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Baclofen and naltrexone effects on alcohol self-administration: Comparison of treatment initiated during abstinence or ongoing alcohol access in baboons

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Abstract

Background—Baclofen, a GABA_B receptor agonist, is under investigation as a pharmacotherapy for alcohol use disorder. Treatment with a pharmacotherapeutic can be initiated during alcohol abstinence or active drinking, which may influence treatment outcomes. This study examined whether baclofen treatment initiated and maintained during alcohol abstinence would reduce alcohol seeking and self-administration upon return to alcohol access, and whether effects differed from treatment initiated and maintained during ongoing alcohol access. Naltrexone was tested under similar conditions for comparison.

Methods—Five baboons self-administered alcohol under a three-component chained schedule of reinforcement that modeled periods of anticipation (Component 1), seeking (Component 2), and consumption (Component 3). Alcohol was only available in Component 3. In Experiment 1, baclofen (0.1–1.8 mg/kg) or naltrexone (1.0–5.6 mg/kg) was administered daily beginning on the first day of a 5-day abstinence period and treatment was continued for 5 days of alcohol access. In Experiment 2, selected doses of both drugs were administered during ongoing alcohol access.

Results—When treatment was initiated during alcohol abstinence, baclofen and naltrexone did not significantly reduce total alcohol intake (g/kg) or alcohol seeking. In comparison, when treatment was initiated during ongoing alcohol access, both baclofen (1.8 mg/kg) and naltrexone (3.2 and 5.6 mg/kg) significantly reduced total alcohol intake (g/kg). Naltrexone (5.6 mg/kg), but not baclofen, significantly reduced alcohol seeking.

Conclusions—Initiation of baclofen treatment (or other alcohol use disorder treatments) during abstinence or active drinking may be an important factor in influencing efficacy and appropriate dose selection.

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Contributions

EW and BJK were responsible for the study concept and design. AFH, EW, and BJK monitored the acquisition of animal data. AFH, EW, and BJK assisted with data analysis and interpretation of findings. AFH wrote the first draft of the manuscript and EW and BJK provided substantive and conceptual feedback on subsequent drafts. All authors contributed to and have approved the final manuscript.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Keywords

baclofen; naltrexone; alcohol; seeking; self-administration; baboons

1. Introduction

Baclofen, a GABA_B receptor agonist, is under investigation as a potential treatment for alcohol use disorder (Agabio and Colombo, 2014). Preclinical studies employing rodent drinking models have reported that baclofen reduced (1) the acquisition and maintenance of alcohol drinking under a two-bottle alcohol versus water choice procedure (Colombo et al., 2000, 2002; Daoust et al., 1987; Quintanilla et al., 2008; but cf. Smith et al., 1992); (2) the increase in alcohol intake after a period of alcohol abstinence (the alcohol deprivation effect, ADE; Colombo et al., 2003a); (3) alcohol intake under oral operant self-administration procedures (Anstrom et al., 2003; Liang et al., 2006; Walker and Koob, 2007); (4) the motivational properties of alcohol measured using extinction (Colombo et al., 2003b; Leite-Morris and Czachowski, 2006; Leite-Morris et al., 2008) and progressive ratio (Maccioni et al., 2008; Walter and Koob, 2007) procedures; (5) and signs of alcohol withdrawal in rats made physically dependent on alcohol (Colombo et al., 2000; Knapp et al., 2007). In one study conducted in baboons, acute doses of baclofen (1.8 and 2.4 mg/kg) reduced self-administration responses for alcohol, decreased total alcohol intake, and facilitated extinction of responding directed towards obtaining alcohol (i.e., alcohol seeking; Duke et al., 2014). Randomized studies to date have shown some promise although treatment efficacy has been mixed (Addolorato et al., 2002, 2007, 2011; Beraha et al., 2016; Farokhnia et al., 2017; Garbutt et al., 2010; Girish et al., 2016; Leggio et al., 2015; Lesouef et al., 2014; Müller et al., 2015; Ponizovsky et al., 2015).

Recent critical reviews of animal models and medications development have provided suggestions for improving predictive validity, including: 1) testing potential alcohol use disorder medications in a wider range of models; 2) utilization of models that generate sufficient volitional alcohol intake to achieve a blood alcohol level (BAL) of 80 mg/dL (0.08%) or more, and include use characteristics of human drinking; and 3) continued evaluations in animal models of medications that reach clinical trials to continue to validate models, optimize therapeutic doses and dosing conditions, and to increase our understanding of treatment effects on basic behavioral processes thought to be associated with alcohol use disorder (i.e., reverse translation; Egli, 2005; Grant and Bennett, 2003; Ripley and Stephens, 2011).

