Original Investigation

Topiramate for the Treatment of Cocaine Addiction
A Randomized Clinical Trial

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IMPORTANCE No medication has been established as an efficacious treatment for cocaine dependence. We hypothesized that dual modulation of the mesocorticolimbic dopamine system by topiramate—a glutamate receptor antagonist and γ-aminobutyric acid receptor agonist—would result in efficacious treatment for cocaine dependence compared with placebo.

OBJECTIVE To determine the efficacy of topiramate vs placebo as a treatment for cocaine dependence.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, randomized, placebo-controlled, 12-week trial of 142 cocaine-dependent adults in clinical research facilities at the University of Virginia between November 22, 2005, and July 25, 2011.

INTERVENTIONS Topiramate (n = 71) or placebo (n = 71) in escalating doses from 50 mg/d to the target maintenance dose of 300 mg/d in weeks 6 to 12, combined with weekly cognitive-behavioral treatment.

MAIN OUTCOMES AND MEASURES For the efficacy period, weeks 6 to 12, the primary outcome was the weekly difference from baseline in the proportion of cocaine nonuse days; the secondary outcome was urinary cocaine-free weeks, and exploratory outcomes included craving and self- and observer-rated global functioning on the Clinical Global Impression scales.

RESULTS Using an intent-to-treat analysis, topiramate was more efficacious than placebo at increasing the weekly proportion of cocaine nonuse days, irrespective of whether missing data were not or were imputed conservatively to the baseline value (13.3% vs 5.3%, 95% CI for the estimated mean difference, 1.4%-14.6%, $P = .02$ or 8.9% vs 3.7%, 95% CI for the estimated mean difference, 0.2%-10.1%, $P = .04$, respectively). Topiramate also was associated, significantly more than placebo, with increasing the likelihood of urinary cocaine-free weeks (16.6% vs 5.8%; odds ratio, 3.21; 95% CI, 1.24-8.32; $P = .02$), as well as decreasing craving and improving observer-rated global functioning (all $P < .05$).

CONCLUSIONS AND RELEVANCE Topiramate is more efficacious than placebo at increasing the mean weekly proportion of cocaine nonuse days and associated measures of clinical improvement among cocaine-dependent individuals.

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No medication has been established as an efficacious treatment for cocaine dependence, although there are 13.2 to 19.7 million cocaine users worldwide among adults aged 15 to 64 years (0.3%-0.4%).[1]

In animals, medications that antagonize the effects of excitatory amino acids or facilitate γ-aminobutyric acid (GABA) action in the mesocorticolimbic dopamine system can reduce cocaine's reinforcing effects[2-5] that are associated with its abuse liability. An intact GABA efferent system from the nucleus accumbens, corpus striatum, and ventral pallidum to cortical structures[6,7] is important for the expression of cocaine reinforcement.[8] Excitatory amino acids, including glutamate, are associated with the acquisition of place preference conditioning and other reinforcing effects of cocaine.[9-11] Furthermore, the enhancement of GABA pathways or the inhibition of corticofugal glutaminergic pathways in the mesocorticolimbic dopamine system can decrease extracellular dopamine release,[12,13] the principal neurotransmitter that mediates cocaine reinforcement.

Chronic cocaine administration impairs GABA's neuronal function relative to that of excitatory amino acids in the mesocorticolimbic dopamine system.[14,15] Thus, a medication that augments GABA function could evince a therapeutic response in treating cocaine dependence. For instance, studies in animals show that medications potentiating the action of GABA in the central nervous system block cocaine-induced dopamine release,[13,16,17] raise brain stimulation reward thresholds,[18] diminish the development and expression of cocaine-associated cues,[16] and inhibit the acquisition and the expression of cocaine-induced conditioned place preference.[19,20] Consistent with this hypothesis, a medication that decreases α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate glutamate receptor function could be an efficacious treatment for cocaine dependence. Thus, AMPA glutamate antagonists have been shown to decrease the locomotor effects of cocaine and other psychostimulants,[21,22] reduce cue-induced reinstatement of cocaine taking,[23,24] and decrease extracellular dopamine release in the mesocorticolimbic dopamine system.[25,26]

We therefore hypothesized that topiramate, a fructopyranose derivative that enhances GABA function[27-30] and inhibits AMPA and kainate glutamate pathways,[31,32] would modulate extracellular dopamine release in the mesocorticolimbic dopamine system and be an efficacious treatment for cocaine dependence.

