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Multi-Center Trial of Baclofen for Abstinence Initiation in Severe Cocaine Dependent Individuals

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Abstract

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Conflict of interest All authors declare they have no conflicts of interest

Background—Cocaine dependence is a major public health problem for which there is no FDA-approved pharmacological treatment. Baclofen is a GABA_B receptor agonist that in preclinical and early pilot clinical trials has shown promise for the treatment of cocaine dependence. The purpose of this multi-site, double-blind study, was to compare the safety and efficacy of baclofen (60 mg/day) versus placebo in an 8-week treatment of individuals with severe cocaine dependence. The primary outcome measure was subjects' self-reported cocaine use substantiated by urine benzoylecgonine (BE). Analysis of the data did not show a significant difference between the groups treated with baclofen and placebo. The current results do not support a role for 60mg baclofen in treating cocaine dependence in the population studied. The contrast of this result to earlier, preclinical and human pilot data with baclofen may reflect the trial's focus on severe cocaine-dependent users, and/or the need for a higher baclofen dose. Baclofen's potential as a *relapse prevention* agent was not tested by the current design, but may be a useful target for future studies.

Keywords

Cocaine; Dependence; Baclofen

1. Introduction

Cocaine dependence is a significant public health problem associated with serious medical, psychiatric, social, and economic consequences. According to the National Survey of Drug Use and Health conducted in 2006, every day approximately 2,700 Americans try cocaine for the first time in their lives and approximately 1.6 million people met Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for cocaine abuse or dependence in the last year. Although many compounds have been evaluated for the treatment of cocaine dependence, none has been approved by the Food and Drug Administration (FDA) for this indication. Psychosocial/behavioral therapy is currently the treatment of choice for cocaine dependence. The National Institute on Drug Abuse (NIDA) is currently pursuing the identification and testing of new pharmacological agents to add to behavioral therapy to treat cocaine dependence.

Baclofen (p-chlorophenyl gamma-aminobutyric acid (GABA)) is a GABA_B receptor agonist with skeletal muscle relaxant activities. For many years it has been prescribed to treat spasticity caused by multiple sclerosis, spinal cord disease, and spinal cord injury. In preclinical studies, baclofen prevents development of cocaine-induced behavioral sensitization and abolishes the motor stimulant actions of cocaine (Kalivas and Steward, 1991). In an extensive series of studies in rats, it was also demonstrated that baclofen reduces intravenous cocaine self-administration (Roberts et al., 1996; Brebner et al., 2002 a,b) and that this effect of baclofen is attenuated by GABA_B receptor antagonist CGP56433A. Importantly, baclofen dose-dependently reduced cocaine-evoked dopamine (DA) release in the shell of rat nucleus accumbens confirming the ability of baclofen to modulate mesolimbic DAergic transmission and indicating its potential as a candidate in the pharmacotherapy of cocaine abuse (Fadda et al., 2003). Consistent with this therapeutic potential, baclofen also attenuated cocaine-seeking in rats (Di Ciano et al., 2003), countered the effect of cocaine on brain self-stimulation reward thresholds (Slattery et al., 2005), reduced cocaine self-administration in rats (Backes et al., 2008), and in non-human primates (Weerts et al., 2007). In a clinical laboratory study in which subjects self-administered a sequence of 12, 25 and 50 mg doses of cocaine, baclofen reduced self-administration of the lowest cocaine dose in the subjects who were also not opioid-dependent (Haney et al., 2006).

Human brain imaging studies indicate that baclofen may blunt the limbic activation that occurs to cocaine cues. Brebner et al. (2002a) reported that cocaine patients, pre-treated with baclofen (10-20 mg twice daily by oral administration) for 7-10 days showed reduced craving and

reduced limbic amygdala, orbital-frontal cortex, and anterior cingulate) activity to visual cocaine cues, as compared to unmedicated cocaine patients. A brain imaging case study (Childress et al., 2000) of a cocaine-dependent paraplegic patient receiving chronic baclofen (for control of his spasms) was also encouraging. This patient reported that chronic baclofen blunted both cocaine euphoria and cocaine desire: his brain imaging data indeed showed blunting of limbic activity to cocaine-related cues.