Our baboon model was designed to model the “*too much, too fast, and too often*” drinking patterns as defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Binge drinking (*drinking too much, too fast*) is defined by the NIAAA as alcohol consumption sufficient to achieve a BAL of 0.08% or more within a 2–3 hour drinking period; this corresponds to about 0.8–1.0 g/kg. Heavy “at risk” drinking also includes drinking an average of more than 14 drinks per week for men and more than 7 drinks per week for women (*drinking too much, drinking too often*). Patterns of “*drinking too much, too fast and too often*” are a key feature of alcohol use disorder. In our chained schedule of

reinforcement (CSR) procedure, baboons consume alcohol at high levels (~1.0 g/kg per day), reach BALs exceeding 0.08%, and maintain this level of consumption 7 days per week for prolonged periods (Kaminski et al., 2008; Holtyn et al., 2014). In addition, drug metabolism and pharmacokinetic parameters in baboons are more similar to humans than rodents (Fridman and Popova, 1988; Jolivet and Ward, 2005; Ward and Smith, 2004), which may yield information on potential drug interactions with alcohol that may not be apparent in rodent models. Thus, our baboon CSR procedure can provide important cross-species validation to bridge the translational research gap between rodents and humans, and improve prediction of efficacy of potential therapeutics in humans.

The present study used our baboon CSR procedure to examine whether baclofen treatment initiated during alcohol abstinence would attenuate alcohol seeking and self-administration upon return to alcohol access and whether effects differed from treatment initiated during ongoing alcohol access. Naltrexone was tested under similar conditions for comparison. Our rationale for this design was that initiation of pharmacotherapeutic interventions can be in the abstinent state, or during active drinking. Treatment efficacy of naltrexone and acamprosate, two of the three FDA-approved medications for alcohol use disorder, is influenced by when treatment is initiated (Maisel et al., 2013).

2. Material and Methods

2.1. Subjects

Five adult male baboons (*Papio anubis*; Southwest Foundation for Biomedical Research, San Antonio, TX), were housed singly in specialized cages that also served as the experimental chambers. All baboons had extensive histories of alcohol self-administration under the CSR paradigm for over 10 years. Prior studies include validation of the CSR model via systematic changes in ethanol dose, duration of alcohol access, response costs, and duration of alcohol abstinence on alcohol seeking and self-administration, as well as testing effects of medications on these behaviors (Weerts et al., 2006; Duke et al., 2014; Holtyn et al., 2014, 2017; Kaminski and Weerts, 2014; Kaminski et al., 2008, 2012, 2013). The use of a within-subject design, in which each subject is exposed to multiple experimental conditions, with baseline criteria met prior to drug treatments, requires fewer subjects than conventional group designs to draw statistically significant, meaningful conclusions. Use of a within-subjects research design is consistent with the recommendations of the National Institutes of Health National Primate Plan and the restrictions of the Animal Welfare Act, to fully utilize each subject and minimize the number of nonhuman primates used in research. The number of subjects used in the present study is the minimal number needed based on results of prior studies using a similar approach, and estimated effect sizes. The baboons were fed standard primate chow (biscuits) adjusted to maintain sufficient caloric intake (e.g., 50–73 kcal/kg) for normal baboons of their size, age, and activity level. They also received 2 pieces of fresh fruit or vegetables (70–120 g each) and a children's chewable multivitamin daily. Water was available ad libitum, except during experimental sessions. The housing room was maintained under a 12-hour light/dark cycle (lights on at 6:00 AM). The facilities were maintained in accordance with USDA and AAALAC standards. The protocol was approved by the Johns

Hopkins University Animal Care and Use Committee and followed the Guide for the Care and Use of Laboratory Animals (2011).