In humans, our hypothesis has been supported indirectly from our demonstration that topiramate is an efficacious treatment for alcohol dependence[33,34] and can reduce relapse in abstinent methamphetamine addicts.[35] More directly, Kampman and colleagues[36] showed in a small (n = 40) placebo-controlled pilot study that topiramate reduced cocaine use after dose titration to 200 mg/d following 8 weeks of treatment. Finally, a recent laboratory study in humans by Johnson and colleagues[37] showed that topiramate (200 mg/d) reduced cocaine craving and decreased the monetary value of experimenter-administered high-dose cocaine (ie, 0.65 mg/kg intravenously), effects suggesting that topiramate can suppress cocaine's reinforcing effects and abuse liability.

To validate our hypothesis and impressions from previous studies in animals and humans, we conducted a randomized, double-blind trial to determine whether topiramate (up to 300 mg/d) would be more efficacious than placebo in treating cocaine dependence.

Methods

Participating Sites

Volunteers were recruited at the University of Virginia (Charlottesville and Richmond sites), where the trial was performed between November 22, 2005, and July 25, 2011. The University of Virginia's institutional review board approved the research protocol, and all enrolled participants provided written informed consent.

Study Design

In a double-blind clinical trial of daily oral topiramate, 142 cocaine-dependent individuals aged 18 years or older, who were diagnosed according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*,[38] were allocated at random into 2 treatment groups: topiramate (n = 71) and placebo (n = 71).

After providing written informed consent, participants were screened to determine eligibility based on diagnosis and health checks. This screening process included 2 weeks of baseline assessment to obtain an accurate recent history of self-reported cocaine use corroborated by urine drug screens. To be randomized into double-blind treatment, participants had to meet the criterion on recent history of cocaine use and eligibility criteria based on diagnosis and health checks. While alcohol-dependent individuals were included in this study, we excluded those with significant withdrawal symptoms that required medical detoxification (see the author material file [http://medschool.umaryland.edu/psychiatry/docs/JAMA_supplement.pdf] for all inclusion and exclusion criteria and additional details of the study design). To meet the criterion on recent history of cocaine use, participants had to provide 1 or more cocaine-positive urine specimens (>300 ng/mL) during screening and 4 or more urine specimens during the 2-week baseline screening period. A diagnosis of cocaine dependence was established using the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[39] All participants who met eligibility criteria for health checks and achieved the criterion on recent history of self-reported cocaine use were allocated at random to treatment.

Study medication was randomized in a 1:1 ratio of daily oral topiramate or matched placebo. Randomization was stratified to balance participants between groups on age, sex, and frequency of cocaine use (>18 vs ≤18 days' use in the past 30 days according to self-report, urine sample, or both) before randomization. After randomization, double-blind treatment medication was provided twice daily (ie, morning and night) for 12 weeks (ie, weeks 1-12) using a double-dummy procedure that ensured that placebo and topiramate recipients received the same number of capsules. At week 1, oral topiramate or the equivalent number of matching placebo capsules

Table 1. Topiramate Dosing Schedule[a]

Week[b]	Morning Dose	Nighttime Dose	Total Daily Dose, mg
0-1	1 × 25-mg capsule	1 × 25-mg capsule	50
1-2	2 × 25-mg capsules	2 × 25-mg capsules	100
2-3	1 × 25-mg capsule + 1 × 50-mg capsule	1 × 25-mg capsule + 1 × 50-mg capsule	150
3-4	1 × 100-mg capsule	1 × 100-mg capsule	200
4-5	1 × 100-mg capsule + 1 × 25-mg capsule	1 × 100-mg capsule + 1 × 25-mg capsule	250
5-6	1 × 100-mg capsule + 2 × 25-mg capsules	1 × 100-mg capsule + 2 × 25-mg capsules	300
6-12	1 × 100-mg capsule + 2 × 25-mg capsules	1 × 100-mg capsule + 2 × 25-mg capsules	300

[a] The placebo and topiramate groups received the same number of capsules; placebo capsules were inactive.

