours before the experiment, to reduce variability in alcohol absorption and, on arrival, smokers were asked to smoke their last cigarette. After baseline assessments, the CR was performed, followed by the ASA. The CR was similar to that of previously published studies (details in: Monti et al., 1987, 1999; McGeary et al., 2006). Participants were exposed to visual, tactile, olfactory, and proprioceptive stimuli associated with the beverage during three 3-minute CR trials. The first consisted on the exposure to neutral cues (i.e. a bottle and glass of water), while the second and the third trials consisted on the exposure to alcoholic cues (commercially-labeled preferred alcohol beverage); at each trial, an audiotape instructed the participant to sniff the glass of water or alcohol according to high/low tones. The three trials were presented in the same order for all participants because of known carryover effects (Monti et al., 1987). At the end of each trial, participants rated their urge and attention to alcohol completing the Alcohol Urge Questionnaire (AUQ; Bohn et al., 1995), and the Alcohol Attention Scale (AAS; Rohsenow et al., 1992). During each trial, participants placed three dental rolls in their mouths (White,

1977) and the saliva produced during cue exposure was indicated by the weight difference determined via an analytical scale (0.0001 gram resolution). Mean arterial pressure (MAP) and HR were continuously monitored. After the CR, participants underwent the ASA (details in: O'Malley et al., 2002; Kenna et al., 2009; George et al., 2010). First, participants were presented with a "priming" drink, whose volume was based on gender, age and body weight (Watson, 1989), and designed to raise blood alcohol levels to 0.03 g/dl. Participants were instructed to consume the priming within 5 minutes; then, 10, 20, 30 and 40 minutes after the priming, BrAC levels, AUQ and alcohol's stimulant and sedative effects – using the Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993) – were assessed. Forty minutes after the priming, a sign indicating "the bar is open" was displayed, and additional alcohol was presented in a form of 2 trays with 4 mini-drinks each (a 4 mini-drink tray per hour). Each mini-drink was calculated to raise the blood alcohol levels by 0.015 g/dl. During the 2-hour alcohol free choice, BrAC, AUQ and BAES were administered every 30 minutes. Participants were allowed to drink any or all glasses and \$3/drink (up to \$24) was provided as an alternative reinforcer for not drinking. At the end of the ASA, participants received a meal and had to wait until BrAC=0.00 before being sent home by taxi. Before being released, participants received a motivational session in order to provide personalized education about AD.

2.6. Moderators

Anxiety levels were assessed with the State-Trait Anxiety Inventory (STAI) scales (Spielberg et al., 1983), FH was assessed with the Family Tree Questionnaire (FTQ; Mann et al., 1985) and age of onset (early onset of alcoholism [EOA] vs. late onset of alcoholism [LOA], i.e. <25 vs. ≥25 year-old at onset) using question B28 of the Comprehensive Drinker Profile (Miller and Marlatt, 1984).

2.7. DNA genotyping

The inside of participant's cheeks was swabbed and genomic DNA was isolated from buccal cells (Freeman et al., 1997; Lench et al., 1988). Details for determining *DRD4* status (*DRD4*-long group [*DRD4-L*] vs. *DRD4*-short [*DRD4-S*]) and 5-HTTLPR status (LL vs. SS/SL) are described elsewhere (McGeary et al., 2006; Kenna et al., 2009).

2.8. Statistical analysis

Most of the analyses presented consist of repeated measures ANCOVAs to accommodate dependent measures assessed at multiple time points. When the dependent measure was just assessed once then a regular ANCOVA was used. The Alcohol Dependence Scale (ADS) (Skinner and Allen, 1982) was hypothesized to moderate the medication effects; however, it was determined that though randomly assigned, the medication group had a higher ADS score [$t(11) = 3.09, p = .01, M = 15.0 (SD = 7.7)$] compared to the active placebo group [$M = 5.1 (SD = 3.40)$]. Baseline ADS was therefore entered as a covariate in all of the main analyses. We examined medication main effects across several different dependent measures. All of the analyses were conducted using SPSS version 18.