2.2. Apparatus

Sessions were conducted in modified primate cages as described in detail previously (Kaminski et al., 2008; Weerts et al., 2006). Briefly, each cage was equipped with a bench along one side of the cage and an aluminum intelligence panel mounted on the same side as the bench. The intelligence panel contained two vertically operated levers (Med Associates, Georgia, VT), two different colored jewel lights mounted above each lever, and a drinkometer (Kandota Instruments, Sauk Center, MN) with two white and two green lights that surrounded a protruding drink spout. All solutions were delivered from a 1000-ml glass bottle positioned above the cage and connected to the drinkometer with tygon tubing. A separate panel on the back wall contained three colored cue lights (red, yellow, and blue). A speaker was mounted above the cages for presentation of auditory stimuli (tones). Experimental events were controlled remotely using Med Associates (East Fairfield, VT) software and hardware interfaced with a personal computer.

2.3. Chained Schedule of Reinforcement (CSR)

Each baboon self-administered alcohol under a 3-component CSR. Each component was associated with distinct stimuli (cues) and behavioral contingencies (schedule requirements), which modeled periods of anticipation (Component 1), seeking (Component 2), and consumption (Component 3). Fulfilling the schedule requirement in each successive component was necessary to progress to the next component, with alcohol available only in the final component. Our laboratory previously validated this baboon procedure (Kaminski et al., 2008; Weerts et al., 2006), which allows for examination of drug effects on responding in the presence of alcohol-related cues that is maintained by conditioned reinforcement (i.e., responding that produces access to alcohol or “seeking”), as well as alcohol self-administration and consumption within the same session. The CSR sessions were conducted seven days per week and began at the same time (8:30 AM) each day. The start of a session was signaled by a 3-s tone and onset of Component 1. During Component 1, a red cue light was illuminated for 20 min and all responses (i.e., lever presses; drinkometer contacts) were recorded but had no programmed consequence.

Component 2 was signaled by the illumination of a yellow cue light and consisted of two links. During the first link, the jewel light over the left lever was turned on, and an alternate fixed-interval (FI) 10-min, fixed-time (FT) 20-min schedule was in effect on the left lever. The first link ended either a) with the first response on the left lever after 10 min elapsed or b) automatically after 20 min, whichever occurred first. During the second link, the jewel light over the left lever flashed and a fixed-ratio (FR) 10 schedule (FR 5 for one baboon) was in effect on the left lever. Completion of the FR response requirement ended Component 2; the yellow cue light and the jewel light were turned off and Component 3 was initiated. Failure to complete the FR response requirement in Component 2 within 90 min resulted in the termination of the session.

During Component 3, the blue cue light was illuminated, the jewel light over the right lever was illuminated, and the opportunity to orally self-administer alcohol was available according to an FR 10 schedule on the right lever. Completion of each FR turned the jewel light off and turned on the white lights on the drinkometer faceplate, indicating drink availability. Contact with the drinkometer spout turned off the white lights, turned on the green lights on the drinkometer faceplate, and operated a solenoid valve that delivered fluid for five seconds (~25–35 ml) or the duration of spout contact, whichever came first. This defined a single drink. Following each drink, all drinkometer lights were turned off and the jewel light over the right lever was again illuminated. Component 3 ended after 120 min and all programmed stimuli were turned off.

2.4. Drugs

All solutions were mixed using reverse osmosis purified drinking water. Ethyl alcohol (190 Proof; Pharmco-AAPER, Brookville, CT, USA) was diluted with reverse osmosis water to a concentration of 4% w/v alcohol. Baclofen and naltrexone hydrochloride (Sigma-Aldrich, St Louis, MO, USA) were dissolved in physiological saline and administered via the intramuscular route (2 ml volume/injection) as detailed below. Vehicle (saline) was administered using the same volume and route of injection for control conditions. Drug doses and vehicle were given in mixed order across baboons.

2.5. Experiment 1: Treatment Initiated During Alcohol Abstinence

Chronic dosing procedures were initiated after the following stability criteria had been met: 1) baseline CSR responding was maintained for two weeks and 2) alcohol self-administration was stable ($\pm 20\%$ intake) for three consecutive CSR sessions. When the stability criteria were met, CSR sessions were suspended; no cues were presented and alcohol was not available (i.e., alcohol abstinence). Beginning on the first day of alcohol abstinence, the same dose of baclofen (0.1–1.8 mg/kg), naltrexone (1.0–5.6 mg/kg), or vehicle was administered at the same time each day (8:00 AM) for 5 consecutive days; and treatment continued when CSR sessions and alcohol availability were reinstated and maintained for an additional 5 days (i.e., 10 days of treatment with baclofen, naltrexone, or vehicle). Drug doses and pre-treatment time (30 min before the CSR session) were based on previous studies with baclofen (Duke et al., 2014; Weerts et al., 2005, 2007) and naltrexone (Kaminski et al., 2012). After completion of a chronic dosing period, a “wash out” period was instituted, in which no test drugs were administered and the CSR sessions continued. Alcohol self-administration under the CSR was re-established and the stability criteria were met before the next abstinence period with chronic drug dosing.