[b] Further explanation is given in the Study Design subsection of the Methods section and in the legend to Figure 2.

was initiated from 50 mg/d and escalated during the first 6 weeks until the ceiling dose of 300 mg/d or the participant's maximum tolerated dose was achieved (see schedule in **Table 1**). During weeks 6 to 12, the maximum achieved dose of topiramate or matching placebo was maintained. If, however, a participant was intolerant of adverse events, the investigator could reduce the daily dose to obtain a minimum topiramate or matching placebo maintenance dose of 200 mg/d. Medication compliance was measured by pill count.

During the 12-week double-blind treatment period, participants had to attend the clinic thrice weekly to provide information on self-reported cocaine use; have their urine tested for cocaine's primary metabolite, benzoylecgonine; and report adverse events and concomitant medication use. Weekly measurements of cocaine craving on the Brief Substance Craving Scale[40] and self- and observer-based assessments of global functioning with the Clinical Global Impression scales[41,42] also were collected. In addition, health checks were performed at scheduled intervals, including urine pregnancy screens every fortnight to ensure that women were not pregnant.

During the 12-week double-blind treatment phase, all participants received, as an adjunct to the medication, weekly cognitive-behavioral treatment, a manual-driven, psychosocial treatment shown to be effective at aiding cocaine abstinence[43] and study participation in pharmacotherapy trials.[44]

Data Analysis

Primary Outcome Variable

The primary outcome variable was the weekly difference from baseline in the proportion of cocaine nonuse days, using the algorithm developed by Elkashef et al,[45] during weeks 6 to 12, the period from when the target topiramate dose or its matching placebo was achieved to the study's end. In their algorithm, they modified the rules from Preston et al[46] by combining self-reported use, urine benzoylecgonine, and the estimated concordance rate between them for each participant to determine whether he or she used cocaine for every study day (see author material file for details of the quantification of benzoylecgonine and the "Guidance Document for Scoring Use and Non-Use Days for Topiramate Trial of Cocaine Dependence," the latter provided courtesy of Shou-Hua Li, PhD, at the National Institute on Drug Abuse). Urine samples were collected thrice weekly.

Secondary Outcome Variable

Urine samples were collected thrice weekly for determining the benzoylecgonine level. The secondary outcome variable was urinary cocaine-free weeks during weeks 6 to 12. One urinary cocaine-free week was defined as when a participant provided 3 urine samples free of benzoylecgonine in 1 week. Those who tested positive on any visit during a week or missed 1 or more visits in any study week were determined to be positive for benzoylecgonine. Because all missing urine samples were coded to the worst possible outcome (ie, as being positive for the cocaine metabolite), we not only accounted for the total amount of possible urine samples that could be collected (ie, there were no missing values) but also derived a conservative estimate of the amount of urinary cocaine-free weeks.

Exploratory Outcome Variables

All exploratory outcomes were analyzed during the predetermined efficacy period from weeks 6 to 12.

Because craving has multidimensional components,[47] we used 2 craving scales that had been well validated in previous pharmacotherapy trials for cocaine dependence[48] to broaden the dimensionality of its assessment. These craving scales included (1) 2 well-validated subscales of the Cocaine Selective Severity Assessment scale (scores 0-7), which measure the highest intensity of craving and the frequency of the urge to use cocaine in the past 24 hours[49] and have been associated with predicting continued abstinence in treatment,[47] and (2) the Brief Substance Craving Scale (scores 1-5), a self-administered assessment that asks the participant to rate his or her craving for cocaine. The Brief Substance Craving Scale used for this study was a modification of the State of Feelings and Cravings Questionnaire.[40]

