A Double-Blind, Randomized, Placebo-Controlled, Prophylaxis Study of Adjunctive Gabapentin for Bipolar Disorder

Eduard Vieta, M.D., Ph.D.; José Manuel Goikolea, M.D.; Anabel Martínez-Arán, Psy.D., Ph.D.; Mercè Comes, Ps.N.; Katia Verger, Ph.D.; Xavier Masramon, B.Sc.; Jose Sanchez-Moreno, Psy.D.; and Francesc Colom, Psy.D., Ph.D.

Objective: To conduct the first randomized, controlled trial assessing the prophylactic efficacy of gabapentin in bipolar disorder.

Method: We conducted a 1-year, double-blind, randomized, comparative, placebo-controlled, parallel-group, multicenter study. As this was a pure prophylactic trial, only euthymic bipolar I and II patients (DSM-IV) were randomly assigned in a 1:1 ratio to gabapentin (N = 13) or placebo (N = 12) added to the current treatment (lithium, valproate, carbamazepine, or any combination but not antipsychotics or antidepressants). Subjects participated in the study for 12 months. The primary efficacy parameter was the Clinical Global Impressions scale for Bipolar Illness, Modified (CGI-BP-M), which was assessed at all visits. Other assessments were the Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), Pittsburgh Sleep Quality Index (PSQI), and the systematic collection of reported adverse events. Data were collected from May 1999 to February 2004.

Results: The change from baseline to month 12 in mean CGI-BP-M scores between groups was statistically significant (p = .0046). Mean score change from baseline to endpoint in the gabapentin group was –2.1, and the mean score change in the placebo group was –0.6. No emerging manic or depressive symptoms were seen in either group as measured with the YMRS, HAM-D, HAM-A, and PSQI. In the PSQI-6 subscale (use of sleeping medication), the mean score change at month 12 in the gabapentin group was 0.9, and the mean score change in the placebo group was 0.05 (p = .0267). Overall, gabapentin was well tolerated.

Conclusion: This small, randomized clinical trial comparing the prophylactic efficacy of adjunctive gabapentin to placebo suggests that, despite lack of acute efficacy, treatment with gabapentin might provide some benefit on the long-term outcome of bipolar disorder.

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Received June 7, 2005; accepted Aug. 25, 2005. *From the Bipolar Disorders Program, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain (Drs. Vieta, Goikolea, Martínez-Arán, Sanchez-Moreno, and Colom and Ms. Comes); the Investigation, Development, and Innovation Department, Pfizer S.A., Madrid, Spain (Dr. Verger); the Euroclin Institute, Barcelona, Spain (Mr. Masramon); the Department of Psychiatry, Autonomous University of Madrid, Madrid, Spain (Dr. Sanchez-Moreno); and the Department of Psychological Medicine, Institute of Psychiatry, London, England (Dr. Colom).*

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Corresponding author and reprints: Eduard Vieta, M.D., Ph.D., Neuroscience Institute, Hospital Clínic, University of Barcelona, IDIBAPS, Villarroel 170, Barcelona 08036, Spain (e-mail: evieta@clinic.ub.es).

Although bipolar disorder is a highly recurrent condition, truly prophylactic trials are scarce. Even rarer are combination prophylactic trials, despite clear evidence that most patients are treated with combinations of several drugs.[1] Most long-term trials assess efficacy starting from an index acute episode, which is generally manic, and randomly assign responders to either study drug or placebo, enriching their samples from both the efficacy and tolerability points of view. The downsides of this approach are limited generalizability and the difficulties of applying this design to drugs that fail to show acute efficacy. However, clinicians are often faced with the need to introduce a second mood stabilizer in patients who are not in an acute episode but have a highly recurrent course and poor outcome. Lithium and especially lamotrigine may be examples of drugs that work better for the prevention of relapse than for the treatment of acute episodes.[2] Gabapentin might be another one.

Gabapentin is an anticonvulsant that has been reported to be effective and well tolerated in several open-label studies involving patients with bipolar disorder.[3–8] However, controlled trials have failed to show any efficacy of this drug on acute episodes,[1,9] and the interest in researching further has progressively declined. However, the real challenge in bipolar disorder is the improvement of the long-term outcome. Some anticonvulsants are better for prevention than for acute treatment, owing to their mechanism of action. For instance, several anticonvulsants, including gabapentin, may be effective for the prevention of seizures or migraine but not for the acute treatment of these conditions.[2] It might well be the same case with bipolar illness. For this reason, we aimed to design a purely prophylactic trial that would address the potential long-term efficacy and safety of gabapentin in bipolar disorder. The trial was designed as a proof-of-concept, pilot study, and, therefore, sample size and assessments are limited.

