A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Extended-Release Carbamazepine Capsules as Monotherapy for Bipolar Disorder Patients With Manic or Mixed Episodes

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Background: Carbamazepine has been used to treat mania for over 2 decades. Most evaluations of carbamazepine have had important limitations, such as absence of a parallel placebo group, small sample size, or the confounding influence of concomitant treatment. All studies have used conventional, immediate-release carbamazepine formulations. We assessed the efficacy and safety of monotherapy with beaded, extended-release carbamazepine capsules (ERC-CBZ; SPD417) in bipolar disorder patients with manic or mixed episodes.

Method: Following a single-blind placebo lead-in, DSM-IV–defined bipolar disorder patients with manic or mixed episodes were randomly assigned to receive ERC-CBZ (N = 101) or placebo (N = 103) for 3 weeks. Patients were hospitalized through the first 7 days of the double-blind period. ERC-CBZ was initiated at 400 mg/day and increased, as necessary and tolerated, up to 1600 mg/day. Efficacy was assessed weekly with the Young Mania Rating Scale (YMRS), Clinical Global Impressions scale (CGI), and Hamilton Rating Scale for Depression (HAM-D). Data were gathered from December 1999 to June 2001.

Results: Ninety-six (47.1%) of 204 patients completed the study. The mean ± SD final ERC-CBZ dose was 756.44 ± 413.38 mg/day with a mean plasma drug level of 8.9 μg/mL. Starting at week 2, ERC-CBZ was associated with significantly greater improvements in YMRS ($p = .032$) using last-observation-carried-forward analyses. At end point, the responder rate (patients with at least a 50% decrease in YMRS score) also favored ERC-CBZ (41.5% vs. 22.4%; $p = .0074$). In a post hoc analysis of mixed patients, HAM-D score was significantly improved in patients remaining on ERC-CBZ treatment on day 21 ($p = .01$). Adverse events occurring more frequently in the ERC-CBZ group than in the placebo group included dizziness, nausea, and somnolence.

Conclusion: We found ERC-CBZ to be effective in the first large, randomized, double-blind, placebo-controlled parallel trial of carbamazepine monotherapy in acute mania. This trial provides important additional evidence supporting the use of carbamazepine in acute mania.

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Current treatments approved by the U.S. Food and Drug Administration for acute mania include lithium, valproate, chlorpromazine, and olanzapine. Many patients do not respond or only partially respond to these treatments, and as adverse effects can also limit management, additional treatment options for acute mania are needed. Carbamazepine has been studied in acute mania in at least 19 controlled trials, in which it consistently demonstrated efficacy and tolerability comparable to lithium (reviewed in McElroy and Keck[1]). However, controlled clinical trials thus far have had important limitations, including the absence of a parallel placebo control group, small sample size (all had fewer than 60 patients), and, frequently, the confounding influence of coadministration of lithium or antipsychotics. In a recent review of controlled carbamazepine monotherapy trials in acute mania, the pooled response rate was 52%.[1] The only placebo-controlled trial of carbamazepine monotherapy in acute mania used a crossover (B-A-B-A, off-on-off-on) design with patients as their own controls and found significant improvement in 12 (63%) of 19 patients on global mania ratings on the Bunney-Hamburg scale.[2]

Trials conducted to date have utilized conventional, immediate-release carbamazepine formulations. Extended-release carbamazepine formulations have been developed in recent years to decrease daily fluctuations in serum carbamazepine concentrations and improve dosing convenience. Clinical studies of extended-release carbamazepine formulations in patients with epilepsy have demonstrated decreased side effects and increased patient-perceived quality of life.[3–5] The objective of this 3-week,

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randomized, double-blind, placebo-controlled, multicenter study was to evaluate the efficacy and safety of carbamazepine monotherapy in bipolar patients with manic or mixed episodes, using twice-daily, beaded, extended-release capsules (ERC-CBZ; SPD417).

