Gabapentin in the Treatment of Cocaine Dependence: A Case Series

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Background: Although multiple medications have been studied for the treatment of cocaine dependence, no medication has been shown to have a robust effect on craving and use. This pilot project was designed to evaluate the safety and tolerability of gabapentin in subjects with cocaine dependence.

Method: Thirty cocaine-dependent subjects (DSM-IV criteria) were enrolled in an 8-week, open-label trial of 1200 mg/day of gabapentin in divided doses. Urine drug screens, subjective measures of craving, and cocaine use interviews were conducted at each weekly visit.

Results: Baseline rating of amount and frequency of craving decreased significantly by week 8 (78% vs. 25% for amount, p = .000; 74% vs. 23% for frequency, p = .004). Positive urine drug screens for cocaine decreased from 86% at baseline to 29% at weeks 4 and 8. There were no reports of significant side effects or adverse events.

Conclusion: This pilot study indicates that gabapentin is safe and well tolerated and may be beneficial in the treatment of cocaine dependence. A placebo-controlled trial would be of interest.

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Multiple medications have been studied in an effort to find an effective pharmacologic treatment for cocaine dependence. While modest treatment effects have been found with tricyclic antidepressants and dopamine agonists, no medication with a robust effect has been identified.[1,2] Most pharmacotherapies for cocaine dependence have focused on the transporter systems for dopamine, serotonin, and norepinephrine since these systems appear to be the main target of cocaine's actions in the brain. However, preclinical studies have shown that mice without the dopamine and/or serotonin transporter still establish cocaine-conditioned place preference.[3] These findings suggest that agents which target other neurotransmitter systems or have multiple mechanisms of action should be evaluated for the treatment of cocaine dependence.

A number of studies have investigated the use of anticonvulsant agents in the treatment of cocaine dependence. Initial uncontrolled reports with the anticonvulsant agent carbamazepine suggested that it decreased cocaine use in cocaine-dependent individuals,[4] but subsequent double-blind studies have not replicated these results.[5–7] More recent double-blind, placebo-controlled trials, however, have suggested that at adequate doses[8] and in subjects with affective disorders,[9] carbamazepine may play a role in the treatment of cocaine dependence. In a double-blind, placebo-controlled study,[10] phenytoin-treated subjects had significantly less cocaine use measured by both urinalysis and self-report compared with placebo. These studies suggest that further research is needed to determine the utility of anticonvulsants as pharmacotherapies for cocaine dependence.

Gabapentin is a relatively new anticonvulsant agent currently approved by the U.S. Food and Drug Administration as an adjunct agent for the treatment of partial seizures with and without secondary generalization. Gabapentin is not hepatically metabolized in humans, does not bind to plasma proteins or induce hepatic enzymes, and is eliminated as an unchanged drug by renal excretion.[11] Although the exact mechanism underlying anticonvulsant activity has not been clearly delineated, gabapentin appears to affect several important neurotransmitter systems. It potentiates γ-aminobutyric acid (GABA) activity, inhibits glutamate synthesis and sodium channels, modulates calcium current, and reduces norepinephrine and dopamine release.[12,13] Because of the broad spectrum of central nervous system activity, gabapentin has been found useful in the treatment of a variety of disorders in addition to epilepsy. It has recently generated interest in psychiatry as a potential treatment for bipolar spectrum disorders, anxiety disorders, behavioral dyscontrol, and alcohol withdrawal.[14,15]

Interest in the use of gabapentin in the treatment of cocaine dependence developed after a cocaine-dependent

patient reported that the use of her husband's gabapentin had decreased her craving and subsequently her use of cocaine.[16] This pilot project is an 8-week, open-label study of gabapentin, 1200 mg/day, in cocaine-dependent individuals. Primary outcome measures included cocaine use as measured by qualitative urine assay and self-report, severity and frequency of cocaine craving, and retention in treatment.

METHOD

Subjects

Subjects were 30 men and women (aged 18–55 years) who met criteria for DSM-IV cocaine dependence and did not endorse an abstinent period longer than 3 weeks during the 3 months prior to evaluation. Additionally, subjects must have used cocaine a minimum of 2 days per week in the month prior to contacting the study coordinator. Primary exclusion criteria were any other current substance dependence, serious medical conditions, or major psychiatric disorders such as major depression, bipolar disorder, or psychoses. Subjects taking psychotropic medications were also excluded. All subjects provided written informed consent approved by the Medical University of South Carolina institutional review board.