2.6. Experiment 2: Treatment Initiated During Alcohol Access

Following Experiment 1, the stability criteria were again met and then selected doses of baclofen (1.8 mg/kg), naltrexone (3.2 and 5.6 mg/kg), or vehicle were each administered for 5 consecutive days during ongoing alcohol access. Based on our prior studies in the baboon, 1.8 mg/kg baclofen is the highest dose without significant adverse effects (Weerts et al., 2005, 2007; Duke et al., 2014). For each drug dose, the stability criteria and wash out procedures were identical to those used in Experiment 1. Only four of the five baboons were

used in Experiment 2; an additional baboon was used in Experiment 1 to confirm that non-significant effects were not due to the sample size.

2.7. Daily Observations

Veterinary technicians completed daily behavioral observations that included the recording of any signs or symptoms of drug side effects (e.g., sedation, muscle relaxation, motor incoordination, gastro-intestinal symptoms, etc.). Observations were completed after the administration of drug or vehicle and after sessions. In addition, daily intake of food (g) and water (ml) was recorded at the same time each day to allow for detection of changes in intake.

2.8. Data Analysis

The primary variables of interest included measures of alcohol seeking (FI responses on the left lever and the latency to complete the FI response requirement in Component 2) and measures of consumption (drinkometer contacts and the total volume of alcohol consumed in Component 3). Total g/kg alcohol intake was calculated based on individual body weights and the total volume of alcohol consumed. The patterning of drinking was analyzed as a function of drinking “bouts” as in our previous studies (Holtyn et al., 2017; Kaminski and Weerts, 2014). A drinking bout was defined as 2 or more drinks with less than 5 minutes between each drink, beginning with the first drink. For each baboon, the mean of the three CSR sessions before each chronic-dosing period was used as the baseline for comparison with vehicle and drug doses, and the mean of the five CSR sessions during each chronic-dosing period was used for vehicle and drug conditions. Data for Days 1–5 of alcohol access were aggregated because alcohol seeking and self-administration on Day 1 of alcohol access was similar to Days 2–5. Effects of chronic administration of baclofen and naltrexone after abstinence and during ongoing alcohol access (i.e., no abstinence) were analyzed separately using repeated measures analysis of variance (ANOVA) for each drug with baclofen (baseline, 0–1.8 mg/kg) or naltrexone (baseline, 0–5.6 mg/kg) dose as a repeated measure. When significant effects were determined, post-hoc Dunnett’s *t*-tests were used for pairwise comparisons. For all statistical analyses, a *p*-value of .05 or less was considered significant.

3. Results

3.1. Experiment 1: Treatment Initiated During Alcohol Abstinence

3.1.1. Alcohol Drinking—During baseline sessions, the grand mean alcohol intake was 0.92 g/kg (SEM = 0.05 g/kg). Mean BAL in excess of 0.08% was previously determined in these baboons after comparable alcohol intake (grand mean of 0.93 g/kg in Kaminski et al., 2008; grand mean of 0.94 g/kg in Holtyn et al., 2014). Baclofen treatment initiated and maintained during alcohol abstinence did not significantly decrease the number of drinks in the first drinking bout when CSR sessions and alcohol access were reinstated [Figure 1, Panel A; $F(6,24) = 2.35, p = .075$]. While exploratory, a Dunnett’s *t*-test revealed a significant difference between the 1.8 mg/kg dose and vehicle. Naltrexone significantly decreased the number of drinks in the first drinking bout [$F(4,16) = 3.92, p = .021$], with a significant decrease relative to vehicle at the 5.6 mg/kg dose. Baclofen did not change the interdrink interval [$F(6,24) = 0.601, p = .726$]. Naltrexone significantly increased the

interdrink interval [$F(4,16) = 3.54, p = .030$], with a significant increase relative to vehicle at the 5.6 mg/kg dose. Baclofen and naltrexone did not significantly reduce total alcohol intake (g/kg) after the return to alcohol access [$F(6,24) = 0.323, p = .916$; $F(4,16) = 2.70, p = .081$; respectively].

