Clinical Experience With Gabapentin in Patients With Bipolar or Schizoaffective Disorder: Results of an Open-Label Study

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Background: This study was carried out to evaluate the efficacy, tolerability, and safety of gabapentin as an adjunctive treatment in patients with bipolar or schizoaffective disorder with manic or hypomanic symptoms.

Method: Twenty-five patients fulfilling DSM-IV diagnostic criteria for bipolar I disorder or schizoaffective disorder underwent a 16-week, open-trial treatment with gabapentin. Symptom severity was measured using the Clinical Global Impressions scale (CGI) and the Brief Psychiatric Rating Scale (BPRS). Baseline scores and final scores were compared by using the Student t test and the Friedman range variance analysis.

Results: Twenty-two patients (88%) completed the 16 weeks of treatment with gabapentin; 19 (76%) had a positive response as measured by changes in CGI and BPRS scores. The mean dose was 1440 mg/day. The only side effect observed was oversedation, which decreased with continuing treatment.

Conclusion: Gabapentin was effective in the treatment of mania and hypomania in patients with bipolar and schizoaffective disorders. If confirmed in controlled studies, these findings suggest that gabapentin represents a well-tolerated, rapidly acting antimanic agent.

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The prophylactic action of antiepileptic drugs was first observed by French[1] and Japanese[2] psychiatrists, and many studies on their value have since been performed. The anticonvulsants carbamazepine and valproate are widely used in both the acute and prophylactic treatment of affective disorders and are recognized as major therapeutic tools for lithium-nonresponsive bipolar patients.[3] Some evidence[4] suggests that the recently approved anticonvulsant lamotrigine could also be effective in both the acute and maintenance phase treatment of patients affected by treatment-resistant bipolar disorders. Although it has not been known if the mechanism of action underlying the antiepileptic properties of these drugs is responsible for their mood-stabilizing effects, it has been suggested that other antiepileptic drugs should be screened for putative thymoleptic properties.[5]

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is a new antiepileptic drug recommended as an adjunctive treatment for patients with refractory partial epilepsy.[6] Although its mechanism of anticonvulsant action is still unknown, its excellent pharmacokinetic profile, lack of interaction with other anticonvulsants, and efficacy and tolerability demonstrated in controlled studies performed in epileptic patients make gabapentin an attractive medication choice for bipolar and schizoaffective patients. At this time, the effectiveness of gabapentin as a treatment for affective disorders has been studied very little. Stanton et al.[7] described a successful treatment of acute mania with gabapentin (at 3600 mg/day) monotherapy in a 40-year-old man with DSM-IV bipolar I disorder and alcohol dependence. Shaffer and Shaffer[8] reported the positive response of 18 of 28 patients treated with adjunctive gabapentin; all patients were diagnosed with a type of bipolar disorder refractory to treatment with standard mood-stabilizing agents. A moderate response was also observed by Bennet et al.[9] in 4 of 5 inpatients with refractory bipolar I and schizoaffective disorders treated with adjunctive gabapentin. Of the 9 patients enrolled in the McElroy et al. open-label study,[10] 8 displayed a moderate or marked reduction in manic symptoms when gabapentin therapy was introduced. Conversely, Short and Cooke[11] and Lee et al.[12] described the occurrence of hypomanic symptoms after gabapentin was added to a regimen of carbamazepine and lamotrigine in the treatment of patients with epilepsy.

In order to further elucidate the efficacy, tolerability, and safety of gabapentin in patients fulfilling DSM-IV[13] diagnostic criteria for either bipolar or schizoaffective disorder, an open-label safety and varying dosage gabapentin trial was undertaken. The purpose of this study

was to evaluate the efficacy of adjunctive gabapentin in the treatment of patients with bipolar or schizoaffective disorder during manic or hypomanic episodes.

METHOD

For participation in the study, patients had to be 18 years of age or older and had to fulfill the DSM-IV diagnostic criteria for bipolar disorder or schizoaffective disorder. To be included in the study, patients had to meet DSM-IV criteria for manic or hypomanic episodes. Exclusion criteria included pregnancy, inadequate contraception, and breastfeeding in women and a recent history of alcohol or drug abuse in both men and women. After informing the subjects and giving them a complete description of the study, consent was obtained.

