ORIGINAL ARTICLE

A Multisite, Double-blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Vigabatrin for Treating Cocaine Dependence

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Importance: Cocaine dependence is a significant public health problem, yet no validated pharmacological treatment exists. The potent γ-aminobutyric acid (GABA) ergic medication vigabatrin has previously been shown to be effective in a double-blind single-site study conducted in Mexico.

Objective: To evaluate the safety and efficacy of vigabatrin for the treatment of cocaine dependence in a US sample.

Design and Setting: Multisite, randomized, double-blind, placebo-controlled, 12-week clinical trial with follow-up visits at weeks 13, 16, 20, and 24 in 11 US sites.

Participants: In total, 186 treatment-seeking participants with cocaine dependence (mean age, 45 years). Approximately 67% were male, and about 60% were of African American race/ethnicity.

Interventions: Participants received twice-daily doses of vigabatrin (total dosage, 3.0 g/d) or matched placebo, plus weekly computerized cognitive behavioral therapy and biweekly individual counseling for 13 weeks. Contingency management encouraged the provision of urine samples.

Main Outcomes and Measures: The primary outcome measure was the proportion of participants with cocaine abstinence during the last 2 weeks of the 12-week treatment phase as assessed by self-reports and quantitative urine drug screens. The weekly fraction of cocaine use days and the number of drug-free urine samples during weeks 1 through 13 were key secondary measures.

Results: No significant differences were observed between the vigabatrin group and the placebo group on the primary outcome measure ($P = .67$), key secondary measures ($P > .99$), or other outcome measures. However, while pill counts and self-reports indicated that more than 66% of all participants (and >63% of the vigabatrin group) took more than 70% of their medication, post hoc vigabatrin urine concentration levels suggested that approximately 40% to 60% of patients taking vigabatrin may not have been adherent. This lack of adherence may have obscured any evidence of vigabatrin efficacy. No visual acuity or visual field deterioration occurred in any of the participants.

Conclusions and Relevance: No protocol-defined differences in efficacy between vigabatrin treatment and placebo were detected for any outcome variable. This may have been due to medication nonadherence or, alternatively, due to the weak efficacy of vigabatrin.

Trial Registration: clinicaltrials.gov Identifier: NCT00611130

JAMA Psychiatry. 2013;70(6):630-637.
Published online April 10, 2013.
doi:10.1001/jamapsychiatry.2013.872

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COCAINE ADDICTION IS A SERIOUS public health concern, with 699 000 patients estimated to have received treatment in 2010 in the United States.[1] It is associated with significant medical, social, and economic consequences and is difficult to treat using traditional psychosocial therapies. No pharmacotherapy has yet been approved by the Food and Drug Administration. The addictive properties of cocaine are related to its ability to increase the levels of dopamine, a neurotransmitter associated with sensations of pleasure and reward.[2,3] Therefore, blocking cocaine-induced increases in dopamine represents a valid pharmaceutical approach to treating cocaine addiction.

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γ-Aminobutyric acid (GABA) suppresses both the firing rate[4,5] and the amount of dopamine released from neurons in the ventral

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tegmental area and nucleus accumbens.[6] Consequently, medications that irreversibly inhibit GABA-transaminase, the enzyme responsible for the catabolism of GABA, and that serve to enhance GABAergic transmission are candidates for the treatment of cocaine addiction.[7,8]

One such medication is vigabatrin, which is an epilepsy treatment marketed as monotherapy for infantile spasms, as well as an adjunctive therapy for adults with refractory complex partial seizures with inadequate response to alternative treatments.[9] Unfortunately, vigabatrin use is associated with visual field defects,[10-14] the incidence of which markedly increases following cumulative doses in excess of 2 kg, with an apparent plateau effect at approximately 3 kg.[15] However, vigabatrin could be used with cumulative doses well below 2 kg to initiate and maintain an initial period of abstinence in patients with cocaine dependence. Three clinical trials[16-18] of vigabatrin in patients with stimulant addiction have been reported; 2 were open-label studies,[17,18] and 1 was a double-blind placebo-controlled study,[16] all completed by Brodie and colleagues in Mexico. The placebo-controlled trial[16] was conducted among treatment-seeking Mexicans from a single parole center who were actively using cocaine and had a history of cocaine dependence. Participants were randomly assigned to 3.0 g/d of vigabatrin (n=50) or matched placebo (n=53) in a 9-week double-blind trial with a 4-week follow-up assessment. The primary outcome was full abstinence for the last 3 weeks of treatment (weeks 6-9), which was achieved in 14 vigabatrin participants (28.0%) compared with 4 placebo group participants (7.5%) (P=.009), with abstinence maintained through the 4-week follow-up assessment by 12 (of 14) vigabatrin group participants (85.7%) compared with 2 (of 4) placebo group participants (50.0%) (P=.002). With respect to safety, no participants reported any visual disturbance throughout their open-label exposure to vigabatrin,[17] and no changes in vital signs or objective measures of visual fields or visual acuity were found with open-label exposure up to 9 weeks.[18,19] In the placebo-controlled trial,[16] no statistically significant differences were observed between the vigabatrin group and the placebo group for adverse events (AEs), visual abnormalities, or medical conditions.