METHOD

Subjects

The protocol was approved by the human subjects panels (institutional review boards) of all participating institutions. Patients provided verbal and written informed consent prior to participation. Data were gathered from December 1999 to June 2001. Patients eligible to enroll were at least 18 years of age and met DSM-IV criteria for bipolar I disorder with current manic or mixed episodes. Since mixed bipolar patients comprise on average 66% of manic presentations, we felt that including mixed patients in the study would be a more accurate reflection of the real world clinical situation. A history of at least 1 previous manic or mixed episode and minimum screen and baseline total score of 20 on the Young Mania Rating Scale (YMRS)[6] were required. Enrollment of treatment-resistant patients was discouraged. Concomitant therapy with antidepressants, cytochrome P450 inhibitors, or anxiolytic or sedative-hypnotic drugs was prohibited (an exception was made with lorazepam, which may have been used in doses up to 6 mg/day during the screening period, up to 4 mg/day during the first week of double-blind treatment, and up to 2 mg/day during the second week of double-blind treatment including any standing or as-needed dosing).

Study Design and Procedures

The 21-day randomized, double-blind, placebo-controlled study followed a 7-day single-blind placebo lead-in period. ERC-CBZ was started at 200 mg twice per day and titrated by daily increments of 200 mg to final doses between 200 mg/day and 1600 mg/day. Investigators were allowed to adjust the dose of medication at their discretion. All patients were hospitalized during the lead-in period and for at least the first 7 days of double-blind treatment. After day 7 of double-blind treatment, patients could be discharged to outpatient status at the discretion of investigators, if sufficiently stable. At screening, baseline, and termination visits, physical examinations and clinical laboratory assessments (including hematology, blood chemistry, and urinalysis) were performed (Quintiles Laboratory, San Diego, Calif.). Each week, adverse events and adherence were recorded, blood was collected for determination of carbamazepine concentrations, and efficacy assessments were performed. The primary outcome measure was the change from baseline to last observation in the YMRS total score. Secondary efficacy assessments included responder rate (percentage of patients with at least a 50% decrease in YMRS scores from baseline to last observation) and change from baseline to last observation in Clinical Global Impressions scale (CGI)[7] and Hamilton Rating Scale for Depression (HAM-D)[8] scores.

Data Analysis

All statistical analyses were carried out using SAS windows (version 8.0) (SAS Institute Inc., Cary, N.C.). SAS Type III estimation was utilized, and the significance level was set at .05 for all statistical tests. The primary efficacy end point was the last-observation-carried-forward (LOCF) value of the decrease from baseline in YMRS total score at day 21 of double-blind treatment for the intent-to-treat (ITT) population. This decrease was assessed by an analysis of covariance (ANCOVA) model using a general linear approach. The percentages of patients showing response at each postrandomization week were analyzed using the Fisher exact test.

Other secondary efficacy variables, such as weekly HAM-D total score, HAM-D depressed-mood item score, and CGI-Severity of Illness (CGI-S) score, were also analyzed for the ITT population using ANCOVA. CGI-Improvement (CGI-I) scores at each week were collapsed into 2 categories ("improved" and "not improved") and analyzed using the Fisher exact test. All efficacy data were also analyzed for, in addition to the ITT population, the observed case population (patients still in treatment at each time point), per protocol population (those in the ITT population who received double-blind study medication for at least 2 weeks and were at least 80% compliant), and completer population (those in the ITT population who completed the protocol). Data on vital signs, electrocardiograms, and laboratory tests were also analyzed using 1-way ANCOVA. The Fisher exact test was used to compare adverse events with an incidence greater than or equal to 1% between treatment groups.

RESULTS

Subjects

At 24 study sites, 204 patients were randomly assigned to double-blind treatment, and 96 (47%) completed the study. The disposition of randomized patients is listed in Table 1. The ITT population for the primary efficacy analysis, 192 patients, excluded 12 patients who did not have a postrandomization YMRS score. Early discontinuation rates were not significantly different between the 2 groups, and reasons for discontinuation were similar. Both treatment groups had a high incidence of "subject choice" given as the reason for discontinuation. As investigators were clearly instructed to be as accurate as possible in noting the reason for discontinuation, it is assumed that very few of these discontinuations in both groups were misclassified lack of efficacy or adverse event discontinuations. Patient demographics and base-

Table 1. Disposition of Bipolar Patients Receiving ERC-CBZ or Placebo

	ERC-CBZ		Placebo		
Variable	N	%	N	%	p Value
Randomized	101	100.0	103	100.0	…
Intent-to-treat	94	93.1	98	95.1	…
Early discontinuation	51	50.5	57	55.3	.5748
Lost to follow-up	3	3.0	3	2.9	1.0000
Adverse event(s)	13	12.9	6	5.8	.0959
Subject choice	17	16.8	19	18.4	.8548
Lack of efficacy	14	13.9	22	21.4	.1991
Protocol violation	1	1.0	2	1.9	1.0000
Other	3	3.0	5	4.9	.7212

Abbreviation: ERC-CBZ = carbamazepine extended-release capsules.

