Original Paper

Can baclofen change alcohol-related cognitive biases and what is the role of anxiety herein?

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Abstract

Background: Baclofen has shown promise in the treatment of alcohol dependence. However, its precise (neuro-) psychological working mechanism is still under debate.

Aims: This study aimed to get a better understanding of baclofen's working mechanism by examining the effect of baclofen on cognitive biases. It was hypothesized that baclofen, compared to placebo, would lead to weaker cognitive biases. Furthermore, given a suggested anxiolytic effect of baclofen, we expected that anxiety would moderate this effect.

Methods: From a larger randomized clinical trial (RCT) with 151 participants, a subset of 143 detoxified alcohol-dependent patients, either taking baclofen or placebo, was examined. Attentional bias for alcohol (500 and 1500 ms), alcohol approach tendencies, implicit alcohol-relaxation associations and trait anxiety were assessed before the administration of baclofen or placebo. Four weeks later, 94 patients were still abstinent (53 in the baclofen and 41 in the placebo condition) and cognitive biases were assessed again.

Results: At baseline, patients showed a vigilance-avoidance pattern for the attentional bias (at 500 and 1500 ms, respectively) and alcohol-negative associations. After 4 weeks, an indication for an attentional bias away from alcohol at 500 ms was found only in the baclofen group; however, cognitive biases did not differ significantly between treatment groups. No moderating role of anxiety on cognitive biases was found.

Conclusions: Baclofen did not lead to a differential change in cognitive biases compared with placebo, and trait anxiety levels did not moderate this. A better understanding of the working mechanism of baclofen and predictors of treatment success would allow prescribing of baclofen in a more targeted manner.

Keywords

Baclofen, working mechanism, implicit processes, cognitive bias, anxiety

Introduction

Almost 4% of all global deaths can be attributed to harmful alcohol consumption (Rehm et al., 2009). In the European Union, prevalence rates for problematic alcohol use are particularly high, with 3.5% of all drinkers meeting criteria for alcohol dependence (AD; Rehm et al., 2013). However, less than 10% of all people with AD receive treatment (Alonso et al., 2004), and for people who do receive treatment, relapse rates typically exceed 50% after 1 year and reach 70% after 3 years (Cutler and Fishbain, 2005). Baclofen, mainly used for the treatment of spasticity, is a new promising drug for the treatment of AD (Chaignot et al., 2015). In first clinical studies with low dosages of baclofen (30 mg/day), a reduction of craving and alcohol intake was demonstrated (Addolorato et al., 2002, 2007), although one study reported null findings (Garbutt et al., 2010). Furthermore, two case studies (Ameisen, 2005; Bucknam, 2007) and a small randomized controlled trial (RCT; Müller et al., 2015) examined high dosages of baclofen (up to 270 mg/day) and confirmed a potential beneficial effect of baclofen in the treatment of AD. In a recent RCT (Beraha et al., 2016), we did not replicate the finding of Müller et al. (2015), likely related to one or more of three important differences between the studies: patients received medication as add-on to psychosocial therapy (not in Müller et al. 2015) leaving less room for improvement, patients had somewhat lower drinking levels and the maximum dosage of baclofen reached in our study was lower (up to 150 mg). In 2014, a temporary recommendation (RTU) for use of baclofen was proclaimed in France, where baclofen is now frequently used as off-label treatment for AD with 200,000 patients initiating baclofen treatment for AD between 2007 and 2013 (Chaignot et al., 2015).

Baclofen acts on the GABA system and is thought to exert its dampening effects on drinking outcomes through the indirect inhibition of dopamine release in the mesocorticolimbic reward pathway (Colombo et al., 2004). Although this pharmacological mechanism has been established, its precise (neuro-) psychological mechanisms of action are still debated. First, it has been argued

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that baclofen causes a suppression of alcohol craving (Addolorato et al., 2000; Colombo et al., 2004; Maccioni and Colombo, 2009). Second, baclofen might act as a partial substitution treatment due to its ethanol-like sedation effects (Chick and Nutt, 2012; Rolland et al., 2013). A third possible mechanism includes a role for anxiety reduction, due to the important role of GABA neurotransmission in anxiety (Cryan and Kaupmann, 2005; Millan, 2003). In line with this, baclofen has been shown to be effective in reducing anxiety in anxiety disorders (Breslow et al., 1989; Drake et al., 2003) and comorbid affective disorders in AD patients (Krupitsky et al., 1993). Furthermore, studies examining the efficacy of baclofen for the treatment of AD found indications for a reduction of anxiety levels (Addolorato et al., 2002; Flannery et al., 2004; Garbutt et al., 2010), although results on anxiolytic effects in AD patients have been inconsistent (Beraha et al., 2016; Müller et al., 2015).