Two clinical studies, one open-label and another double-blind, placebo-controlled, assessing the effects of baclofen on cocaine use and craving in cocaine-dependent subjects suggest that baclofen shows promise in the treatment of cocaine dependence and warrants an expanded efficacy trial. In the open-label pilot study, 10 cocaine-dependent subjects were treated with baclofen 20 mg three times a day in conjunction with three times per week cognitive behavioral group counseling. The results of this study showed a trend towards reduced cocaine craving and self-reported cocaine use verified by urine toxicology, during at least a portion of the 17-week treatment period (average of 5 weeks) in 9 of the 10 cocaine-dependent subjects (Gudeman et al., 1996; Ling et al., 1998).

Shoptaw et al (2003) conducted a double-blind, placebo-controlled trial of cocaine-dependent subjects who were treated for 16 weeks with baclofen 20 mg three times daily or placebo in conjunction with cognitive behavioral therapy (CBT) three times per week. No statistically significant differences were identified for craving or cocaine use between subjects receiving baclofen vs placebo in the intent-to-treat or the evaluable groups. In a post hoc analysis using a Markov Transition model, a trend was identified towards reduced cocaine use in baclofen-treated subjects during weeks 3-8 in the subset of subjects with heavier cocaine use as evidenced by a higher frequency of BE-positive urines during the baseline period.

Based on the early clinical trial results, we chose to concentrate on non-abstinent cocaine patients for the current multi-site study of baclofen's potential benefits. By focusing on non-abstinent ('heavy') cocaine users, our study tested baclofen's ability to help cocaine patients initiate abstinence.

2. Methods

2.1. Study design

This was a multi-site, double-blind, placebo-controlled comparison of two groups of cocaine-dependent adults who volunteered to participate in a medication trial to achieve abstinence from or reduction of cocaine use. In order to be eligible, subjects were required to meet Diagnostic and Statistical Manual of Mental Disorders Fourth Edition-Text Revision (DSM-IV-TR) criteria for cocaine dependence, determined by structured clinical interview (SCID), and be at least 18 years of age and otherwise in good health.

Abstinence initiation vs. relapse prevention—The study selected adult male and female volunteers who were actively using cocaine at the time of study entry, and were defined as “severely” dependent based on the criterion that they provided three or more urine samples that were positive for benzoylecgonine (BE) in the 14-day screening period leading up to randomization. Subjects, however, were not instructed that there was any requirement for providing three BE-positive urines. By selecting non-abstinent patients, the study design thus tested for abstinence initiation. Though the relapse prevention potential of baclofen was also of interest, this would have entailed a doubling of the trial size (in order to recruit abstinent cocaine patients), length and costs. We thus restricted our examination to abstinence initiation for this initial multi-site trial.

Exclusion criteria included current dependence, defined by DSM-IV-TR criteria, on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana or physiological dependence on alcohol requiring medical detoxification; court ordered treatment for drug dependence; potential for incarceration during the study; psychiatric or neurologic diagnosis with the potential for endangering the subject as a result of participation; history of electroconvulsive therapy in the prior 3 months; serious medical illness that could potentially be affected by treatment with baclofen; intercurrent medications that could affect or be affected by the action or metabolism of baclofen; and known or suspected hypersensitivity to baclofen. Female participants were excluded if pregnant or lactating. Potential participants with an established diagnosis of AIDS were excluded, but HIV positive individuals were not excluded, and testing of HIV status and HIV education were offered to candidates.

Qualifying subjects were randomized by 1:1 ratio to receive baclofen 20 mg three times a day or matched placebo orally for 8 weeks, followed by follow-up assessments for 4 weeks. Adaptive randomization was used to balance the groups for clinical site and gender. In addition the participants received weekly psychosocial therapy consisting of 1h of individual cognitive behavioral therapy (CBT) during the 8-week treatment period. CBT was standardized across sites where the subjects were audio-taped, with the subjects' consent, in order to monitor drift and assure adherence to manual-guided therapy. A random proportion of the tapes were reviewed by the Boston Behavioral Treatment Training Center to evaluate the therapist's treatment adherence.