3. Results

3.1. Sample description

Of 43 telephone screenings, 19 signed the consent document; five individuals were not eligible while 14 were eligible and randomized. Demographics were as follows: age: 41.6 (25–51) years; 10 males/4 females; 6 Black/2 Hispanic/5 White/1 Multi-racial; 12.6 (8–17) years of education; 7 FH+/7 FH–; baseline average of drinks per day 7.92 (2.86–31.50).

3.2. Clinical profile

SCID symptoms ranged from 3 to 7 ($M=4.1$, $SD=1.3$). The average score on the Drinking Inventory of Consequences (DrInC) was 30.6 ($SD=18.7$). Years of problem drinking ranged from 6 to 30 ($M=18.9$, $SD=8.0$). The average score on the items on the trait scale of the State and Trait Anxiety Inventory (STAI) was 1.8 ($SD=0.5$). Means (and SD s) for liver tests (AST, ALT, GGT, and bilirubin) were 31.0 (31.4), 27.2 (21.7), 46.1 (48.2), and 0.52 (0.14), respectively.

One participant did not perform the CR/ASA because of significant non-compliance with the medication (62.5%); therefore 13 (93%) individuals were included in the analysis. The mean compliance rate was 94.25% (range=87 to 100%) assessed via pill count, participants' interview, and verified by urine riboflavin check (using ultraviolet light detection of a urinary riboflavin tracer). During the study, there were no serious adverse events and the medication was generally well tolerated by all the participants.

3.3. Group differences on baseline measures

In addition to the previously reported difference between the baclofen and the active placebo group on the ADS score, the SCID indicated that the baclofen group also had a greater number of alcohol dependence symptoms ($M=5.0$, $SD=1.3$) than the active placebo group [$M=3.1$ ($SD=0.4$), $t(12)=3.65$, $p<.01$]. Though the group difference in symptoms was greater than the group difference on the ADS, we used the ADS score as a covariate, since the symptom count distribution evidence a restriction of range (i.e., half the sample had a value of 3). There was also a group difference on the DrInC [baclofen: 41.4 (19.9) compared to placebo 19.9 (9.7), $t(12)=2.58$, $p=.02$]. There were no other group differences on any of the other clinical profile variables, nor FH, nor baseline drinks per day.

3.4. Alcohol cue-reactivity (CR)

A repeated measures ANCOVA with AUQ scores for the water trial showed no medication effect. Similarly, no effect was found on the AAS, nor for HR during the alcohol trials. Repeated measures ANCOVA for MAP indicated a significantly higher MAP for the baclofen group, compared to the active placebo [$F(1,25)=5.36$, $p=.03$]. A repeated measures ANCOVA on saliva during the CR was significant [$F(1,24.4)=15.97$, $p<.01$] indicating greater salivation with baclofen than active placebo [mean difference=1.87 ($SE=0.48$)].

3.5. Alcohol self-administration (ASA)

After consuming the priming drink, there was a significant effect of baclofen, compared to active placebo, on the biphasic effects of alcohol, i.e. significant increases in alcohol

stimulation and alcohol sedation. Repeated measures ANCOVA for BAES stimulation [$F(1,92.5)=11.30$, $p=.001$, mean difference=1.67 (SE=0.50)] across 8 time points. When just the pre ad-libitum consumption period was examined, this was also statistically significant [$F(1,44.4)=11.78$, $p=.001$, mean difference=2.40 (SE=0.69)] (Fig. 1a). When the ad-libitum consumption period alone was examined, the medication effect was no longer significant [$F(1,51.3)=2.29$, $p=.14$, mean difference=1.04 (SE=0.69)] (Fig. 1b). When the number of drinks consumed during the ad-libitum period was entered as a covariate, the medication effect became a statistical trend [$F(1,51.4)=2.93$, $p=.09$, mean difference 1.34 (SE=0.79)]. When all 8 time points were analyzed with BAES sedation as the dependent measure a medication effect was apparent [$F(1,90)=9.99$, $p<.01$; mean difference=1.10 (SE=0.35)]. However, when just the first four time points were analyzed, the medication effect was not significant [$F(1,51.4)=0.87$, $p=.37$, mean difference=0.53 (SE=0.57)]. When the last 4 time points were analyzed, the medication effect was significant [$F(1,47.7)=11.28$, $p=.002$, mean difference=1.42 (SE=0.42)] even when the number of drinks consumed during the ad-libitum period was entered as a covariate [$F(1,48.1)=5.36$, $p=.03$, mean difference=1.11 (SE=0.48)]. In summary, a medication effect for stimulation was significant for the “pre ad-libitum” (post-priming) period, but not during the “ad-libitum” period, while a medication effect for sedation was significant for the “ad-libitum” period, but not pre. These results indicate that the medication effects on stimulation and sedation did not occur simultaneously, i.e. the increase in stimulation occurred before the increase in sedation.