The present 12-week clinical trial, which was completed in the United States and used a randomized, double-blind, placebo-controlled design, evaluated the safety and efficacy of vigabatrin for the treatment of cocaine dependence. It was predicted that vigabatrin, relative to placebo, would significantly increase abstinence in individuals with cocaine dependence. In addition, the target dosage selected, 3.0 g/d, resulted in a cumulative dose of only 218.0 g; therefore, it was predicted that no significant difference in the development of visual field defects would be observed between groups.

METHODS

PARTICIPANTS

Participants were recruited by 11 US sites, primarily through radio, newspaper, and television advertisements, as well as by referrals, posters, and flyers. All participants were given a thorough explanation of the study and signed an informed consent form that was approved by the institutional review boards of the participating sites. Eligible participants were at least 18 years old, had normal visual fields as measured by a Humphrey field analyzer, and were in good physical health as determined by the results of a medical history, physical examination, electrocardiogram, and standard laboratory tests. Participants were required to meet *DSM-IV* criteria for cocaine dependence as assessed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders,[20] to be seeking treatment for cocaine dependence, and to have at least 1 positive (benzoylecgonine [BE] level ≥300 ng/mL) urine drug screen during the 14-day baseline.

Participants were excluded from the study if they required detoxification from alcohol, if they had been court-ordered to seek cocaine-dependence treatment, or if they met *DSM-IV* criteria for dependence for any substance other than cocaine, alcohol, nicotine, or marijuana. Pregnant and lactating women and women unwilling to use an adequate method of birth control were also excluded, as were patients who had ever taken vigabatrin, had received electroconvulsive therapy within 3 months of randomization, or had been enrolled in an opioid substitution program in the past 2 months. Finally, participants were excluded if they had taken a drug with known major organ toxic effects, including retinotoxic effects, within 30 days of randomization or if they had clinically significant ophthalmologic disease or were undergoing treatment for ocular disease or intended to have any ocular surgery or procedure during their participation in the trial.

PROCEDURES

Participants completed screening and a 2-week baseline, after which those meeting study criteria were randomized in a 1:1 ratio to vigabatrin or placebo, stratified by sex, primary route of cocaine administration (ie, smoked or intravenous vs nasal), and frequency of cocaine use during the last 30 days before screening (≤18 vs >18 days). During the 12-week treatment phase, participants were scheduled to attend 3 research visits per week for safety and efficacy assessments. Single follow-up visits were scheduled at weeks 13, 16, 20, and 24. Following randomization, participants were instructed to take 3 identical tablets twice daily throughout the 12-week treatment phase. Each week's worth of medication came in a blister package labeled with which pills were to be taken on each day of the trial week. The vigabatrin dosage escalation was managed through the packaging of the vigabatrin kits, in which the amount of vigabatrin contained in the tablets increased from 0.0 g of vigabatrin in the first dose on day 1 to 0.5 g of vigabatrin per tablet (total dosage, 3.0 g/d) on study days 15 to 77. Dosage reduction was completed in a similar manner, with vigabatrin reduced to 2.0 g/d on study day 78 and to 1.0 g/d on study day 82.

All participants received weekly computerized cognitive behavioral therapy[21] plus biweekly half-hour individual sessions with a counselor. Participants were compensated for their time and travel. In addition, contingency management was used to reinforce the provision of valid urine samples (based on temperature and creatinine level). Reinforcement started at $7.25 per urine sample and increased by $0.25 for each consecutive urine sample provided. A missed visit reset the compensation to the original $7.25 per urine sample. In addition, a bonus was earned for every week of the provision of 3 urine samples ($10 for weeks 1-10 and $25 for weeks 11 and 12) and for the provision of a urine sample at each follow-up visit ($25). Reinforcements were provided in the form of vouchers (minimum, $5 value), with the provision of cash for reinforcements of less than $5.