Table 2. Demographics and Disease Characteristics in Bipolar Patients Receiving ERC-CBZ or Placebo[a]

Characteristic	ERC-CBZ (N = 101)	Placebo (N = 103)	Total (N = 204)	p Value
Age, mean (SD), y	38.0 (10.94)	38.1 (11.01)	38.0 (10.95)	.9341
Female	41 (40.6)	56 (54.4)	97 (47.5)	.0489
White	73 (72.3)	75 (72.8)	148 (72.5)	.2924
Mixed episode	60 (59.4)	48 (46.6)	108 (52.9)	.0670

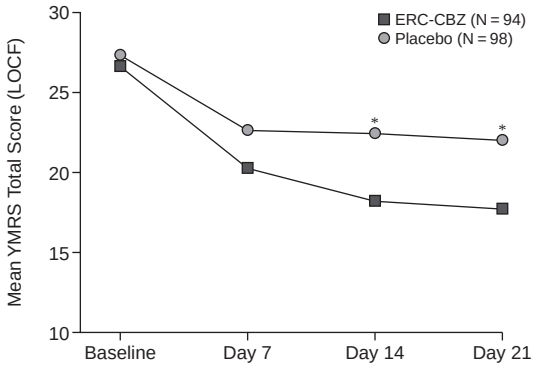
[a]Values shown as N (%) unless otherwise noted.
Abbreviation: ERC-CBZ = carbamazepine extended-release capsules.

line disease characteristics are listed in Table 2. The ERC-CBZ treatment group included a slightly greater number of male patients than the placebo group and a greater proportion of patients with mixed episodes (59.4% vs. 46.6%).

Concomitant medications. The overall percentage of patients taking an allowed concomitant medication (89.1%, ERC-CBZ patients; 90.3%, placebo patients) and the types of concomitant medication were similar in the 2 treatment groups. The most common medication was lorazepam (71.3%, ERC-CBZ patients; 67.0%, placebo patients; p = .55, Fisher exact test), followed by paracetamol and ibuprofen. Lorazepam could be given as needed during the initial 2 weeks of the double-blind treatment (only up to 2 mg/day during the second week), and there was no significant difference in p.r.n. use between the treatment groups. For the 83 subjects with available dose information, the mean daily lorazepam dose was 2.2 mg for both treatment groups.

Final daily dose of study medication and compliance. The mean ± SD final daily dose of ERC-CBZ was 756.44 ± 413.38 mg, with a mean plasma drug level of 8.9 µg/mL. Of 192 ITT patients, the numbers (percentages) of patients with a final daily dose of 200 mg, 400 to 600 mg, 800 to 1000 mg, 1200 to 1400 mg, and 1600 mg during double-blind treatment were 6 patients (3.1%), 31 patients (16.1%), 62 patients (32.3%), 31 patients (16.1%), and 62 patients (32.3%), respectively. As expected, more placebo patients (42.9%) were taking the maximum daily dose of 1600 mg as compared with ERC-CBZ patients

Figure 1. YMRS Total Scores at Baseline and Each Week by Treatment Group Using LOCF Analysis for the ITT Population



*p < .05.
Abbreviations: ERC-CBZ = carbamazepine extended-release capsules, ITT = intent-to-treat, LOCF = last-observation-carried-forward, YMRS = Young Mania Rating Scale.