Implicit cognitive motivational processes

With prolonged alcohol and drug use, the motivational system becomes more sensitive to drug cues, and automatically activated motivational processes gain importance (Robinson and Berridge, 2008). Drug cues may then relatively automatically capture attention (i.e. attentional bias), trigger approach tendencies (i.e. approach bias) or activate implicit affective drug-related memory associations, collectively called implicit cognitive motivational biases (see for a review Stacy and Wiers, 2010).

For alcohol cues, these cognitive biases are well studied. Studies show that heavy social drinkers compared to occasional social drinkers have an attentional bias towards alcohol-related stimuli (Field et al., 2004; Townshend and Duka, 2001), and an attentional bias for alcohol in AD in-patients has also been found (Noël et al., 2006). However, findings have not been consistent and an important moderator could be presentation time, with some evidence for an attentional bias for alcohol at short presentation times, and no bias or even an avoidance bias at longer presentation times, a so-called vigilance-avoidance pattern (Field et al., 2006; Ingjaldsson et al., 2003; Noël et al., 2006).

Concerning alcohol approach tendencies, studies indicate that heavy drinkers have stronger approach tendencies for alcohol-related stimuli compared to light drinkers (Wiers et al., 2009), and indications for an approach bias for alcohol have been found in patients with AD (Wiers et al., 2011). However, findings have not always been consistent and appear to depend on details of the task employed (Barkby et al., 2012; Field et al., 2010; Spruyt et al., 2013; Wiers et al., 2013b).

Finally, implicit affective memory associations are often assessed with the Implicit Association Task (IAT; Greenwald et al., 1998), and studies show that heavy drinkers have negative and arousal associations with alcohol (Houben and Wiers, 2006; Wiers et al., 2002). Similar results have been found in a clinical sample of patients with AD (De Houwer et al., 2004). Although the task has been used in many varieties in non-dependent drinkers (see for a meta-analysis Rooke et al., 2008), relatively few studies have reported alcohol associations in AD patients and how they are influenced by treatment (see Dickson et al., 2013 and Wiers et al., 2011 for an exception). Given the hypothesized relevance of anxiety in the effects of baclofen, we here focused on memory associations between alcohol and relaxation.

It has been shown that cognitive biases are positively correlated with craving and future drug use (Cousijn et al., 2011; Field and Eastwood, 2005; Houben and Wiers, 2008; but see Christiansen et al., 2015 for a critical review). Furthermore, since negative emotions may cause alcohol craving and consumption in patients with AD (Baker et al., 2004) due to the tension-reducing effect of alcohol, it is suggested that negative emotions can strengthen alcohol-related cognitive biases (Field and Powell, 2007; Field and Quigley, 2009; Grant et al., 2007; Lindgren et al., 2009; Salemink et al., 2015; Stewart et al., 2002). Furthermore, studies have found that re-training maladaptive cognitive biases, when added to regular therapy, can lead to a reduction of alcohol use and relapse rates (see for a review Wiers et al., 2013a). These training studies illustrate the possibility to influence drinking behaviour by changing alcohol-related cognitive biases, and the question arises whether this could also be part of the working mechanism of a pharmacological agent used for the treatment of AD, such as baclofen. One indication therefore comes from a recent functional magnetic resonance imaging (fMRI) study, which showed that baclofen could inhibit drug cue-induced motivational processing with subliminal cues in cocaine-dependent patients (Young et al., 2014). We wanted to extend this finding to behavioural measures assessed in patients with AD.

Therefore, the present study examined the effect of baclofen on cognitive biases. The aims of the current study were twofold: First, it was examined whether baclofen had an effect on alcohol-related cognitive biases. Second, since baclofen has been found to reduce anxiety, we further investigated the role of anxiety herein. This study was part of an RCT, in which alcohol-dependent patients received either a low or a high dosage of baclofen, or placebo (Beraha et al., 2016). Alcohol-related cognitive biases were assessed at baseline and after 4 weeks. More specifically, attentional bias at 500 ms and 1500 ms (for vigilance and avoidance, respectively), approach bias for alcohol and alcohol associations with relaxation were examined. Furthermore, trait anxiety levels were measured at baseline. In order to strengthen cognitive biases and account for the anxiolytic effect of baclofen, we induced negative mood prior to the assessment of the tasks.

