Randomized Placebo-Controlled Trial of Baclofen for Cocaine Dependence: Preliminary Effects for Individuals With Chronic Patterns of Cocaine Use

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Background: This screening trial evaluated whether the $GABA_B$ agonist baclofen demonstrated sufficient clinical efficacy to recommend an adequately powered trial of the medication as a pharmacotherapy for cocaine dependence.

Method: Participants with cocaine dependence verified by the Structured Clinical Interview for DSM-IV were randomly assigned to baclofen (N = 35; 20 mg t.i.d.) or placebo conditions (N = 35; identical in appearance and dosage rate) using a 2-group, experimental, 16-week double-blind design featuring thrice-weekly cognitive-behavioral drug counseling groups. Outcomes were retention, cocaine use, cocaine craving, and adverse events.

Results: A generalized estimating equation (GEE) model showed that participants assigned to receive baclofen demonstrated statistically significant reductions in cocaine use over those assigned to receive placebo as indicated by urine drug screening results ($\chi^2 = 5.34$, df = 1, p = .021). Confirming the GEE model, longitudinal analyses showed that participants assigned to receive baclofen demonstrated significant and stepwise increases in the probability of providing benzoylecgonine-free urine samples throughout the trial as the number of benzoylecgonine-positive samples increased during baseline ($\chi^2 = 10.63$, df = 1, p = .001). Participants assigned to placebo demonstrated no such association. Univariate analyses of aggregates of urine drug screening showed generally favorable outcomes for baclofen, but not at statistically significant levels. There was no statistical significance observed for retention, cocaine craving, or incidence of reported adverse events by treatment condition.

Conclusions: Project findings demonstrated initial clinical efficacy of baclofen over placebo in reducing cocaine use when delivered concurrent with thrice-weekly drug abuse counseling sessions. The effects of baclofen were particularly apparent for those participants with chronic levels of cocaine use at baseline and provide support for a full-scale efficacy trial for baclofen, especially among this subgroup of patients.

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Despite intensive investment of resources and the completion of many clinical trials, no medication has demonstrated clear evidence of efficacy for the treatment of cocaine dependence.[1] The search for effective pharmacotherapies has focused largely on dopaminergic agents, due to the central role of that neurotransmitter system in the reinforcing effects of cocaine and other stimulants.[2,3] Having come up largely empty-handed from this search, investigators are increasingly looking to other brain mechanisms that modulate the behavioral effects of cocaine and other drugs of abuse.[4]

There is preclinical evidence that medications that act on the inhibitory neurotransmitter system, γ-aminobutyric acid (GABA), may represent viable candidates as treatments for cocaine dependence.[5] Both inhibitory and excitatory amino acid systems may be involved in the reinforcing effect of cocaine.[6–13] It is understood that the bulk of GABA activities in the central nervous system are inhibitory in nature, exerting a generally dampening effect on the overall activities of the reward system.[14,15] Specifically, GABA has been shown to exert an inhibiting effect on the tonic activity of dopamine neurons in the ventral tegmental area[16] and in the nucleus accumbens,[17] and this may attenuate the reinforcing effects of cocaine through modulation of dopamine transmission.[18]

Vigabatrin, a GABA transaminase inhibitor that increases GABA neurotransmission, reduced cocaine-induced dopamine release by 25% or more in laboratory animals.[19] Although vigabatrin has exceptional preclinical

support for reducing consumption of alcohol and cocaine[20] and acceptable cardiovascular and hepatotoxicity profiles in the presence of cocaine,[21] the medication causes unacceptable visual field defects in approximately one third of those exposed to the medication for long periods.[22]

Another GABAergic medication, the $GABA_B$ agonist, baclofen, also modulates cocaine self-administration in laboratory animals.[23] Baclofen consistently reduces cocaine self-administration at low doses using a fixed ratio-1 schedule[24] and dramatically reduces response behaviors at all cocaine dose levels when tested using a progressive ratio schedule.[25] Effects for baclofen on cocaine self-administration in laboratory animals show sensitivity to levels of cocaine dose and response requirements.[26] Baclofen may also show differential effects in humans that depend upon such factors as pattern and level of cocaine exposure, although this is as yet untested.

Our initial experience with baclofen as a treatment agent involved a 10-patient, open-label study, which found that the medication was safe when used in conjunction with cognitive-behavioral counseling 3 times a week.[27] Data from preclinical and human experiences using baclofen led our group to mount a randomized, placebo-controlled screening trial of baclofen (20 mg t.i.d.) administered in the context of thrice weekly cognitive-behavioral drug counseling groups for reducing cocaine use. This screening trial was undertaken to determine whether baclofen produces effects significant enough to warrant a full-scale efficacy trial. We predicted that in measures of cocaine use, treatment retention, and cocaine craving, participants assigned to receive baclofen would significantly outperform participants assigned to receive placebo.

METHOD

Participants

A total of 131 treatment-seeking, cocaine-dependent volunteers began screening procedures for this study. Following a 2-week, nonmedication screening period to collect baseline measures, 70 participants were randomly assigned to receive baclofen (N = 35) or placebo (N = 35). Analysis comparing whether the 61 participants who terminated prior to randomization differed systematically from those randomized to the trial showed that there were no statistically significant differences in any of the measured demographic or drug use characteristics.