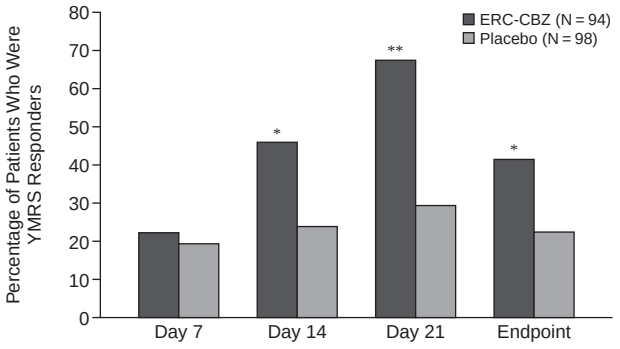
(21.3%; p = .002, Fisher exact test). One third (33.0%) of ERC-CBZ patients were taking a final daily dose of 800 to 1000 mg. About the same numbers of ERC-CBZ patients were taking a final daily dose of 400 to 600 mg (20.2%), 1200 to 1400 mg (19.1%), and 1600 mg (21.3%). Mean daily adherence rates during the double-blind treatment period were similar for ERC-CBZ (92.4%) and placebo (93.4%) patients.

Efficacy

Figure 1 depicts YMRS total scores by treatment group using LOCF analysis in the ITT sample. Patients receiving ERC-CBZ had greater decreases in YMRS total scores compared with patients receiving placebo beginning at week 2 (p = .032) and at primary end point, day 21 (p = .033). Figure 2 depicts rates of response (decrease in YMRS total score of at least 50%) at different time points during the study. Compared with placebo patients, patients receiving ERC-CBZ had higher response rates at day 14 (p = .0093), day 21 (p = .0003), and end point (p = .0074).

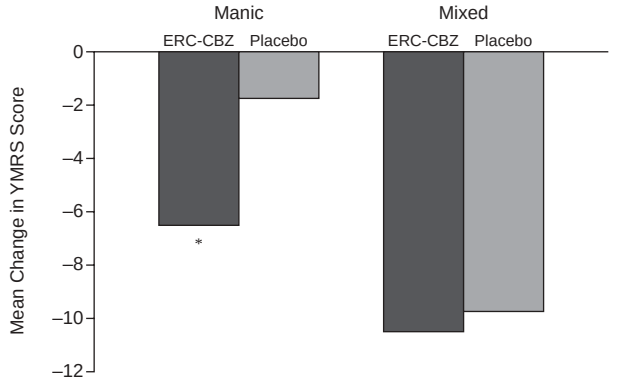
Subgroup analyses of the YMRS total score (performed for men vs. women, 3 age groups, white vs. nonwhite, and manic vs. mixed bipolar disorder at baseline) revealed similar moderate treatment effects in favor of ERC-CBZ in all subgroups. As depicted in Figure 3, ERC-CBZ led to similar decreases in YMRS total score in patients with manic versus mixed bipolar disorder at baseline (mean change in YMRS score from baseline: manic, –6.44; mixed, –10.31). However, due to a larger placebo effect in the patients with mixed bipolar disorder, the change in YMRS score was statistically significantly different from placebo only in the patients with manic bipolar disorder (p = .0092 vs. placebo at end point).

Figure 2. Response According to YMRS Score in the ITT Population[a]



[a]Patients with at least a 50% decrease in total YMRS scores from baseline are considered responders.
*p < .01.
**p < .001.
Abbreviations: ERC-CBZ = carbamazepine extended-release capsules, ITT = intent-to-treat, YMRS = Young Mania Rating Scale.

Figure 3. Change in YMRS Total Score by Treatment Group for Subjects Diagnosed as Manic or Mixed at Baseline



*p < .01 vs. placebo.
Abbreviations: ERC-CBZ = carbamazepine extended-release capsules, YMRS = Young Mania Rating Scale.

Compared with placebo, ERC-CBZ also yielded greater improvement in end point/day 21 CGI-S scores (3.66 vs. 4.07; p = .0254) and yielded larger mean percentages of improvement on the CGI-I at day 21 (66.7% vs. 35.3%; p = .0035) and at end point (43.6% vs. 24.0%; p = .0067). Mean ± SD HAM-D total scores at baseline were similar for ERC-CBZ (14.77 ± 6.41) and placebo (13.44 ± 5.05) patients. There were no significant differences in HAM-D total scores between the treatment groups at any visit, although there was a trend toward greater HAM-D decreases in the ERC-CBZ group at day 21 (mean change from baseline: ERC-CBZ patients, –5.35; placebo patients, –1.58; p = .09). Post hoc analysis of the subgroup of mixed patients found a significantly greater decrease in HAM-D score in patients remaining on ERC-CBZ treatment on day 21 (mean change from baseline: ERC-CBZ mixed patients, –7.62; placebo mixed patients, –2.44; p = .01).