Global functioning was assessed on the Clinical Global Impression-Observer and Clinical Global Impression-Self scales. The Clinical Global Impression-Observer scale required the clinician or nurse practitioner to rate the global severity of the participant's cocaine dependence symptoms and the improvement of those symptoms since the beginning of the study. The severity of the participant's cocaine dependence was rated according to 8 specific problem areas often associated with cocaine dependence. The global severity of, as well as global improvement in, cocaine dependence was rated.[41,42] The Clinical Global Impression-Self scale, a self-administered assess-

ment, asked the participant to rate the global severity of his or her cocaine dependence symptoms and the improvement of those symptoms since the beginning of the study.[41,42]

Data Quality

We managed the data according to the Food and Drug Administration guidelines of good clinical practice[50] (see the author material file for additional details of data quality).

Statistical Analysis

All data were analyzed using the intent-to-treat principle, whereby all participants allocated at random to treatment were included in the statistical analyses. For the primary outcome variable, a mixed-effects linear regression model was used to assess the treatment effect, the time effect, and the interaction effect between them. The statistical model, which included random intercept and slope (for temporal trend), was adjusted for participants' weekly mean proportion of cocaine nonuse days before randomization (ie, during the 2-week baseline screening period using the algorithm by Elkashef et al[45]), age at onset of cocaine use, sex, race, and frequency of self-reported cocaine use in the 30 days before informed consent as covariates. To account for missing data during the present study, we conducted a sensitivity analysis whereby we imputed data for all dropouts as relapse to each participant's baseline measure (ie, data on weekly mean proportion of cocaine nonuse days during the 2-week baseline screening period) to provide a conservative estimate for the difference in treatment effect between topiramate and placebo. We therefore conducted analyses for data with and without imputing missing data for dropouts. Cohen's effect size was computed for the primary outcome variable to provide the estimated magnitude of the treatment effect.[51] Effect sizes of 0.2, 0.5, and 0.8 represent small, medium, and large effects, respectively (see the author material file for complete details of the statistical analysis for all outcome measures, handling of missing data, and power analysis).

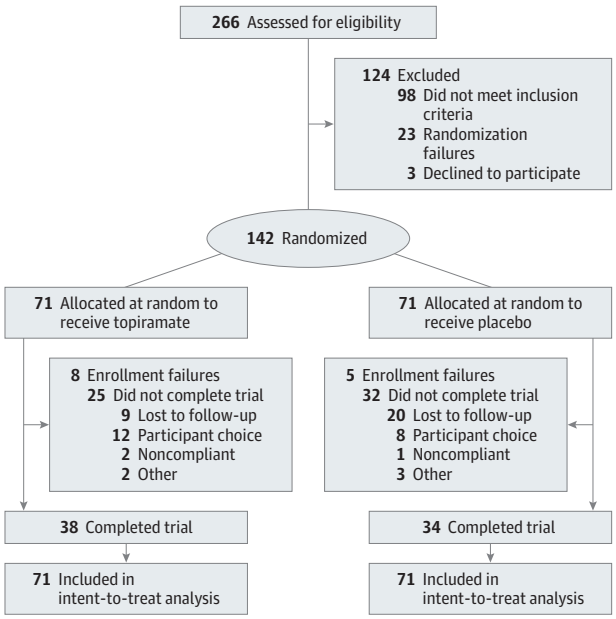
Results

Participants

Of 266 volunteers screened, 124 (46.6%) were ineligible, and 142 were allocated at random to receive either topiramate or placebo. Of the 142 participants, 72.5% were male and 27.5% were female, and 28.9% were white, 70.4% were black, and 0.7% were Asian. Thirteen of the 142 participants failed enrollment (8 and 5 in the topiramate and placebo groups, respectively)—that is, they were allocated at random to treatment but did not return to the clinic for the first double-blind visit. Nevertheless, all 142 participants allocated to treatment were included in the intent-to-treat analysis. The disposition of the participants during the trial is presented in **Figure 1**.

The topiramate and placebo groups were well matched demographically (**Table 2**). No statistically significant difference existed between them in the mean (SD) number of days of self-reported cocaine use during the 30 days before informed consent—13.3 (7.7) and 12.3 (7.9), respectively.