Participants met all of the following inclusion criteria: (1) cocaine dependence, current, diagnosed using the Structured Clinical Interview for DSM-IV (SCID); (2) aged 18 to 65 years; (3) English literacy sufficient to complete measures and scales; (4) understand risks/benefits to participation; and (5) provide voluntary informed consent. Participants also met none of the following exclusion criteria: (1) dependence on alcohol or other substances, current (SCID-verified); (2) current psychiatric disorder requiring treatment; (3) active medical conditions that interfere with participation (e.g., uncontrolled diabetes); (4) history of seizures; (5) unstable behavior during screening period (e.g., transportation problems, erratic attendance); and (6) asthma (current or lifetime) requiring treatment.

Baseline demographic variables indicated that the baclofen and placebo groups were fundamentally similar (Table 1). Compared to those assigned to placebo, participants assigned to receive baclofen were significantly more likely to report possession of a valid drivers license, fewer days of work, and fewer days of cannabis use in the 30 days prior to baseline. Baclofen participants also scored significantly higher at baseline on subscales of the Addiction Severity Index,[28] indicating greater disturbance in employment compared to placebo-treated participants.

Design

This 2-group, randomized, placebo-controlled, double-blind trial of baclofen (20 mg t.i.d.) was conducted from October 1997 to May 1999 as part of a National Institute on Drug Abuse (NIDA)–funded project to screen theoretically promising medications for cocaine dependence. A placebo identical in appearance to the baclofen pill was delivered at the same rate as the active condition. The study design was conducted at the lower ranges of statistical power for detecting medication effects and used an alpha level of $p < .05$, power equal to 0.80, and a moderate medication effect size between conditions using indices of urine drug screening.

Measures

Participant characteristics at baseline were assessed using the Addiction Severity Index[28] and the SCID.[29] Four domains of treatment outcome were measured: retention, urine drug testing, cocaine craving, and adverse events. Compliance with medication taking was monitored using pill counts.

Addiction Severity Index. The Addiction Severity Index, a standardized 40-minute clinical interview used in addiction research to quantify problem areas experienced by substance abusers, was collected at baseline. The measure has excellent interrater and test-retest reliability and discriminant and concurrent validity.[28] Composite scales measure medical status, employment, drug use, alcohol use, legal status, family/social status, and psychiatric functioning.

Structured Clinical Interview for DSM-IV (SCID). The SCID[29] was administered to verify cocaine dependence, to exclude participants with concomitant alcohol or other illicit drug dependence, and to assess comorbid psychiatric conditions that would preclude study participation.

Retention. Retention was the number of days that participants received medication from the first observed dose

Table 1. Demographic, Drug Use, and Psychiatric Characteristics by Assignment to Treatment Condition

Variable	Baclofen (N = 35)	Placebo (N = 35)
Gender, N (%) male	25 (71.43)	23 (65.71)
Ethnicity, N (%)		
White	9 (25.71)	5 (14.29)
African American	11 (31.43)	17 (48.57)
Asian/other	2 (5.71)	0 (0)
Latino/a	13 (37.14)	13 (37.14)
Age, mean ± SD, y	34.03 ± 6.4	36.34 ± 9.4
Education, mean ± SD, y	12.83 ± 2.5	12.51 ± 13.1
Days worked in month prior to baseline, mean ± SD[a]	10.11 ± 9.8	12.51 ± 7.7
Valid drivers license, N (%)[b]	28 (80.00)	18 (51.43)
Days cocaine used in past 30, mean ± SD	13.43 ± 9.4	12.63 ± 9.2
Lifetime cocaine use, mean ± SD, y	11.26 ± 5.1	10.57 ± 7.1
Route of administration, N (%)		
Oral	1 (2.86)	0 (0)
Intranasal	4 (11.43)	4 (11.43)
Smoking	27 (77.14)	31 (88.57)
Injection	3 (8.57)	0 (0)
Days cannabis used in past 30, mean ± SD[c]	3.56 ± 6.9	5.66 ± 1.5
Baseline ASI composite scores, mean ± SD		
Medical	0.15 ± 0.3	0.16 ± 0.1
Employment[d]	0.49 ± 0.3	0.35 ± 0.6
Alcohol	0.21 ± 0.2	0.22 ± 0.2
Drug	0.25 ± 0.1	0.26 ± 0.2
Legal	0.08 ± 0.2	0.07 ± 0.1
Family/social	0.22 ± 0.2	0.24 ± 0.2
Psychiatric	0.13 ± 0.2	0.11 ± 0.1
Psychiatric variables (SCID verified), N (%)		
Substance abuse secondary to cocaine dependence		
Current	13 (37.14)	14 (40.00)
Lifetime	25 (71.43)	28 (80.00)
Non–substance-related mood disorders		
Current	3 (8.57)	3 (8.57)
Lifetime	5 (14.29)	4 (11.43)
Non–substance-related anxiety disorders		
Current	2 (5.71)	4 (11.43)
Lifetime	2 (5.71)	4 (11.43)
Substance-induced Axis I disorders		
Current	8 (22.86)	12 (34.29)
Lifetime	10 (28.57)	12 (34.29)

[a] $t = 2.11$, df = 68, $p = .04$.
[b] $\chi^2 = 6.34$, df = 1, $p = .01$.
[c] $t = 2.65$, df = 40.4, $p = .01$.
[d] $t = -3.67$, df = 68, $p < .001$.
Abbreviations: ASI = Addiction Severity Index, SCID = Structured Clinical Interview for DSM-IV.

of study medication to the last clinic visit. Early termination occurred when participants failed to return to clinic for 6 consecutive visits (2 weeks).

