Extended-Release Carbamazepine Capsules as Monotherapy for Acute Mania in Bipolar Disorder: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Although carbamazepine has long been used for the treatment of acute mania, only recently was its efficacy confirmed in a large, multicenter, parallel-group, placebo-controlled, randomized trial. In the present study, we further evaluated the efficacy and safety of monotherapy with beaded, extended-release carbamazepine capsules (ERC-CBZ) in patients with bipolar I disorder experiencing manic or mixed episodes.

Method: Hospitalized bipolar I disorder (DSM-IV criteria) patients (N = 239) with manic or mixed episodes were randomly assigned on a double-blind basis to receive ERC-CBZ or placebo for 3 weeks, following a single-blind placebo lead-in. Treatment with ERC-CBZ was initiated at 200 mg twice daily, and investigators were encouraged to increase doses, as necessary and tolerated, by 200 mg/day 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. The study was conducted from July 23, 2002, to April 1, 2003.

Results: 144 patients (60.3%) completed the study, with a significant number of placebo patients discontinuing due to lack of efficacy ($p < .001$). Extended-release carbamazepine treatment was associated with significant improvements in mean YMRS total and CGI total scores, using last-observation-carried-forward analyses, beginning at day 7 ($p < .05$). Adverse events occurring more frequently in the ERC-CBZ–treated group included dizziness (39.3%), somnolence (30.3%), and nausea (23.8%). Patients taking ERC-CBZ experienced a significant increase in total cholesterol, composed of increases in both high-density and low-density lipoproteins.

Conclusion: Extended-release carbamazepine monotherapy had significantly greater efficacy compared with placebo in the treatment of acute mania in this large, randomized, double-blind, placebo-controlled trial.

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A complete list of the members of the SPD417 Study Group is given at the end of the article.

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The range of therapeutic options for bipolar disorder is expanding rapidly, and approved therapies include a number of anticonvulsant and antipsychotic medications. Due to the limitations in overall response to and tolerability of many agents, the availability of additional options is likely to improve outcomes significantly in patients with bipolar disorder. Although patients with bipolar disorder are often treated concurrently with multiple mood-stabilizing agents, monotherapy is preferable, when possible, to minimize side effects, drug interactions, and costs for both medication and monitoring. Clinical trials of agents used as monotherapy remain essential to rigorously demonstrate the agents' efficacy for acute bipolar mania. Carbamazepine has long been considered a therapeutic option for bipolar disorder, even though the U.S. Food and Drug Administration has yet to approve a preparation of carbamazepine for such an indication. Until recently, carbamazepine had been evaluated primarily in small trials that were rarely placebo-controlled and used exclusively immediate-release preparations that must be administered 3 or 4 times daily to avoid potentially problematic serum drug level fluctuations.[1,2]

A recent 3-week, multicenter, placebo-controlled, parallel-group trial found significant improvement in manic symptoms in bipolar I patients receiving monother-

apy with twice-daily beaded, extended-release carbamazepine capsules (ERC-CBZ).[3] The objective of the current 3-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial was to evaluate further the efficacy and safety of carbamazepine monotherapy in bipolar I patients with manic or mixed episodes, using ERC-CBZ.

METHOD

Subjects

The protocol was approved by the institutional review boards of all participating centers. After thorough explanation of the study, patients provided written informed consent prior to participation. Patients eligible to enroll were at least 18 years of age and met DSM-IV criteria for bipolar I disorder with most current episode manic or mixed. A history of at least 1 previous manic or mixed episode and a minimum baseline total score of 20 on the Young Mania Rating Scale (YMRS)[4] were required. Patients who had been treated with electroconvulsive therapy (ECT) or clozapine within 3 months of baseline or antidepressants within 4 weeks of baseline were not eligible to enroll. Concomitant therapy with antidepressants, antipsychotics, lithium, ECT, or anxiolytic or sedative-hypnotic drugs was prohibited, with the exception of lorazepam. Lorazepam was permitted on an as-needed basis for agitation or sleep 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 through the second week of double-blind treatment. No lorazepam or other rescue drug was permitted after the second week.