We hypothesized that: (1) baclofen, compared to placebo, would weaken cognitive biases for alcohol. In addition, as cognitive biases following a negative mood induction were expected to be stronger for patients with higher levels of trait anxiety, we hypothesized that (2) the effect of baclofen on cognitive biases would be moderated by baseline trait anxiety: a stronger reduction of cognitive biases through baclofen in patients with higher levels of trait anxiety. The goal of the present study was to improve our understanding of the working mechanism of baclofen in order to gain knowledge on how its potential beneficial effect in the treatment of AD can be explained.

Materials and methods

Participants

The study was part of an RCT on the efficacy of high-dose baclofen for the treatment of AD (Netherlands Trial Register, no. 3681; Beraha et al., 2016). In the original trial, 151 patients with AD participated. Participants were recruited from two inpatient treatment centres and three outpatient treatment centres. Fifty-eight patients were randomly assigned to high-dose baclofen (up

Table 1. Baclofen dosage for the baclofen group at t2.

N	Baclofen dosage (mg/day)
20	30
1	40
3	50
2	60
9	80
18	110

to 150 mg), 31 to low-dose baclofen (30 mg) and 62 to placebo. Since the inclusion of patients fell behind schedule, the inclusion of patients in the low-dose group was stopped halfway in order to ensure a valid comparison between the two extreme groups (see Beraha et al., 2016). From the 151 patients, the 143 patients who completed the computer tasks at baseline were included in the present study (high-dose baclofen: 54; low-dose baclofen: 29; placebo: 60). For the aim of the present study, the high-dose and the low-dose baclofen groups were merged. This resulted in a (high- and low-dose) baclofen group (N= 83), with participants taking between 30 and 110 mg/day baclofen and a placebo group (N=60); see Table 1 for the distribution of baclofen dosages within the baclofen group at t2. The study was approved by the ethics committee of the Academic Medical Center in Amsterdam.

Inclusion and exclusion criteria

Inclusion and exclusion criteria from the original trial were met. Inclusion criteria were: (a) between 18 and 70 years; (b) DSM-IV AD-diagnosis; (c) <0.5% breath alcohol concentration at the screening visit; (d) an average alcohol consumption of ≥ 14 units (1 unit contained 10 g of ethanol) for women and ≥ 21 units for men per week over a consecutive 30-day period in the 90-day period before the start of the study and at least 2 heavy drinking days (women ≥ 5 units; men ≥ 6 units) in the past 90 days; (e) ≥ 96 h and ≥ 21 days abstinence prior to the initiation of the study medication; (f) Dutch language skills; and (g) provision of a contact person in the event of loss of contact. Exclusion criteria were: (a) current severe axis I disorder (other than depression, anxiety and bipolar disorder); (b) a primary diagnosis of substance dependence other than AD (excluding nicotine dependence); (c) severe physical illness (e.g. Parkinson's disease, gastric ulcer, duodenal ulcer, cerebrovascular disease, respiratory insufficiency, hepatic or renal insufficiency, and epilepsy); (d) medication for hypertension; (e) risk of suicide; (f) cognitive impairment; (g) current or recent (past 3 months) pharmacological treatment for AD (i.e. acamprosate, naltrexone, disulfiram or topiramate); (h) pregnancy or breastfeeding; (i) ≥ 7 days inpatient treatment for substance disorder in the past 30 days; and (j) the use of baclofen in the past 30 days. Informed consent was obtained from all participants.

Medication

The original trial consisted of a 6-week titration phase and a 10-week high-dose phase, where dosage was stabilized. Pills were provided in identical tablets and were taken three times a day. Participants started with 30 mg/day (three times 10 mg) baclofen or placebo, and the dose was increased with 10 mg baclofen for the high-dose group or placebo for the low-dose and the placebo group every other day, resulting in an increase of 30 mg/week and a maximum dosage of 150 mg/day within 6 weeks. In case of prolonged side effects, the dosage was reduced to the previous dosage and increased again. Hence, participants in the high-dose baclofen group could reach a daily dosage of up to 150 mg within 6 weeks depending on tolerance (see Beraha et al., 2016 for a detailed description of the RCT). In the present study, participants could reach a maximal daily dosage of up to 110 mg within 4 weeks.