3.1.2. Alcohol Seeking—In Component 2, five days of alcohol abstinence produced a significant increase in the number of left lever responses when CSR sessions and alcohol access were reinstated under baclofen and naltrexone dosing conditions [data not shown; $F(6,24) = 4.69, p = .005$; $F(4,16) = 3.75, p = .033$; respectively]. Pairwise comparisons showed that baclofen and naltrexone did not significantly reduce the number of left lever responses relative to vehicle. Five days of alcohol abstinence also produced a significant decrease in the response latency under baclofen and naltrexone dosing conditions [Figure 1, Panel B; $F(6,24) = 4.70, p = .005$; $F(4,16) = 4.25, p = .023$; respectively]. Pairwise comparisons showed that baclofen and naltrexone did not significantly increase the response latency relative to vehicle.

3.2. Experiment 2: Treatment Initiated During Ongoing Alcohol Access

3.2.1. Alcohol Drinking—During baseline sessions, the grand mean alcohol intake was 1.05 g/kg, comparable to intake which has previously been reported to produce BALs greater than 0.08% in baboons (Holtyn et al., 2014; Kaminski et al., 2008). Baclofen and naltrexone treatment initiated and maintained during ongoing alcohol access significantly decreased the number of drinks in the first drinking bout [Figure 2, Panel A; $F(2,6) = 9.33, p = .014$; $F(3,9) = 5.24, p = .023$; respectively]; with decreases relative to vehicle at the 1.8 mg/kg dose of baclofen and at the 3.2 and 5.6 mg/kg doses of naltrexone. Baclofen and naltrexone did not significantly change the interdrink interval [$F(2,6) = 0.89, p = .458$; $F(3,9) = 1.07, p = .410$; respectively]. Baclofen and naltrexone significantly decreased total g/kg alcohol intake [$F(2,6) = 7.09, p = .026$; $F(3,9) = 17.86, p < .001$; respectively]; with decreases relative to vehicle at the 1.8 mg/kg dose of baclofen and at the 3.2 and 5.6 mg/kg doses of naltrexone.

3.2.2. Alcohol Seeking—Baclofen did not significantly change the number of left lever responses [data not shown; $F(2,6) = 3.29, p = .109$] or the response latency [Figure 2, Panel B; $F(2,6) = 3.79, p = .086$] in Component 2. Naltrexone significantly decreased the number of left lever responses [data not shown; $F(3,9) = 4.49, p = .034$] and significantly increased the response latency [Figure 2, Panel B; $F(3,9) = 6.12, p = .015$] in Component 2, with statistically significant differences relative to vehicle at the 5.6 mg/kg dose.

3.3. Daily Observations

Daily observations of baboons revealed adverse behavioral effects of baclofen (Table 1). In the first 48 hrs of 1.8 mg/kg/day baclofen treatment during the abstinence period and during ongoing alcohol access, all baboons vomited, and showed reduced or complete food suppression. Lethargy (inactivity and lying on the cage floor) was also observed in some baboons in the first 48 hrs of baclofen treatment. The adverse effects of baclofen were transient, as none of these behaviors were observed beyond the first 48 hrs of baclofen treatment despite continued dosing. None of the baboons showed these behaviors under

vehicle test conditions (Table 1) or under any of the naltrexone test conditions (data not shown).

4. Discussion

The present study examined whether alcohol seeking and self-administration could be reduced by initiation and maintenance of chronic baclofen and naltrexone treatment during abstinence from alcohol. We also examined if effects differed from treatment initiated during ongoing alcohol access. Doses of baclofen (1.8 mg/kg) and naltrexone (3.2 mg/kg) that significantly reduced alcohol self-administration when administered during ongoing access conditions in prior studies (Duke et al., 2014; Kaminski et al., 2012), did not significantly reduce total g/kg alcohol intake when treatment was initiated and maintained during abstinence in the current study. The highest naltrexone dose (5.6 mg/kg), however, did affect drinking pattern. The number of drinks in the first drinking bout was reduced and the duration of intervals between drinks was extended. When treatment was initiated and maintained during ongoing alcohol access in the current study, 1.8 mg/kg baclofen and 3.2–5.6 mg/kg naltrexone significantly reduced total alcohol intake and reduced the number of drinks in the first drinking bout. In sum, lower doses of baclofen and naltrexone initiated during active alcohol drinking were effective when compared to treatment initiated during abstinence.