During the ASA, there was a lower amount of alcohol consumed, expressed as standard drinking units (SDUs) in the baclofen group; baclofen $M(SD)$: 0.17 (0.41), placebo $M(SD)$: 1.43 (2.30); $d=.76$, $t(6.4)=1.43$, $p=.20$. Although the difference did not reach a statistical difference, there was a robust medication effect ($d=.76$). When ADS was entered as a covariate, the medication effect became stronger, though it was still not significant [$F(1,10)=3.15$, $p=.11$]. Alcohol drinking for the 7 days prior to the CR/ASA was also collected via the Timeline Follow-Back (TLFB). Group differences for SDUs consumed the day before [baclofen $M(SD)$: 2.67 (4.25), placebo $M(SD)$: 8.91 (12.86); $d=.65$, $t(7.5)=1.21$, $p=.26$] and 2 days before [baclofen $M(SD)$: 4.75 (7.29), placebo $M(SD)$: 9.91 (10.90); $d=.56$, $t(11)=0.98$, $p=.35$] the CR/ASA were similar to group differences for alcohol consumed during the ASA. Given the small sample, we conducted an additional post-hoc analysis aimed to analyze the data with a repeated measures ANCOVA with all 3 time points on the same metric, i.e. drinks during the ASA were “scaled up” to the SDUs for the 2 days before, by multiplying by eight (the sample mean for the 2 days before was 7.0, and the sample mean for the day before was 5.7; the average of these two values is 6.4; the sample mean for ASA drinks consumed was 0.8. $6.4/0.8=8$.) These three dependent measures were entered into repeated measures ANCOVA with ADS as a covariate. The medication effect was significant in this test [$F(1,35.69)=10.98$, $p<.01$, baclofen: -0.35 (SE=2.60), placebo: 12.9 (SE=2.35), with a negative SDU value obtained by covarying the ADS score, which was associated with alcohol consumption and which was higher in the medication group] (Fig. 2).

3.6. Moderator analyses

We explored hypothesized moderators on the two treatment main effects that were the most pronounced — the dependent measures of BAES stimulation and sedation. Five moderators were tested in turn each on stimulation and sedation: *DRD4* status, 5-HTTLPR status, FH, age of onset of alcoholism, and baseline state anxiety (dichotomized by median split). Moderator and respective main effects were tested, with ADS included as a covariate. Moderator effects were significant for eight of the ten tests, and a trend was apparent when FH status was tested as a moderator on BAES sedation (Table 1). Six of the eight significant moderation effects were very pronounced ($p < .001$; Table 1). We also explored the possible effects of the same five moderators on the drinking-related variable whose effect was the most pronounced (the composite drinking variable). Moderator and respective main effects were tested, with ADS included as a covariate (Table 2). Moderator effects were significant for the *DRD4* status [Fig. 3a, $F(1,31.6)=11.0$, $p < .01$] and 5-HTTLPR status [Fig. 3b, $F(1,26.6)=33.1$, $p < .001$].