Questionnaires

The following patient characteristics were collected: demographic data, severity of alcohol-related problems (Alcohol Use Disorder Identification Test; AUDIT; Saunders et al., 1993), drinking history (European Addiction Severity Index; EuropASI; Blanken et al., 1994), alcohol use in the past 30 days (Timeline Follow Back; TLFB; Sobell and Sobell, 1992) and craving (Obsessive Compulsive Drinking Scale; OCDS; Anton et al., 1995). Trait anxiety was measured with the trait version of the State-Trait Anxiety Inventory (STAI trait; Spielberger, 2010). Current affective and arousal state was assessed with the Self Assessment Manikin (Bradley and Lang, 1994) in order to examine the manipulation of affect. Participants indicated their affective and arousal state on a 9-point scale, with the lowest score indicating unhappy or relaxed and the highest score indicating happy or excited, respectively.

Negative mood induction

Before each measure of cognitive biases, a negative mood induction procedure took place. Negative affect was induced with a personalized stress imagery task based on Sinha et al. (1999). In this task, participants identified and reported a stressful event that was not related to alcohol. They were asked to concentrate on cognitions, emotions and physiological responses while describing the event.

Measures of cognitive biases

Dot Probe Task (DPT). Attentional bias was assessed with the alcohol-DPT (Field et al., 2004). After 10 practice trials, 15 alcohol images paired with 15 soda images were shown in 60 critical trials, and 14 negative images were used for 28 negative filler trials. A trial started with a fixation cross presented for 500 ms. Thereafter the picture pairs were presented at the left and the right side of the screen. For half of the trials presentation time was 500 ms and for the other half 1500 ms, presented in random order. After images disappeared, a small arrow pointing up or down appeared in the location of one of the images, and participants were instructed to respond to it, as quickly and accurately as possible, by pressing a corresponding key (e- or i-key, counterbalanced) to indicate whether it pointed up or down. Probes replaced images with equal frequency, and there was an equal number of trials with each probe type. Images were presented in random order. Incorrect trials were repeated.

Approach-Avoidance Task (AAT). Implicit alcohol-related action tendencies were assessed with the alcohol-AAT (Wiers et al., 2009). Following 20 practice trials, 15 alcohol images, 15 soda images and 15 negative images were shown semi-randomly (at most three similar rotations and image categories in a row) in 120 critical trials and 60 negative filler trials. Each image was presented twice, rotated 3° to the left or to the right (Cousijn et al., 2011). Participants were instructed to push or pull a joystick depending on the rotation direction. Half of the patients pulled images rotated right and pushed images rotated left, the other half did the opposite. Image size increased or decreased by pulling or pushing the joystick mimicking an approach or avoidance action, respectively. Incorrect trials were repeated.

Brief Implicit Association Test (BIAT). Implicit alcohol-related memory associations, specifically alcohol-relaxation associations, were assessed with the BIAT (Salemink et al., 2015). The BIAT is a short version of the IAT and requires participants to focus on just two of the four categories of each block (we used the traditional seven-block structure). Two target categories, alcohol and soda, and two attribute categories, relaxed and negative, were used. For each category three images were individually presented as category exemplars. At the top of the screen the question 'Does this image belong to' appeared subjacent to the target or attribute words and 'Yes' and 'No' on the left and right as a reminder of the meanings of the corresponding keys. The BIAT consisted of seven blocks including three practice blocks (1, 2 and 5) and four combination blocks (3, 4 and 6, 7). In the practice blocks (12 trials) only one category (alcohol, soda or relaxed) appeared on the screen, and each category exemplar was presented twice. Combination blocks consisted of 16 practice trials (block 3 and 6; 16 trials) and 24 assessment trials (block 4 and 7; 24 trials) where one target and one attribute category (alcohol and relaxed or soda and relaxed) were presented together. One attribute category (negative) never appeared on the screen as a word. Target and attribute category exemplars were presented alternately. Participants were instructed to categorize exemplars to the category word(s) by pressing a corresponding key. The order of the combination blocks was counterbalanced. Incorrect trials were repeated.