The dose of baclofen was escalated from 10 mg to 60 mg in the first week of the treatment period. This dosing regimen represents the standard method for administration of baclofen for other clinical indications in order to avoid undesirable side effects, such as drowsiness, which might impact retention. In weeks 2-7, the subjects received 60 mg of baclofen or matched placebo daily. In week 8, a tapering schedule was employed in order to avoid potential adverse events, particularly seizures. However, as the subject population had no prior seizure history, there was an extremely low risk of seizures that might emerge with abrupt discontinuation of baclofen.

2.2. Subjects

A total of 160 subjects with cocaine dependence were enrolled in the study-80 subjects per treatment group (Figure 1). Subjects were enrolled in the study at eight participating clinics. These sites were located in the following cities with the number of subjects recruited at each site in parentheses: San Francisco (16), Fairfax (12), Philadelphia (21), Torrance (28), Baltimore (20), Denver (26), Salt Lake City (27), and San Antonio (10). Entry into this study was open to both men and women and to all racial and ethnic subgroups. Subjects were recruited from a variety of sources. The primary source was subjects seeking treatment for cocaine dependence via referrals from local treatment providers and word of mouth between subjects themselves and others who were also seeking treatment; additional subjects were recruited from the community by means of advertising in local media.

The study was approved by the Human Rights Committee of the Veterans Affairs Cooperative Studies Program Coordinating Center (VACSPCC, Perry Point, MD) and by the institutional review boards of participating sites. It was conducted in accordance with the Declaration of Helsinki and was registered with clinicaltrials.gov under NCT00439413. All the subjects provided written informed consent. A data and safety monitoring board provided independent monitoring of the study.

2.3. Study agent

Baclofen and matched placebo were supplied by Murty Pharmaceuticals (Lexington, KY) as white 10 mg round tablets for oral administration. Investigational agents were distributed through the Department of Veterans Affairs (DVA) Pharmacy Coordinating Center (PCC) in Albuquerque, NM.

Study medication was provided to subjects using medication cards that contained a 1-week supply of tablets in blister packaging. Subjects were required to take six tablets per day at the (full dose of medication), and were required to bring their remaining medication supply to the clinic each week, at which time another week of medication was provided. The number of tablets each subject returned to the clinic was used to calculate drug compliance, which was expressed as a percentage: number of tablets presumably taken (not returned) divided by the total number of tablets that should have been taken, multiplied by 100%.

2.4. Data analysis

For the primary outcome measure, the weekly mean proportion of days of cocaine non-use as determined by subject self-report confirmed with urine assays for BE was utilized. Each day of the study week during the 14-day screening period and the 8-week treatment phase was coded as a cocaine “use” or “non-use” day based upon self-report, confirmed or disproved by urine drug screening results. The urine drug screen results were first coded for “new use” according to modifications of the algorithm by Preston et al. (1997): (1) BE > 300 ng/ml in the first urine sample during screening; (2) BE > 300 ng/ml in any sample collected more than 2 calendar days after the previous sample; (3) an increase in BE concentration over the immediately previous sample to any value over 300 ng/ml; (4) urine BE > 300 ng/ml and greater than one-half of the BE concentration in the immediately previous sample; or (5) creatinine < 20 mg/dl and BE/creatinine ratio is increased compared to the immediately previous sample.

Once this urine sample new use classification was completed, results were integrated with self-report to “score” each day as a use or non-use day (the first day of the 8-week treatment phase was not scored). Days a subject self-reported using cocaine were always scored as use days, regardless of the urine results. Non-use days required participants to self-report no cocaine use and were verified by no “new use” results from urine drug screening. Days when self-report of no new use was discrepant from the urine results, the immediately preceding day was scored as a use day. Subject-reported days of non-use were re-scored to missing if not followed by a urine BE assessment within 7 days. In the cases where the concordance rate between self-report and urine BE for an individual was < 70% overall, the subject's self-reported days of non-use were re-scored to missing if they were not followed by a urine BE assessment within 3 days. The weekly mean proportions of cocaine non-use days for the 8-week treatment phase were analyzed as a repeated measure using Generalized Estimation Equations (GEE) (Liang and Zeger, 1986; Zeger and Liang, 1986). The model included study week as the time variable, treatment group, the first order treatment and study week interaction term, and the 14-day screening mean proportion of cocaine non-use days as a baseline covariate. An autoregressive correlation structure was used to model the within-subject correlations between the weekly repeated proportions of cocaine non-use days.