The initial daily dose of gabapentin was 300 mg/day, given orally in 1 dose at night. Doses were subsequently increased by 300 mg/day every 4 days, according to patient response and side effects, to a maximum dose of 2400 mg/day. Doses were usually given b.i.d. or t.i.d.

Psychotropic agents such as benzodiazepines and neuroleptics already prescribed at baseline were maintained, while other mood stabilizers such as lithium, carbamazepine, and valproate were tapered off. The changeover from other mood stabilizers to gabapentin was simultaneous over a period of 4 weeks. The substitution of the mood stabilizer was necessary because of the presence of severe side effects. The substitution or addition of gabapentin was the only manipulation during the course of the study (16 weeks), and gabapentin was the only mood stabilizer used in our patients.

An extensive physical and neurologic examination was performed on all patients prior to initiation of the trial, and plasma samples were obtained at baseline and 2 weeks after the initiation of the therapy for laboratory tests including measures of electrolytes and thyroid, renal, hepatic, and hematologic status. Urine analysis was carried out at the same intervals. Patients were visited every 15 days (or more frequently if needed) to assess response and side effects, to record compliance, and to adjust doses as necessary. Throughout the study period, patients were rated by the same clinician. Patients could be withdrawn from participation in the study at their request or on the basis of clinical judgment or abnormal safety assessments.

Psychopathologic evaluation and severity assessments were performed at baseline and every 2 weeks using 2 psychiatric rating scales: (1) the Clinical Global Impressions scale (CGI),[14] which contributes to the formulation of an overall opinion in 3 areas: the seriousness of the illness, the general improvement, and the rate of therapeutic efficacy; and (2) the Brief Psychiatric Rating Scale (BPRS),[15] which includes an 18-item assessment of various psychiatric symptoms, including affective and psychotic symptoms, and on which individual item scores range from 1 (not present) to 7 (extremely severe).

Table 1. Clinical Characteristics of Patients

Characteristic	N
Number of patients	
Entering study[a]	25
Completing study	22
Sex	
Male	12
Female	13
Diagnosis	
Bipolar I disorder	16
Schizoaffective disorder, bipolar type	9
Symptomatology	
Manic symptoms	9
Hypomanic symptoms	16

[a]Mean age = 44.5 years; range, 19–82 years.

The primary assessment of the therapeutic effect was the BPRS total score, the CGI severity of illness score, the CGI change score, and the BPRS change score (or "improvement score," baseline score minus week 16 score). Statistical analysis was performed by using the Student t test for paired data with the degree of freedom indicated in each case, and the range variance analysis with the Friedman method. Values are given as the mean ± SD.

RESULTS

Subjects

Twenty-five patients (12 men, 13 women; mean age = 44.5 years; range, 19–82 years) who met the inclusion criteria for participation in the study were enrolled. The diagnosis was DSM-IV bipolar I disorder in 16 cases and schizoaffective disorder bipolar type in 9 cases; 16 patients presented hypomanic episodes and 9 manic episodes (6 of them were dysphoric). None of the patients presented a history of rapid cycling. The clinical characteristics of the patients are summarized in Table 1.

Clinical Response

Twenty-two patients completed the 16-week study, while 3 patients (2 with hypomanic symptoms and 1 with manic symptoms) discontinued in the second week of treatment, 2 because of noncompliance and 1 because of inadequate clinical response (increase of hypomanic symptoms and the occurrence of behavioral agitation in an 82-year-old patient). Of the 22 patients treated with gabapentin for at least 16 weeks, 19 (76% of the original 25) had a positive response as judged by both the treating psychiatrist and the patient. The CGI severity rating at baseline was 4.0 ± 1.2 and at week 16 was 2.3 ± 1.1. The CGI change score was statistically significant ($t = 8.5$, $df = 21$, $p < .0001$). The BPRS score at baseline for these patients was 29.1 ± 7.1 and at week 16 was 21.3 ± 3.3. The BPRS score showed statistically significant reduction ($t = 28.2$, $df = 11$, $p < .0001$). In the patients with manic

episodes (N = 8), the BPRS score at baseline was 37.1 ± 5.8 and at week 16 was 22.7 ± 3.0. The analysis of variance indicated that the reduction in scores was statistically significant ($\chi^2 = 51.2$, df = 8, $p < .001$). In the patients with hypomanic episodes (N = 14), the BPRS score at baseline was 24.5 ± 1.8 and at week 16 was 20.5 ± 3.3. The analysis of variance indicated that the reduction in scores was statistically significant ($\chi^2 = 53.4$, df = 8, $p < .001$).