Urine drug testing. Urine samples for drug testing were collected on Mondays, Wednesdays, and Fridays during the baseline and treatment periods and analyzed using radioimmunoassay methods by Northwest Toxicology (Salt Lake City, Utah). Quantitative values with dilution to benzoylecgonine 150,000 ng/mL (urinary metabolite of cocaine) were available. The qualitative level for determining samples positive for cocaine metabolite was benzoylecgonine 300 ng/mL . New use criteria[30] were applied to quantitative values to define qualitative results (0 = no new use; 1 = new use) such that an index sample was interpreted to indicate no new use of cocaine if the quantitative benzoylecgonine value of the index sample was at least 50% less than the immediately prior sample. If the previous sample was missing and the quantitative value exceeded benzoylecgonine 300 ng/mL, the sample was considered a new use. Qualitative results were compiled using 4 typical aggregates: joint probability index,[31] percentage of urine samples negative for benzoylecgonine, longest period of continuous abstinence verified by urine drug testing (in days), and percentage of participants that provided 3 consecutive weeks of urine samples negative for cocaine metabolite.[32]

Cocaine craving. Cocaine craving ratings were recorded once per week using a visual analogue scale (0 = "not at all" to 100 = "strongest ever") that asked participants to indicate on a 100-mm line their "most intense craving for cocaine that occurred at any time during the past 24 hours."

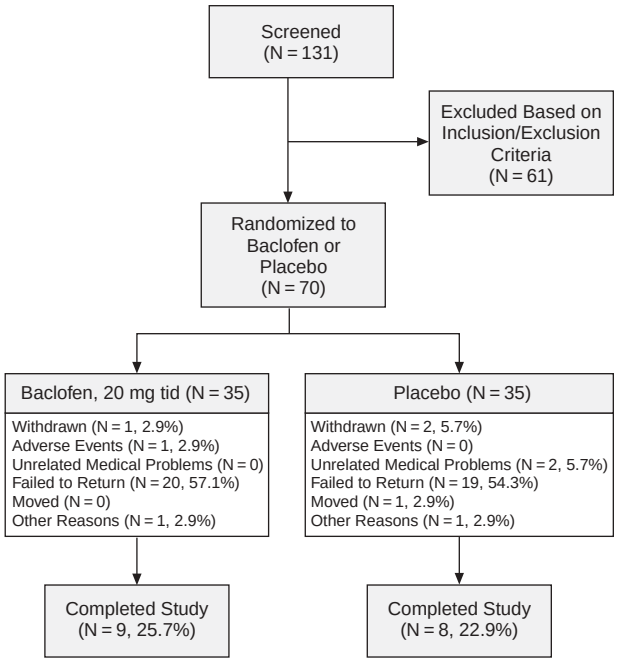
Adverse events. Adverse events were reported by participants or observed by medical staff members. Those adverse events rated in severity as moderate or higher that occurred during the trial were tallied, and these adverse events were collapsed into categories. Moderate adverse events were reported as the incidence of each event category per condition. Serious adverse events were described individually.

Compliance. Pill counts served as the primary marker of medication adherence and were calculated as the total number of pills dispensed minus the number of pills returned divided by the total number of pills dispensed. Only pills that were returned were included in this pill count. For those who terminated their participation early by not returning to the clinic, only those pills that were verified from returned medication bottles were included in the pill counts. No inferences were made regarding pills taken from bottles that were not returned to clinic. Self-report of pill taking was used to explain discrepancies that occasionally occurred between actual pill counts and self-report of pill taking. To test whether fatigue, a common side effect of baclofen, might aid baclofen-treated participants in decoding their condition assignment, participants were polled during the second week on their belief of whether they received baclofen or placebo as their study medication.

Procedure

All activities involved in this study were overseen by the Friends Research Institute West Coast Institutional Review Board (Los Angeles, Calif.). Participants re-

Figure 1. Study Design Flow Chart



sponded to newspaper or radio ads about this treatment research project through a central recruitment number, which scheduled the individual for an intake interview. At this interview, study procedures were explained fully. Following provision of voluntary, signed informed consent, participants began a 2-week, nonmedication baseline period. This baseline period was to identify and exclude those whose cocaine dependence was inappropriate for outpatient intervention, to collect information that documented inclusion and exclusion criteria, and to deliver interventions that taught early recovery skills. Those cleared for study participation were randomly assigned to condition at the first clinic visit following the baseline period and received their first week of study medication in take-home bottles (Figure 1). Ingestion of the first dose of study medication was observed by the research nurse. Study medication was returned at the end of each research week for pill counts, following which participants received a new bottle of medication. Clinic was held in the evening hours, which facilitated observed dosing from each new bottle of study medication dispensed. Participants continued the treatment protocol until they either completed 16 weeks of medication or terminated early. Participants were assessed by telephone or a clinic visit 30 days following their last clinic visit to verify their medical safety.