Figure 1. Trial Profile



Disposition of the participants during the trial.

Study Retention

Adjusting for the 13 who failed enrollment, 72 of the 129 participants who received 1 or more weeks of double-blind treatment completed the 12-week trial. Of these, 38 were topiramate recipients and 34 had received placebo, with no significant difference between the groups in time to dropout ($P = .40$, log-rank test) or number of missed visits (mean [SEM], 16.0 [1.5] for topiramate recipients and 17.6 [1.5] for placebo recipients; $P = .45$, t test). At week 6, the retention rates were 77.8% for topiramate recipients and 74.2% for placebo recipients; this decreased to 63.5% and 53.0%, respectively, by the end of week 11. Three participants did not return for the termination visit at week 12. Figure 1 presents the reasons for dropout.

Compliance

Medication compliance rate was the total dose (in milligrams) dispensed minus the total dose returned divided by the recommended dose, multiplied by 100. The mean (SD) compliance rate was 57.6% (11.4%) and 60.4% (9.3%) for the topiramate and placebo groups, respectively, with no significant difference between the groups.

Primary Outcome Variable

For the weekly mean proportion of cocaine nonuse days during weeks 6 to 12, there was a significant effect of topiramate vs placebo, irrespective of whether missing data were not (13.3% vs 5.3%; 95% CI, 1.4%-14.6%; effect size, 0.48; $F = 5.66$; $P = .02$) or were imputed to the baseline value (8.9% vs 3.7%; 95% CI, 0.2%-10.1%; effect size, 0.35; $F = 4.15$; $P = .04$). **Figure 2** shows the effect of topiramate vs placebo during the entire trial period.

Table 2. Baseline Demographics and Drug Use Histories of Cocaine-Dependent Participants, by Treatment Group[a]

Characteristic	Topiramate (n = 71)	Placebo (n = 71)	Total (N = 142)
Age, mean (SD), y	43.6 (8.0)	43.8 (8.3)	43.7 (8.1)
Body mass index, mean (SD)			
Male	28.7 (6.4)	25.6 (5.2)	27.6 (5.8)
Female	27.9 (6.6)	32.7 (10.0)	30.3 (8.3)
Sex			
Male	51 (71.8)	52 (73.2)	103 (72.5)
Female	20 (28.2)	19 (26.8)	39 (27.5)
Race or ethnicity			
White	24 (33.8)	17 (23.9)	41 (28.9)
Black	46 (64.8)	54 (76.1)	100 (70.4)
Asian	1 (1.4)	0	1 (0.7)
Employment			
Full time	42 (59.2)	44 (62.0)	86 (60.6)
Part time	17 (23.9)	15 (21.1)	32 (22.5)
Retired or disabled	3 (4.2)	2 (2.8)	5 (3.5)
Unemployed	9 (12.7)	9 (12.7)	18 (12.7)
Other	0	1 (1.4)	1 (0.7)
Marital status			
Married or cohabiting	33 (46.5)	45 (63.4)	78 (54.9)
Widowed, separated, or divorced	17 (23.9)	16 (22.5)	33 (23.2)
Never married	19 (26.8)	9 (12.7)	28 (19.7)
Refused to disclose	2 (2.8)	1 (1.4)	3 (2.1)
Social class[b]			
1-3	12 (16.9)	18 (25.4)	30 (21.1)
4-6	46 (64.8)	45 (63.4)	91 (64.1)
7-9	13 (18.3)	7 (9.9)	20 (14.1)
Refused to disclose	0	1 (1.4)	1 (0.7)
Years of education, mean (SD)	12.6 (2.0)	13.2 (2.3)	12.9 (2.1)
Self-reported days of alcohol use in the past 30 d before baseline, mean (SD)	7.2 (8.9)	7.0 (8.3)	7.1 (8.6)
Self-reported days of cocaine use in the past 30 d before baseline, mean (SD)	13.3 (7.7)	12.3 (7.9)	12.8 (7.8)
Lifetime years of cocaine use, mean (SD)	16.0 (9.0)	16.2 (10.3)	16.1 (9.6)
No. of lifetime drug abuse treatments before baseline, mean (SD)	1.8 (2.9)	1.6 (2.1)	1.7 (2.5)
US dollars spent on drugs in the past 30 d before baseline, mean (SD)	861.9 (823.3)	764.4 (1090.4)	813.1 (963.9)
Route of cocaine administration[c]			
Oral	1 (1.4)	1 (1.4)	2 (1.4)
Nasal	13 (18.3)	8 (11.3)	21 (14.8)
Smoking	59 (83.1)	64 (90.1)	123 (86.6)
Injection	0	0	0

