Gabapentin Treatment of Mood Disorders: A Preliminary Study

S. Nassir Ghaemi, M.D.; Jacob J. Katzow, M.D.; Sonal P. Desai; and Frederick K. Goodwin, M.D.

Objective: To determine if gabapentin is effective either as adjunctive treatment or as monotherapy for major affective disorders in a naturalistic setting.

Method: All charts of patients meeting DSM-IV criteria for bipolar disorder or unipolar major depressive disorder treated with gabapentin in a private psychiatric practice were reviewed and clinical response was assessed retrospectively using the Clinical Global Impressions scale for Improvement (CGI-I).

Results: Gabapentin was moderately to markedly effective in 30% (15/50) of patients, with statistically nonsignificant differences between patients with bipolar disorder type I, bipolar disorder type II and NOS, and unipolar major depressive disorder. 70% reported side effects, mainly sedation, with 16% of the total sample discontinuing treatment due to adverse events.

Conclusion: Gabapentin appears to be somewhat effective as add-on treatment in a subgroup of patients with mood disorders in a naturalistic setting. Prospective, controlled studies are required to clarify these pilot data.

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Received Oct. 3, 1997; accepted Jan. 12, 1998. *From the Psychopharmacology Research Center, Department of Psychiatry, The George Washington University, Washington, DC.*

Reprint requests to: S. Nassir Ghaemi, M.D., George Washington University, Department of Psychiatry, 2150 Pennsylvania Ave NW, 8th Floor, Washington, DC 20037.

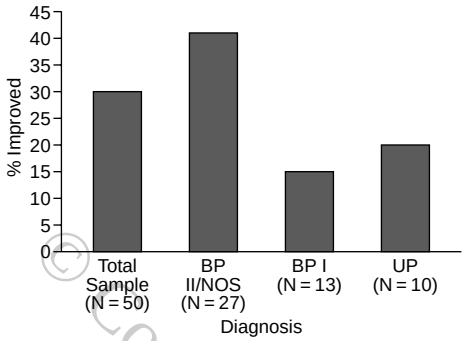
Gabapentin, a new anticonvulsant with gabaergic and glutaminergic properties, has demonstrated some anxiolytic and mood-altering effects in initial clinical trials in patients with epilepsy.[1,2] These reports are consistent with the possible role of the neurotransmitter gamma-aminobutric acid (GABA) in the pathophysiology of mood disorders,[3] although gabapentin's exact mechanism in treating seizures or mood symptoms is unknown. It has few side effects, with no known potentially fatal effects, and minimal drug interactions. Patients frequently express an interest in using gabapentin rather than standard mood-stabilizing agents (like lithium carbonate, divalproex sodium, or carbamazepine) due to its limited side effect profile. Thus, clinical interest regarding its use in mood disorders has grown. To date, there are 3 preliminary abstracts, 4 letters to the editor, and 1 original article regarding its effect in mixed samples of psychiatric patients. These reports vary in quality. One is double-blind and compares gabapentin with lamotrigine in monotherapy treatment of bipolar disorder, type I or II; however, at this date, only preliminary results are available, with the gabapentin response rate reported to be 39%.[4] A number of others did not identify how treatment response was established or how diagnoses were established, and the indications for treatment were not limited to mood disorders; in these studies, reported responses ranged from 63% to 92%.[5–7] One study was a case report of a single patient with acute mania who improved with gabapentin alone,[8] and another a case series of moderate to marked improvement in 4 of 5 patients with bipolar or schizoaffective disorders receiving adjunctive gabapentin.[9] Only 2 studies defined their diagnostic methods using DSM-IV criteria and utilized rating scales to assess treatment response, 1 finding a 53% (8/15) response (alone or with mood stabilizers) in bipolar depression (type I or type II),[10] and another finding a 78% (7/9) response in adjunctive treatment of hypomania, mania, or mixed episodes.[11] In some of these studies, the effect of concomitant medications may be either to erase or to enhance the perceived effectiveness of gabapentin, particularly in patients with bipolar disorder. It is known, for instance, that patients with bipolar disorder, type I, may respond poorly to otherwise effective medications if they are also treated with antidepressant medications.[12]

Since this study is also naturalistic and retrospective, it shares many of the limitations of the above reports. However, it does provide initial pilot data in the same sample regarding the possible effectiveness of gabapentin in bipolar disorder type I, other parts of the bipolar spectrum (bipolar disorder type II and NOS), and unipolar major depressive disorder.