Table 3. Summary of Treatment-Emergent Adverse Events (AEs) in Bipolar Patients Receiving ERC-CBZ or Placebo

	ERC-CBZ (N = 101)		Placebo (N = 103)	
Variable	N	%	N	%
Total AEs	89	88.1	75	72.8
Possibly related/related AEs	78	77.2	59	57.3
AEs causing discontinuation	13	12.9	6	5.8
Serious AEs	4	4.0	4	3.9

Abbreviation: ERC-CBZ = carbamazepine extended-release capsules.

As expected (in view of autoinduction), mean serum carbamazepine concentrations in ERC-CBZ patients declined with time (11.5, 10.1, 8.7, and 8.9 µg/mL on days 7, 14, and 21 and at end point, respectively). Serum carbamazepine concentrations did not have significant correlations with absolute scores or change in YMRS total scores at any postrandomization visit.

Safety

Treatment-emergent adverse events. Treatment-emergent adverse events are outlined in Table 3. Compared with placebo, ERC-CBZ yielded more patients with any adverse event (ERC-CBZ, 88.1%; placebo, 72.8%; p = .0078), possibly related or related adverse events (ERC-CBZ, 77.2%; placebo, 57.3%; p = .0029), and discontinuations due to adverse events (ERC-CBZ, 12.9%; placebo, 5.8%; p = .0959). In the ERC-CBZ group, 2 subjects discontinued for each of the following adverse events: nausea, dizziness, mania, pruritus, and rash. In the placebo group, 2 subjects discontinued for diarrhea and 2, for rash. ERC-CBZ yielded similar (low) numbers of patients with serious adverse events (ERC-CBZ, 4.0%; placebo, 3.9%). The 8 serious adverse events included 7 instances of worsening or exacerbation of bipolar symptoms (4 with ERC-CBZ, 3 with placebo) and 1 rehospitalization for suicidality (placebo). All of these events were judged to be unrelated to the study drug, and 3 patients discontinued due to serious adverse events. No patient died during the study. A significantly greater incidence was found in the ERC-CBZ group compared with the placebo group for the following adverse events: dizziness, nausea, somnolence, vomiting, dyspepsia, dry mouth, pruritus, and speech disorder (Table 4). Rash was reported in 8.9% of ERC-CBZ patients and 5.8% of placebo patients (p = .4335), led to discontinuation in 2.0% of ERC-CBZ patients and 1.9% of placebo patients, and was considered severe in only 1.0% of ERC-CBZ patients and in no placebo patients.

Laboratory evaluations and vital signs. Generally, differences between treatment groups for laboratory tests were small and not clinically significant. Mean values

Table 4. Notable Treatment-Emergent Adverse Events in Bipolar Patients Receiving ERC-CBZ or Placebo[a]

	ERC-CBZ (N = 101)		Placebo (N = 103)	
Event	N	%	N	%
Any[b]	89	88.1	75	72.8
Dizziness[b]	49	48.5	13	12.6
Nausea[b]	38	37.6	11	10.7
Somnolence[b]	33	32.7	16	15.5
Headache	23	22.8	25	24.3
Vomiting[b]	22	21.8	4	3.9
Dyspepsia[b]	19	18.8	6	5.8
Pain	15	14.9	14	13.6
Dry mouth[b]	12	11.9	3	2.9
Constipation	12	11.9	7	6.8
Insomnia	11	10.9	6	5.8
Pruritus[b]	9	8.9	2	1.9
Speech disorder[b]	7	6.9	0	0.0

[a]Adverse events reported by more than 10% of patients in either treatment group or significantly different between treatment groups.
[b]Treatment-emergent adverse events with a significant difference between treatment groups.
Abbreviation: ERC-CBZ = carbamazepine extended-release capsules.