METHOD

Twenty-five subjects aged from 18 to 75 years with a diagnosis of bipolar I or II disorder (according to DSM-IV criteria) treated with any standard mood stabilizer like lithium, valproate, carbamazepine, or any combination during the last year were recruited. Other inclusion criteria were as follows: 2 bipolar episodes or more during the last year, Clinical Global Impressions scale for Bipolar Illness, Modified (CGI-BP-M)[10] score ≥ 4, last episode having occurred within 6 months prior to randomization, and, if the subject was treated with thyroxine, stable treatment during the last year. Importantly, the patients had to be euthymic at randomization, defined as a score of 8 or less on the Hamilton Rating Scale for Depression (HAM-D)[11] and 4 or less on the Young Mania Rating Scale (YMRS).[12] Therefore, patients had to be in clinical remission at study entry, allowing the assessment of the actual prophylactic effects of the therapy. Indeed, this rather unusual design caused a number of protocol violations, as some patients who were initially enrolled had to be excluded because they were not in remission at study entry.

Excluded patients were those with previous hypersensitivity to gabapentin; women who were pregnant or nursing or planning to become pregnant during the study period; patients receiving an experimental drug within 3 months prior to the screening period; patients with a history or clinical evidence of any cardiovascular, hematologic, liver, or renal disorder; patients with a history of severe diseases requiring continued medical treatment during the previous 6 months; and those with current illegal drug or alcohol abuse/dependence.

The primary efficacy parameter was the CGI-BP-M, which was assessed at all study visits. The CGI-BP-M is a modified version of the CGI-BP,[13] which includes a subscale for the assessment of long-term outcome and 2 subscales for the assessment of acute manic and depressive symptoms.[10] This clinician-rated instrument measures the severity of symptoms (subscales for manic and for depressive symptoms) and the severity of the disorder (primary outcome of this trial on a 7-point scale ranging from 1 [not ill at all] to 7 [the most extremely ill patient]). This scale has been used in several studies before.[14,15]

Other assessments include the YMRS, the HAM-D, the Hamilton Rating Scale for Anxiety (HAM-A),[16] the assessment of sleep quality by the Pittsburgh Sleep Quality Index (PSQI),[17] and the time from randomization to first new episode. Side effects were systematically collected.

The protocol was approved by the ethics committee of each participating center. Seven centers participated in this trial across Spain. The study was planned and conducted in accordance with the Declaration of Helsinki. Twenty-five subjects were eligible to take part in the study according to the above-mentioned criteria. All provided signed consent after a detailed explanation of the study procedures. The randomization was generated confidentially by the sponsor (K.V. and X.M., Pfizer S.A., Spain) prior to the study using the SAS Statistical Package (SAS Institute, Inc.; Cary, N.C.) for the computer. Both subjects and clinicians were blinded regarding gabapentin/placebo assignment.

Subjects received medication daily in 1:1 ratio. Thirteen subjects were included in the gabapentin group, and 12 subjects were included in the placebo group. Treatment started the day after randomization. Randomly assigned patients were titrated during 1 week, and they received gabapentin or placebo added to the previous treatment (lithium, valproate, carbamazepine, or any combination) and no treatment with antipsychotics or antidepressants. Patients who received gabapentin started with an initial dosage of 1200 mg/day; this dosage was maintained until the end of the study. In the presence of emerging symptoms, the dosage could be increased up to 2400 mg/day in either arm, and, in the presence of a drug-related adverse event, the dosage could be reduced to 900 mg/day. The drug was taken 3 times a day. At each visit, the patient was assessed for any mood disorder according to DSM-IV criteria. Lithium, carbamazepine, and gabapentin levels were monitored, but gabapentin levels were maintained blinded until the end of the study. Additional visits could be scheduled if the patient showed symptoms of a potential episode during the interval between follow-up visits. The trial duration was 1 year.