[a] Values are presented as number (percentage) unless otherwise indicated. No significant differences existed for any variable when the topiramate and placebo groups were compared (all $P > .05$).

[b] Defined by Hollingshead and Redlich.[52]

[c] A few participants used both the nasal and smoking methods.

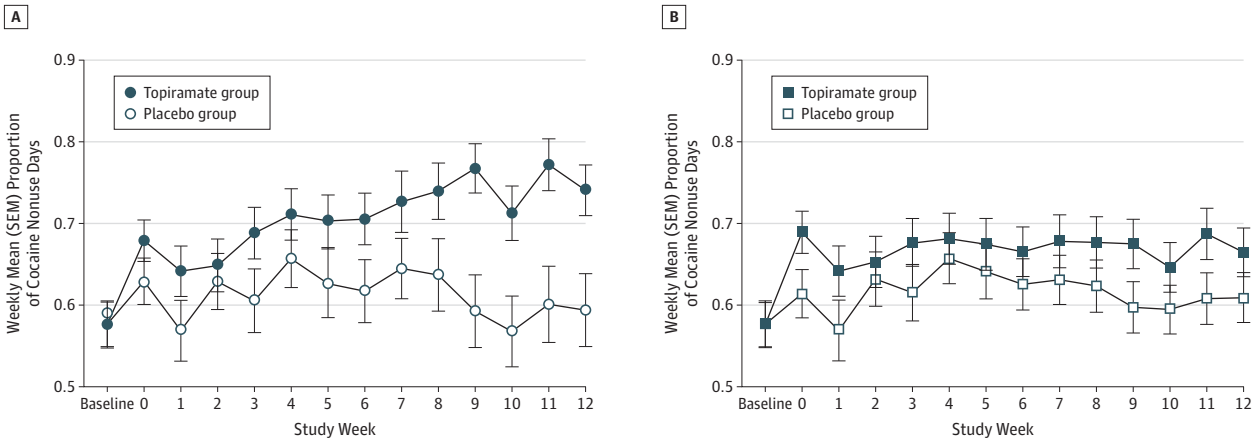
Secondary Outcome Variable

For the urinary cocaine-free weeks during weeks 6 to 12, those who received topiramate compared with placebo had a significantly greater likelihood of achieving urinary cocaine-free weeks (16.6% vs 5.8%; odds ratio [OR], 3.21; 95% CI, 1.24-8.32; $F = 5.77$; $P = .02$). Interestingly, when the results were expanded as a sensitivity test to include study weeks 1 to 12, topiramate was still associated, significantly more than placebo, with an increasing likelihood of urinary cocaine-free weeks (13.5% vs 6.7%; OR, 2.17; 95% CI, 1.00-4.71; $P = .049$).

Exploratory Outcome Variables

For the 2 craving subscales of the Cocaine Selective Severity Assessment scale, the estimated proportions of topiramate vs placebo were 0.573 vs 0.402 (OR, 2.00; 95% CI, 1.01-3.97; $P = .048$) for having "reportedly no desire at all for cocaine in the last 24 hours"; 0.572 vs 0.379 (OR, 2.19; 95% CI, 1.08-4.42; $P = .03$) for having "reportedly no urge at all to use cocaine in the last 24 hours"; and 0.553 vs 0.364 (OR, 2.16; 95% CI, 1.08-4.34; $P = .03$) for having "reportedly no desire and no urge at all for cocaine in the last 24 hours."