Several secondary assessments evaluating treatment effects on use reduction were also performed. The proportion of subjects who (1) reduced their days of cocaine use to 75% or less of their frequency of use at baseline, or (2) reduced their use to 50% or less, of their frequency of use at baseline was analyzed using Fisher's exact test. The maximum number of consecutive days of cocaine abstinence, was analyzed using the nonparametric Wilcoxon rank-sum test. Study retention by treatment group was compared using the log rank test. The severity of cocaine dependence was assessed by comparing composite scores of the Addiction Severity

Index (ASI-Lite and ASI-Lite Follow-up) (McLellan et al., 1985), Brief Substance Craving Scale (BSCS) (Mezinskas et al., 1998), Cocaine Selective Severity Assessment (CSSA) (Kampman et al., 1998) and Clinical Global Impression as assessed by the subject (CGI-S) and an observer (CGI-O) (Tracy et al., 2000). The ASI-Lite was performed at screening and ASI-Lite Follow-up at the first visit of weeks 4 and 8. The Wilcoxon rank-sum test was performed on the change scores between screening and each follow-up assessment. The BSCS, CSSA, CGI-S, and CGI-O were performed weekly during screening and at the first visit of each on-treatment study week. GEE analysis was performed on all four of these repeated measures (Liang and Zeger, 1986; Zeger and Liang, 1986). A treatment effect on human immunodeficiency virus (HIV) risk-taking behavior hypothesized to be associated with drug use was assessed by the HIV Risk-Taking Behavior Scale (HRBS). The HRBS was conducted at screening and week 8, and the change score was analyzed by the Wilcoxon rank-sum test. Safety of baclofen was assessed by occurrences of adverse events (AEs) collected at each clinic visit, laboratory data, physical exams, the Hamilton Depression Rating Scale (HAM-D) and vital signs. All statistical tests performed were two-sided at an alpha level of 0.05.

3. Results

3.1. Baseline demographics and drug use

The baseline demographics and drug use characteristics were very similar in the baclofen and the placebo groups (Table 1). On average, the subject cohort was 43 years old and 80% male. In both groups, blacks represented the majority of the subjects (63% in the baclofen group and 54% in the placebo group). In the 30 days prior to study participation, subjects used cocaine for an average of 18 - 19 days and spent about \$550 - \$570 on drugs. The majority of subjects smoked cocaine as opposed to insufflation or other routes of administration.

3.2. Treatment retention

The overall retention for the baclofen trial was 67%, and there was no significant difference (log-rank p-value = 0.84) between the retention rates in the two treatment groups.

3.3. Efficacy as assessed by self-report of cocaine use and confirmed by urine BE levels

The repeated measures analysis of the weekly mean proportions of cocaine non-use days for the 8-week treatment phase indicates that, in the ITT population, baclofen failed to increase the number of cocaine non-use days significantly compared to placebo (p-value = 0.77). Figure 2 shows the mean weekly percentage of cocaine non-use days in both treatment groups over the entire treatment period.

The same outcome measure was also analyzed with additional model terms to control for variations due to site, gender, cocaine use in the 30 days prior to consent, and the baseline HAM-D score. This GEE analysis again failed to detect any significant difference between the treatment groups (p-value = 0.75).

Table 2 illustrates the findings for three of the secondary outcome measures, the definitions of which were based on self-report of use and confirmatory urine BE analysis. Fisher's exact test failed to detect a difference between the two treatment groups for the proportions of subjects who reduced cocaine use days to 75% or less (p = 0.75) and to 50% or less (p = 0.67) of baseline rates. Subjects in the baclofen group and in the placebo group showed an average of 6 and 7 days of consecutive cocaine non-use, respectively. This difference was also statistically insignificant (p = 0.37).