4. Discussion

This study provides preliminary information on the biobehavioral mechanisms and moderators of how baclofen affects alcohol consumption in AD individuals. The strongest result was the ability of baclofen to amplify alcohol's biphasic effects and the effect of baclofen in reducing alcohol consumption during both the naturalistic phase and the ASA. First of all, it should be noted that while participants reported an increase in sedation in the BAES scale, no clinically significant sedative side-effects (sedation, tiredness, sleepiness) were reported while participants took the medication, confirming the already reported safety of baclofen in AD patients. The ability of baclofen to increase alcohol's sedating effect on the BAES is consistent with the human laboratory study by Evans and Bisaga (2009). Hence, the main biobehavioral mechanism of how baclofen reduced drinking could be the ability of baclofen to increase alcohol's unpleasant effects (i.e. sedation). In fact, the effects of baclofen on alcohol's sedation may exert an aversive effect on the subjective experiences of alcohol consumption, reducing individuals' motivation to drink more alcohol after an alcohol priming, as we observed during the ASA.

On the contrary, the effect of baclofen for increasing alcohol's stimulating effect was not reported by Evans and Bisaga (2009). Indeed, baclofen's effect on stimulation is somewhat counter-intuitive as one may expect that an effective medication should reduce alcohol's rewarding effects. This difference between our results and those by Evans and Bisaga (2009) might be related to the enrollment of a different population, the use of different doses of baclofen, and the use of different doses of alcohol administered in the laboratory. Nonetheless, the effect of baclofen in increasing stimulation did not result in increased drinking during the ASA; rather, baclofen reduced alcohol consumption during the experiment. As Schuckit et al. (2004) have shown, FH+ individuals have a decreased sensitivity to alcohol and this could be increased by baclofen, as discussed below.

Baclofen's effect on alcohol consumption did not reach statistical significance although the effect size was robust both during the ASA and the 2 days prior to the ASA. Additionally, a post-hoc analysis of the SDUs consumed during the ASA and the 2 days

before with a repeated measures ANCOVA found a statistically significant medication effect. Altogether, these findings on alcohol consumption may suggest an effect of baclofen on alcohol consumption in this population of non-treatment seeking AD individuals — such effect may be due to the effects of baclofen on the biphasic effects of alcohol, as reported during the lab experiment. However, given the very small sample, a larger study is needed to investigate the magnitude of the effect of baclofen on drinking.

We also explored possible moderators of baclofen's effects on the biphasic effects of alcohol (Table 1). Greater sedation associated with baclofen was apparent in those with *DRD4* 7 repeats, while the opposite was observed in those with <7 repeats, i.e., sedation was lower for those receiving baclofen compared to active placebo. For BAES stimulation, FH(+) individuals demonstrated increase in stimulation associated with baclofen while the opposite pattern was observed in those with FH(−). As for anxiety, those with low state anxiety showed an increase in both stimulation and sedation when receiving baclofen relative to active placebo, while those with high state anxiety showed a decrease in stimulation and sedation when receiving baclofen. In summary, these preliminary results suggest that *DRD4* status, FH and state anxiety might moderate baclofen's effects on alcohol's biphasic effects. Particularly interesting is the potential moderator role of FH. In fact, FH+ individuals have a decreased sensitivity to alcohol (Schuckit et al., 2004) and in this study, FH status moderated baclofen's effects on stimulation, that is FH(+) individuals demonstrated increase in stimulation associated with baclofen while the opposite pattern was observed in those with FH(−). In other words, the increase in stimulation suggests that baclofen may have increased perceived alcohol intoxication, perhaps by increasing alcohol sensitivity and this effect was only observed in FH(+) individuals who have low sensitivity to alcohol, while baclofen reduced stimulation in FH(−) individuals.

We also explored the possible role of the same moderators on baclofen's effects on alcohol consumption (Table 2) and found that both *DRD4* and *HTTLPR* status moderated alcohol consumption. In fact, less drinking was associated with baclofen in those with *DRD4* 7 repeats, while the opposite was observed in those with <7 repeats (Fig. 3a). Furthermore, baclofen, as compared to placebo, reduced alcohol consumption regardless of *HTTLPR* status; however, baclofen-treated individuals with LL genotype drank significantly less compared to those baclofen-treated individuals with SS/SL genotype (Fig. 3b). These moderator analyses with a small sample size can only detect very large effect sizes, and therefore future attempts to replicate these findings are encouraged.