All statistical analyses were done by intention to treat and last observation carried forward. Changes from baseline were analyzed by analysis of covariance including effects for treatment, center, number of previous episodes before randomization, and baseline value as a covariate in the model. The primary outcome measure was the CGI-BP-M endpoint score for severity of the disease;

Table 1. Demographic and Clinical Characteristics of Patients With Bipolar Disorder at Baseline

Variable	Gabapentin (N = 13)	Placebo (N = 12)	Total (N = 25)
Sex, N (%)			
Men	3 (23.1)	4 (33.3)	7 (28.0)
Women	10 (76.9)	8 (66.7)	18 (72.0)
Age, mean (SD), y	46.2 (14.3)	47.6 (15.8)	48.6 (14.7)
Weight, mean (SD), kg	74.6 (13.8)	63.8 (12.1)	69.4 (13.9)
Seasonal pattern, N (%)[a]	3 (25.0)	2 (16.7)	5 (20.8)
Rapid cycling, N (%)	5 (38.5)	6 (50.0)	11 (44.0)
Bipolar II, N (%)	1 (7.7)	5 (41.7)	6 (24.0)
Time from diagnosis, mean (SD), y	20.9 (11.5)	16.5 (10.5)	18.8 (11.0)
No. of episodes, mean (SD)			
Total	33.8 (25.1)	17.8 (18.7)	25.8 (23.1)
Manic	6.8 (8.3)	4.1 (6.3)	5.5 (7.4)
Hypomanic	6.6 (7.9)	5.1 (7.6)	5.8 (7.6)
Depressive	19.3 (19.0)	8.3 (7.9)	13.8 (15.3)
Mixed	0.8 (1.6)	0.4 (0.9)	0.6 (1.3)
No. of hospitalizations, mean (SD)	4.1 (5.4)	2.4 (2.3)	3.3 (4.2)

[a]Data missing for 1 of the gabapentin patients.

this score reflects long-term outcome rather than cross-sectional symptoms, which are addressed with the mania and depression CGI-BP-M subscales. Other secondary efficacy parameters such as time from randomization to first new episode were analyzed using a Cox proportional hazards model including effects for treatment, center, number of previous episodes before randomization, and baseline value as a covariate in the model. Output from the Cox model included the hazard ratio point estimate and 95% confidence interval for treatment, along with its associated p value. Kaplan-Meier curves were constructed to summarize time from randomization to first new episode by treatment group. Data were collected from May 1999 to February 2004.

RESULTS

The patients' demographic and clinical baseline data at the time of randomization are shown in Table 1. At the beginning of the study, both groups, gabapentin and placebo, had similar CGI-BP-M, YMRS, HAM-D, HAM-A, and PSQI scores, and there were not relevant clinical differences. Of the 25 patients with bipolar disorder in remission who were randomly assigned, 13 subjects in the gabapentin group and 12 subjects in the placebo group, 13 subjects (52%) completed the study, 7 subjects (54%) from the gabapentin group and 6 subjects (50%) from the placebo group. The reasons for discontinuation in the gabapentin group were as follows: 2 subjects (15%) no longer wanted to participate in the study, 2 subjects (15%) had lack of efficacy, 1 subject (8%) had adverse events, and 1 subject (8%) had other reasons. The reasons for discontinuation in the placebo group were as follows: 3 patients (25%) no longer wanted to participate in the study, 1 subject (8%) had lack of efficacy, 1 subject (8%) had adverse events, and 1 subject (8%) had other reasons.

Mean score changes from baseline to month 12 in both groups are summarized in Table 2. The change in CGI-BP-M score between groups was statistically significant (gabapentin –2.1, placebo –0.6, p = .0046). As expected, because patients had to be in remission at baseline, no significant differences between groups were found in YMRS, HAM-D, HAM-A, and PSQI scores. However, for the PSQI-6 subscale (use of sleeping medication), the score change at month 12 in the gabapentin group was –1.1 and the change in the placebo group was –0.6 (p = .0267). Figure 1 shows the evolution of the CGI-BP-M scores in both groups and p values at all visits. Time from randomization to first new episode is shown in Figure 2. There was no significant difference between placebo and gabapentin with regards to this variable (p = .6658). The associated hazard ratio was 1.344.