Procedure

Participants were recruited after detoxification. Following the screening, the first test session (t1) was scheduled. After the completion of questionnaires, the first negative mood induction took place and the three tasks were conducted. The mood induction was repeated between the tasks, and negative images were included in the tasks in order to sustain the induced negative affect. Participants rated their affective and arousal state before the first mood induction (baseline measure), after each mood induction (before the task) and after completing each task, resulting in seven mood and arousal ratings. After the first test session, patients were randomized to high-dose baclofen, low-dose baclofen or placebo. After 4 weeks, a second test session (t2) was scheduled in which the procedure of the first test session was repeated and questionnaires and tasks following a negative mood induction were assessed again. Since in-patients stayed in the clinic for the duration of 4 weeks, t2 was scheduled before they left. Outpatients who relapsed before t2 were excluded. Relapse was defined as having a heavy drinking day after a lapse (any intake of alcohol). In the original trial a third test session was conducted after 16 weeks, repeating the procedure of t1 and t2. The results of this third test session are not included in the present study, due to the small number of participants who completed the tasks in the final test session at 16 weeks. Tasks were presented in three different counterbalanced orders with the E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Alcohol images and matched soda images were taken from the Amsterdam Beverage Picture Set (Pronk et al., 2015), and emotional images were taken from the International Affective Picture System (IAPS; Lang et al., 1997).

Data preparation of RT data

Practice trials, negative trials and error trials from the DPT and the AAT were discarded. Attentional bias scores were calculated by subtracting median RTs to probes replacing alcohol images from median RTs replacing soda images, with positive scores reflecting an attentional bias towards alcohol. Attentional bias scores were calculated for the presentation duration of 500 ms and 1500 ms separately. Alcohol approach bias scores were calculated by subtracting median approach RTs from median avoid RTs for alcohol images, with positive scores reflecting faster approach reactions (Rinck and Becker, 2007; Wiers et al., 2009). The strength of alcohol-relaxation associations from the BIAT was determined with the D2SD measure using the scoring algorithm from Greenwald et al. (2003). Outliers were identified using the outlier labelling rule, which is based on multiplying the interquartile range by a factor of 2.2, adding the resulting value to the third quartile and subtracting it from the first quartile, and defining outliers as values outside of these boundaries (Hoaglin et al., 1986; Iglewicz and Banerjee, 2001). At t1, one outlier was identified for the DPT 500 ms and three for the alcohol approach bias. At t2, one outlier was identified for the attentional bias at 1500 ms. For the extreme values 'winsorizing' was applied, meaning that extreme values were replaced with the highest acceptable value (Tukey, 1962). At t1, internal reliability was extremely low for the DPT, with a Cronbach's alpha of 0.01. For the AAT Cronbach's alpha was 0.51 for alcohol images. The BIAT had good internal reliability with a Cronbach's alpha of 0.80.

Results

Participants

From the original sample of 151, 143 participants completed at least one task at t1. A total of 138 participants completed the DPT, 138 the AAT and 138 the BIAT. The difference was caused by technical errors, discontinuation of the tasks due to the impact of the negative images or lack of time. DPT scores of three participants and BIAT scores of five participants were excluded from analysis, because of excessive error rates (>25%), resulting in an analytical sample of 135 participants for the DPT, 138 for the AAT and 133 for the BIAT. Groups did not differ significantly at baseline in demographic or clinical measures (see Table 2).

Table 2. Demographic and clinical characteristics of study participants at baseline.

	Total (N = 143)	Baclofen (N = 83)	Placebo (N = 60)	t-value or chi-square
Demographics				
Age (years)	44.7 (9.7)	45.2 (9.9)	44.1 (9.3)	t = 0.727
Men	98 (68.5%)	56 (67.5%)	42 (70.0%)	χ^2 = 0.103
Married	77 (53.9%)	45 (54.2%)	32 (53.3%)	χ^2 = 0.011
Employed	84 (58.7%)	46 (55.4%)	38 (63.3%)	χ^2 = 0.899
Alcohol use				
Alcohol (g/day)	143.1 (85.9)	145.0 (85.9)	140.4 (86.5)	t = 0.314
Duration of alcohol abuse (years)	19.5 (11.5)	19.8 (11.7)	19.1 (11.3)	t = 0.330
Duration of abstinence (days)	11.9 (4.7)	11.9 (4.3)	11.9 (4.4)	t = –0.037
Number of previous detoxifications	1.6 (2.9)	1.3 (2.1)	2.1 (3.7)	t = –1.536
Questionnaires				
AUDIT	28.5 (5.2)	29.0 (5.6)	27.7 (4.5)	t = 1.505
OCDS	29.4 (10.1)	28.9 (10.1)	30.2 (10.2)	t = –0.720
STAI trait	49.9 (11.2)	51.0 (11.5)	48.4 (10.6)	t = 1.364

Data are mean (SD) or n (%). AUDIT: Alcohol Use Disorder Identification Test; OCDS: Obsessive Compulsive Drinking Scale; STAI trait: State-Trait Anxiety Inventory-trait version. *p < 0.05.