Altogether, the main results of this pilot study and the exploratory analyses of the moderators suggest that baclofen's ability to reduce alcohol consumption may be related to its ability to increase alcohol's unpleasant effects (i.e. sedation), but this might be limited to specific endophenotypes, i.e. AD individuals with *DRD4* 7 repeats (by contrast, perhaps baclofen should be avoided in AD individuals with *DRD4* <7 repeats) or is more pronounced in other endophenotypes, i.e. AD individuals with LL genotype. The very small sample limits significantly possible conclusions on the role of these moderators, which are reported here mostly to guide possible fully powered studies on these specific genetic moderators.

From a neurobiological standpoint, activation of D₄ receptors in the VTA inhibits the accumulation of intracellular cAMP, which in turn leads to greater motivation for dopaminergic rewards (Knapp et al., 2001). Although it would be premature to speculate possible neurobiological explanations of the present study, Ray et al. (2009) pointed out how the *DRD4* 7 variant may be associated with greater cAMP accumulation that, in turn, may lead to more alcohol use. Thus, hypothetically the magnitude of baclofen's effect in suppressing alcohol-stimulated dopamine release in the VTA and reducing alcohol use might be greater in AD individuals with *DRD4* 7. Interestingly, we had hypothesized that baclofen is more likely to have a significant effect on patients with a high severity of AD (Leggio et al., 2010), and the present study suggests that baclofen is more likely to affect alcohol drinking in carriers of *DRD4* 7 repeats, an endophenotype that is significantly related with more alcohol-related problems (Hutchison et al., 2002; Ray et al., 2009). Furthermore, a study by Schuckit et al. (1999) reported that the 5-HTTLPR status increases the risk of alcohol-related problems only in interaction with other neurotransmitter systems, such as GABAergic neurotransmission, an observation consistent with our findings on the interaction between the LL vs. SS/SL genotype and the effects of the GABAergic baclofen on alcohol-related sedation and alcohol consumption.

The inconsistency of baclofen's effects on alcohol drinking among previous treatment RCTs suggests that different AD individuals may respond differently to baclofen (Leggio et al., 2010). Although caution is required given the small sample, this study tentatively identified possible specific endophenotypes that may have a different response to baclofen on alcohol effects and consumption.

We noted previously that baclofen unexpectedly increased BAES stimulation. Interestingly, while this was true in the main analysis, baclofen reduced stimulation in those individuals with FH(−) or high anxiety levels. This might suggest that baclofen's effects on alcohol-related stimulation might be dependent on FH status and state anxiety. However neither FH status nor anxiety moderated alcohol drinking; thus the clinical relevance of these moderators remains unclear at this stage.

In this study we did not find an effect of baclofen in reducing alcohol craving nor in the attention to alcohol cues during the CR. Reported previously, there was an effect of baclofen in reducing self-reported alcohol craving in treatment-seeking AD individuals (Addolorato et al., 2002, 2007), while here we tested cue-elicited alcohol craving in non-treatment seeking AD individuals. The different samples and study settings, as well as the small sample, might explain these differences. Furthermore, during the CR, we found a significant increase in MAP and saliva in the baclofen group. The increase in MAP is consistent with the laboratory study (Evans and Bisaga, 2009), where baclofen was associated with small increases in blood pressure. Also, we used an active placebo (cypheptadine), which side-effects may include dry mouth, and this might explain the higher saliva mass in the baclofen group. In summary, there was not a beneficial effect of baclofen on the subjective and physiological responses to the CR experiment. On the other hand, the results on the CR outcomes might raise the question on a possible abuse liability of baclofen in this population. It should be noted that in treatment trials that lasted longer, AD patients never abused of baclofen (reviewed in: Leggio et al., 2010), thus making this hypothesis unlikely.