3.4. Efficacy based on urine benzoylecgonine test results

The raw quantitative urine BE values had a very wide range (min. = 0 and max = 2,470,000 ng/ml) and the distribution of these scores was extremely skewed. The $\log_{10}$ transformation of the raw scores resulted in a narrower range (min = 0 and max = 6.39) and a more well-behaved, approximately bell-shaped distribution. Mean weekly $\log_{10}$ transformed urine BE levels were analyzed using GEE with treatment and study week as main effects, the baseline mean as a covariate, and the first order interaction term between treatment and study week. Baclofen did not show any significantly different effect on the urine BE values compared to placebo ($p = 0.99$).

3.5. CGI results

Mean weekly severity and improvement scores on the CGI-O and CGI-S were analyzed separately with GEE models including treatment and study week as main effects, the baseline mean score as a covariate, and the first order interaction term between treatment and study week. Overall, baclofen did not show any significantly different effect on the weekly severity or improvement scores compared to placebo in any of the models ($p = 0.46 - 0.95$).

3.6. Results from the CSSA

Mean weekly severity scores on the CSSA were analyzed using GEE with treatment and study week as main effects, the baseline mean severity score as a covariate, and the first order interaction term of treatment and study week. The analysis showed that baclofen failed to lessen the severity in cocaine dependence as assessed by this score ($p\text{-value} = 0.14$).

3.7. Analysis of severity scores on the BSCS

A similar analysis of mean weekly severity scores of the BSCS was done and the analysis suggested that the baclofen subjects did not experience significantly less craving compared to the placebo subjects over the entire length of the trial ($p\text{-value} = 0.59$).

3.8. Analysis of the HAM-D score

GEE analysis of the mean weekly scores of the HAM-D indicated no significant treatment effects ($p\text{-value} = 0.66$).

3.9. Results from the HRBS

The HRBS has two subscale scores—a drug subscale which ranges from 0 to 30, and a sexual behavior subscale, which ranges from 0 to 25—and the overall score which can range from 0 to 55. A lower score overall on each either subscale indicates less risk-taking behavior. The change in HRBS scores from baseline to week 8 was compared between the two treatment groups using t-tests. The change score comparisons on drug subscale scores ($p\text{-value} = 0.99$), sexual behavior subscale scores ($p\text{-value} = 0.12$) and overall scores ($p\text{-value} = 0.13$) show no significant differences in the two treatment groups. The analysis suggests that subjects on baclofen showed no significant difference in their risk-taking behavior.

3.10. ASI results

The ASI has seven distinct components—medical, employment, alcohol, drug, legal, family/social, and psychiatric. Four change scores (baseline and week 4, baseline and week 8, baseline and the last visit, and weeks 4 and weeks 8) are compared between treatment groups for all seven components using t-tests. A positive change score is indicative of improvement and a negative change score is indicative of worsening between the respective time points during the treatment phase of the trial. No significant differences between the two treatment groups were detected when mean change scores in each of the seven components were compared.

3.11. Safety

Baclofen was safe and well tolerated in this trial. There was no difference between groups in overall incidence of AEs ($p=1.00$). Ninety-one percent of subjects taking baclofen and 90% of subjects taking placebo experienced AEs. Somnolence, headache, and dizziness were experienced by 45%, 39%, and 20%, respectively, in the baclofen group compared to 35%, 31% and 18% in the placebo group. Nausea was reported by 26% in the baclofen group and 14% in the placebo group ($p=0.07$). Vomiting was reported by 14% for baclofen and 6% for placebo. Diarrhea was reported by 11% and 9%, respectively. Dry mouth was reported by 6% for baclofen and 13% for placebo. Other common AEs (baclofen vs placebo) were cough (15% vs 14%), nasal congestion (8% vs 6%), rhinorrhea (6% vs 6%), anxiety (10% vs 4%), depression (5% vs 9%), insomnia (4% vs 6%), back pain (9% vs 11%), myalgia (8% vs 10%), and arthralgia (10% vs 9%). There were no effects on blood chemistries or QTc intervals, and there were no seizures.