Assessments

Substance use was assessed using the Time-Line Follow-Back (TLFB)[17] modified to ask about cocaine use for the 30 days prior to study entry, the Quantitative Cocaine History[18] to quantify the amount of cocaine used over longer periods of time, and a 100-mm visual analog scale to measure craving for cocaine. The Global Assessment of Severity (GAS) was used to measure degree of cocaine dependence. Psychiatric diagnoses were made using the Structured Clinical Interview for DSM-IV.[19] Psychological symptomatology was assessed using the Beck Depression Inventory (BDI),[20] the Beck Anxiety Inventory (BAI),[21] the Young Mania Rating Scale,[22] and the Symptom Checklist-90, Revised (SCL-90R)[23] at baseline. The TLFB and craving analog scale were administered at weekly intervals during medication treatment. Urine drug screens were conducted weekly. The BDI, BAI, and SCL-90R were administered at weeks 4 and 8. Patients were asked about medication side effects at weeks 1 through 8.

All patients received a medical evaluation, physical examination, electrocardiogram (ECG), liver function tests, hematologic tests, and urine drug screen at baseline. Urine samples were analyzed for drugs of abuse at the Clinical Neurobiology Laboratory at the Institute of Psychiatry using the AxSYM Cocaine Metabolite assay (Abbott Laboratories, Abbott Park, Ill.). Urine screen results were considered positive for cocaine at a benzoylecgonine concentration of 300 ng/mL or greater.

Design

Gabapentin treatment was begun at 600 mg/day and dosed twice daily for 3 days (300 mg b.i.d.) and then increased to 1200 mg dosed twice daily (600 mg b.i.d.). Patients were seen weekly, and at each clinic visit, they provided a urine sample and self-report of cocaine use, and cocaine craving was assessed. Hematology profiles and ECGs were repeated at weeks 4 and 8. A 10-day supply of medication was dispensed at each visit. No formal psychotherapy or psychosocial component was included in the study, but subjects were not prohibited from engaging in psychosocial treatments.

Data Analysis

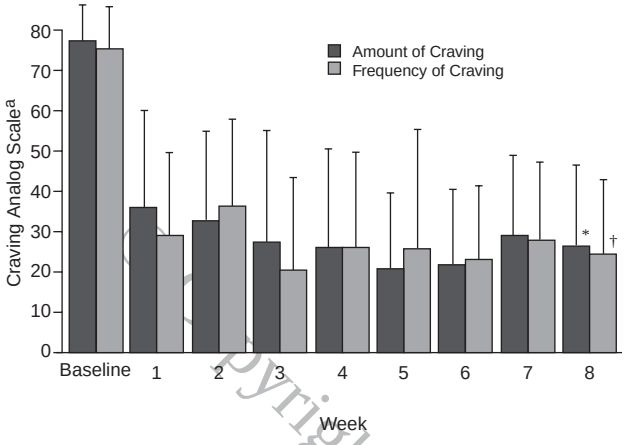
Data were entered into SPSS software (version 6.1, Chicago, Ill.) and double-checked against the hard copy to ensure accuracy. Baseline differences between those who completed the study and those who dropped out were analyzed using chi-square tests for categorical data and 2-tailed t tests for comparison of means. For measures that were collected only at baseline and week 8, comparisons were performed using a t test. Data that were collected only at baseline and visits 4 and 8 as well as data collected weekly were analyzed using a repeated measures analysis of variance design with last observation carried forward. All statistical tests were considered significant at $p < .05$.

RESULTS

Of the 30 subjects who consented to participate in the study, 12 individuals failed to return after their week 1 appointment. Of the remaining 18 patients, 14 individuals (47%) completed week 4 and 6 (20%) completed the 8-week treatment phase. No statistically significant differences were found in demographics, psychopathology, or cocaine use history between those who entered the treatment phase (N = 18) and those who did not (N = 12). Those individuals who completed week 4 follow-up assessments were included in the intent-to-treat analysis.