Overall, patients showed improvement 2 to 4 weeks after the addition of gabapentin to their ongoing psychotropic regimens.

Dosage

The mean dose used to treat our psychiatric patients was 1440 mg/day (range, 900–2400 mg). There was no clear relationship between the daily dosage of gabapentin and the clinical response.

Adverse Effects

The most common side effect was oversedation that was initially of moderate intensity in 11 patients (44%), decreasing to mild intensity with continuing treatment. With the low dosage used, no other undesirable side effects occurred. There were no clinically significant abnormalities in vital signs throughout the study.

DISCUSSION

These data in 25 patients suggest that gabapentin may have antimanic efficacy in bipolar and schizoaffective disorders. Twenty-two patients completed 16 weeks of treatment, and 19 of the 22 patients showed a positive response during the course of the treatment with gabapentin. Clinical improvement was evident after 14 days of treatment with gabapentin and reached maximum effects over 7 or 14 days of full dosage. The mean dose used to treat our psychiatric patients was 1400 mg/day. There was no clear relationship between the daily dosage of gabapentin and the clinical response.

Gabapentin is a relatively safe medication according to neurologic literature.[16] In our study, gabapentin showed an acceptable degree of overall tolerability, there being only 1 adverse event (oversedation) reported during the course of the 16 weeks of treatment, and it was transient and of only mild intensity.

At present, it is not possible to determine whether gabapentin represents only an adjunct treatment or is the relevant factor in the treatment of acute mania, since complete withdrawal of all other drugs has not been attempted in patients for ethical reasons. The evidence suggests that although gabapentin alone may be suitable for the control of the hypomanic or mildly disturbed manic patient who retains some insight, neuroleptics are necessary for immediate control of behavior and mood in more active patients.

This type of therapy appears rather specific insofar as it is nonsedative and, apparently, from a psychopathologic point of view, acts specifically on the core symptoms of mania (elation, megalomania, decreased sleep requirements, pressure of speech, flight of ideas, distraction, and psychomotor agitation). It has a significant antianxiety and antiagitation effect.

The hypothesis that hypofunction of GABA in the central nervous system may be involved in the pathogenesis of manic syndromes was initially proposed by Van Kammen.[17] This concept, which has received verification in experiments targeting the role of GABA in major affective disorders,[18–20] is supported by the finding that GABAergic anticonvulsants possess antimanic properties and are also used in the prophylaxis of manic depression. Involvement of GABAergic transmission in the mode of action of gabapentin may not, however, represent the only possible explanation for the effects of gabapentin in affective disorders. A further, highly interesting, possible alternative regarding the mode of the action of lithium-like compounds is their calcium antagonistic property. The effects of anticonvulsants on neuronal calcium fluxes are under current investigation.[21]

Although the question as to the molecular mode of action of anticonvulsants in the treatment of affective disorders cannot, as yet, be answered, the application of these compounds appears highly promising and is an important addition to the therapeutic arsenal for the management of these types of psychoses. The pattern of response and nonresponse to gabapentin therapy is similar to that seen in most studies of the acute treatment of bipolar and schizoaffective patients with carbamazepine and lithium (50%, marked or moderate response; 25%, slight response).[3]

The findings of our study must be regarded as preliminary and in need of replication in double-blind or placebo-controlled trials. A longer trial period might have rendered more definitive results. If confirmed in controlled studies, these findings suggest that gabapentin represents a well-tolerated, rapidly acting antimanic agent. Gabapentin may become an alternative treatment approach for patients with resistant affective illness or for those patients who are unable to tolerate the side effects of lithium.

Drug name: carbamazepine (Tegretol and others), gabapentin (Neurontin), lamotrigine (Lamictal).

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