Nine serious adverse events (SAEs) were reported during the study. Three were judged to be possibly related to medication. One SAE was in a 46-year-old male who experienced chest pain and was admitted to the hospital in atrial fibrillation. After failing to respond to procainamide he was cardioverted back to sinus rhythm with electrical shock. The incident occurred on his last day of study medication and he returned to the study for follow up. He revealed that he had had two previous episodes of atrial fibrillation in his life; he was taking placebo. A second subject with a possibly related SAE was a 40-year-old male treated in an emergency room for dizziness and disorientation after heavy use of cocaine. After stabilization he was admitted to a detoxification center for 48 hours, after which he returned to the study; he was also taking placebo. A third subject was a 52-year-old male who was hospitalized for attempted overdose with alcohol and the study medication. After recovery, he was discharged from the study at week 6. While this was considered an unrelated SAE at the time of the subject's participation, it was later determined that the subject was taking baclofen. Consequently, and in consultation with the DSMB, this SAE was reclassified as possibly related. Other SAEs that were unrelated to medication were abdominal pain and hematochezia, injury from a motor vehicle, urticaria after albuterol use, hospitalization for suicidal thoughts during the follow-up period, and jaundice and liver enzyme elevation due to hepatitis C.

4. Discussion

This multi-center trial did not succeed in corroborating the findings of previous single-center investigators who identified baclofen as an effective medication for reducing craving for and use of cocaine, particularly those with severe cocaine dependence.

Based on both preclinical and imaging studies of baclofen's cocaine-relevant effects, we posited that baclofen was a strong therapeutic candidate as it is safe, well tolerated, and readily available as a generic medication. In Shoptaw and colleagues' double-blind, placebo-controlled trial of 70 subjects, there was no significant effect on cocaine use reduction in the baclofen treated subjects compared to placebo; however, by week 9 less than 50% of subjects were still enrolled, and only 25.7% (baclofen) and 23.9% (placebo) completed the study. A post hoc analysis using GEE and Markov 1 Transition Models identified a positive medication effect for baclofen in weeks 3-8, while retention was still greater than 50%. A strong positive correlation for treatment effect was observed between the baseline frequency of BE-positive urine samples and medication, and no such correlation was seen in the placebo group. The current trial, in which subjects with similar frequencies of cocaine use were selected and where retention over 8 weeks of study treatment was higher, we were unable to replicate a similar outcome in primary or secondary measures of cocaine use reduction.

The effects of baclofen as assessed from measures of craving and withdrawal did not differ significantly from placebo. Symptoms of depression did not emerge during the trial regardless of treatment or length of participation; rather, HAM-D scores improved in both groups.

Recent preclinical (Walker et al., 2007, Maccioni et al., 2008) and clinical trials of baclofen for treatment of alcohol dependence have shown benefits for reducing withdrawal symptoms, craving, and reducing alcohol intake (Colombo et al., 2004, Addolorato et al., 2007). Post hoc subgroup analyses, including using baseline cocaine use and alcohol dependence as covariates failed to show a differential effect for baclofen over placebo. Although our study did not use adaptive randomization to balance the groups according to their history of alcohol use, the number of subjects who reported alcohol dependence was identical in both groups. To test whether there was a differential response to treatment depending on history of alcohol dependence, we performed repeated measures analysis using GEE separately on the non-alcohol dependent and the alcohol dependent groups. For the non-alcohol dependent subjects the treatment main effect ($p = 0.66$) and the treatment-by-week first order interaction ($p = 0.88$) were not significant at the 5% level. For the alcohol dependent group these terms were likewise non-significant at the 5% level ($p = 0.39$ and 0.73 , respectively). For this reason, we believe that the presence of alcohol dependence in some of the cocaine-dependent subjects did not contribute to the failure to show a medication effect. When this study was conducted, we did not anticipate a possible treatment effect on alcohol abuse, so the subjects were not asked to report on their ongoing alcohol use during the course of the study, but this question would be of interest in future clinical trials.

The dose we tested in the current study, 60 mg/day, was the same dose that was assessed to be safe and well tolerated in both the prior open-label trial of Ling et al. (1998) and the placebo-controlled proof-of-concept trial reported by Shoptaw et al. (2003). Though a similarly modest dose of baclofen (10-20 mg, twice daily for 7-10 days) successfully blunted limbic activation to drug video cues in treatment-seeking cocaine patients (Brebner et al., 2002a), its brain effects were significantly diminished when administered more than 4h prior to the video challenge. These findings are a reminder that baclofen (or any medication) may demonstrate robust effects on sensitive brain imaging endpoints under dosing conditions that might not yield reliable clinical effects. Even though our subjects' mean compliance with medication was acceptable (86.1% for baclofen and 87.9% for placebo), the standard dose and schedule for baclofen that is recommended for spasticity may need to be titrated upward for replicable clinical outcomes in addiction. Case reports subsequent to the current trial (Ameisen, 2005; Bucknam, 2007) have reported success in reducing alcohol craving/drinking with doses of baclofen exceeding 120mg daily.