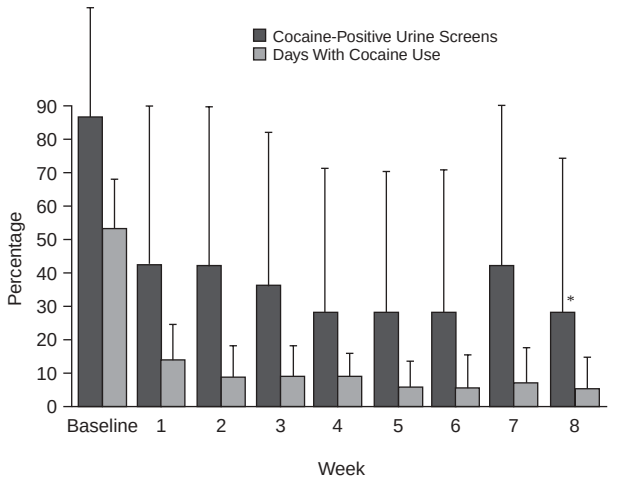
Of the intent-to-treat sample (N = 14), 86% (12/14) were men with a mean ± SD age of 33.4 ± 5.5 years and 12.77 ± 1.68 years of education. Seventy-one percent (10/14) were white, and 50% (7/14) were employed. Comorbid substance disorders included current alcohol (14%; 2/14) and cannabis (7%; 1/14) abuse. History of alcohol dependence (36%; 5/14) and alcohol (43%; 6/14), cannabis (64%; 9/14), sedative (14%; 2/14), and amphetamine (14%; 2/14) abuse was also noted. At baseline, study subjects reported a mean ± SD of 11.93 ± 8.86 years of cocaine use with $14,424.29 ± $11,504.67 worth of cocaine used in the last year. In the 30-day baseline period, subjects reported a mean ± SD of $1663.50 ± $1196.49 spent on cocaine and 16.0 ± 5.59 days of use with mean ± SD of $107.15 ± $85.20 spent

Figure 1. Subjectively Reported Ratings of Craving Amount and Frequency on the Craving Analog Scale



[a]Range, 0–100.
*p = .000 vs. baseline.
†p = .004 vs. baseline.

Figure 2. Percentage of Cocaine-Positive Urine Screens and Percentage of Days With Cocaine Use at Baseline, Week 4, and Week 8



*p = .001 vs. baseline.

each day of use. Crack cocaine was preferred by 92.9% (13/14) of the subjects.

As can be seen in Figure 1, the amount and frequency of cocaine craving was high before medication treatment, but decreased dramatically in the first week of treatment with modest decreases thereafter ($F = 28.79$, $df = 8,80$; $p = .000$ and $F = 11.98$, $df = 8,80$; $p = .004$, respectively). A statistically significant decrease was found in the self-report of number of days using cocaine ($F = 20.41$, $df = 8,80$; $p = .002$), which was supported by a significant decrease in the percentage of cocaine-positive urine samples (Figure 2; $F = 3.60$, $df = 8,80$; $p = .001$).

The self-report of dollar amount spent on cocaine per day of use decreased from $107 ± $85.2 at baseline to $13 ± $30.2 at week 8; however, this did not reach statistical significance ($F = 2.93$, $df = 8,80$; $p = .124$), possibly owing to variability and/or small sample size. The mean ± SD number of days until relapse was 21 ± 24.0 days. GAS scores for cocaine dependence decreased significantly during the study period ($F = 21.16$, $df = 8,80$; $p = .001$).

The BDI scores showed a marked decrease from 19.6 ± 10.7 at baseline to 8.7 ± 8.1 at week 8 ($F = 5.83$, $df = 2,20$; $p = .024$). BAI scores showed a similar decrease, from 14.2 ± 8.8 at baseline to 5.1 ± 4.7 at week 8 ($F = 10.76$, $df = 2,20$; $p = .004$).

Safety and tolerability measurements by side effect interviews and laboratory monitoring revealed no significant difficulties. There were no significant differences in laboratory findings or vital signs throughout the treatment period. Reported side effects included nausea (N = 1) and sedation (N = 1). These side effects were generally time limited and dissipated within 3 days.

DISCUSSION

In this open-label pilot study, gabapentin treatment decreased the self-report of amount and frequency of cocaine craving as well as the percentage of days with cocaine use during the study period. Similarly, the percentage of individuals with a positive urine drug screen for cocaine decreased from 86% (12/14) at baseline to 29% (4/14) at week 4 and 29% (4/14) at week 8.

Gabapentin was safe and well tolerated in this population of cocaine users. No subject who discontinued treatment early complained of adverse events or side effects prior to discontinuation. At study conclusion, no significant changes from baseline were noted in ECGs, vital signs, weight, or hematologic parameters.