Figure 2. Weekly Mean Proportion of Cocaine Nonuse Days From Baseline Through Study Week 12



Each symbol represents the mean proportion of cocaine nonuse days for each study week, and the error bars indicate standard error (SEM). Weekly mean proportion of cocaine nonuse days was analyzed (A) without imputing missing data and (B) imputing missing data using baseline values. Mean (SEM) values for the weekly proportion of cocaine nonuse days at baseline (ie, mean cocaine use during the 2-week baseline period) for the 2 groups receiving topiramate and placebo were 0.5775 (0.0294) and 0.5665 (0.0302), respectively. Participants were allocated to treatment groups at the end of the 2-week baseline period. Study medication was provided at week 0 and, therefore, week 1 contains those individuals who had received 1 or more weeks of double-blind treatment.

For the craving subscales of the Brief Substance Craving Scale, the estimated proportions of topiramate vs placebo were 0.499 vs 0.300 (OR, 2.33; 95% CI, 1.15-4.71; $P = .02$) for having "reportedly no craving at all" in terms of the intensity, frequency, and duration of craving in the past 24 hours and 0.501 vs 0.271 (OR, 2.70; 95% CI, 1.38-5.29; $P = .004$) for having "reportedly no craving at all" in the intensity of craving on the worst day.

For the Clinical Global Impression-Observer scale, the estimated proportions of topiramate vs placebo were 0.374 vs 0.161 (OR, 3.11; 95% CI, 1.49-6.52; $P = .003$) for having "reportedly no symptoms or borderline symptoms" in the global severity of cocaine dependence and 0.754 vs 0.561 (OR, 2.40; 95% CI, 1.26-4.58; $P = .01$) for being "reportedly very much improved or much improved" in the global improvement of cocaine dependence. Topiramate compared with placebo also was associated with a significant reduction in the total scores of the severity of participants' cocaine dependence (estimated mean difference, -1.74; 95% CI, -3.12 to -0.35; $P = .02$).

For the Clinical Global Impression-Self scale, the estimated proportions of topiramate vs placebo were 0.502 vs 0.310 (OR, 2.25; 95% CI, 1.05-4.83; $P = .04$) for having "reportedly no symptoms or borderline symptoms" in the global severity of cocaine dependence and 0.704 vs 0.550 (OR, 1.95; 95% CI, 0.91-4.17; $P = .09$) for being "reportedly very much improved or much improved" in the global improvement of cocaine dependence.

Safety

Sixty topiramate recipients (84.5%) and 57 placebo recipients (80.3%) experienced adverse events during the trial ($P = .66$, Fisher exact test). The 6 most commonly reported adverse events with 1 or more occurrences in topiramate and placebo recipients were decreased weight (63.5% and 49.3%, respectively, $P = .13$), fatigue (45.1% and 35.2%, $P = .30$), headache (38.0% and 38.0%, $P > .99$), paresthesia (50.7% and 21.1%, $P < .001$), taste perversion (42.3% and 23.9%, $P = .03$), and diarrhea (33.8% and 25.4%, $P = .36$). Difficulty with concentration also was significantly different between the treatment groups (26.8% for topiramate and 11.3% for placebo, $P = .03$). No serious adverse events were reported, no pregnancy test in women was positive, and no deaths occurred.

Discussion

Topiramate was significantly more efficacious than placebo at achieving the primary outcome during the efficacy period of increasing the mean weekly proportion of cocaine nonuse days, even when missing data were imputed to the baseline value, a conservative method to determine the robustness of the data.

Topiramate also was significantly more efficacious than placebo at achieving the secondary outcome during the efficacy period of increasing the likelihood of urinary cocaine-free weeks (ie, with urine samples free from cocaine's primary metabolite, benzoylecgonine). Furthermore, topiramate compared with placebo was significantly associated with reductions in the intensity and frequency of craving in the past 24 hours as well as improvements in observer-rated global functioning during the same period.