The 5-day abstinence period reduced the response latency and increased the number of seeking responses in Component 2 to gain access to the daily supply of alcohol. Baclofen and naltrexone did not significantly reduce alcohol seeking when treatment was initiated and maintained during alcohol abstinence. When administered during ongoing alcohol access, naltrexone, but not baclofen, decreased the number of seeking responses and increased the response latency (i.e., prolonged time to gain access to alcohol). Alcohol-seeking behaviors in Component 2, which provide a measure of the motivation to drink in the CSR, are resistant to change (Duke et al., 2014; Holtyn et al., 2014; Kaminski et al., 2012). The current findings are consistent with those of Duke et al., (2014); acute doses of baclofen (0.1–2.4 mg/kg) did not significantly alter the number of Component 2 seeking responses or the response latency. Kaminski et al., (2012) reported that acute doses of naltrexone (0.32–3.2 mg/kg) tended to decrease the number of left lever responses, but did not increase the latency to obtain alcohol. Both baclofen and naltrexone may not have robust effects on alcohol seeking, particularly when treatment is initiated in the abstinent state, suggesting that they may be less effective for reducing craving/urges to drink and seeking behaviors prior to alcohol exposure. Human laboratory studies (Evans and Bisaga, 2009; Leggio et al., 2013; Farokhnia et al., 2017) have shown that baclofen did not attenuate self-reports of alcohol craving or cue-elicited alcohol craving, but did affect participants' subjective response to alcohol, including reports of sedation (Evans and Bisaga, 2009; Leggio et al., 2013) and intoxication/feeling high after alcohol intake (Farokhnia et al., 2017). Based on these findings, it has been suggested that a mechanism by which baclofen may reduce alcohol consumption is by amplifying subjective responses to alcohol (Leggio et al., 2013; Farokhnia et al., 2017).

Prior preclinical studies have not directly compared effects of baclofen treatment during alcohol abstinence versus active drinking. However, studies investigating effects of acute administration of baclofen during ongoing alcohol access in both rodents and primates are consistent with the present findings (for a review, see Agabio and Colombo, 2014). For example, in Indiana alcohol-preferring (P), Sardinian alcohol-preferring (sP), and Alko Alcohol (AA) rats, baclofen (3.0 mg/kg; i.p.) reduced self-administration responses and g/kg alcohol consumed under an FR 4 schedule of reinforcement and reduced the breaking point for alcohol under a progressive ratio schedule (Maccioni et al., 2012). In baboons that self-administered alcohol under the 3-component CSR, acute doses of baclofen (1.8 and 2.4 mg/kg) administered during ongoing alcohol access reduced self-administration responses and total g/kg alcohol intake (Duke et al., 2014).

The dose of baclofen (1.8 mg/kg/day or ~50–60 mg total dose) needed to reduce behaviors did produce overt effects during initial dosing. All of the baboons administered 1.8 mg/kg/day during abstinence and ongoing alcohol access vomited, and showed reduced or complete food suppression, inactivity and lying on the cage floor in the first 48 hours of administration. These effects were transient and were not observed with continued dosing. When treatment was initiated during the abstinence condition, no aversive effects were evident when alcohol access was reinstated. During the ongoing alcohol access condition, adverse effects were observed on Days 1 and 2 of alcohol access. Because significant reductions in alcohol intake were only observed when 1.8 mg/kg baclofen was administered during ongoing alcohol access, it is possible that baclofen side effects may have contributed to the reduction in alcohol intake. However, alcohol intake was similar across the five days of alcohol access, suggesting that aversive effects were not the primary factor in drinking reduction. Nevertheless, the duration of baclofen side effects observed in the present study is consistent with clinical reports suggesting that side effects of baclofen administration are generally transient and subside with continued treatment (Agabio et al., 2013). Clinical trials have reported that baclofen was well tolerated in heavy drinkers and alcohol-dependent patients (Addolorato et al., 2002, 2007, 2011; Müller et al., 2015; Ponizovsky et al., 2015), although treatment efficacy has been mixed. In three double-blind placebo-controlled clinical trials, alcohol-dependent adults treated with 30–270 mg per day baclofen were more likely to achieve complete abstinence compared to those who received placebo (Addolorato et al., 2002, 2007; Müller et al., 2015). In contrast, four other trials found no significant differences in alcohol abstinence among alcohol-dependent adults given 30–150 mg per day baclofen or placebo (Addolorato et al., 2011; Beraha et al., 2016; Garbutt et al., 2010; Ponizovsky et al., 2015).