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1. The participant provided ≥4 urine samples during weeks 11 and 12 and 1 urine sample in week 13.
2. The last urine sample of week 12 had been collected ≥9 calendar days after the first urine sample of week 11.
3. No more than 4 clinic days (usually weekdays) or 5 calendar days (could include weekends or holidays), whichever resulted in a shorter gap, had elapsed between any 2 successive urine samples.
4. All urine samples collected during weeks 11 through 13 had a benzoylecgonine level of <300 ng/mL and a creatinine level of >20 mg/dL (to convert creatinine level to micromoles per liter, multiply by 88.4).
5. A self-report value existed for all 14 days of this 2-wk period, and all those days were self-reported as "no use."

Figure 1. Criteria for being scored as cocaine abstinent on the primary outcome measure.

MEASURES

The primary outcome measure was the proportion of participants in each group with cocaine abstinence during the last 2 weeks of the 12-week treatment phase. The following 2 independent measures of cocaine use were used to determine the value of the binary abstinence variable for each participant: (1) self-report of cocaine use (ie, use vs no use) on each day of the 2-week period using the time line follow-back procedure[22,23] and (2) quantitative measurements of BE and creatinine from at least 4 adequately spaced urine samples, with a cocaine-positive result defined as a BE level of at least 300 ng/mL. To be scored as being cocaine abstinent during the last 2 weeks of the treatment phase, all criteria listed in **Figure 1** must have been met. Participants not meeting those criteria were scored as not being cocaine abstinent. Some cocaine-dependence trials[24,25] have used as an outcome measure weekly fractions of cocaine use days, as calculated using the SelfReportPHarmacoKinetic1 (SRPHK1) procedure. This procedure combines self-reported cocaine use, urine BE levels, and the concordance between the 2 to determine the cocaine use status of each trial day. The daily values are then used to calculate the fraction of cocaine use days for each week. Therefore, this measure was included as a key secondary outcome variable, with the number of drug-free urine samples provided during weeks 1 through 13 as a second key secondary outcome.

Other secondary outcome measures included cocaine craving, addiction severity, and Substance Clinical Global Impression (SCGI) scores.[26] Cocaine craving was assessed on a weekly basis using the Brief Substance Craving Scale.[27] The Brief Substance Craving Scale instructed the participant to use a 5-point scale to rate the intensity, frequency, and length of time spent craving cocaine during the past 24 hours; these scores were summed to yield a total craving score. The Fifth Edition of the Addiction Severity Index,[28] a structured clinical interview that yields scores for 7 areas of functioning, was administered by a trained staff member at baseline and weeks 4, 8, and 12. Clinician and participant global impression ratings of the severity of the participant's cocaine-dependence symptoms were obtained on a weekly basis using the SCGI-observer scale and the SCGI-self scale.[26] In accord with National Institutes of Health policy, participants self-reported their race/ethnicity; reporting was based on the race/ethnicity classifications used in the 2000 US Census.

Safety measures included vital signs once per week, AEs and concomitant medication assessments 3 times per week, and laboratory assessments (hematology, blood chemistry, and urinalysis) during screening and baseline and at trial weeks 4, 8, and 12. Physical examination and electrocardiogram were performed during screening and baseline and at trial week 12. Participants underwent visual field testing using a Humphrey visual field analyzer (model 2 or 2i with program 60-4; Carl Zeiss Group) during screening and baseline and again during weeks 12 to 14. In addition, because electroretinography-measured cone voltages are known to be associated with (and perhaps predictive of) visual field loss,[29-31] electroretinography testing was conducted on all patients in 5 sites where it was available on the same days as the visual field measures. Because cocaine abuse itself can produce electroretinography changes in a small fraction of users,[32] participants exhibiting such changes during screening were excluded from the study.