During the trial, participants attended clinic thrice weekly to complete measures, provide urine samples, and attend counseling groups. To monitor safety during the trial, blood panels (complete blood counts with differential), urinalyses, and ECG were conducted at baseline and at weeks 4, 8, 12, and 16. No incentives were provided for participation throughout the trial.

Psychosocial Activities

Cognitive-behavioral group counseling sessions were held at each clinic. The counseling program is manual driven[33] and has been shown to be an excellent platform when conducting cocaine pharmacotherapy trials.[33–35]

Data Analysis

The cardinal analysis of project data involved evaluation of urine samples for benzoylecgonine to determine the effects of baclofen on cocaine use. Univariate tests of aggregate indices of urine sample results provided clinically useful information. Longitudinal models were applied to more accurately evaluate the effects of baclofen and maximize the information contained in the data matrix, i.e., thrice weekly urine samples (6 samples during baseline, 48 samples during treatment). Missing samples were not imputed for univariate or multivariate analyses. Aggregate measures of urine drug screens were analyzed separately: joint probability index scores were compared between conditions at the end of 8 and 16 weeks of treatment using differences between uncorrelated proportions tests, which yield a z statistic.[36]

The primary method for determining intervention effects using longitudinal analysis involved calculation of a generalized estimating equation model (GEE).[37,38] Each of these analyses included the baseline variables that were different between conditions as covariates. In order to describe medication effects, we calculated the probabilities for baclofen and placebo in instilling (i.e., transitioning from a benzoylecgonine-positive urine sample to benzoylecgonine-free urine sample) and maintaining cocaine abstinence (i.e., consecutive benzoylecgonine-free urine samples). We calculated the transitional probabilities that a specific urine sample was free of benzoylecgonine given the result of the previous urine drug screen (e.g., Markov order 1). This also allowed calculation of the probabilities of treatment failure (i.e., transitioning from a benzoylecgonine-free sample to a benzoylecgonine-positive sample or maintaining consecutive benzoylecgonine-positive samples). This approach accounts for the non-independence of events in a cocaine clinical trial, i.e., the correlation among different measurements of the same individual represents values assumed to influence the index of observation. Transition models retain a dynamic aspect because by describing the transition from one observation to the next, the history is taken into account.[39] Retention was tested using a log-rank analysis. Craving scores were analyzed using GEE.

In order to determine whether missing data differentially affected our analysis, we evaluated the pattern of

Figure 2. Survival Analysis Depicting the Proportion of Participants Retained in Each Condition (Baclofen or Placebo) Throughout Each of the 16 Weeks of Treatment

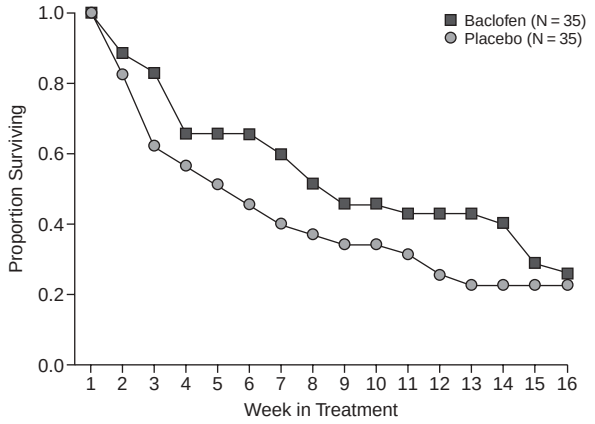


Table 2. Aggregate Measures of Urine Drug Screening for Cocaine Metabolite by Assignment to Treatment Condition

Measure	Baclofen (N = 35)	Placebo (N = 35)
Joint probability index[a]		
8 Weeks	0.20	0.14
16 Weeks	0.20	0.11
Weeks 3–8	0.30	0.18
Treatment effectiveness score, mean ± SD[b]	12.66 ± 13.5	9.03 ± 12.9
Percentage of samples negative for cocaine metabolite, mean ± SD	64.23 ± 36.3	52.44 ± 40.4
Longest consecutive period of cocaine abstinence, mean ± SD, d	11.81 ± 17.7	11.06 ± 21.5
Patients with 3 consecutive weeks of cocaine abstinence, N (%)	6 (17.14)	4 (11.43)

[a]Calculated as the proportion of patients that provided samples negative for cocaine metabolite divided by the number of patients assigned to the condition (N = 35). Values represent joint probability indexes for the end of week 8, for the end of week 16, and for the average of each of the points between weeks 3–8.
[b]Represents the average of the sums of samples negative for cocaine metabolite for each condition.

"missingness" (both for dropouts and for intermittent missing values) observed for the baclofen and placebo conditions by applying a GEE model. We recoded data into a dichotomous variable of either observed or missing as the outcome for this analysis.