Study Design and Procedures

The 21-day, randomized, double-blind, placebo-controlled study followed a 5-day, single-blind placebo lead-in period. Extended-release carbamazepine treatment was initiated at 200 mg twice a day and titrated by increments of 200 mg/day to final doses between 200 mg/day and 1600 mg/day, at the discretion of the investigator. 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 displaying adequate improvement could be discharged at the discretion of investigators. 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, 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 ≥ 50% decrease in YMRS scores from baseline to last observation), mean change from baseline to last observation in Clinical Global Impressions scale (CGI)[5] and Hamilton Rating Scale for Depression (HAM-D)[6] total scores, HAM-D depressed mood item (item 1) score, and time to outpatient status.

Data Analysis

All statistical analyses were carried out using SAS statistical software, version 8.0 (SAS 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 mean YMRS total score at day 21 of double-blind treatment for the intent-to-treat (ITT) population. The mean YMRS total score, CGI-Severity of Illness (CGI-S) score, HAM-D total score, and HAM-D depressed mood item score at each post-randomization visit and end point were analyzed using a 2-way analysis of covariance (ANCOVA) model with treatment and site as the main factors and the baseline value as the covariate for the ITT population. A 2-way analysis of variance was performed on baseline data for these variables with treatment and site as the main factors. The number of subjects with an improved CGI score, the number of subjects demonstrating a response at each post-randomization visit (days 7, 14, and 21), and the number of subjects showing a sustained response were analyzed using the χ^2 test with continuity adjustment. Data on vital signs, electrocardiograms, and laboratory tests were also analyzed using 1-way ANCOVA. Fisher exact test was used to compare adverse events of incidence greater than or equal to 1% between treatment groups.

RESULTS

Subjects

At 25 study sites (19 in the United States and 6 in India), 239 patients were randomly assigned to double-blind treatment, and 144 (60.3%) completed the study, which was conducted from July 23, 2002, to April 1, 2003. The disposition of randomized patients is listed in Table 1. The ITT population for the primary efficacy analysis excluded 4 patients who did not have a post-randomization YMRS score. The overall early discontinuation rates of the 2 treatment groups were not significantly different. For subjects randomly assigned to ERC-CBZ, the most frequent reasons for discontinuation were adverse events (9.0%), subject choice (9.0%), and protocol violation (7.4%). For subjects in the placebo group, the most frequent reasons for discontinuation were lack of efficacy (23.1%) and subject choice (9.4%). Significantly more subjects in the placebo group than subjects in the ERC-CBZ group discontinued because of lack of efficacy (23.1% vs. 6.6%; $p < .001$). More subjects receiving ERC-CBZ than receiving placebo discontinued therapy because of an adverse

Table 1. Disposition of Patients, N (%)

Variable	ERC-CBZ	Placebo	p Value
Randomized patients	122 (100)	117 (100)	…
Intent-to-treat sample	120 (98.4)	115 (98.3)	…
Early discontinuation	42 (34.4)	53 (45.3)	.1124
Lost to follow-up	2 (1.6)	2 (1.7)	1.0000
Adverse event(s)	11 (9.0)	6 (5.1)	.3162
Subject choice	11 (9.0)	11 (9.4)	1.0000
Lack of efficacy[a]	8 (6.6)	27 (23.1)	.0004
Protocol violation	9 (7.4)	4 (3.4)	.2548
Other	1 (0.8)	3 (2.6)	.3616

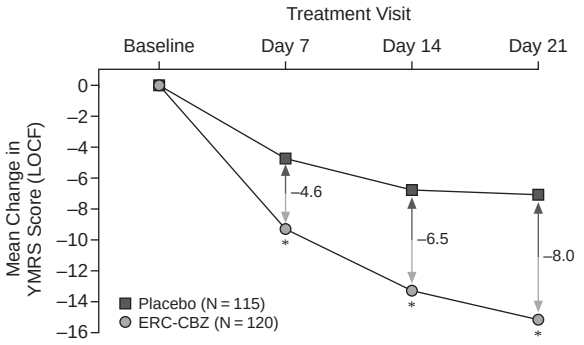
[a]Statistically significant.
Abbreviation: ERC-CBZ = extended-release carbamazepine capsules.

