Gabapentin Reduces Cocaine Use Among Addicts From a Community Clinic Sample

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Background: Individuals with chronic psychiatric conditions display a high rate of cocaine use. Gabapentin was hypothesized to reduce cocaine use by restoring inhibitory GABAergic feedback on ascending dopaminergic projections to nucleus accumbens neurons.

Method: Nine participants with DSM-IV cocaine dependence were selected from patients attending a large community psychiatric clinic. During a 24-week open-label trial of gabapentin (800–2400 mg/day), qualitative urine drug screens were collected from the participants up to 3 times per week. Data were collected from September 1999 to May 2001.

Results: With gabapentin, the mean ± SD number of cocaine-positive urine screens decreased from 53.11 ± 13.23 to 35.22 ± 14.84 ($t = 3.58$, $N = 9$, $p < .01$). The number of weeks of abstinence from cocaine increased from 2.1 ± 1.5 to 8.0 ± 5.5 ($t = 3.21$, $N = 9$, $p < .01$).

Conclusion: Gabapentin appeared to be a safe and efficacious medication to reduce cocaine usage in a community sample of psychiatric patients.

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The rates of substance use among people with serious mental illness exceed the rate encountered in the general population.[1] Estimates of comorbidity have ranged between 27% and 60%.[2] Except for alcohol, cocaine is one of the drugs most extensively used in this population.[3] Use of cocaine can undermine the potential benefits of treatment in a panoply of ways, including more frequent hospitalization, increased suicidality and violence, homelessness, increased persistence of symptoms, and poor social and vocational reintegration.[2] Many behavioral and pharmacologic approaches have been investigated to curb the use of cocaine among addicts, but cocaine addiction has proved to be a recalcitrant problem (see Kosten and Singha[4] for review). Recurrent cocaine use depletes γ-aminobutyric acid (GABA) from nucleus accumbens axon terminals contacting mesolimbic dopaminergic neurons. Hence, it was hypothesized that if GABA levels could be raised by a pharmacologic intervention, the GABAergic inhibitory tone on the activity of dopaminergic neurons projecting to the nucleus accumbens could perhaps be restored.[5] Approved as an anticonvulsant, gabapentin increases brain GABA and enhances GABA release when used in the recommended range of 800 to 2400 mg/day.[6] Experience with 2 addicts previously suggested that gabapentin was a safe and well-tolerated addition to most psychotropic medication regimens, and that it appeared to significantly alleviate cocaine use.[7] Here, we report results from a 24-week open-label trial with 9 additional psychiatric patients with cocaine dependence receiving care at a community clinic.

METHOD

After thorough discussion of the protocol, 11 patients receiving care at the Inwood Clinic of the Washington Heights Community Service (WHCS) (New York, N.Y.) consented in writing to participate in this institutional review board–approved open-label trial. Despite varying severity of mental illness, all patients displayed understanding of the purpose, method, and goal of the study. All had been referred by their therapist or psychiatrist because of severe and persistent cocaine dependence (DSM-IV criteria). Two participants were removed from the trial after 3 and 5 weeks, respectively, due to noncompliance. Of the remaining 9 participants, 7 were men, and 2 were

women. Seven also participated in the Mentally Ill, Chemically Addicted (MICA) program. This structured group activity focused on substance use lasts for 1 hour and takes place 3 times a week. Four of those 7 individuals also participated in a day program, and 3 attended only the MICA group. Two participated strictly as outpatients. These 2 participants worked at the clinic, met with a physician (W.N.R.) weekly, and provided urine samples 3 times per week. Participant ages ranged between 24 and 43 years (mean ± SD = 36 ± 6.2 years). DSM-IV diagnoses based on clinical evaluation and chart review were paranoid schizophrenia (5/9), psychosis not otherwise specified (2/9), major depression (1/9), and dysthymia (1/9). Five of the 9 participants also met criteria for cannabis dependence. Consistent with the philosophy of the WHCS, participation in this study did not modify any ongoing treatment. Medications taken by participants were haloperidol, olanzapine, fluphenazine, bupropion, trazodone, imipramine, perphenazine, risperidone, or paroxetine, either singly or in combination.

Participants received gabapentin in a dose range of 800 to 2400 mg/day under the supervision of a nurse if participating in the day program. If they participated as an outpatient (N = 2) or strictly as an MICA group participant (N = 3), gabapentin was dispensed by a physician (W.N.R.) who provided a supply sufficient until their next scheduled visit. During a typical titration, participants first received 200 mg p.o. b.i.d. for 2 days, then 400 mg p.o. b.i.d. for 2 days, then 600 mg p.o. b.i.d. for 2 days, then 1200 mg p.o. b.i.d. thereafter, 2400 mg/day being the maximum daily dose. Medication was administered in 2 divided doses per day. Participants were questioned about side effects at each medication visit. Dosage was determined and adjusted on the basis of side effect burden, thus reflecting conditions routinely encountered in a clinic setting.