Table 3. Valence and arousal scores at t1 and t2.

	Valence scores	Arousal scores
t1 (N=133)		
Baseline	6.27 (1.48)	3.50 (1.80)
After first mood induction	3.14 (2.11)*	6.38 (2.27)*
After second mood induction	3.29 (1.86)*	5.82 (2.15)*
After third mood induction	3.53 (2.10)*	5.70 (2.22)*
t2 (N=94)		
Baseline	6.91 (1.46)	2.70 (1.62)
After first mood induction	3.80 (1.91)*	5.15 (2.16)*
After second mood induction	4.04 (2.02)*	4.97 (2.32)*
After third mood induction	4.09 (1.01)*	4.87 (2.02)*

Data are mean (SD). * p < 0.001.
Higher scores indicate positive mood (valence) and higher arousal levels (arousal).

At t2 (after 4 weeks), 94 participants (53 (low- and high) baclofen group, 41 placebo group) completed at least one task. BIAT scores of five participants were excluded because of error rates above 25%. In the baclofen group, 49 participants completed the DPT, 50 participants completed the AAT and 46 participants the BIAT. In the placebo group, 36 participants completed the DPT, 40 participants completed the AAT and 39 the BIAT.

Preliminary analyses

Mood manipulation. Since valence and arousal scores were not normally distributed, a Wilcoxon Signed Rank Test was used in order to examine the mood manipulation. Baseline valence and arousal scores were compared with each of the valence and arousal scores assessed after the three negative mood inductions. Scores indicated a significant increase of negative mood (all p's < 0.001) and arousal (all p's < 0.001) following all negative mood inductions for t1 as well as t2, indicating that the induction of negative mood was successful (see Table 3).

Bias scores. One-sample t-tests with a test-value of zero were used in order to test the overall presence of cognitive biases. At t1, participants had a significant attentional bias towards alcohol at 500 ms (p = 0.043) and a significant attentional bias away from alcohol at 1500 ms (p = 0.037). Furthermore, while participants showed no significant alcohol approach bias (p = 0.101), they had significantly strong alcohol-negative (vs. alcohol-relaxation) associations (p < 0.001). At t2, only in the baclofen group attentional bias at 500 ms changed from a significant vigilance (attend alcohol) to a significant avoid alcohol bias (p = 0.027), a pattern not seen in the placebo group (p = 0.425). No significant alcohol approach tendencies but significant alcohol-negative associations were found in both treatment groups (all p's < 0.001) (see Table 4).

Main analyses

Effects of baclofen on cognitive biases and the role of anxiety. STAIT scores at t2 were 39.3 (SD=11.5) for the baclofen group and 38.5 (SD=10.2) for the placebo group (p = 0.701). In order to examine the effect of baclofen on cognitive biases and the potential moderating role of anxiety herein, four ANCOVAs on t2 bias scores were conducted, separately for each bias score (attentional bias at 500 ms, attentional bias at 1500 ms, approach bias for alcohol and alcohol-relaxation associations) with treatment group (baclofen or placebo) as the between-subject factor. In order to control for cognitive bias scores at t1, this variable was added as a covariate (Van Breukelen, 2006). Furthermore, to investigate the role of anxiety, trait anxiety measured at t1 was added as a covariate and the interaction between trait anxiety and treatment group was examined.[1]

For the attentional bias scores for alcohol at 500 ms and 1500 ms, neither the main effects nor the interaction between treatment

Table 4. Bias scores at baseline (t1) and at t2.