The source of the discrepancy between the clinical trials is unclear, but whether treatment was initiated during active drinking or abstinence could be a contributing factor. In the four clinical trials that used similar dosing conditions, the two trials that reported null effects (Addolorato et al., 2011; Garbutt et al., 2010) required 3 days of alcohol abstinence prior to the initiation of dosing with baclofen or placebo. In contrast, in the two trials that reported positive effects (Addolorato et al., 2002, 2007) abstinence was not a requirement; dosing could be initiated during active drinking. Nevertheless, it has been speculated that the differences between the patient populations with regard to severity of alcohol dependence

and the dose of baclofen treatment may be important contributing factors underlying the discrepancy among the clinical trials (Agabio and Colombo, 2014; Leggio et al., 2010).

The current findings with naltrexone are also consistent with the clinical literature. For example, it appears that naltrexone is primarily effective for helping patients who cannot remain abstinent to reduce drinking behaviors (Leavitt, 2002). The current findings also suggest use of a higher dose of naltrexone during abstinence may be needed to improve treatment success (Yoon et al., 2011, 2016). In the current study, naltrexone treatment initiated during active drinking reduced total alcohol intake (g/kg) and seeking behaviors at lower doses (3.2–5.6 mg/kg) when compared to treatment initiated under abstinence conditions. Higher dosing may be needed under abstinence conditions, as alcohol seeking and consumption are augmented by abstinence, and are resistant to change (Weerts et al., 2006). Taken together, these data suggest that initiation of baclofen (or other alcohol use disorder treatments) during abstinence or active drinking may be an important factor in influencing efficacy and appropriate dose selection of a pharmacotherapeutic. The identification of boundary conditions such as these is important to developing and refining treatment strategies that will benefit a greater majority of individuals with alcohol use disorders.

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Highlights

- Baclofen and naltrexone reduced alcohol intake when initiated during alcohol access
- Baclofen and naltrexone failed to reduce alcohol intake when initiated during abstinence
- Baclofen did not decrease alcohol seeking when initiated during alcohol access or abstinence
- Naltrexone decreased alcohol seeking only when initiated during alcohol access
- Lower doses were more effective when initiated during active drinking than abstinence

Figure 1. Experiment 1

Effects of chronic administration of baclofen (0.1–1.8 mg/kg), naltrexone (1.0–5.6 mg/kg), or vehicle (VEH) on alcohol drinking in Component 3 (A) and alcohol seeking in Component 2 (B) during the return to alcohol access after five days of alcohol abstinence. For Panel B, note that the minimum latency to complete the FI response requirement was 600 seconds (i.e., 10 minutes). The dashed horizontal line within each graph shows the grand mean baseline from the last three days of alcohol access before each abstinence period. Data shown for the vehicle and drug test conditions are the grand means (+SEM)

from Days 1–5 of alcohol availability after abstinence. *Indicates a significant ($p < .05$) difference from vehicle.

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Treatment Initiated During Active Drinking

A. Alcohol Drinking

B. Alcohol Seeking

Figure 2. Experiment 2

Effects of chronic administration of baclofen (1.8 g/kg), naltrexone (3.2 and 5.6 mg/kg), or vehicle (VEH) on alcohol drinking in Component 3 (A) and alcohol seeking in Component 2 (B) during ongoing alcohol access. For Panel B, note that the minimum latency to complete the FI response requirement was 600 seconds (i.e., 10 minutes). The dashed horizontal line within each graph shows the grand mean baseline from the last three days of alcohol access before each drug or vehicle test condition. Data shown for the vehicle and drug test

conditions are the grand means (+SEM) from Days 1–5 of each drug or vehicle test condition. *Indicates a significant ($p < .05$) difference from vehicle.

Table 1

Number of baboons showing adverse behavioral effects of vehicle (VEH) or 1.8 mg/kg baclofen during the first two days of treatment during alcohol abstinence or ongoing alcohol access.

	VEH		1.8 mg/kg baclofen	
	Alcohol Abstinence	Ongoing Alcohol Access	Alcohol Abstinence	Ongoing Alcohol Access
Vomiting	0/5	0/4	5/5	4/4
Decreased food intake	0/5	0/4	5/5	4/4
Lethargy	0/5	0/4	1/5	2/4