RESULTS

Missing Data

There were similar patterns of missing data observed for both treatment conditions ($\chi^2 = 0.57$, df = 1, p = .45). We concluded that there were no systematic biases for our findings by differential rates or patterns of missing data by treatment condition.

Retention

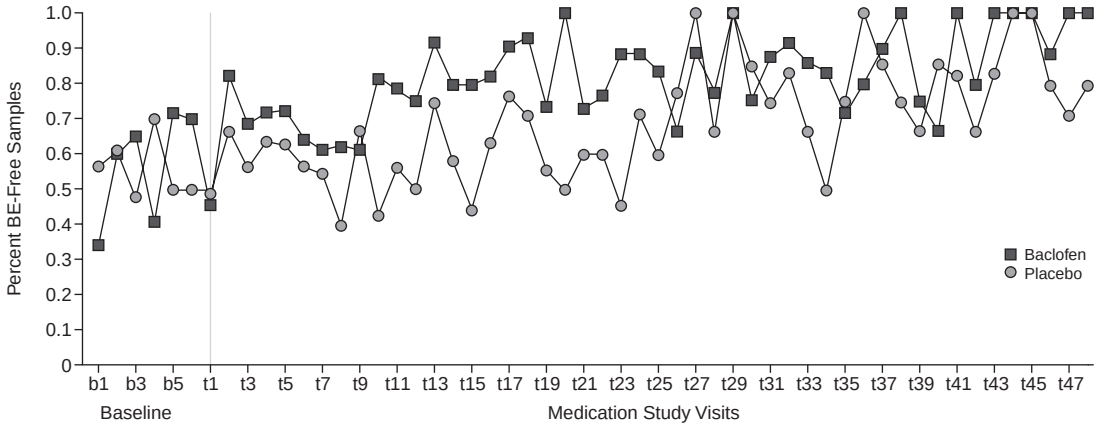
Survival analyses indicated that there were no statistically significant differences as tested by log rank ($\chi^2 = 0.54$, df = 1, p = .46) in retention by assignment to condition (Figure 2). Baclofen-treated subjects were retained in the protocol a mean (SD) of 56.87 (± 43.41) days, whereas those in the placebo condition averaged 48.27 (± 40.57) days. Similar percentages of participants completed the 16-week treatment period in the baclofen (N = 9; 25.7%) and placebo (N = 8; 22.9%) conditions.

Urine Drug Screening Results

Univariate analyses of aggregate variables showed that participants assigned to the baclofen condition performed better than those assigned to placebo, although not at statistically significant levels (Table 2). Post hoc analyses of the joint probability showed baclofen-treated participants were significantly more likely to provide urine samples that were cocaine metabolite–free between weeks 3 to 8 than were participants treated with placebo (t = 5.98, df = 34, p < .001). Figure 3 depicts the favorable performance of the baclofen condition over placebo during the first 8 weeks of the trial using the percentage of benzoylecgonine-free urine samples.

Results of the longitudinal analysis, both GEE and Markov order 1 transition models, evaluating medication effects showed a strongly significant effect for baclofen. In these analyses, the baseline Addiction Severity Index employment composite and reported cannabis use in the 30 days prior to baseline were included as covariates. These baseline variables were not statistically significant predictors in the models and were dropped from the analyses presented. The GEE solution showed a significant effect of baclofen over placebo ($\chi^2 = 5.34$, df = 1, p = .021) in reducing cocaine use as measured using urine drug screening results. The transitional analysis confirmed the GEE solution and identified a strongly significant interaction between baclofen and baseline level of cocaine use ($\chi^2 = 10.63$, df = 1, p = .001). The transitional model also found that the treatment effects increased as the number of benzoylecgonine-positive samples increased over the baseline period (Figure 4). By contrast, those assigned to the placebo condition demonstrated no such association. Placebo-treated participants who provided more benzoylecgonine-positive urine samples during the baseline period showed stepwise increases in the likelihood of providing fewer metabolite-free urine samples during the treatment period. A post hoc strategy to describe the clinical significance of this effect calculated the number of benzoylecgonine-free urine samples during the trial for participants who provided 3 or more samples during baseline that were positive for cocaine metabolite. Participants who met this criterion and who were assigned to the placebo condition (N = 16) averaged 3.38 benzoylecgonine-free urine samples, com-

Figure 3. Percentage of Urine Samples Provided by Participants in Each of the 2 Treatment Conditions That Tested Free of Cocaine Metabolite (Benzoylecgonine[BE]) at Each Point During the Trial[a]



[a]The first 6 points (b1 to b6) represent the percentage of BE-free urine samples by condition during the baseline period. The line through t1 denotes randomization into treatment condition and the initiation of study medication. Points t1 to t48 represent the percentage of BE-free urine samples by condition during the treatment period. The upward drift for both lines over the treatment period represents the effect of attrition on these proportions.

pared with 11.42 samples for those assigned to the baclofen condition (N = 12).

Cocaine Craving

There was no statistically significant difference between participant ratings of cocaine craving for the 24 hours prior to the clinic visit by medication condition as evaluated using GEE.