Table 2. Demographic and Clinical Characteristics of Study Population

Characteristic	ERC-CBZ (N = 122)	Placebo (N = 117)	Total (N = 239)	p Value
Age, mean (SD), y	37.4 (11.04)	36.5 (10.88)	37.0 (10.95)	.5164
Female, N (%)	41 (33.6)	30 (25.6)	71 (29.7)	.1779
White, N (%)	54 (44.3)	56 (47.9)	110 (46.0)	.3042
Manic episode, N (%)	96 (78.7)	93 (79.5)	189 (79.1)	.8794

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

Figure 1. Change in YMRS Total Scores From Baseline at Each Week by Treatment Group Using LOCF Analysis for the Intent-to-Treat Population[a]



[a]In the ERC-CBZ group, YMRS scores were 28.46 at baseline and 13.38 at end point; in the placebo group, scores were 27.93 at baseline and 20.82 at end point.
*p < .0001 compared with placebo following analysis of covariance with baseline score as covariate.
Abbreviations: ERC-CBZ = extended-release carbamazepine capsules, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

event (9.0% vs. 5.1%) or protocol violation (7.4% vs. 3.4%), although these differences were not significant. Lack of efficacy was the only reason for discontinuation with a statistically significant difference between the treatment groups.

There were no important differences between the treatment groups in any demographic or clinical characteristics at baseline in the randomized subjects (Table 2) or the ITT population. Of the 239 subjects randomized, 148 (62%) were from the United States and 91 (38%) from India. There were more men than women (70% vs. 30%) in this study. The mean (± SD) age was 37.0 (± 10.95) years, and 46% were white, 12% were black, and 42% were of other ethnicities, including subjects in India. More subjects were experiencing manic (79%) as compared with mixed (21%) episodes of bipolar I disorder.

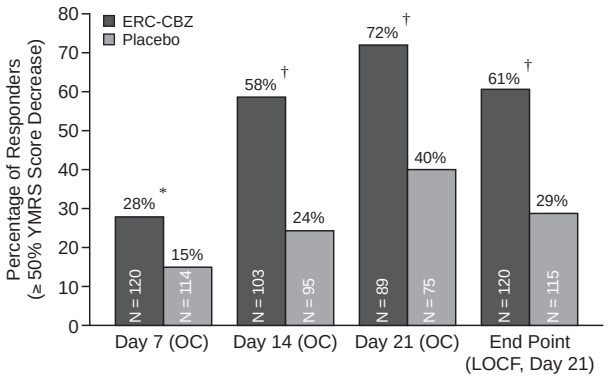
Concomitant medications. Concomitant medication use was similar in the 2 treatment groups (ERC-CBZ, 91.8%; placebo, 86.3%). The most common concomitant medications were lorazepam (ERC-CBZ, 73.8%; placebo, 78.6%), acetaminophen, and ibuprofen. Lorazepam was the only relevant concomitant medication, as no other psychotropic medications were allowed during the study. Lorazepam was not allowed after the second week of double-blind treatment.

Compliance and final daily dose of study medication. The average treatment compliance rates, evaluated by capsule counts, were approximately 98% in both treatment groups during the double-blind treatment period. The mean ± SD final dose of randomized patients in the ERC-CBZ group was 642.6 ± 369.2 mg/day (N = 122). In the ITT population, most patients in the ERC-CBZ group were titrated to a final daily dose of 2 to 3 capsules (400–600 mg) (48.3%) or 4 to 5 capsules (800–1000 mg) (24.2%), while most subjects in the placebo group were titrated to a final daily dose of 4 to 5 capsules (53.9%) or 8 capsules (29.6%).