Table 1. Baseline Characteristics of Participants

Characteristic	Treatment Group: Vigabatrin (n = 92)	Treatment Group: Placebo (n = 94)
Age, mean (SD), y	44.6 (7.6)	45.0 (8.3)
Male sex, %	65.2	68.1
Hispanic race/ethnicity, %[a]	5.4	19.1
Race/ethnicity, %		
African American	65.2	55.3
White	29.3	33.0
Native American or Alaskan native	0.0	2.1
Other	5.4	9.6
Primary route of cocaine administration, %		
Smoked or intravenous	84.8	86.2
Nasal	15.2	13.8
Frequency of cocaine use during the last 30 d before screening, %		
≤18 d	69.6	66.0
>18 d	30.4	34.0
Addiction Severity Index subscale, mean (SD)		
Medical	0.179 (0.3)	0.204 (0.3)
Employment	0.628 (0.3)	0.580 (0.3)
Alcohol	0.217 (0.2)	0.165 (0.2)
Drug	0.270 (0.1)	0.257 (0.1)
Legal	0.054 (0.1)	0.071 (0.2)
Family/social	0.204 (0.2)	0.192 (0.2)
Psychiatric[b]	0.124 (0.2)	0.225 (0.4)

[a] Significant difference between treatment groups ($P < .01$).
[b] Significant difference between treatment groups ($P < .05$).

IDENTITY OF THE INVESTIGATIONAL PRODUCT

Vigabatrin and its matching placebo were supplied as white, film-coated, capsule-shaped 500-mg tablets with a bisect on one side. They were custom manufactured for Catalyst Pharmaceutical Partners, Inc.

DATA ANALYSIS

Per study protocol, the primary outcome measure (the proportion of intent-to-treat participants abstinent during the last 2 weeks of the 12-week treatment phase) was compared between treatment groups using a logistic regression with covariates (sex, treatment group, primary route of cocaine administration, and frequency of cocaine use during the last 30 days before screening, as well as the US site). All weekly secondary variables, including the key secondary measure (the weekly fraction of cocaine use days during treatment), were compared between treatment groups using a by-participant random-intercept mixed-model regression with the following covariates: trial week, treatment group, trial week × treatment group interaction, and the measure of interest evaluated at baseline. For some of these weekly measures, a binomial sign test was also performed as a post hoc exploratory assessment to indicate

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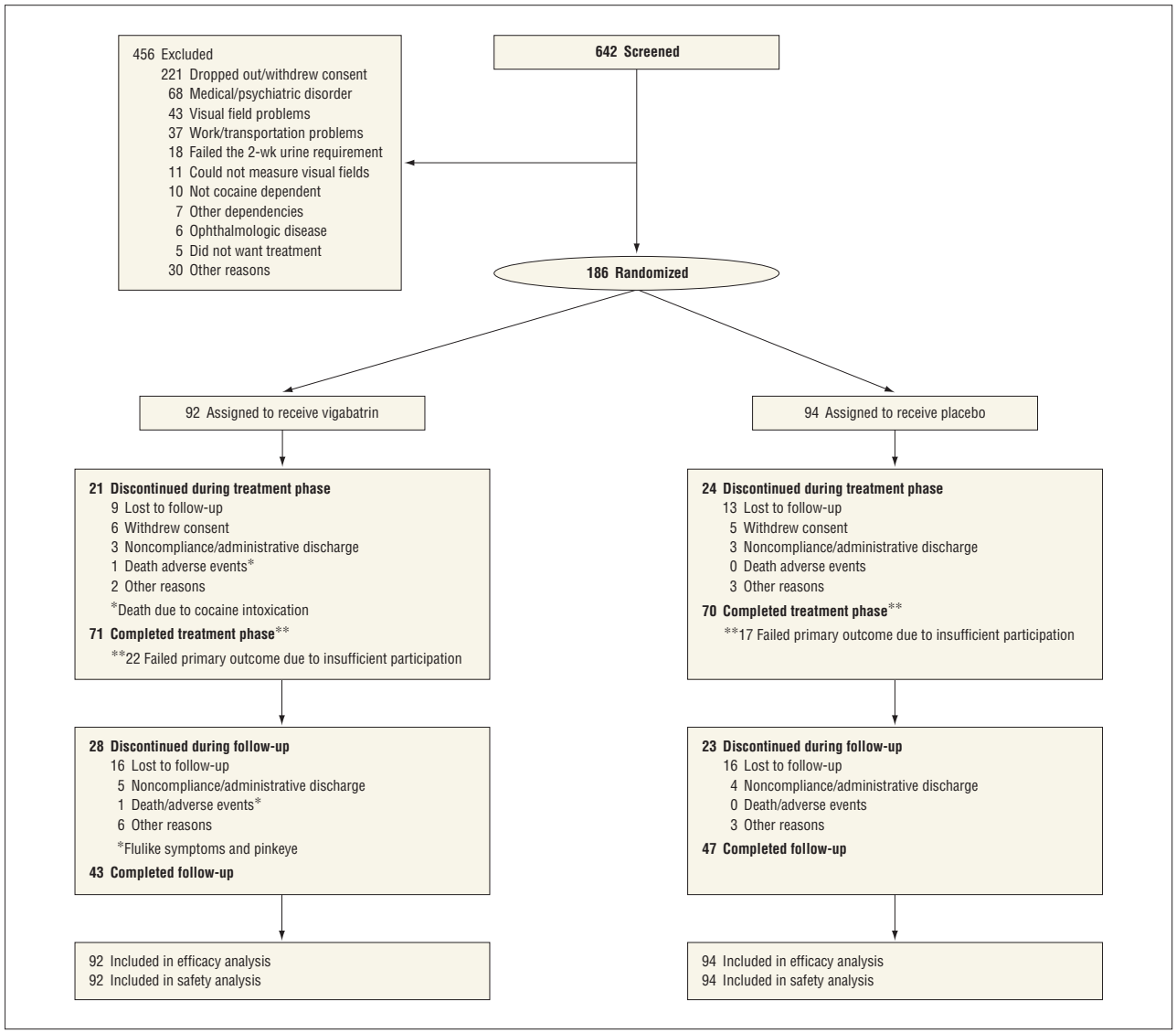