Adverse Events

Over the course of the trial, there were no clinically significant changes observed in cardiovascular functioning, serology, vital signs, or physical examinations for any study participants. Three serious adverse events occurred during the study, all of which occurred to participants receiving baclofen, and none of which was judged to be related to study medication. All 3 serious adverse events involved a worsening of the participants' cocaine problems; each required overnight hospitalization, and 1 required concomitant treatment for depression. The incidence, by condition, of reported adverse events rated moderate in severity is shown in Table 3. Participants in the baclofen condition were generally more likely to experience headaches, whereas those in the placebo condition were more likely to experience colds and flu, although there were no statistically significant differences between conditions for incidence or percentage of total for these experiences.

Compliance

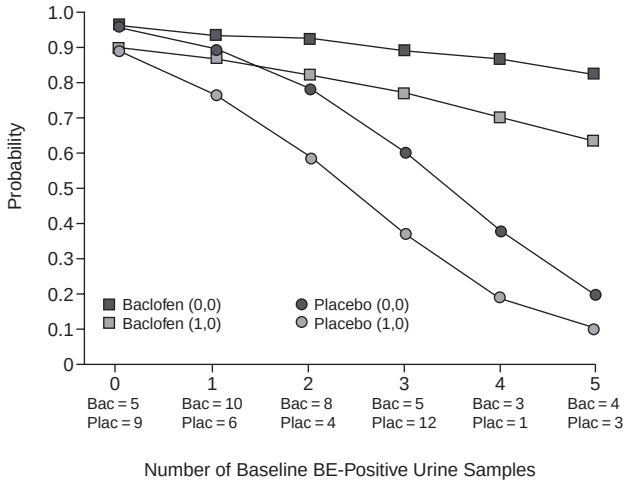
Participants in the placebo condition took a mean of 69.85% (± 22.82%) of their study medication doses. By comparison, participants assigned to receive baclofen took a mean of 72.50% (± 22.82%) of their study medication doses, a nonsignificant difference. Participants were polled as to which medication they believed they received at the beginning of the second study week; a total of 18 (60.0%) of 30 participants assigned to receive baclofen correctly guessed their condition, compared to 10 (62.5%) of 16 participants assigned to receive placebo, a nonsignificant difference.

DISCUSSION

This study tested the effectiveness of baclofen as a pharmacotherapy for cocaine dependence when administered in the context of thrice weekly cognitive behavioral drug counseling. Standard, univariate measures of treatment response using aggregates of urine drug screening results showed no statistically significant differences for the baclofen over the placebo condition, although all indices were in the predicted direction. Post hoc analyses using the joint probability index evaluated during weeks 3 and 8 showed statistically significant differences for baclofen over placebo in reducing cocaine use. Admittedly, this finding provides only a suggestion of a treatment effect. Aggregate indices are particularly sensitive to the effect of attrition, especially in screening trials utilizing relatively small sample sizes. Identification of medication effects is made more difficult beyond 8 weeks in this and other trials of cocaine pharmacotherapies, likely due to reductions in power associated with early termination.

Significant medication effects for baclofen over placebo were detected when using longitudinal models (GEE), including transitional models calculating the tran-

Figure 4. Transitional Probability That a Participant Will Provide a Benzoylecgonine (BE)-Negative Urine Sample Given the Result of the Immediately Previous Urine Sample as a Function of the Number of Urine Tests Provided at Baseline That Were BE-Positive[a]



[a]The numbers of participants by condition that provided each level of BE-positive urine samples during baseline are represented across the top of the figure. No participants provided 6 BE-positive urine samples during baseline; hence, the range was 0–5 BE-positive urine samples. These transitional probabilities depict the effect of successful treatment at any point during the medication period and are represented by the probability of providing 2 consecutive BE-free urine samples ("0,0"—maintaining cocaine abstinence) and of providing a BE-free urine sample following a BE-positive urine sample ("1,0"—initiating cocaine abstinence).

Table 3. Incidence and Percentage of Total of Adverse Events Rated Moderate in Severity by Assignment to Treatment Condition

	Baclofen		Placebo	
Adverse Event	No. of Events	%	No. of Events	%
Headache	32	39.51	13	19.70
Flu/colds	10	12.35	19	28.79
Body aches/pain	12	14.81	11	16.67
Nausea/upper GI	8	9.88	9	13.64
Fatigue	1	1.23	3	4.55
Accidents	4	4.94	3	4.55
Insomnia	1	1.23	3	4.55
Lower GI problems	2	2.47	1	1.52
Toothache	1	1.23	2	3.03
Dizzy, light-headed	3	3.70	0	0
Visual/eye	3	3.70	0	0
Hearing/ear	2	2.47	0	0
Chest pain	1	1.23	1	1.52
Anxiety	0	0	1	1.52
Irritability	1	1.23	0	0

Abbreviation: GI = gastrointestinal.

sitional probabilities of treatment response at different levels of cocaine use observed at baseline. The agreement of these solutions yields confidence in the results that baclofen treatment provided a differential response compared with placebo. The finding that baclofen effects are observed in stepwise fashion with the extent of cocaine use detected at baseline implies that those who have a more chronic and severe form of cocaine dependence are more likely to show a response to baclofen. These individuals engage in consistent exposure to cocaine, which resembles the cocaine exposure frequency delivered in laboratory studies. This similarity in administration may be the theoretical link between study findings and preclinical investigations that show that effects of baclofen are dependent upon elements related to the delivery of cocaine in the experimental paradigms, i.e., dose level and reinforcement schedules.[26] The observation that participants assigned to the placebo condition demonstrated no such effects provided further support for demonstration of medication effects and not artifacts of statistical analyses. Together, these findings provide an exciting suggestion for the role of GABAergic medications and the generally dampening effects for GABA on the reward mechanisms involved during recovery from chronic levels of cocaine dependence.