Efficacy

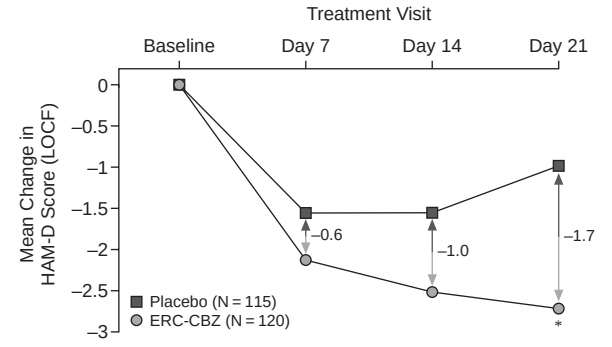
Patients treated with ERC-CBZ had highly significant decreases in YMRS total scores compared with patients receiving placebo beginning at day 7 and also at day 14 and at primary end point, day 21 (LOCF analysis, ITT sample; $p < .0001$ at all time points). Using the LOCF analysis, the difference in the mean change from baseline to each post-randomization week between the treatment groups was 4.6 points, 6.5 points, and 8.0 points for day 7, day 14, and day 21, respectively, which showed a trend of increased treatment effect from day 7 to day 21 in favor of ERC-CBZ (Figure 1). Figure 2 depicts YMRS response rates (patients showing a decrease in YMRS total score of at least 50%) at different time points during the study. Patients treated with ERC-CBZ had significantly higher response rates than patients treated with placebo at day 7 (observed case [OC] analysis; $p < .05$), day 14 (OC analysis; $p < .0001$), day 21 (OC analysis; $p < .0001$), and end point (LOCF analysis; $p < .0001$). Subgroup analyses (by age, gender, country, and manic or mixed presentation) revealed similar decreases in YMRS total scores. Compared with placebo, ERC-CBZ treatment was associated with significantly improved scores on both the CGI-S and CGI-Improvement (CGI-I) scales at day 7 (both OC analysis; $p < .05$), as well as on days 14 and 21 (all OC analysis; $p < .0001$) and at end point ($p < .0001$).

Figure 2. Percentage of Patients Considered Responders at Each Post-Randomization Week and End Point, by Treatment Group, for the Intent-to-Treat Population



*p < .05 compared with placebo based on χ^2 test with continuity adjustment.
†p < .0001 compared with placebo based on χ^2 test with continuity adjustment.
Abbreviations: ERC-CBZ = extended-release carbamazepine capsules, LOCF = last observation carried forward, OC = observed case, YMRS = Young Mania Rating Scale.

Figure 3. HAM-D Total Scores at Baseline and Each Week by Treatment Group Using LOCF Analysis for the Intent-to-Treat Population[a]



[a]In the ERC-CBZ group, HAM-D scores were 9.60 at baseline and 6.88 at end point; in the placebo group, scores were 9.45 at baseline and 8.47 at end point.
*p < .01 compared with placebo following analysis of covariance with baseline score as covariate.
Abbreviations: ERC-CBZ = extended-release carbamazepine capsules, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

The HAM-D total score (Figure 3) was also significantly improved in ERC-CBZ–treated patients compared with placebo-treated patients at end point (p < .01). In a subgroup analysis of the 188 ITT subjects with a manic episode, there was a statistically significant difference on the HAM-D between the treatment groups at end point (p < .05). For the smaller subgroup of 47 ITT subjects with a mixed episode, the difference in the improvement

Table 3. Summary of Treatment-Emergent Adverse Events (AEs), N (%)

Variable	ERC-CBZ (N = 122)	Placebo (N = 117)
Total AEs	112 (91.8)	66 (56.4)
AEs possibly related/related to treatment	100 (82.0)	42 (35.9)
AEs causing discontinuation	11 (9.0)	6 (5.1)
Serious AEs	4 (3.3)	6 (5.1)

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

on HAM-D was not significant at end point (p = .0607). There was no significant difference in mean HAM-D depressed mood item number 1 score between treatment groups at any post-randomization visit or at end point.