	N	Mean (SD)	*t*-value
Attentional bias 500 ms	135	13.5 (76.7)	2.04*
Attentional bias 1500 ms	135	−12.9 (71.1)	−2.11*
Approach bias alcohol	138	−10.8 (76.8)	−1.65
Alcohol-relaxation associations	133	−0.8 (0.7)	−13.37**

Bias scores at baseline. *$p < 0.05$; **$p < 0.001$.
Note: Positive bias scores indicate an attentional bias towards alcohol, an approach bias towards alcohol and alcohol-relaxation associations.

	Baclofen			Placebo		
	N	Mean (SD)	*t*-value	*N*	Mean (SD)	*t*-value
Attentional bias 500 ms	49	−20.1 (61.1)	−2.28*	36	10.8 (80.7)	0.81
Attentional bias 1500 ms	49	0.7 (61.1)	−0.09	36	−13.6 (52.9)	−1.54
Approach bias alcohol	50	−0.8.0 (79.6)	−0.07	40	4.2 (55.7)	0.48
Alcohol-relaxation associations	46	−1.1 (0.5)	−14.86**	39	−1.1 (0.5)	−14.19**

Bias scores at t2 in the baclofen and the placebo group. *$p < 0.05$; **$p < 0.001$.
Note: Positive bias scores indicate an attentional bias towards alcohol, an approach bias towards alcohol and alcohol-relaxation associations.

group and trait anxiety were significant (all *p*-values > 0.264). Further, also for approach bias scores, neither the main effects nor the interaction between group and trait anxiety were significant (all *p*-values > 0.568). Finally, for alcohol-relaxation associations, no significant main effects nor a significant interaction effect were found (all *p*-values > 0.494).

Discussion

This study examined the effect of baclofen on cognitive biases in AD and the role of anxiety herein. The most important findings were as follows: consistent with the literature, after negative mood induction, patients showed an attentional bias for alcohol at baseline with the typical vigilance-avoidance pattern – bias towards alcohol at 500 ms and bias away from alcohol at 1500 ms. However, unexpectedly, patients showed no significant approach bias for alcohol and no alcohol-relaxation associations but strong alcohol-negative associations at baseline. Regarding the main aims of the study, we found indications for a change from an attentional bias towards alcohol at 500 ms at baseline away from alcohol after 4 weeks of baclofen treatment. However, baclofen did not lead to a change in cognitive biases compared with the placebo group, and no evidence for a moderating role of anxiety herein could be found.

For cognitive biases at baseline, the pattern of results was mixed, with findings on attentional biases confirming previous research (a pattern of vigilance-avoidance, Field et al., 2006; Noël et al., 2006; Snelleman et al., 2015). No overall approach bias for alcohol was found, which is contrary to an earlier study showing indications for an approach bias in AD patients (Wiers et al., 2011), but in accordance with another study (Eberl et al., 2013). It is argued that this could have been caused by individual differences or ambivalence between approach and avoidance associations towards alcohol in patients with AD, in particular in AD patients that are receiving treatment. Finally, patients in the present study showed strong alcohol-negative (vs. alcohol-relaxation) associations, which is in accordance with earlier studies demonstrating negative implicit associations with alcohol and alcohol-arousal associations in heavy drinkers and patients with AD (De Houwer et al., 2004; Wiers et al., 2002). However, in the present study stronger alcohol-relaxation (vs. alcohol-negative) associations were expected, caused by the induction of negative mood prior to the assessment of implicit alcohol associations (Lindgren et al., 2009; Ostafin and Brooks, 2010).

Concerning the effects of baclofen on cognitive biases, the results did not clearly confirm our hypotheses. Our findings suggest that baclofen does not have an effect on approach bias or on implicit alcohol-relaxation (and/or alcohol-negative) associations. Concerning attentional bias, our sample showed an attentional bias at 500 ms towards alcohol at baseline, which changed into an attentional bias away from alcohol only in the baclofen group after 4 weeks. This inhibitory effect of baclofen on attention to alcohol was further confirmed by a moderate within-group effect size in the baclofen group from baseline to t2 (Cohen's $d = 0.49$) compared with a negligible within-group change in the placebo group (Cohen's $d = 0.03$) and is in accordance with earlier research (Young et al., 2014). However, note that attentional bias did not differ between the groups at t2, which could be due to the high variability within the placebo group at t2 and the very low internal reliability of the DPT (Cronbach's alpha of 0.1). In accordance, the literature suggests that the DPT often suffers from low internal reliability, and possible causes are discussed by Ataya et al. (2012). Furthermore, it should be taken into consideration that with the (rather) long presentation duration of 500 ms and 1500 ms, maintained attention, rather than initial orienting may have been measured in the present study, especially with the long presentation time of 1500 ms. Therefore, further studies are warranted that examine the effect of baclofen on attentional bias taking these issues into consideration.