remained within the normal range for all laboratory tests. For both alkaline phosphatase and cholesterol, the mean percentage change from baseline was approximately 12% in ERC-CBZ and 2% in placebo patients (mean change in alkaline phosphatase, 8.035 vs. 1.686 U/L; $p = .0108$; mean change in cholesterol, 21.365 vs. 1.116 mg/dL; $p < .0001$). Mean white blood cell count change was $-1.151 \times 10^3/\mu L$ with ERC-CBZ (to $6.473 \times 10^3/\mu L$) versus $-0.053 \times 10^3/\mu L$ with placebo ($p < .0001$). There were no reports of leukopenia, agranulocytosis, or aplastic anemia. A significant ($p < .05$) difference between treatment groups was found for the mean change from baseline to end point for 3 variables: first supine diastolic blood pressure (ERC-CBZ, 3.1 mm Hg; placebo, –0.7 mm Hg), pulse rate (ERC-CBZ, 1.2 beats per minute; placebo, –2.0 beats per minute), and weight (ERC-CBZ, 2.4 lb [1.1 kg]; placebo, –0.2 lb [–0.1 kg]). No patient in either treatment group experienced significant (7% or more) weight gain during the study.

DISCUSSION

ERC-CBZ was more effective than placebo in the treatment of acute mania in this multicenter, randomized, double-blind, placebo-controlled trial. Compared with placebo, patients treated with ERC-CBZ had significantly greater improvements in manic symptoms on the YMRS, CGI-I, and CGI-S. At end point, 41.5% of ERC-CBZ–treated patients were considered YMRS responders (vs. 22.4% with placebo; $p = .0074$). A significant effect of ERC-CBZ treatment on efficacy measures was first detected in this study at day 14, similar to other published trials.[9,10] This is slightly longer than is typically reported in trials of atypical antipsychotic agents; however, the design of the YMRS is not sensitive to early improvements. Mean serum concentrations of carbamazepine decreased during the 3 weeks of this study, as would be expected due to enzymatic autoinduction, despite likely dose increases, and were within previously recommended ranges for the treatment of affective disorders[11] (7–12 μg/mL) and acute mania[12] (6–12 μg/mL). Despite documented correlations between serum concentrations of carbamazepine and anticonvulsant efficacy, the current findings are in agreement with several previous studies that found no correlation between serum carbamazepine concentrations and antimanic responses.[13–15] There is clearly room for further study of this issue with larger sample sizes.

Overall, a nonsignificant trend toward improved HAM-D scores during ERC-CBZ treatment was observed. For the ERC-CBZ treatment group, 40.6% of patients were in a manic state with a low mean HAM-D score at baseline (ERC-CBZ baseline HAM-D score = 11.79 for manic patients). This low mean score may have made the analysis assessing change in the overall group more difficult. Post hoc analysis of the subgroup of mixed patients found that, compared with placebo subjects, ERC-CBZ subjects who were still taking medication at day 21 showed significant improvement in HAM-D scores (mean change from baseline: ERC-CBZ, –7.62 [mean score decreased from 16.87 to 9.25]; placebo, –2.44 [mean score decreased from 14.44 to 12.00]; $p = .01$). For the mixed patients, the magnitude of difference between the ERC-CBZ and placebo treatment groups (5.18) at day 21 was comparable to the effect seen in many trials in both bipolar depression[16] and unipolar depression.[17–19] Since an antidepressant response typically takes longer to achieve than an antimanic response, antidepressant trials are more often 6- to 8-week trials, and a complete response would not be expected to be captured in this 3-week trial. This substantial improvement in mixed patients remaining in the study at day 21 suggests that additional trials of sufficient duration conducted in the bipolar I and II mixed and depressed populations may be enlightening.

Several small open-label trials and a few small double-blind trials reviewed by Post et al.[20] have previously demonstrated efficacy of carbamazepine in the treatment of acute bipolar depression. This review of studies carried out in both unipolar and bipolar acute depression reported an overall response rate of 65% in open-label trials and 44% in controlled trials.[20] There have also been at least 10 double-blind, randomized trials evaluating carbamazepine as maintenance therapy in bipolar disorder, with response rates to carbamazepine ranging from 30% to 60%. Many trials have compared carbamazepine with lithium, and although the overall response rate is similar, some have suggested superiority of lithium.[21] In one recent trial following 171 patients for 2.5 years, lithium was more effective maintenance treatment overall[22] and in a post hoc analysis of 67 "classical" bipolar I patients,[23] but in a post hoc

analysis of 104 patients with bipolar II, bipolar not otherwise specified, mixed states, mood-incongruent delusions, and comorbidity, carbamazepine tended to be more effective.