The GEE solution applied current biostatistical methods, while the application of a transitional probability analysis, complete with calculation of the probability of treatment response at differing levels of cocaine use at baseline, represents a solid contribution to the task of identifying subgroups of patients that might respond positively to medications. The probabilities depicted provide useful information to clinicians who might consider which patients may benefit from treatment with baclofen when administered in the context of cognitive-behavioral group drug counseling. Descriptive information showing reductions in cocaine use for those treated with baclofen who were heavy users of cocaine during the baseline period indicates the clinical relevance of this medication. The findings appear clear: Patients who present for treatment with chronic levels of cocaine use may benefit from using baclofen in the early phases of recovery from cocaine dependence. Those who present for treatment with more episodic patterns of cocaine use would likely respond positively to behavioral drug counseling approaches alone.

Despite 15 years of medication trials, none have demonstrated significant effects as cocaine pharmacotherapies when evaluated using placebo-controlled, double-blind procedures. Hence, outcome measures in cocaine pharmacotherapies must extend beyond absolute abstinence and consider reductions in use as a viable measure of medication performance. Measures of partial response (i.e., reductions in cocaine use) raise questions of how to quantify those reductions in use, while at the same time maintaining an emphasis on clinically meaningful differences. This study used a variety of statistical techniques to more precisely quantify the effects of missing data and baseline performance in evaluating the strength of the signal for baclofen. The preliminary nature of this study

and small sample size preclude determining the clinical significance of the signal measured, a task that remains for an adequately powered replication trial.

A limitation of this study is the small size of the sample used to calculate these transitional probabilities. Probabilities calculated at the extreme high end of cocaine use during baseline are based on small samples due to the low number of participants meeting those criteria. Still, the documented effects for baclofen in doubling or tripling the probability of a positive response to treatment for those with chronic cocaine use at treatment entry when compared to placebo provide compelling empirical support for using the medication in combination with behavioral drug counseling for this subgroup of patients, particularly in the early phase of recovery from cocaine dependence.

Findings from this study also are limited in that they represent a single efficacy trial of baclofen as a cocaine pharmacotherapy. Results may only generalize to that group of cocaine-dependent individuals who are willing to join an intensive outpatient medication research trial. Yet, the data indicate strongly that a larger trial of baclofen is warranted. These medication findings in the subgroup of participants with chronic cocaine use at baseline also correspond with recent findings from a placebo-controlled trial of amantadine,[40] in which participants with higher ratings of cocaine severity at baseline showed significant response to amantadine. Combination strategies that integrate both of these medications may provide new directions for the continuing search for an effective cocaine medication.

Drug names: amantadine (Symmetrel and others), baclofen (Lioresal and others).