Figure 2. The flow of study participants through the various phases of the clinical trial.

whether a consistent difference might exist between treatments that was too small to be detected by the regression. An efficacy variable that was not trial week related (the treatment-phase number of drug-free urine samples as a percentage of scheduled urine samples) was compared between treatment groups using a Wilcoxon rank sum test stratified for sex, primary route of cocaine administration, and frequency of cocaine use during the last 30 days before screening. Adverse events included all untoward events reported by the participants, as well as significant changes in laboratory values and vital signs. The AEs were tabulated by body system and preferred term, seriousness, and relationship to study medication. The AEs were compared between treatment groups using the Pearson χ^2 test or the Fisher exact test depending on marginal frequency counts. As summarized in **Table 1**, demographic and baseline characteristics were compared between treatment groups using the *t* test, Pearson χ^2 test, Fisher exact test, or Wilcoxon rank sum test depending on which was most appropriate for the particular measure.

RESULTS

SPECIMEN ANALYSIS

Urine samples were assessed for BE with an immunoassay using gas chromatography–mass spectrophotometry in a Substance Abuse and Mental Health Services Administration–certified laboratory. During the study, 5917 urine samples were measured quantitatively. Overall, 25.6% (26.2% for the vigabatrin group and 25.0% for the placebo group) of the expected urine samples were missing; of these, 11.4% (11.3% for the vigabatrin group and 11.4% for the placebo group) were missing intermittently during the time participants were active in the study, while 14.3% (15.0% for the vigabatrin group and 13.6% for the placebo group) were missing because of study dropout.

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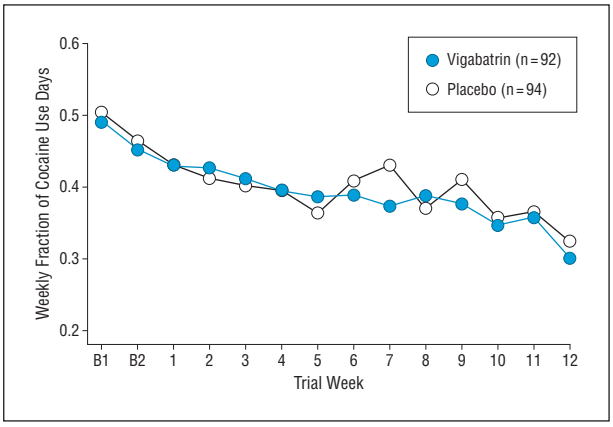

Figure 3. The mean weekly fraction of cocaine use days by treatment group. Weekly fractions of cocaine use days were estimated using the SelfReportPHarmacoKinetic1 algorithm[24] based on self-reports and quantitative urine benzoylecgonine levels. B1 and B2 indicate baseline 1 and baseline 2, respectively.