We decided to examine associations between alcohol and relaxation, since we expected a reduction of anxiety through

baclofen, causing a weakening of these associations. However, all patients showed significant alcohol-negative (vs. alcohol-relaxation) associations throughout the whole study (De Houwer et al., 2004; Wiers et al., 2002), which seemed not to be affected by baclofen. Since this is the first study examining the effect of baclofen on alcohol-relaxation associations in a clinical sample, more research is needed to draw any conclusions.

Results of the present study do not support the hypothesis of a moderating role of trait anxiety on the influence of baclofen on cognitive biases after the induction of negative mood. Several earlier studies found indications of an anxiolytic effect of baclofen (Addolorato et al., 2002; Flannery et al., 2004; Garbutt et al., 2010; Krupitsky et al., 1993; but see Müller et al., 2015 and Beraha et al., 2016 for null findings). Based on these findings it was suggested that patients with higher trait anxiety levels would respond better to baclofen. However, similar to our results, other studies also failed to confirm a moderating role of trait anxiety on the effect of baclofen (Garbutt et al., 2010; Leggio et al., 2013). The present study extends these findings with a null effect of baclofen on cognitive biases after negative mood induction.

Several shortcomings of the present study have to be taken into consideration. First, we included a negative mood induction prior to the tasks in order to study the effect of baclofen on negative affect strengthened cognitive biases. The majority of studies found indications for a strengthening of cognitive biases after the induction of negative mood (Field and Powell, 2007; Field and Quigley, 2009; Grant et al., 2007; Lindgren et al., 2009; Ostafin and Brooks, 2010; Salemink et al., 2015; Stewart et al., 2002); however, this was the first study examining the effect of negative mood on cognitive biases in AD patients. Although subjective pre- and post-measures indicate that negative mood increased, the precise effect of the negative mood induction on cognitive biases in the present study is not clear, since no control condition with a neutral or positive mood induction was included (this was done to optimize the power for finding an effect of baclofen on these biases), and cognitive biases were only measured after the induction of negative mood. Therefore, studies examining the effect of baclofen on cognitive biases without any induction of mood, or with the addition of groups undergoing a neutral or positive mood induction, are warranted. Second, cognitive biases are not sufficiently examined in clinical populations, especially in treatment-seeking patients with AD. Studies indicate that patients receiving clinical treatment, contrary to heavy drinkers, show negative attentional bias (Townshend and Duka, 2007; Vollstädt-Klein et al., 2009) or no bias at all (Barkby et al., 2012). Regarding attentional bias, presentation time of the stimuli is likely to play an important role, with some evidence for a vigilance-avoidance pattern (Field et al., 2006) and more reliable assessment is important, where the tracking of eye-movements is promising (Field and Quigley, 2009). Additionally, the relationship between cognitive biases and treatment outcome is not clear. More research is warranted regarding the assessment of cognitive biases and their relationship to alcohol use and relapse in specific groups of drinkers. Third, the majority of the participants in the present study were in-patients receiving intensive psychosocial treatment. As argued in the recent study of Beraha et al. (2016), baclofen (and other medications) might not have a strong additional effect to psychotherapy, which could also have reduced the likelihood of finding an effect of baclofen on cognitive biases. Furthermore, since patients were treated in a clinic, they might have experienced relatively low levels of craving and anxiety, causing the absence of cognitive biases (Field et al., 2013) and subsequently group differences. Further outpatient treatment studies are warranted. Finally, cognitive biases at t2 are only reassessed in patients who did not relapse. However, since it is possible that baclofen might affect cognitive bias measures differently in relapsing and non-relapsing patients, it would be important to examine cognitive biases in both groups.

The present study is the first study examining the effect of baclofen on cognitive biases in AD. We found no clear evidence for a weakening of cognitive biases through baclofen or a moderating role of anxiety herein. Given the current contradictory findings regarding the efficacy of baclofen, a better understanding of the precise working mechanism and the identification of predictors of treatment success would represent valuable knowledge, in order to prescribe baclofen in a more directed manner.

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Note

1. Analyses with the original three groups (placebo, low-dose baclofen and high-dose baclofen) yielded similar results.

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