Our study design did not test for baclofen's ability to prevent relapse in cocaine users who have achieved a period of abstinence. Preclinical studies suggest that baclofen may be a good candidate for relapse prevention. Studies in rats indicate efficacy against cue-triggered drug seeking (Di Ciano et al., 2003), and cocaine-primed reinstatement (Campbell et al., 1999). It was noted that, when tested against two doses of cocaine in a self-administration paradigm on a fixed-ratio schedule, baclofen was more effective against the lower dose of cocaine (Brebner et al., 2000). Other investigators have observed attenuation of the reinstatement response to heroin (Spano et al., 2007), nicotine (Paterson et al., 2004; Fattore et al., 2002) and amphetamine (Brebner et al., 2005) in animal models. Baclofen has recently demonstrated effects in several addiction-relevant clinical populations: smoking reduction, (Franklin, et al., 2009, in press); alcohol drinking, (Addolorato, et al. 2007); and binge eating provided encouraging results, (Broft et al., 2007) which suggests that further systematic testing at higher doses and with longer acting formulations, as well as in a relapse prevention paradigm for stimulant addiction is warranted.

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Figure 1.
Subject flow in the clinical trial of baclofen for the treatment of cocaine dependence.

Figure 2.
Mean weekly percentage of cocaine non-use days by treatment based on self report confirmed by urine BE.

Table 1**Subject Characteristics**

Variable	Baclofen (N=80)	Placebo (N=80)	p-value
Age (mean (SD))	42.3 (8.2)	43.0 (8.0)	0.68
% Male	78.8%	80.0%	1.00
Race			
White	24.0%	27.5%	0.13
Black	63.3%	53.7%	
Hispanic	8.9%	18.8%	
Asian/Pacific	2.5%	0%	
American Indian	1.3%	0%	
Years of Education	13.0 (2.1)	13.0 (2.0)	0.42
Days of cocaine use past 30 days	19.9 (8.2)	18.1 (7.8)	0.15
Yrs of cocaine use, lifetime	13.9 (8.1)	15.5 (8.3)	0.25
\$ spent on drugs in past 30 days	555.6 (561.8)	567.2 (637.2)	0.78
ASI Composite Drug Score	0.29 (0.09)	0.27 (0.07)	0.15
ASI Composite Alcohol Score	0.22 (0.23)	0.24 (0.24)	0.71
ASI Composite Employment Score	0.54 (0.30)	0.57 (0.30)	0.50
ASI Composite Legal Score	0.07 (0.13)	0.08 (0.16)	0.86
ASI Composite Family/Social Score	0.23 (0.24)	0.21 (0.21)	0.90
ASI Composite Psychiatric Score	0.16 (0.18)	0.17 (0.18)	0.95
ASI Composite Medical Score	0.23 (0.32)	0.20 (0.29)	0.73
Hamilton Depression Rating Score	11.8 (9.2)	10.6 (8.4)	0.47
Usual route of cocaine use			
Smoked	85.0%	76.3%	0.26
Nasal	8.8%	17.5%	
Other	6.3%	6.3%	
Alcohol Use			
Number of Subjects with Alcohol Dependence	37	37	1.00
Number of Years of Alcohol Use (mean±SD)	15.7±12.7	18.8±11.9	0.12

Table 2

Secondary outcome measures based on self-report of cocaine use and confirmed by urine BE

Outcome	Baclofen (N=77)	Placebo (N = 78)	p-value
Percentage of subjects who reduced cocaine use days to 75% or less of baseline rate	42.9	46.1	0.75
Percentage of subjects who reduced cocaine use days to 50% or less of baseline rate	15.6	19.2	0.67
Longest consecutive period (in days) of cocaine abstinence (SD)	6.1 ± 6.8	7.4 ± 9.7	0.37