Adverse events were mostly mild to moderate and were typical of those expected with carbamazepine based on trials in patients with mood disorders and epilepsy. The carbamazepine product information carries a black box warning for agranulocytosis and aplastic anemia. However, no patient in the present study experienced any of the serious side effects that have rarely been associated with carbamazepine, such as agranulocytosis, aplastic anemia, or Stevens-Johnson syndrome. This study was unlikely to detect such problems, as the incidence of agranulocytosis (1.4 per 1 million patients treated per year) and of aplastic anemia (5.1 per 1 million patients treated per year) with carbamazepine is very low.[24] In addition, there was no evidence of benign leukopenia, which by some estimates may occur in 10% of patients.[25]

Similar to previous large trials of carbamazepine in epilepsy patients, a minimal weight increase of 1.3% was reported during this study. There were no potentially clinically significant (7% or greater) weight increases seen in any patient with ERC-CBZ. Weight gain and obesity are common problems in bipolar patients, and several frequently used therapies, such as olanzapine, lithium, and valproate, have been associated with clinically significant weight gain.

The rate of rash with ERC-CBZ was 8.9%. No patient experienced a serious rash. Anticonvulsants such as carbamazepine, lamotrigine, and valproate may, rarely, yield serious rashes. Indeed, the lamotrigine product information includes a black box warning regarding serious rash. The product information for other treatment options for acute mania also includes black box warnings—lithium for toxicity close to therapeutic levels, and valproate for hepatotoxicity, teratogenicity, and pancreatitis. These treatments are associated with additional important dose-related adverse events. Up to 75% of patients taking lithium experience adverse effects, some of which can be managed by lowering the dose or altering the dosing schedule. Valproate is associated with gastrointestinal distress, hair loss, and clinically significant weight gain. Extended-release preparations are available for carbamazepine, lithium, and valproate and are considered to be better tolerated than immediate-release preparations, as they yield lower peak serum concentrations.

Medication adherence in patients with bipolar disorder has been reported to be as low as 40%. Conventional carbamazepine immediate-release formulations can require 3- or 4-times-daily dosing to avoid intermittent adverse effects. Extended-release compared with immediate-release carbamazepine formulations have been associated with lower peak serum concentrations,[4] decreased circadian toxicity,[26] and decreased central nervous system side effects, such as sedation, diplopia, confusion, and ataxia. Also, extended-release carbamazepine formulations such as ERC-CBZ allow twice-daily dosing, which is associated with better adherence. Compared with extended-release tablets, capsules may potentially increase adherence further by providing the flexibility to take the medication with or without meals, and their contents can be sprinkled on soft food.[27]

This study has several limitations. First, the sample size, although sufficient to detect efficacy and common adverse events, was insufficient to detect rare carbamazepine adverse events. Second, the early discontinuation rate was high. This rate of 53% is, however, comparable to those found in other 3-week monotherapy inpatient trials in bipolar patients, which have reported dropout rates ranging from 38.6% to 68.4%.[28–30] Polypharmacy is often required in order to achieve optimal outcomes in patients with bipolar disorder. Since multiple psychotropic medications are currently available to treat bipolar disorder, retaining patients in a placebo-controlled clinical trial of a single agent would be expected to be challenging. The LOCF analyses in part address this limitation. Third, although the incidence of lorazepam use was similar in the 2 treatment groups, and the mean dose, when available, was the same, the mean dose was not collected for all subjects receiving lorazepam, and it remains a possibility that a higher dose was being taken by the ERC-CBZ subjects. Finally, extensive history of treatment resistance to other medications was not obtained, so the generalizability of findings to patients with treatment-resistant bipolar disorders cannot be determined.

CONCLUSION

Ours is the first randomized, double-blind, placebo-controlled trial to confirm that carbamazepine is effective in the treatment of acute mania. It is also the first trial evaluating an extended-release formulation of carbamazepine in bipolar disorder. Adverse events were typical of those expected with carbamazepine, and ERC-CBZ was generally well tolerated. These results establish the efficacy of ERC-CBZ in acute mania and confirm the role of carbamazepine as an effective treatment for acute mania.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine and others), ibuprofen (Motrin and others), lamotrigine (Lamictal), lorazepam (Ativan and others), olanzapine (Zyprexa).