PARTICIPANTS AND DISPOSITION

As shown in **Figure 2**, study consent was obtained from 642 candidates, of whom 186 were randomized. Of these, 141 (75.8%) completed the 12-week treatment phase, with no treatment group differences. Among the 141 participants who completed the 12-week treatment phase, the primary outcome could not be determined for 39 participants, with no differences between groups, because of insufficient study participation (Figure 1). As summarized in Table 1, the study sample was approximately 67% male, and about 60% were of African American race/ethnicity; participants were 45 years old on average and primarily (85.5%) used cocaine by the smoked or intravenous route. No statistically significant treatment group differences were observed in demographic or baseline characteristics except for race/ethnicity, with more participants of Hispanic race/ethnicity in the placebo group ($P < .001$), and the Addiction Severity Index psychiatric subscale, which was higher among the participants receiving placebo compared with those receiving vigabatrin ($P < .03$). The cognitive behavioral therapy and counseling sessions were well attended, with no significant group differences in the mean (SD) numbers of cognitive behavioral therapy sessions attended (9.52 [4.19] for the vigabatrin group and 9.68 [4.20] for the placebo group) and counseling sessions attended (5.01 [2.29] for the vigabatrin group and 5.11 [2.17] for the placebo group).

EFFICACY OUTCOMES

The primary outcome analysis revealed no significant difference between treatment groups in the proportion of participants with cocaine abstinence during the last 2 weeks of the 12-week treatment phase ($P = .67$). In total, 7 of 92 vigabatrin group participants (7.6%) had cocaine abstinence during the last 2 weeks of the treatment phase, while 5 of 94 placebo group participants (5.3%) had cocaine abstinence during the last 2 weeks of the treatment phase. Using logistic regression, analysis of one key secondary outcome, the weekly fraction of cocaine use days, revealed no significant treatment effect ($P > .99$) (**Figure 3**). Also, the Wilcoxon rank sum test of the percentage of drug-free urine samples provided during weeks 1 through 13 failed to indicate a difference between treatment groups ($P = .60$). However, the results of a subsequent binomial sign test suggested that the vigabatrin group consistently used less cocaine than the placebo group during the 12-week treatment phase as measured by urine BE levels ($P = .006$).

The SCGI-self scale, SCGI-observer scale, and Brief Substance Craving Scale scores as a function of trial week and treatment group are summarized in eTable 1 (http://www.jamapsych.com), which shows that both groups reported less craving and significant improvement in global functioning during the course of the study, consistent with the significant trial week effect ($P < .001$). The mean Addiction Severity Index–drug composite scores as a function of treatment group and trial month are also summarized in eTable 1. Both groups improved during the course of the study, which is again consistent with the significant trial week effect ($P < .001$). No significant medication effect was observed for any of these analyses.

SAFETY OUTCOMES

Adverse Events

No significant treatment group differences were observed in the occurrence of AEs, in medication-related AEs, or in the number of participants discontinued from study medication because of AEs (eTable 2). The only group difference in AE frequency was for headache, which occurred at a significantly higher rate in the placebo group. Eleven participants collectively experienced a total of 14 serious adverse events (SAEs). The 3 SAEs involving placebo group participants (manic episode, hip replacement, and insomnia) were determined to be unrelated to the study medication. Of 11 SAEs experienced by 8 vigabatrin group participants, 8 (experienced by 5 participants) were deemed to be unrelated or unlikely to be related to the study medication. These were pneumonia (2 participants), meningitis, left eye trauma from a fight, major depression, tachycardia, gunshot to the right tibia, and procedural complications stemming from the gunshot. Two SAEs (acute hepatitis and death from acute cocaine intoxication) were deemed to be possibly related. For 1 SAE (a motor vehicle crash with injury), no decision could be made as to relatedness.

Ophthalmologic AEs

Results of the eye examinations showed no clinically significant decreases in visual acuity during the study. In the case of visual field defects, no statistically significant differences between the treatment groups were found in the change from baseline to posttreatment assessments. Results of the electroretinography performed on 37 participants (19 in the vigabatrin group and 18 in the placebo group) showed no clinically significant changes from baseline, defined as at least a 50% decrease in any wave amplitude or at least a 50% increase in the mean implicit time. A possibly new safety finding was the occurrence of photopsia (perceived flashes of light) for periods ranging from

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Table 2. Comparison Between the Present Trial and the Mexican Trial by Brodie et al[16]