METHOD

Charts of all patients with mood disorders treated in a private outpatient psychiatric practice with gabapentin for

Figure 1. Treatment Response to Gabapentin for Mood Disorders in 50 Patients*



*Abbreviations: BP II/NOS = bipolar disorder, type II, or bipolar disorder, NOS; BP I = bipolar disorder, type I; UP = unipolar major depressive disorder. Response based on moderate to marked improvement on Clinical Global Impressions scale for Improvement (score ≥ 2). Differences were not statistically significant (p = .16 for BP II/NOS vs. BP I; p = .44 for BP II/NOS vs. UP; Fisher exact test).

any duration in a 1-year time frame were collected. Informed consent was obtained for chart review. Fifty-seven patients were identified, and 7 were excluded from further review due to insufficient data in the charts regarding response or side effects with gabapentin treatment or due to refusal of informed consent. Fifty patients were included in the study (10 with unipolar major depressive disorder; 13 with bipolar disorder, type I; 19 with bipolar disorder, type II; and 8 with bipolar disorder, NOS). Their charts were reviewed for the following clinical and demographic variables: age, sex, concurrent medications, mood stabilizer use and dosage, evidence regarding poor response to standard mood stabilizers before gabapentin use, evidence regarding whether during gabapentin treatment mania or hypomania occurred, adverse events, maximum and maintenance gabapentin dose and duration of treatment, indications for treatment with gabapentin, whether or not gabapentin was discontinued, reason for discontinuation of gabapentin, family history of psychiatric disorders, age at onset of illness, and current substance abuse. Concomitant medications for bipolar disorder were lithium, valproate, and carbamazepine and for unipolar depression were tricyclic antidepressants, serotonin selective reuptake inhibitors, bupropion, venlafaxine, and nefazodone. Treatment response was established based on the retrospective application after chart review of the Clinical Global Impressions of Improvement scale (CGI-I) as follows: –3 = very much worse, –2 = much worse, –1 = slightly worse, 0 = unchanged, +1 = slightly improved, +2 = much improved, +3 = very much improved. Treatment response scores were assigned on the basis of chart review by 1 of the psychiatrists (S.N.G.) through a consensus agreement with the treating clinician (J.J.K.). Diagnoses were assigned after chart review through a consensus agreement between the treating clinician (J.J.K.) and 1 of the other psychiatrists with expertise in affective disorders (S.N.G.) by the application of DSM-IV criteria for unipolar major depressive disorder, bipolar disorder type I, and bipolar disorder type II. The diagnosis of bipolar disorder, NOS, was made using DSM-IV criteria augmented by the recommended criteria of Akiskal,[13] in order to assess possible effects of gabapentin on a broad definition of the bipolar spectrum. Indications for treatment (acute depression, mood elevation, or mood cycling) were established based on a similar review of the chart and clinician report. While some of these patients had not responded sufficiently to standard antidepressant and mood-stabilizing treatments, many refused to take standard treatments and preferred a trial of gabapentin despite its lack of proven efficacy.

Statistical analyses consisted of descriptive statistics and unpaired t test comparisons between groups.

RESULTS

The mean age ± standard deviation of the sample was 44.6 ± 12.3 years (range, 18–73), with 22 males, and 28 females. The mean dose of gabapentin used was 1597 ± 1195 mg/day (range, 100–5600) for a mean duration of 12.8 ± 9.9 weeks (range, 1–38). The mean maximum dose used was 1699 ± 1237 mg/day (range, 100–6000).