These results should be interpreted in light of the study's strengths and limitations. This is the first human laboratory alcohol study testing baclofen in AD individuals, after having taken baclofen for a reasonable period of time before performing laboratory procedures. This is also the first study ever providing data, albeit preliminary, on the potential role of candidate genetic moderators and proposing possible endophenotypes for baclofen's response in AD patients. Moreover, this is one of the first studies (see: Hammarberg et al., 2009) combining CR and ASA, thus providing a more comprehensive assessment of biobehavioral mechanisms of the drug. The most important limitation was the small sample, which raises the issue of possible type II errors, especially for the moderators' analyses. As such, the overall goal of this study is to provide preliminary findings that may guide future larger trials. Furthermore, baclofen was only tested at the 10 mg t.i.d. dose, the most common dose that showed efficacy in reducing alcohol drinking and promoting abstinence in RCTs. A post-hoc analysis of another RCT (Addolorato et al., 2011) suggested that baclofen 60 mg/day may be even more effective than 30 mg/day in reducing alcohol drinking, and other preliminary reports point out the potential role of higher doses of baclofen in treating AD (e.g. Ameisen, 2005; Rigal et al., 2012). Therefore, future controlled studies should assess baclofen's efficacy at different doses in treatment and human laboratory studies (even with different doses of alcohol administered). Finally, future studies are needed to evaluate the effects of baclofen on psychiatric symptoms that may be common in alcoholics (e.g. depressive symptoms and anhedonia; Martinotti et al., 2008).

In conclusion, these preliminary findings show that biobehavioral mechanisms of baclofen's response in AD individuals may include its effects on the biphasic effects of alcohol and the possible role of *DRD4* and *HTTLPR* as possible genetic moderators.

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Fig. 1.

Stimulation and sedation subscales of the Biphase Alcohol Effects Scale (BAES) between the baclofen and active placebo groups during the alcohol “priming” (a) and the alcohol self-administration (ASA) experiment (b). After consuming the priming drink, there was a significant effect of baclofen, compared to active placebo, in the biphasic effects of alcohol, i.e. significant increased stimulation and sedation. Fig. 1a shows the biphasic effects of alcohol after the alcohol priming, but before the ad-libitum session; Fig. 1b shows the biphasic effects of alcohol during the ad-libitum session.

Fig. 2.

Estimated means (and standard error bars) for the Standard Drink Units (SDUs) assessed 2 days prior and during the alcohol self-administration (ASA). In order to post-hoc analyze the data with a repeated measures ANCOVA with all 3 time points (ASA and self-reported alcohol drinking 1 day and 2 days before ASA), on the same metric, drinks during the ASA were “scaled up” to the standard drinking units (SDUs) for the 2 days before, by multiplying by eight (the sample mean for the 2 days before was 7.0, and the sample mean for the day before was 5.7; the average of these two values is 6.4; the sample mean for ASA drinks consumed was 0.8. $6.4/0.8=8$.) These three dependent measures were entered into repeated measures ANCOVA with ADS as a covariate.

Fig. 3. Moderating effects for Standard drinking units (SDUs) consumed during 2 days prior and during the Alcohol Self-Administration (ASA). Moderation effects (Fig. a — DRD4 Status, Fig. b — 5-HTTLPR status) for Standard Drink Units (SDUs) consumed during the 2 days prior and during the laboratory session.

Table 1
Moderation effect cell estimated means and standard errors, and *p*-values for main effects and moderation effects.

Moderation effect cell estimated means and standard errors						
	BAES stimulation		BAES sedation			
	Active placebo	Baclofen	Active placebo	Baclofen		
	<i>M</i> (SE)	<i>M</i> (SE)	<i>M</i> (SE)	<i>M</i> (SE)		
DRD4 <7 repeats	1.37 (.32)	5.96 (.60)	1.91 (.24)	-0.02 (.44)		
DRD4 7 repeats	0.15 (.38)	2.08 (.27)	0.17 (.28)	2.08 (.20)		
SS or SL	4.59 (.47)	2.34 (.24)	0.80 (.42)	2.04 (.22)		
LL	1.14 (.29)	-3.04 (.90)	0.54 (.26)	4.63 (.81)		
FH+	0.18 (.39)	3.62 (.33)	0.16 (.32)	1.83 (.27)		
FH-	2.13 (.31)	1.02 (.41)	1.40 (.25)	1.97 (.33)		
EOA	1.63 (.34)	2.98 (.34)	0.88 (.22)	1.64 (.23)		
LOA	0.36 (.43)	2.79 (.55)	0.54 (.29)	3.43 (.36)		
State anxiety low	0.32 (.37)	3.23 (.35)	1.22 (.22)	2.84 (.21)		
State anxiety high	2.67 (.41)	2.19 (.46)	0.81 (.24)	0.57 (.28)		