Overall, 48.3% of ERC-CBZ–treated subjects and 34.8% of placebo-treated subjects (p < .05) were discharged from the hospital during the double-blind treatment period.

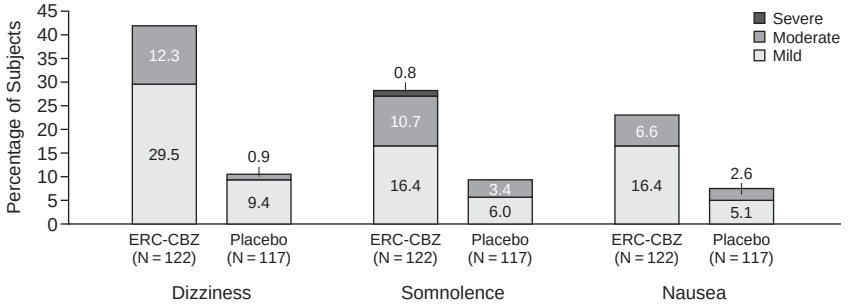
Effect size. Effect size is an index that measures the magnitude of a treatment effect. Unlike significance tests, these indices are independent of sample size. An effect size of 0.2 is considered small, 0.5 is considered medium, and 0.8 or greater is a large effect size. The effect size for this trial was 0.85, indicating a large effect by Cohen's standard.

Safety

Treatment-emergent adverse events. Study-related adverse events are listed in Table 3. Overall, subjects in the ERC-CBZ group had a statistically significantly higher incidence of these events compared with the placebo group (91.8% vs. 56.4%; p < .0001). Most treatment-emergent adverse events were of mild or moderate severity and were reported during the first week (Figure 4). The most frequently reported treatment-emergent adverse events in the ERC-CBZ group were dizziness (41.8%), somnolence (27.9%), and nausea (23.0%). More ERC-CBZ–treated subjects (9.0%) than placebo-treated subjects (5.1%) had a treatment-emergent adverse event that caused study termination, but this difference was not statistically significant. Similar to previous studies, pruritus was reported in 10 patients (8.2%) in the ERC-CBZ group, compared with 3 patients (2.6%) in the placebo group (Table 4). Rash was reported in 3 placebo patients (2.6%) and 6 patients treated with ERC-CBZ (4.9%) (Table 4). One patient in the ERC-CBZ treatment group discontinued the study due to rash. There were no reports of severe rash.

A serious adverse event was defined as any adverse drug experience that resulted in death, was life threatening, resulted in persistent or significant disability, resulted in a congenital abnormality or birth defect, or required inpatient hospitalization or prolongation of existing hospitalization. The incidence of serious adverse

Figure 4. Percentage of Subjects (ERC-CBZ and placebo) Experiencing a Mild, Moderate, or Severe Episode of Common Adverse Events in the Current Study



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

Table 4. Notable Treatment-Emergent Adverse Events, N (%)[a,b]

Event	ERC-CBZ (N = 122)	Placebo (N = 117)	p Value
Any[c]	112 (91.8)	66 (56.4)	< .0001
Dizziness[c]	48 (39.3)	14 (12.0)	< .0001
Somnolence[c]	37 (30.3)	12 (10.3)	.0001
Nausea[c]	29 (23.8)	11 (9.4)	.0032
Ataxia[c]	23 (18.9)	0 (0.0)	< .0001
Vomiting[c]	20 (16.4)	3 (2.6)	.0003
Blurred vision[c]	11 (9.0)	2 (1.7)	.0194
Asthenia	10 (8.2)	3 (2.6)	NS
Pruritus	10 (8.2)	3 (2.6)	NS