Ten patients (77%) in the gabapentin group and 7 taking placebo (58%) reported adverse events, mostly mild. The most frequent ones, involving more than 10% of patients in the gabapentin group, were constipation, N = 4 (31%); headache, N = 3 (23%); nausea, N = 3 (23%); dizziness, N = 2 (15%); insomnia, N = 2 (15%); and tremor, N = 2 (15%). Only 1 patient in each group discontinued the study owing to an adverse event, including a patient who was randomly assigned to gabapentin and suffered a myocardial infarction that was not considered to be related to the treatment.

DISCUSSION

This is, to the best of our knowledge, the first "pure" prophylactic study in bipolar disorder conducted to date. Although a number of studies have assessed the efficacy of several different drugs as compared to placebo in relapse prevention,[18–20] the concept of prophylaxis has a rather different meaning: relapse prevention is the outcome of trials with enriched designs, in which the drug tested is administered acutely and responders are subsequently randomly assigned to either the same drug or placebo. Those studies[18–20] assessed, in fact, whether it was worthwhile or not to continue with the drug after remission from the acute episode. Examples of trials that had 100% enriched samples are the long-term lamotrigine studies[19,21] and the long-term olanzapine studies.[20,22,23] These 5 modern trials benefited from the lessons learned with a previous failed, long-term study comparing divalproex, lithium, and placebo[24,25] that did not enrich 100% of the sample, failing to separate on the primary outcome.[25,26] Other modern long-term studies comparing lithium with carbamazepine[27,28] assessed partially enriched samples as well.

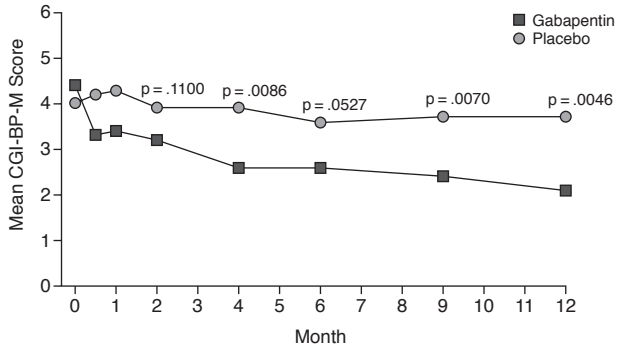
Pure prophylactic trials are designed to assess the long-term outcome of patients who initially received the

Table 2. Efficacy Parameter Scores at Month 12 and Change in 12-Month Scores From Baseline for Patients With Bipolar Disorder Randomly Assigned to Adjunctive Gabapentin Treatment or Placebo

	Gabapentin (N = 13)		Placebo (N = 12)		Change From Baseline				
Scale	Mean	SD	Mean	SD	Gabapentin (N = 13), Mean	Placebo (N = 12), Mean	Difference,[a] %	95% CI	p Value[b]
CGI-BP-M	2.1	1.6	3.7	1.4	–2.1	–0.6	1.5	0.5% to 2.5%	.0046
YMRS	5.5	9.3	1.8	3.8	3.1	–0.6	3.7	–2.2% to 9.5%	.2038
HAM-D	6.3	7.5	7.5	6.0	1.3	2.5	1.2	–4.9% to 7.4%	.6753
HAM-A	7.4	7.5	6.9	5.6	–0.3	–0.9	0.6	–5.4% to 6.5%	.8443
PSQI-Total	6.0	4.1	7.4	3.6	–1.3	0.2	1.5	–1.7% to 4.6%	.3362
PSQI-1[c]	1.0	0.9	1.1	0.9	–0.1	0	0.1	–0.7% to 0.9%	.7949
PSQI-2[c]	1.3	1.1	1.7	1.0	0	0.4	0.4	–0.5% to 1.4%	.3117
PSQI-3[c]	0.5	0.7	0.4	0.9	0.3	0.2	0.1	–0.6% to 0.8%	.7888
PSQI-4[c]	0.5	0.5	0.6	0.9	0.2	0.3	0.1	–0.4% to 0.8%	.5518
PSQI-5[c]	1.0	0.4	1.0	0.3	0	0	0.0	–0.3% to 0.3%	.9521
PSQI-6[c]	0.9	1.5	1.5	1.3	–1.1	–0.6	0.5	0.1% to 1.0%	.0267
PSQI-7[c]	1.0	1.0	1.1	1.0	–0.3	–0.2	0.1	–0.7% to 0.9%	.7842