Variable	Present Trial	Mexican Trial
Participating sites, No.	11	1
Patients screened, No.	642	225
Intent-to-treat patients randomized, No.	186	103
Demographics		
Female sex, %	33.3	3.9
Mean age, y	44.8	29.1
Completed treatment, No./total No. (%)		
Overall	**141/186** (75.8)	**53/103** (51.5)
Vigabatrin group	71/92 (77.2)	31/50 (62.0)
Placebo group	70/94 (74.5)	22/53 (41.5)
Vigabatrin dosage, g	3 Total (3 tablets twice daily)	3 In orange juice once daily
Medication adherence	66.2% Took >70% of their pills (by pill count and self-report)	100% At attended visits, during which medication dosing was observed
Treatment duration, wk	12	9
Primary route of cocaine administration, %		
Smoked or intravenous	85.5	Unknown
Nasal	14.5	Unknown
Source of study participants	Individuals seeking treatment, through radio, newspaper, and television advertisements	Released prisoners seeking treatment at parole center
Treatment platform	Computerized weekly cognitive behavioral therapy and biweekly individual counseling	Group therapy and lottery
Urine sample collection	3 Times per week, quantitative	2 Times per week, qualitative
Serious adverse events, No.	14	0
Achieved primary outcome		
Definition	Abstinence at weeks 11 and 12	Abstinence at weeks 7-9
P value for difference between treatment groups	.67	<.009
Overall, No./total No. (%)	**12/186** (6.5)	**18/103** (17.5)
Vigabatrin group, No./total No. (%)	7/92 (7.6)	14/50 (28.0)
Placebo group, No./total No. (%)	5/94 (5.3)	4/53 (7.5)

1 day to 3 months, which was reported by 8 vigabatrin group participants and 1 placebo group participant. In all cases, the photopsia was reported to have resolved, and in no case did a participant discontinue treatment. Five of 8 photopsia events in the vigabatrin group were judged to be possibly related to the study drug, while the event in the placebo group was rated as unrelated.

MEDICATION ADHERENCE

The number of pills taken as a percentage of those expected to be taken was measured by counts of pills remaining in returned blister packs. Participant self-report was accepted when a blister pack was missing. Based on pill counts, 55.4% of participants were more than 90% compliant, and 66.2% of participants were more than 70% compliant, with no statistically significant difference between the treatment groups.

POST HOC MEDICATION ADHERENCE EVALUATION

Given the unexpected negative efficacy results, post hoc analyses were performed to determine if a more accurate assessment of adherence might reveal a potential explanation for the lack of treatment effect. The evaluation is based on the knowledge that vigabatrin is largely unmetabolized and that more than 80% of the drug is excreted in urine.[33] The vigabatrin concentrations were measured using a validated gas chromatography–mass spectrophotometry method, with a quantitation limit of 2 μg/mL and a detection limit of 0.4 μg/mL. The post hoc analysis was completed among 125 participants who had adequate urine sample counts at week 11 and week 12. This group is referred to as the complier verification analysis subgroup, which was defined before unblinding.

A maximum of 12 urine samples per participant were tested of a possible 37 specimens collected during the treatment phase, for a total of 1326 total samples among 125 complier verification analysis subgroup participants. Vigabatrin levels between the limit of quantitation and 15 533 μg/mL were observed, with a peak in the distribution of results occurring between 1450 and 2900 μg/mL for the subgroup of 61 complier verification analysis subgroup participants who were treated with vigabatrin. Once the medication assignment became known, it was apparent that approximately 40% of the vigabatrin-assigned participants had minimal or undetectable vigabatrin levels in their urine samples among at least 70% of the specimens. A subjective assessment of the patterns of vigabatrin urine concentrations in the remaining vigabatrin group participants suggested that as many as 20% were also noncompliant.

COMMENT

This 12-week, randomized, double-blind, placebo-controlled clinical trial of vigabatrin suggests that vigabatrin did not significantly decrease cocaine use. In contrast to the planned analyses, the results of a post hoc analysis of urine BE levels suggest that vigabatrin might have some

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efficacy. The present results are consistent with previous trials of GABAergic medications for cocaine dependence, which have had mixed efficacy results.[34] However, our results are in sharp contrast to recently published findings from a similar but smaller (N = 103) single-site vigabatrin clinical trial conducted in Mexico.[16] Several key participant differences between the trials could account for the divergent results, including variation in the demographics of the samples, with the Mexican trial comprising a younger (mean age, 29 vs 45 years) and more homogeneous sample compared with the present trial, with fewer women (4% vs approximately 33%). Notably, while our study participants had 14 SAEs, the Mexican trial reported no SAEs. Significant cultural differences also likely existed between the 186 Americans recruited for our trial through radio, newspaper, and television advertisements and the 103 Mexicans recruited from a single parole center. A comparison of the present trial with the Mexican trial is given in **Table 2**. The following 2 design differences are likely of greatest importance.