Taken together, it is reasonable to propose that topiramate treatment was associated with a clinically meaningful improvement in the severity of cocaine dependence. Because no medication with which to compare our findings directly has been approved for the treatment of cocaine dependence, we propose that our observations are relevant clinically, since topiramate's effect size of 0.48 to promote nonuse of cocaine exceeds that of other medicines, such as naltrexone (0.12) or acamprosate (0.36),[53] which have been approved by the Food

and Drug Administration to promote abstinence in another addictive disorder, alcohol dependence.

One mechanistic explanation for topiramate's therapeutic effect to increase cocaine abstinence could be its apparent ability to decrease craving. While the craving reductions could have been the consequence rather than the cause of increased cocaine abstinence, supporting experimental evidence from a laboratory study in humans showed that topiramate compared with placebo pretreatment was associated with a significant reduction in craving, reinforcement, and the abuse liability of self-administered cocaine.[37] Notably, however, the relationship between craving and cocaine consumption is not necessarily linear[54-56]; it can vary depending on the timing or context in which craving occurs,[47] or both. Cocaine consumption can take place in the absence of craving,[57] and other mechanisms not measured directly in the present study might be related to topiramate's therapeutic effect in treating cocaine dependence.

While difficulties in concentration were reported more often among topiramate recipients compared with placebo recipients, these were generally transient and did not interfere with normal daily functioning. Despite previously reported concerns regarding topiramate's potential to impair cognition,[58,59] slow dose escalation during several weeks appears to reduce the frequency and intensity of these cognitive difficulties.[60,61]

In general, we had 2 caveats to our findings. First, as is common with pharmacotherapy studies in stimulant users, attrition can be a notable problem.[62] Although our retention rates were on target with study projections and compared favorably with contemporary outpatient clinical trials in stimulant dependence[35,63,64] (see the author material file for examples), additional study compliance-enhancing techniques could have proved useful. As a suggestion for future research, which would require empirical validation, stimulant pharmacotherapy trials could include an additional or alternative brief psychosocial adjunct specifically designed to promote both study and medication compliance,[65] which has been shown to achieve medication compliance rates as high as 94.5%.[66] In addition, or as an alternative, an increase in compensation—which in our study was modest but typical of pharmacotherapy-focused trials in the field—including a more pronounced escalating level of compensation for increasing durations of participation, with a sizable completion bonus in a contingency management-type protocol,[67] could reduce dropout. Second, topiramate's therapeutic effects appeared to increase during the trial. Hence, a lengthier period of assessment would be needed to optimize topiramate's treatment effect. Indeed, it would be reasonable to propose that an important next step to extend our findings in the present shorter-term study of topiramate's efficacy in treating cocaine dependence would be to perform a longer-term study of 6 months or more, thereby enabling determination of the sustainability of topiramate's therapeutic effect in treating cocaine dependence. Such a phase III–type study, especially if industry sponsored, could be powered appropriately to test even more conservative outcomes to foster Food and Drug Administration approval. Including a follow-up period of 6 to 12 months in future studies would enable determination of whether, and for how long, the therapeutic effects of topiramate treatment in cocaine-dependent individuals can be sustained after medication discontinuation.

We have proposed that both a personalized approach to optimize the adverse events vs efficacy profile of topiramate to treat cocaine dependence and performing studies in populations comorbid for alcohol or other substance dependence could be fruitful areas for future research (see the author material file for additional comments on future trials).

In conclusion, before the present study, no medication had been established as an efficacious treatment for cocaine dependence despite more than 3 decades of intense scientific effort. Building on evidence from a previous pilot study[36] and our recent laboratory study in humans,[37] we suggest that the present data, at the very least, provide an important building block from which to establish topiramate as an efficacious medicinal treatment for cocaine dependence.

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Study concept and design: Johnson, Ait-Daoud.
Acquisition of data: Johnson, Ait-Daoud, Penberthy, Javors.
Analysis and interpretation of data: Johnson, Ait-Daoud, Wang, Penberthy, Seneviratne, Liu.
Drafting of the manuscript: Johnson, Wang, Penberthy, Javors, Liu.
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