<i>p</i> -Values for main effects and moderation effects						
	BAES stimulation		BAES sedation			
	Medication Main effect	Moderator main effect	Interaction term	Medication main effect	Moderator main effect	Interaction term
DRD4 <7 vs. 7	<i>p</i> <.001	<i>p</i> <.001	<i>p</i> <.01	n.s.	n.s.	<i>p</i> <.001
SS/SL vs. LL	<i>p</i> <.001	<i>p</i> <.001	<i>p</i> =.03	<i>p</i> <.001	<i>p</i> <.05	<i>p</i> <.001
FH+ vs. FH-	<i>p</i> <.01	n.s.	<i>p</i> <.001	<i>p</i> <.01	<i>p</i> <.05	<i>p</i> =.06
EOA vs. LOA	<i>p</i> <.01	<i>p</i> =.06	n.s.	<i>p</i> <.001	<i>p</i> <.01	<i>p</i> <.001
Low vs. high state anxiety	<i>p</i> <.05	<i>p</i> =.07	<i>p</i> <.001	<i>p</i> <.05	<i>p</i> <.001	<i>p</i> <.001

DRD4=dopamine receptor D4.

SS or SL=short/short or short/long variant genotypes of the serotonin transporter-linked polymorphism region.

LL=long/long variant genotype of the serotonin transporter-linked polymorphism region.

FH= 1st degree family history of alcoholism.

EOA/LOA=early vs. Late age of onset of alcoholism. Early onset is <25 years old.

M=mean.

SE=standard error.
n.s.=Not significant.

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Table 2

Moderation effect cell estimated means and standard errors, and *p*-values for main effects and moderation effects.

Moderation effect (interaction) cell estimated means and standard errors		
Standard drinking units (SDUs) (3-days composite variable)		
	Active placebo	Baclofen
	<i>M</i> (SE)	<i>M</i> (SE)
DRD4 <7 repeats	5.86 (2.60)	9.05 (4.82)
DRD4 7 repeats	18.02 (3.05)	0.05 (2.20)
SS or SL	13.05 (3.21)	-0.60 (1.73)
LL	16.91 (1.99)	-30.78 (6.34)
FH+	18.31 (3.46)	2.91 (2.91)
FH-	10.72 (2.75)	-3.66 (3.62)
EOA	19.11 (2.62)	3.76 (2.82)
LOA	6.54 (2.67)	-2.73 (2.90)
State anxiety low	16.09 (3.00)	1.66 (2.93)
State anxiety high	11.85 (3.28)	-1.99 (4.02)

***p*-Values for main effects and moderation effects (Interactions)**

SDUs (3-days composite variable)			
	Medication main effect	Moderator main effect	Interaction term
DRD4 <7 vs. 7	<i>p</i> =.07	n.s.	<i>p</i> <.01
SS/SL vs. LL	<i>p</i> <.001	<i>p</i> <.001	<i>p</i> <.001
FH+ vs. FH-	<i>p</i> <.001	<i>p</i> <.05	n.s.
EOA vs. LOA	<i>p</i> <.01	<i>p</i> <.01	n.s.
Low vs. high state anxiety	<i>p</i> <.01	n.s.	n.s.

DRD4=dopamine receptor D4.

SS or SL=short/short or short/long variant genotypes of the serotonin transporter-linked polymorphism region.

LL=long/long variant genotype of the serotonin transporter-linked polymorphism region.

FH=1st degree family history of alcoholism.

EOA/LOA=early vs. late age of onset of alcoholism. Early onset is <25 years old.

M=mean.

SE=standard error.

n.s.=Not significant.