The subject retention rate for this trial was low, although similar to rates often seen in cocaine treatment trials.[24] Many cocaine pharmacotherapy treatment trials have used a psychotherapy component or contingency management to decrease attrition. Although the current study had no formal psychotherapy component or contingency strategy, subjects were seen weekly by research staff for approximately 30 minutes each. During this period of time, research assistants and the study physician stressed compliance with the medication, assessed side effects of the medication, and supported the subject's desire for abstinence.

The exact mechanism by which gabapentin may decrease cocaine craving and use is not completely understood. Previous investigators have suggested that anticonvulsants may decrease cocaine use by preventing cocaine-induced kindling.[8] Interestingly, gabapentin was recently reported to have the highest protective index, as compared with 14 newly approved or potential anticonvul-

sant agents, in a murine model of cocaine-induced seizures.[25] Therapeutic effects of anticonvulsant agents in cocaine dependence may also be mediated by mood-stabilizing properties, GABAergic effects, or interaction with multiple neurotransmitter systems.

It is well recognized that anticonvulsant agents have demonstrated mood-stabilizing properties in individuals with bipolar disorder.[26] Preliminary studies indicate that gabapentin may be effective in bipolar disorder.[27] Mood instability and depression are often seen during the early abstinence period in cocaine-dependent subjects.[28] This subtle mood dysregulation is thought to be part of a protracted withdrawal syndrome. Cocaine-dependent individuals may relapse in an attempt to self-medicate mood instability, depressive symptoms, and other symptoms of protracted abstinence. Despite excluding major psychiatric illnesses, significant improvement in psychological functioning was found at weeks 4 and 8 on the BAI and the BDI. However, without a placebo group, it is impossible to determine the relationships among medication treatment, mood symptoms, and cocaine use.

Increasing preclinical and clinical evidence suggests that the GABAergic agents warrant further investigation as medication treatments for cocaine dependence. Dewey and colleagues[29] found that agents which can increase GABAergic activity can attenuate cocaine's ability to increase extracellular concentrations of dopamine and gross locomotor activity in laboratory animals. The GABAergic drug gamma-vinyl GABA (vigabatrin) was found to significantly reduce cocaine-induced increases in dopamine, as measured by positron emission tomography in a baboon model, and abolish both the expression and acquisition of cocaine-induced conditioned place preference.[30] This rise in dopamine is thought to underlie the reinforcement properties of cocaine. Roberts and Andrews[31] found that cocaine self-administration in rats was suppressed after treatment with the GABAergic agent baclofen. In addition, Ling and colleagues[32] in an open-label trial found that baclofen decreased cocaine craving in human subjects. While these findings support the use of GABAergic medications as potential treatments for cocaine dependence, considerable work is needed to delineate the exact mechanism by which these agents may decrease cocaine craving.

This study is limited by the small sample size, high dropout rate, and open-label design. Open-label treatments of cocaine dependence have yielded positive results that cannot be replicated in placebo-controlled trials.[33] This is particularly true when outcome is measured without the use of objective measures such as urine drug screens (i.e., self-report only). Although we did find a significant decrease in cocaine use by urine drug screen, the high dropout rate makes this result difficult to interpret. While placebo effects may be caused by various psychosocial interventions that often accompany pharmacotherapy trials, the current study had no formal psychosocial component, which strengthens the assumption that the results seen could be because of a medication effect. Clearly, a double-blind, placebo-controlled trial would be necessary to explore this assumption. Second, while urine drug screens were obtained as an objective measure of drug use, they were only obtained once per week. This would allow missed cocaine use if the client had used prior to 48 to 72 hours before the study visit. Batki and colleagues[34] have suggested that urine drug screens be obtained at least twice per week to identify use that is short of abstinence. Finally, the dose of gabapentin used, 1200 mg/day, may have been too low to generate a maximum response. The 1200-mg dose was based on the typical dose of gabapentin found in the psychiatric literature at the time the protocol was written. More recent trials in psychiatric populations have used much higher dosages (e.g., 2000–3000 mg/day).[35]

In conclusion, the results of this pilot study suggest that gabapentin is safe and well tolerated in cocaine-dependent subjects. Gabapentin may be beneficial in reducing the craving for cocaine and cocaine use. Well-controlled studies are needed to further delineate the role of gabapentin as a potential treatment for cocaine dependence.

Drug names: carbamazepine (Tegretol and others), gabapentin (Neurontin), phenytoin (Dilantin and others).

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