Qualitative urine drug screens (cocaine, stimulants, opiates, methadone, cannabinoids) were collected up to 3 times a week as part of the MICA program for 24 weeks before and 24 weeks after the initiation of gabapentin treatment, for an expected total of 72 urine drug screens during the baseline period and 72 during the treatment period. Missed samples were counted as cocaine positive. The period of 24 weeks was chosen to evaluate the longer-term effect of continued gabapentin on cocaine use. Urine samples were sent to a commercial laboratory for a qualitative screen for drugs of abuse. The length of abstinence periods was evaluated by computing the highest number of consecutive weeks within the 24-week period with negative urine toxicology screens prior to and during treatment with gabapentin. Responders were identified as participants who displayed at least a 50% decrease in the number of sampled urine screens found positive for cocaine and who displayed at least a 50% increase in the number of weeks of abstinence from cocaine. Statistical analysis of the results of the urine toxicologies and duration of abstinence consisted of a t test for matched pairs.[8] Gabapentin levels were sampled at week 12.

RESULTS

Six (67%) of 9 participants reported a noticeable decrease in their cocaine use, while 3 (33%) of 9 did not. All participants complied with their medication. Gabapentin could be added to antipsychotic, antidepressant, or anxiolytic medications without significant side effects. Two of the 9 participants reported sedation requiring that their gabapentin dosage be reduced. The mean ± SD dose was 1266.7 ± 317.7 mg/day. The average proportion of missed urine toxicology samples was 18% (13/72) before and 21% (15/72) during treatment with gabapentin ($t = 0.98$, $N = 9$, $p > .5$).

Analysis of the data for all participants revealed that gabapentin reduced the average number of cocaine-positive urine screens from 53.11 ± 13.23 to 35.22 ± 14.84 ($t = 3.58$, $N = 9$, $p < .01$). The length of abstinence periods increased from 2.1 ± 1.5 to 8.0 ± 5.5 weeks ($t = 3.21$, $N = 9$, $p < .01$). All responders participated in the MICA program. For 4/6 responders with regular cocaine use, a lag period of 2 to 3 weeks could be detected preceding the appearance of cocaine-negative urine screens. For the other 2/6 responders, a binge pattern of use prevented determination of a lag period. Serum concentrations of gabapentin ranged between 7 and 43 mg/L and did not correlate with the decrease in the number of cocaine-positive urine screens ($r = 0.02$).

DISCUSSION

In an uncontrolled, 24-week, open-label trial carried out at a community clinic with patients in a day program, patients in a MICA group, and outpatients, gabapentin was associated with a reduction in cocaine use as evidenced by a decrease in the number of cocaine-positive urine screens and an increase in the length of abstinence periods. Gabapentin was well tolerated and could be easily added to ongoing medication regimens for medical and psychiatric conditions. While responders preponderantly carried a diagnosis of paranoid schizophrenia, an association between diagnosis and response to gabapentin must await data from a larger sample. All responders were participants in the MICA program prior to this open trial and had experienced great difficulty in achieving and maintaining abstinence from cocaine.

Participants commented on how gabapentin modified their experience of cravings and modified their pattern of cocaine use. The most frequent comments about gabapentin related to how cravings seemed easier to overcome during treatment and how gabapentin seemed to reduce the extent of cocaine use when relapses occurred.

Gabapentin is a structural analog of GABA that is permeable through the blood-brain barrier. It is surmised, as a result of its action at a neuronal, presynaptic, and widely but unevenly distributed binding site,[9] that gabapentin increases the synthesis and the release of GABA in the substantia nigra, amygdala, and thalamus.[10] In the nucleus accumbens, gabapentin antagonized evoked dopamine release.[11] Therefore, if chronic cocaine use leads to depletion of GABA terminals, this could result in an enhancement of the effect of cocaine via a relative disinhibition of mesencephalic dopamine neurons projecting to the nucleus accumbens, amygdala, and cortex. In keeping with this hypothesis, gabapentin would abate cocaine use by restoring a GABAergic inhibitory drive to mesencephalic dopamine neurons and thus reverse the allostasis that subserves cocaine addiction.[12]

In 5 of 9 participants, marijuana dependence coexisted with cocaine dependence. Gabapentin did not alter marijuana use in any of these participants; this suggests that manipulation of GABA, which may be effective in alleviating cocaine use, does not modify the distinct physiology of cannabinoids.[13]

This trial corroborates the results of a previous open trial in which the authors reported a 66% reduction in cocaine use in a group of cocaine addicts without other psychiatric comorbidity who received a fixed dose of 1200 mg/day of gabapentin for 8 weeks.[14] A significant limitation of open-label trials is the absence of a placebo. Notwithstanding the possibility of a placebo response in this trial, these results suggest that gabapentin is a promising, safe, easily tolerated, and effective adjunct treatment for cocaine use among those attending a community clinic. Results from randomized double-blind trials being conducted at our center are awaited to confirm these pilot data.

Drug names: bupropion (Wellbutrin and others), fluphenazine (Prolixin and others), gabapentin (Neurontin), haloperidol (Haldol and others), imipramine (Tofranil and others), olanzapine (Zyprexa), paroxetine (Paxil), perphenazine (Etrafon and others), risperidone (Risperdal), trazodone (Desyrel and others).

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