First, participants in the Mexican study[16] took their study medication under observation on clinic visit days (twice per week). Participants in the present study took all of their doses at home (except on the randomization visit), and medication adherence was assessed entirely by pill counts in returned blister packs and by self-report when a blister pack was missing. Second, participants in the Mexican study provided urine samples only twice per week, making it difficult to fully validate self-report of cocaine use. In the present study, we not only obtained thrice-weekly urine samples but also required participants to meet certain criteria (Figure 1) to ensure that all new cocaine use during the last 2 weeks of the 12-week treatment phase (when abstinence was evaluated) was likely to be detectable. The findings from these criteria were that approximately 28% of the participants had large enough time gaps between consecutive urine samples that they could have had new (and undetectable) use of cocaine during these periods. Such patients were deemed to be unevaluable for detecting abstinence and (per protocol) were not considered to have cocaine abstinence. In the Mexican study, with larger time gaps between consecutive urine samples, undetected new cocaine use could have occurred.

Because of the unexpected negative results in the present study, a post hoc evaluation of medication adherence was completed using vigabatrin concentration in the urine samples of the vigabatrin group participants among the complier verification analysis subgroup. Clearly, these participants were compliant in following study procedures unrelated to medication. However, based on the post hoc medication adherence evaluation, it seems that only about 40% of this group could be classified as having been medication adherent. Because of the possible significant medication nonadherence, it is impossible to draw definitive conclusions concerning the efficacy of vigabatrin.

Therefore, the lack of significant vigabatrin efficacy may have been due to weak efficacy of the drug or due to significant nonadherence with taking the drug as prescribed. A third vigabatrin clinical trial, funded by the National Institute on Drug Abuse, is ongoing in several US sites and is designed to more adequately address medication adherence (eg, with once-daily dosing, observed dosing 3 times per week, and riboflavin level monitoring to measure compliance).

Submitted for Publication: May 19, 2012; final revision received August 7, 2012; accepted September 29, 2012.
Published Online: April 10, 2013. doi:10.1001/jamapsychiatry.2013.872
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Author Contributions: Dr E. C. Somoza had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conflict of Interest Disclosures: Dr Gorodetzky reported being a consultant to US WorldMeds, Helicon, and Cypress Bioscience, as well as holding stock options in Catalyst Pharmaceutical Partners, Inc. Dr Sheehan reported being on the speakers bureau for Reckitt Benckiser. Dr Roache reported having consulted for Reckitt Benckiser and in the past several years has received contract funding from Ovation Pharma, Eli Lilly, and Pfizer. Dr Bickel reported being a principal in HealthSim, LLC, which specializes in the research and development of prevention science products.
Funding/Support: Funding and support for this study were provided by Catalyst Pharmaceutical Partners, Inc. The study medication and matching placebo were provided by the company at no cost.
Role of the Sponsor: The sponsor provided funding to a clinical research organization, Health Decisions (Durham, NC), which provided day-to-day data collection management and analysis and initial interpretation of the data.
Participating Sites: Addiction Pharmacology Research Laboratory, St Luke's Hospital, San Francisco, California; Be Well Center, The University of Texas Health Science Center at San Antonio; Boston University School of Medicine, Boston, Massachusetts; Center for Chemical Dependence, The Johns Hopkins Bayview Medical Cen-

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ter, Baltimore, Maryland; Department of Veterans Affairs Medical Center, Cincinnati, Ohio; Department of Veterans Affairs Medical Center, Dayton, Ohio; Friends Research Institute, Torrance, California; Operation PAR, Largo, Florida; Segal Institute for Clinical Research, North Miami, Florida; University of Arkansas for Medical Sciences Addiction Treatment Clinic, Little Rock; and Veterans Affairs New York Harbor Healthcare System, New York, New York. The 5 sites completing electroretinography testing were Addiction Pharmacology Research Laboratory, St Luke's Hospital, San Francisco, California; Be Well Center, The University of Texas Health Science Center at San Antonio; Department of Veterans Affairs Medical Center, Cincinnati, Ohio; University of Arkansas for Medical Sciences Addiction Treatment Clinic, Little Rock; and Veterans Affairs New York Harbor Healthcare System, New York, New York.

Online-Only Material: The eTables are available at http://www.jamapsych.com.

Additional Contributions: Malcolm S. Reid, PhD, was the site principal investigator from Veterans Affairs New York Harbor Healthcare System, New York, New York. He died of leukemia on April 23, 2010. All study data from his site were completed and have been included in this article; however, he died before the manuscript was begun and could not be listed as an author.

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