REFERENCES

1. Ling W, Shoptaw S. Integration of research in pharmacotherapy for addictive disease: where are we? where are we going? In: Miller NS, Stimmel B. Binghamton NY, eds. The Integration of Pharmacological and Nonpharmacological Treatments in Drug/Alcohol Addictions. The Haworth Press, Inc.; 1997:83–102
2. Self DW, Nestler EJ. Molecular mechanisms of drug reinforcement and addiction. Annu Rev Neurosci 1995;18:463–495
3. Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl) 1999;146: 373–390
4. Kleber HD. Treatment of cocaine abuse: pharmacotherapy. CIBA Foundation Symposium 1992;166:195–200
5. Wise RA. D1-and D2-type contributions to psychomotor sensitization and reward: implications for pharmacological treatment strategies. Clin Neuropharmacol 1995;18:S74–S83
6. Cameron DL, Williams JT. Dopamine D1 receptors facilitate transmitter release. Nature 1993;366:344–347
7. Engberg G, Klingpetersen T, Nissbrandt H. GABA(B) receptor activation alters the firing pattern of dopamine neurons in the rat substantia nigra. Synapse 1993;15:229–238
8. Klitenick MA, DeWitte P, Kalivas PW. Regulation of somatodendritic dopamine release in the ventral tegmental area by opioids and GABA: an in vivo microdialysis study. J Neurosci 1992;12:2623–2632
9. Rick CE, Lacey MG. Rat sustantia nigra pars reticulata neurons are tonically inhibited via GABBA, but not GABAB, receptors in vitro. Brain Res 1994;659:133–137
10. Seutin V, Johnson SW, North RA. Effect of dopamine and baclofen on N-methyl-D-asparate induced burst firing in rat ventral tegmental neurons. Neuroscience 1994;58:201–206
11. Santiago M, Cano J, Westerink BHC. Are bilateral nigrostriatal dopaminergic pathways functionally linked in the rat brain: a microdialysis study in conscious rats. Brain Res 1993; 628:187–192
12. Santiago M, Machado A, Cano J. Regulation of the prefrontal cortical dopamine release by GABAA and GABAB receptor agonists and antagonists. Brain Res 1993;630:8–31
13. Santiago M, Machado A, Cano J. In vivo release of dopamine from rat striatum, substantia nigra and prefrontal cortex: differential modulation by baclofen. Br J Pharmacol 1993;109:814–818
14. Kushner SA, Dewey SL, Kornetsky C. Gamma-vinyl GABA attenuates cocaine-induced lowering of brain stimulation reward thresholds. Psychopharmacology (Berl) 1997;133:383–388
15. Kushner SA, Unterwald EM. Chronic cocaine administration decreases the functional coupling of GABA(B) receptors in the rat ventral tegmental area as measured by baclofen-stimulated 35S-GTPgammaS binding. Life Sci 2001;69:1093–1102
16. Wood PL. Actions of GABAergic agents on dopamine metabolism in the nigrostriatal pathway of the rat. J Pharmacol Exp Ther 1982;222: 674–679
17. Pycock C, Horton R. Evidence for an accumbens-pallidal pathway in the rat and its possible gabaminergic control. Brain Res 1976;110:629–634
18. Cousins MS, Roberts DC, de Wit H. GABA(B) receptors agonists for the treatment of drug addiction: a review of recent findings. Drug Alcohol Depend 2002;65:209–220
19. Morgan AE, Dewey SL. Effects of pharmacologic increases in brain GABA levels on cocaine-induced changes in extra cellular dopamine. Synapse 1998;28:60–65
20. Stromberg MF, Mackler SA, Volpicelli JR, et al. The effect of gamma-vinyl-GABA on the consumption of concurrently available oral cocaine and ethanol in the rat. Pharmacol Biochem Behav 2001;68:291–299
21. Molina PE, Ahmed N, Ajmal M, et al. Co-administration of gamma-vinyl GABA and cocaine: preclinical assessment of safety. Life Sci 1999;65:1175–1182
22. Harding GF, Spencer EL, Wild JM, et al. Field-specific visual-evoked potentials: identifying field defects in vigabatrin-treated children. Neurology 2002;58:1261–1265
23. Roberts DC, Brebner K. GABA modulation of cocaine self-administration. Ann NY Acad Sci 2000;909:145–158
24. Brebner K, Phelan R, Roberts DC. Effect of baclofen on cocaine self-administration in rats reinforced under fixed-ratio 1 progressive-ratio schedules. Psychopharmacology (Berl) 2000;148:314–321
25. Roberts DC, Andrews MM, Vickers GJ. Baclofen attenuates the reinforcing effects of cocaine in rats. Neuropsychopharmacology 1996;14:1–7
26. Campbell UC, Lac ST, Carroll ME. Effects of baclofen on maintenance and reinstatement of intravenous cocaine self-administration in rats. Psychopharmacology (Berl) 1999;143:209–214
27. Ling W, Shoptaw S, Majewska D. Baclofen as a cocaine anti-craving medication: a preliminary clinical study Neuropsychopharmacology 1998;18:403–404
28. McLellan AT, Kushner H, Metzger D. The fifth edition of the Addiction Severity Index. J Subst Abuse Treat 1992;9:199–213
29. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for the DSM-IV (SCID). Washington DC: American Psychiatric Press, 1995
30. Preston KL, Silverman K, Schuster CR, et al. Use of quantitative urinalysis in monitoring cocaine use. NIDA Res Monogr 1997;175: 253–264
31. Ling W, Shoptaw S, Wesson D, et al. Treatment effectiveness score as an outcome measure in clinical trials. NIDA Res Monogr 1997;175: 208–220
32. Gawin FH, Morgan C, Kosten TR, et al. Double-blind evaluation of the effect of acute amantadine on cocaine craving. Psychopharmacology (Berl) 1989;97:402–403
33. Rawson RA, Shoptaw SJ, Obert JL, et al. An intensive outpatient approach for cocaine abuse treatment. The Matrix model. J Subst Abuse Treat 1995;12:117–127
34. Shoptaw SJ, Rawson RA, McCann MJ, et al. The Matrix model of outpatient stimulant abuse treatment: evidence of efficacy. J Addict Dis 1995;13:23–35

35. Shoptaw SJ, Kintaudi PC, Charuvastra C, et al. A screening trial of amantadine as a medication for cocaine dependence. Drug Alcohol Depend 2002;66:217–224
36. Guilford JP, Fruchter B. Fundamental Statistics in Psychology and Education, 6th ed. New York, NY: McGraw-Hill; 1978:159–163
37. Liang KY, Zeger SL. On the use of concordant pairs in matched case-controlled studies. Biometrics 1988;44:1145–1156
38. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics 1988; 44:1049–1060
39. Stram DO, Wei LJ, Ware JH. Analysis of repeated ordered categorical outcomes with possibly missing observations and time dependent covariates. J Am Stat Assoc 1988;83:631–637
40. Kampman KM, Volpicelli JR, Alterman AI, et al. Amantadine in the treatment of cocaine-dependent patients with severe withdrawal symptoms. Am J Psychiatry 2000;157:2052–2054