As shown in Figure 1, the overall response rate in the total sample based on moderate to marked response on the CGI-I (score ≥ 2) was 30% (15/50). Response in the other parts of the bipolar spectrum (bipolar disorder, type II, and bipolar disorder, NOS; 11/27, 41%) was over twice that of bipolar disorder type I (2/13, 15%, p = .16, Fisher's exact test) or unipolar major depressive disorder (2/10, 20%, p = .44, Fisher's exact test), but these differences were not statistically significant.

The most common indications for treatment were major depressive symptoms (N = 29, 58%) and rapid-cycling bipolar episodes (N = 12, 24%) followed by mixed bipolar symptoms (N = 6), hypomanic symptoms (N = 2), and manic symptoms (N = 1). Response rates remained similar when assessed based on indication of treatment for acute major depressive symptoms (8/29, 28%) or for rapid-cycling episodes (3/12, 25%).

Among all bipolar spectrum patients (type I, type II, and NOS; N = 40), 18 (45%) were receiving standard mood-stabilizing agents, and 29 (73%) were receiving antidepressant medications. Thus, a number of patients were receiving both antidepressant and mood-stabilizing medications. Response rates remained similar when assessed only in bipolar patients not taking antidepressant medications (3/11, 27%), and somewhat lower in bipolar patients also receiving concomitant standard mood-stabilizer pharmacotherapy (2/18, 11%). These differences were not

Table 1. Cases of Hypomania Induced by Gabapentin (N = 4)

Patient	Indication	Concomitant Medications (mg/day)	Diagnosis[a]	Discontinued Gabapentin
1	Depression	Fluoxetine (10)	BP II	No
2	Depression	Paroxetine (30)	BP I	Yes
3	Depression	Alprazolam (dose unclear)	BP NOS	Yes
4	Mixed symptoms	Bupropion (200) Lithium (600)	BP II	No

[a]BP I = bipolar disorder, type I; BP II = bipolar disorder, type II; BP NOS = bipolar disorder, NOS.

statistically significant when compared with response rates in the diagnostic groups of Figure 1. Doses of mood stabilizers used were as follows: lithium, 850 ± 366 mg/day, in 17 patients; valproate, 913 ± 699 mg/day, in 13 patients; carbamazepine, 500 ± 424 mg/day, in 2 patients. Sufficient data points were not available on serum levels to provide representative mean results. Only 4 patients received gabapentin alone, with 2 improving, 1 unchanged, and 1 much worse.

Seventy percent (35/50) reported some side effects, usually sedation (48%, N = 24), followed by increased appetite (N = 5) with noticeable weight gain in 2 patients, cognitive and memory difficulties (N = 3), anxiety and agitation (N = 3), dizziness (N = 2), decreased appetite, headache, ataxia, acne, and tremor (N = 1 each). Twenty-one (42%) eventually stopped gabapentin treatment, 13 (26%) due to lack of effectiveness, and 8 (16%) due to adverse events. Adverse events leading to discontinuation were increased depression and sedation (N = 2 each), dizziness, increased agitation, memory difficulties, and weight gain (N = 1 each).

Manic symptoms appeared to occur in 4 patients. As can be seen in Table 1, none of these patients were receiving gabapentin alone, 3 were receiving antidepressant medications with gabapentin, and 1 was receiving a medication (alprazolam) that may have antidepressant properties. Only 1 patient was receiving mood stabilizers (lithium) and at a subtherapeutic mood-stabilizing dose. In 2 cases (patients 1 and 4), the manic symptoms consisted of a possible mild initial hypomanic episode followed by improvement and continuation on the medication. In the other 2 cases (patients 2 and 3), patient 2 reported "extreme mood swings" within 2 days of starting gabapentin, "a speedy feeling" which diminished when concomitant paroxetine was discontinued; later, divalproex sodium, 250 mg/day, was added to gabapentin, and olanzapine treatment was also added, but there was no better than mild improvement overall, and gabapentin was discontinued after 32 weeks. In patient 3, gabapentin added to alprazolam resulted in a hypomanic episode lasting 6 weeks, which was followed by a severe major depressive episode, leading to gabapentin discontinuation.