[a]Treatment-emergent adverse events reported by ≥ 5% of ERC-CBZ–treated patients and at least twice the rate of placebo.
[b]Rash was reported by 6 (4.9%) of the ERC-CBZ–treated patients and 3 (2.6%) of the placebo-treated patients (NS).
[c]Treatment-emergent adverse events with a significant difference between treatment groups.
Abbreviation: ERC-CBZ = extended-release carbamazepine capsules.

events was similar between treatment groups (ERC-CBZ: 4 subjects, 6 events; placebo: 6 subjects, 6 events). Of the 10 subjects who experienced a serious adverse event during the double-blind treatment period, 7 subjects (3 ERC-CBZ and 4 placebo) discontinued the study. Serious adverse events in the ERC-CBZ group included 2 instances of manic-depressive reaction, worsening of 2 depressive episodes, 1 personality disorder, and 1 fever with rash. Serious adverse events for the placebo group included 2 manic reactions, 1 depressive reaction, exacerbation of chronic obstructive pulmonary disease, nausea, and 1 accidental injury. Only 1 serious adverse event was deemed possibly related to the study drug. Three days after initiating ERC-CBZ, a male subject developed a fever and an erythematous macular rash over the trunk and lower extremities that was associated with a low white blood cell (WBC) count of $1.7 \times 10^3/\mu L$ (normal range, $4.1–12.3 \times 10^3/\mu L$). The event resolved 6 days after discontinuation of the study drug.

Laboratory evaluations and vital signs. The percent change in WBC values from baseline to end point was greater in the ERC-CBZ group compared with the placebo group (ERC-CBZ, –11.7% vs. placebo, 0.3%; p = .0001). These and other laboratory values are shown in Table 5. Shifts from normal at baseline to low at end point in WBC were observed in 4.3% of ERC-CBZ subjects versus 1.8% of placebo subjects. One ERC-CBZ–treated subject had a clinically significant decrease in WBC count ($1.7 \times 10^3/\mu L$), which resolved 6 days after discontinuation of study drug, as mentioned previously.

The percent change from baseline to end point was also greater in the ERC-CBZ group compared with the placebo group for total cholesterol (ERC-CBZ, 13.2% vs. placebo, 2.0%; p < .0001), calculated low-density lipoprotein cholesterol (LDL-C) (ERC-CBZ, 28.2% vs. placebo, 11.5%; p < .0001), and direct high-density lipoprotein cholesterol (HDL-C) (ERC-CBZ, 9.7% vs. placebo, 3.2%; p < .01). The percentage of subjects with a shift from normal at baseline to high at end point was higher (> 5% difference) in the ERC-CBZ treatment group than in the placebo group for total cholesterol (28.4% vs. 9.5%), calculated LDL-C (20.0% vs. 9.2%), and direct HDL-C (5.6% vs. 0.0%). One ERC-CBZ–treated subject had a clinically significant increase in LDL-C during the study, from 141 to 171 mg/dL (normal range, 0–130 mg/dL), and 1 subject had a clinically significant increase in triglycerides, from 478 mg/dL to a final value of 686 mg/dL (normal range, 45–250 mg/dL).

The percentage of subjects with a shift from normal at baseline to high at end point was also higher (> 5% difference) in the ERC-CBZ treatment group than in the placebo group for alanine aminotransferase (11.4% vs. 4.2%), urine ketones (6.8% vs. 0.9%), and urine protein (6.0% vs. 0.9%). The percentage of subjects with a shift from normal at baseline to low at end point was higher (> 5% difference) in the ERC-CBZ treatment group than in the placebo group for hematocrit (6.3% vs. 1.0%), reticulocytes (17.9% vs. 7.1%), total bilirubin (7.7% vs. 0.9%), and uric acid (10.9% vs. 2.8%). None of these increases or decreases was considered to be clinically