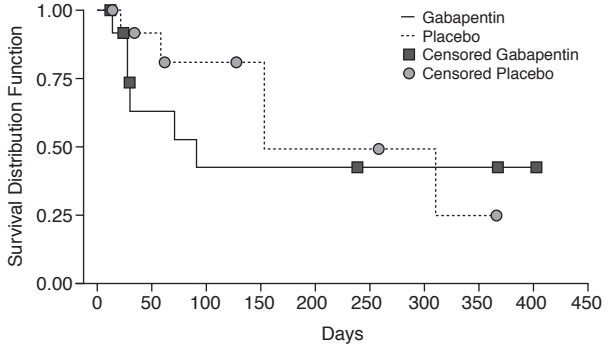
[a]Difference between the 2 groups in reduction in score from initial evaluation to month 12.
[b]Analysis of covariance.
[c]PSQI subscales are as follows: PSQI-1 = sleep quality, PSQI-2 = sleep latency, PSQI-3 = sleep duration, PSQI-4 = habitual sleep efficiency, PSQI-5 = sleep duration, PSQI-6 = use of sleeping medication, PSQI-7 = daytime dysfunction.
Abbreviations: CGI-BP-M = Clinical Global Impressions scale for Bipolar Illness, Modified; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; PSQI = Pittsburgh Sleep Quality Index.

Figure 1. CGI-BP-M Score Change From Baseline to 12-Month Endpoint for Patients With Bipolar Disorder Randomly Assigned to Gabapentin Treatment or Placebo[a]



[a]p Values represent the difference between groups in reduction in score from initial evaluation (baseline).
Abbreviation: CGI-BP-M = Clinical Global Impressions scale for Bipolar Illness, Modified.

Figure 2. Time From Randomization to First New Episode in Patients With Bipolar Disorder Assigned to Gabapentin Treatment or Placebo



experimental drug when not in an acute episode of illness. These trials are particularly useful in highly recurrent conditions, such as asthma or migraine, for which some therapies that have acute efficacy are not suitable for prophylaxis, and vice versa. Bipolar disorder may also be one such condition. Whereas there is no indication that gabapentin may have acute antimanic or antidepressant effects,[9,29] this trial suggests that gabapentin may still carry some benefits on the long-term outcome. Besides, in this trial, there was no sign of destabilization of mood and there were few side effects. However, the specific nature of the long-term benefits is a bit unclear, because improvements were only significant in the CGI-BP-M long-term outcome subscale (primary outcome measure) and the PSQI-6 subscale. The CGI-BP-M long-term outcome subscale is a valid and reliable measure of long-term efficacy[10] but lacks specificity. Improvement in the CGI-BP-M, as in this study, indicates that the clinician, who was blinded to the drug, had a significant perception of improvement in the long-term outcome of gabapentin-treated patients. However, owing to the experimental nature of the design, and limited sample size, the number of secondary outcomes was very limited and we could not correlate the findings on the CGI-BP-M with a significant increase of time to relapse, which would have provided more consistency to the findings. The main reason for the absence of positive findings in survival analysis is likely to be the extremely high number of previous episodes in the gabapentin arm. It seems that randomization failed to

balance such variables, particularly the number of previous depressive episodes, which was 19 in the gabapentin arm as compared to 8 in the placebo arm at baseline. Interestingly enough, looking into the Kaplan-Meier curves in Figure 2, all relapses in the gabapentin arm occurred during the first 3 months, whereas placebo-treated patients experienced recurrence regularly throughout 1 year. This might suggest some carry-over effects of the high frequency of relapse in the gabapentin arm at baseline. This is, however, mere speculation, and only a larger sample size or a longer follow-up would have likely provided a better balance during randomization and perhaps confirmed this hypothesis.

In conclusion, despite the apparent lack of acute efficacy of gabapentin, this study suggests that this drug is likely to provide some benefits on the long-term outcome of the disorder, confirming what some clinicians and open-label studies have suggested before. The nature of this benefit is, however, not completely clear, except for significant improvement in some items related to the quality of sleep and less need of benzodiazepines. Despite some limitations, this study also provides some indirect support to the notion that some drugs might possess mood-stabilizing properties regardless of their lack of efficacy for the acute treatment of manic or depressive episodes.

Drug names: carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote), gabapentin (Neurontin and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), thyroxine (Synthroid, Levo-T, and others).

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