DISCUSSION

Gabapentin appeared effective in about one third of patients with mood disorders, consistent with part of our hypothesis. While response in the other parts of the bipolar spectrum (type II or NOS) seemed better than in bipolar disorder type I or unipolar major depressive disorder, these differences were not statistically significant, possibly due to type II error. These results are less robust than in the previous initial open reports of gabapentin response in psychiatric disorders. This may be the product of the methodological differences between this study and the other reports, as discussed in the introduction. When statistical analysis controlled for the effect of concomitant medications, such as mood stabilizers and antidepressants, no significant differences in treatment response were noted. Too few patients were treated in monotherapy (N = 4) to more cleanly gauge the effect of gabapentin in these patients. However, these data are similar to a preliminary report on double-blind treatment with gabapentin monotherapy, in which the response rate in bipolar disorder type I was reported to be 39%.[4]

It can be difficult to clearly detect the effect of gabapentin when added to complicated treatment regimens in a naturalistic setting, such as this one. Nonetheless, a 30% treatment effect was clinically significant and was judged to be an important and useful treatment alternative by the clinicians and patients involved. Since most of these patients were not treatment-resistant, gabapentin seemed most helpful in those who preferred not to take other mood-stabilizing medications, such as lithium or carbamazepine, due to the higher risk of significant side effects. Although not statistically significant, there appeared to be some advantage in clinical response to gabapentin in bipolar disorder type II or NOS compared with bipolar disorder type I. Given these patients' limited mood-elevation symptoms (by definition, in bipolar disorder type II or NOS compared with bipolar disorder type I) and their unwillingness to take standard mood-stabilizing agents due to perceived excessive side effect risks, gabapentin appeared to be a good choice in a risk-benefit analysis for the bipolar spectrum.

The few cases of apparent mania or cycling after gabapentin treatment should be interpreted with caution given the uncontrolled nature of these observations. However, a few other reports of gabapentin-induced hypomania or possibly mania have been reported.[5,14] It should be emphasized that the cases noted in our study involved patients with bipolar disorder who were receiving less than therapeutic doses of mood stabilizers and also were receiving antidepressant medications. These 2 factors in combination with gabapentin may put susceptible individuals at risk of hypomania or mania. Even so, in 2 of the 4 cases, the hypomania was transient and followed by mild clinical improvement.

Limitations of the Current Study

The results of this study should be interpreted with caution because of a number of limitations. First, these data are open, uncontrolled, and retrospective; also, treatment assessments partially involved the assessment of the treating clinician; thus, these data are open to bias in testing hypotheses. Second, the lack of statistically significant differences may reflect type II error, i.e., absence of statistical power due to small sample sizes. Third, the naturalistic circumstances of treatment, especially the frequent use of concomitant therapy may have obscured the real treatment affect of gabapentin. We tried to control somewhat for these effects in the subanalyses of bipolar patients not taking antidepressants, for example, and failed to find any significant differences in response; however, the small sample sizes in subanalyses may again have limited statistical power.

CONCLUSION

Gabapentin appears to be effective in a subgroup of patients with mood disorders. It may be particularly useful in milder segments of the bipolar spectrum, where its effectiveness and its low side effect profile maximize the risk-benefit analysis in its favor. Further prospective controlled data are required to clarify the efficacy of gabapentin in mood disorders.

Drug names: alprazolam (Xanax), bupropion (Wellbutrin), carbamazepine (Tegretol and others), divalproex sodium (Depakote), gabapentin (Neurontin), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), venlafaxine (Effexor).

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