Table 5. Laboratory Values, Mean

	ERC-CBZ (N = 122)		Placebo (N = 117)		
Value	Baseline	End Point	Baseline	End Point	p Value
Hematologic					
WBC count, × $10^3/\mu L$	8.1	7.1	8.6	8.4	.0001
Hematocrit, %	43.3	42.5	43.6	43.9	NS
Lymphocytes, %	28.5	28.0	26.7	27.7	NS
Hepatic					
Albumin, g/dL	4.3	4.2	4.3	4.4	.01
Alkaline phosphatase, IU/L	92.2	95.1	92.9	94.2	NS
Serum urea nitrogen, mg/dL	11.8	11.8	12.0	11.7	NS
Creatinine, mg/dL	0.86	0.83	0.87	0.86	NS
Glucose, mg/dL	97.0	97.2	92.4	93.6	NS
Other					
Total cholesterol, mg/dL	178.5	199.1	178.8	180.4	< .0001
HDL-C, mg/dL	44.1	47.5	41.9	42.1	< .01
LDL-C, mg/dL	98.8	117.4	98.6	103.4	< .0001
Triglycerides, mg/dL	186.6	176.0	202.2	174.4	NS

Abbreviations: ERC-CBZ = extended-release carbamazepine capsules, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, WBC = white blood cell.

important. Additionally, no evidence of aplastic anemia or of agranulocytosis was observed.

There were no statistically significant differences between treatment groups in the mean change from baseline to end point in vital sign measurements except for weight. Extended-release carbamazepine–treated subjects had a mean increase in weight of 1.0 kg as compared with 0.1 kg for placebo-treated subjects ($p < .001$). This difference, although statistically significant, is not considered clinically relevant.

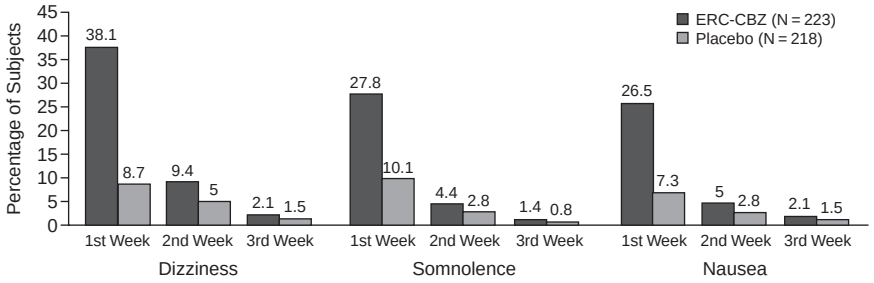
DISCUSSION

Treatment with ERC-CBZ was more efficacious than placebo in the treatment of acute bipolar mania in this multicenter, randomized, double-blind, placebo-controlled trial in 239 bipolar I patients. Patients treated with ERC-CBZ had significantly greater improvements on the YMRS, CGI-I, CGI-S, and HAM-D than those treated with placebo. At end point, 60.8% of ERC-CBZ–treated patients were considered YMRS responders, defined as a reduction of at least 50% in YMRS score, compared with 28.7% of placebo-treated patients ($p < .0001$). This finding is comparable to a recent multicenter trial utilizing ERC-CBZ in bipolar disorder that found a 42% YMRS response rate in those treated with ERC-CBZ versus 22% in those treated with placebo ($p < .01$).[3] The rates are also comparable to response rates reported in a review of controlled carbamazepine monotherapy trials in acute mania, where the pooled response rate to carbamazepine was 52%.[7] Additionally, the YMRS response rate of 60.8% at end point for the ERC-CBZ–treated group is higher than previously reported for a number of therapeutic agents (weighted average response rate = 52%; range, 40%–59%).[8–14] Significant improvements in YMRS and CGI total scores were detected in this study beginning on day 7, the first day of rating scale administration after baseline. This length of time to improvement is earlier than that reported in a recent multicenter trial of ERC-CBZ,[3] perhaps due to the fact that there was a smaller percentage of patients with mixed disease in the current study, who are thought to respond more slowly and less completely. This robust response at 1 week was also earlier than reported in previous evaluations of lithium, carbamazepine, and valproate in acute mania,[15,16] though trials with other agents have shown antimanic efficacy in earlier measurements.[8,13,14] The fact that this trial first recorded responses at day 7 limits comparison to these other trials in terms of speed to response.