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REFERENCES

1. McElroy SL, Keck PE Jr. Pharmacologic agents for the treatment of acute bipolar mania. Biol Psychiatry 2000;48:539–557
2. Post RM, Uhde TW, Roy-Byrne PP, et al. Correlates of antimanic response to carbamazepine. Psychiatry Res 1987;21:71–83
3. Persson LI, Ben Menachem E, Bengtsson E, et al. Differences in side effects between a conventional carbamazepine preparation and a slow-release preparation of carbamazepine. Epilepsy Res 1990;6:134–140
4. Canger R, Altamura AC, Belvedere O, et al. Conventional vs controlled-release carbamazepine: a multicentre, double-blind, cross-over study. Acta Neurol Scand 1990;82:9–13
5. Mirza WU, Rak IW, Thadani VM, et al. Six-month evaluation of Carbatrol (extended-release carbamazepine) in complex partial seizures. Neurology 1998;51:1727–1729
6. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–435
7. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impression (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73:159–171
8. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
9. Okuma T, Yamashita I, Takahashi R, et al. Comparison of the antimanic efficacy of carbamazepine and lithium carbonate by double-blind controlled study. Pharmacopsychiatry 1990;23:143–150
10. Vasudev K, Goswami U, Kohli K. Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. Psychopharmacology (Berl) 2000;150: 15–23
11. Ballenger JC, Post RM. Carbamazepine in manic-depressive illness: a new treatment. Am J Psychiatry 1980;137:782–790
12. Okuma T. Therapeutic and prophylactic effects of carbamazepine in bipolar disorders. Psychiatr Clin North Am 1983;6:157–174
13. Post RM, Uhde TW, Ballenger JC, et al. Carbamazepine and its -10,11-epoxide metabolite in plasma and CSF: relationship to antidepressant response. Arch Gen Psychiatry 1983;40:673–676
14. Lerer B, Moore N, Meyendorff E, et al. Carbamazepine versus lithium in mania: a double-blind study. J Clin Psychiatry 1987;48:89–93
15. Petit P, Lonjon R, Cociglio M, et al. Carbamazepine and its 10,11-epoxide metabolite in acute mania: clinical and pharmacokinetic correlates. Eur J Clin Pharmacol 1991;41:541–546
16. Calabrese JR, Bowden CL, Sachs GS, et al, for the Lamictal 602 Study Group. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
17. Thase ME, for the Venlafaxine XR 209 Study Group. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. J Clin Psychiatry 1997;58:393–398
18. Kiev A, Feiger A. A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients. J Clin Psychiatry 1997;58:146–152
19. Rudolph RL. Achieving remission from depression with venlafaxine and venlafaxine extended release: a literature review of comparative studies with selective serotonin reuptake inhibitors. Acta Psychiatr Scand Suppl 2002;415:24–30
20. Post RM, Ketter TA, Denicoff K, et al. The place of anticonvulsant therapy in bipolar illness. Psychopharmacology (Berl) 1996;128:115–129
21. Greil W, Ludwig-Mayerhofer W, Erazo N, et al. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders: a randomised study. J Affect Disord 1997;43:151–161
22. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. Neuropsychobiology 2000;42(suppl 1):2–10
23. Greil W, Kleindienst N, Erazo N, et al. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. J Clin Psychopharmacol 1998;18:455–460
24. Pellock JM. Carbamazepine side effects in children and adults. Epilepsia 1987;28(suppl 3):S64–S70
25. Hart RF, Easton JD. Carbamazepine and hematological monitoring. Ann Neurol 1982;11:309–312
26. Haefeli WE, Meyer PG, Luscher TF. Circadian carbamazepine toxicity. Epilepsia 1994;35:400–402
27. McLean A, Browne S, Zhang Y, et al. The influence of food on the bioavailability of a twice-daily controlled release carbamazepine formulation. J Clin Pharmacol 2001;41:183–186
28. Bowden CL, Brugger AM, Swann AC, et al, for the Depakote Mania Study Group. Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA 1994;271:918–924
29. Pope HG Jr, McElroy SL, Keck PE Jr, et al. Valproate in the treatment of acute mania: a placebo-controlled study. Arch Gen Psychiatry 1991; 48:62–68
30. Tohen M, Sanger TM, McElroy SL, et al, and the Olanzapine HGEH Study Group. Olanzapine versus placebo in the treatment of acute mania. Am J Psychiatry 1999;156:702–709