Significant improvements in HAM-D total score were detected in this study at end point, consistent with earlier findings of a trend toward improvement at 21 days in the previous multicenter trial of ERC-CBZ, as well as in several trials demonstrating symptomatic improvement in patients with bipolar and unipolar depression treated with carbamazepine.[3,17] This finding is encouraging, given the relatively mild overall depressive symptoms seen in this population, which included 80% manic patients at baseline. Additionally, the 3-week duration of this study may have been too brief to detect the full extent of improvements in depression ratings. Given the relatively few options available to treat this phase of the illness, larger controlled trials of ERC-CBZ in patients with bipolar depression would appear to be warranted to assess efficacy for both acute episodes and for prophylaxis.

The ERC-CBZ discontinuation rate in the present study was 34%, which is at the lower end of the range of reported dropout rates for other 3-week, monotherapy inpatient trials in acutely manic bipolar disorder (overall treatment group dropout = 41%; range, 39%–58%).[8,10–14] Adverse events reported in this trial were typical of those reported in previous trials of carbamazepine in epilepsy and bipolar disorder. Adverse events were more common

Figure 5. Pooled Data From the Current Study and a Previous Study Showing the Weekly Incidence of the Most Common Adverse Events for ERC-CBZ and Placebo Groups Over Time[a,b]



[a]Data are from the current study pooled with Weisler et al.[3]
[b]Aggressive ERC-CBZ titration protocol for hospitalized patients (200 mg/day as tolerated) was used in both studies.
Abbreviation: ERC-CBZ = extended-release carbamazepine capsules.

in the ERC-CBZ group and consisted largely of central nervous system and gastrointestinal side effects. Although a small weight increase (1.0 kg) was reported during this study, this was not considered clinically relevant.

Most treatment-emergent adverse events were reported in the first week and were of mild to moderate severity (Figure 4). Although 16.4% of patients experienced emesis and a significant portion of patients experienced nausea, somnolence, and dizziness, adverse events such as these were less frequently reported in the second and third weeks of the trial. This is important because most of these adverse events were transient and not severe enough for patients to discontinue treatment. In a post hoc pooled analysis (data on file [Study 304], Shire, Wayne, Pa., 2003) of the current study and another 3-week, double-blind, placebo-controlled, randomized trial of ERC-CBZ,[3] the incidence of typical ERC-CBZ–associated adverse events decreased over time (Figure 5; compare with Figure 4) with continued treatment. Increases in total cholesterol (average 20 points) in this trial were not unexpected. Recent literature has concluded that several anticonvulsants, including carbamazepine and phenobarbital, can lead to modest increases in cholesterol.[18] However, a 6-month open-label extension study that enrolled patients from this trial demonstrated that patients who were previously on carbamazepine treatment did not experience a further increase in their cholesterol beyond that which was seen in the original 3-week trial period.[19] Patients who were on placebo treatment in the 3-week trial, however, experienced a similar 20-point increase in total cholesterol during the 6-month extension trial.

Conclusion

These results confirm previous findings regarding the efficacy of ERC-CBZ as monotherapy for acute mania. Additionally, the results show ERC-CBZ to be safe and well tolerated. Together, these are the largest trials of any carbamazepine preparation in the treatment of acute mania. They provide evidence of efficacy and safety of ERC-CBZ to help guide clinicians in their treatment of patients with bipolar I disorder.

Drug names: carbamazepine (Carbatrol, Equetro, and others), ibuprofen (Motrin, Ibu-tab, and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others).

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