A 6-Month, Multicenter, Open-Label Evaluation of Beaded, Extended-Release Carbamazepine Capsule Monotherapy in Bipolar Disorder Patients With Manic or Mixed Episodes

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Background: Carbamazepine is frequently used for treating bipolar disorder, but few large trials have assessed its efficacy in preventing relapse. We evaluated open-label monotherapy with beaded extended-release carbamazepine capsules (ERC-CBZ; SPD417) as continuation and short-term maintenance therapy in bipolar disorder patients with manic and mixed episodes.

Method: A 6-month, open-label study enrolled 92 patients with DSM-IV bipolar disorder (most recent episode: 67% [N = 62] mixed, 33% [N = 30] manic) who had participated in 2 previous 3-week, double-blind, placebo-controlled studies. Subjects received beaded ERC-CBZ (200–1600 mg/day), titrated at investigators' discretion to a final mean dose of 938 mg/day and serum carbamazepine concentration of 6.6 µg/mL. The primary efficacy measure was time to relapse, and secondary efficacy measures included Young Mania Rating Scale (YMRS), Clinical Global Impressions scale (CGI), and Hamilton Rating Scale for Depression (HAM-D) scores. Data were gathered from January 2000 to January 2002.

Results: Of 77 patients analyzed in the intent-to-treat population, 11 (14.3%) relapsed. Fifty-three patients (68.8%) discontinued early, including 18 (23.4%) due to adverse events. Observed mean time to relapse was 61.1 days, while estimated mean time to relapse based on the Kaplan-Meier model was 141.8 days. Improvements on the YMRS, CGI, and HAM-D from the beginning of prior double-blind treatment were maintained. The most common adverse events were headache, dizziness, and rash. No significant weight gain was noted.

Conclusion: We noted a low relapse rate with beaded ERC-CBZ in this 6-month trial. Adverse events were generally mild to moderate and were typical of those associated with carbamazepine. Controlled studies are warranted to further explore the efficacy of beaded ERC-CBZ in preventing relapse in bipolar disorder.

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A list of the members of the SPD417 Study Group appears at the end of the article.

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Evidence supporting the efficacy of carbamazepine in acute mania includes small trials, primarily comparing immediate-release carbamazepine with active controls,[1] and one recent, large, randomized, double-blind, placebo-controlled trial using twice-daily beaded extended-release carbamazepine capsules (ERC-CBZ; SPD417).[2] In addition, double-blind trials have suggested that carbamazepine maintenance therapy in bipolar disorder has efficacy similar to lithium, with response rates ranging from 30% to 62%.[3,4] A long-term trial in 171 patients over 2.5 years found lithium superior to carbamazepine for "classical bipolar disorder" (bipolar I disorder with classic euphoric mania), but carbamazepine tended to be superior to lithium for "atypical bipolar disorder" (patients with bipolar II disorder, bipolar disorder not otherwise specified, comorbidity, substance abuse, and mixed states).[5]

Lithium's adverse effect profile and inadequate prophylactic efficacy in up to 50% of patients point to the need for additional therapeutic options. Other available treatment options include valproate and olanzapine; these agents have prophylactic efficacy, but their use can be limited in some patients due to adverse effects such as sedation and weight gain. Recent controlled data support the efficacy of lamotrigine maintenance treatment in bipolar disorder,[6] with more robust prevention of recurrence of depressive compared with manic episodes. However, the utility of this agent may be limited by the occurrence of nonserious rash in roughly 1 in 10 patients and serious rash in as many as about 1 in 1000 patients.[7]

Previous evaluations of the prophylactic efficacy of carbamazepine exclusively used conventional immediate-

release carbamazepine formulations. Extended-release formulations may have important advantages, including smaller peak-to-trough serum carbamazepine concentration fluctuations, which can potentially yield less peak-related neurotoxicity.[8–10] In addition, the more convenient twice-daily dosing may improve adherence, which has been correlated with improved outcomes in bipolar disorder[11] and is known to improve with decreased daily dosing frequency.[12,13] Indeed, extended-release carbamazepine treatment decreases serum carbamazepine concentration fluctuations and adverse effects.[14,15] A recent retrospective chart review of epilepsy patients switched to extended-release carbamazepine from immediate-release carbamazepine reported significant decreases in dose-related central nervous system adverse effects, such as sedation, diplopia, confusion, and ataxia.[16]

This open-label study was designed to monitor the safety and continued response to beaded ERC-CBZ treatment over 6 months in manic or mixed bipolar patients who had completed a 3-week, double-blind, placebo-controlled study of beaded ERC-CBZ.

METHOD

Subjects

This protocol was approved by the human subjects panels (institutional review boards) of all participating institutions, and data were gathered from January 2000 to January 2002. Patients provided verbal and written informed consent prior to participation. Subjects were at least 18 years of age, met DSM-IV criteria for bipolar disorder with most recent episode either manic or mixed, and had previously completed one of 2 previous trials of beaded ERC-CBZ. Both trials were 3-week, double-blind, placebo-controlled evaluations, one in 204 manic or mixed patients, and the other in 59 manic or mixed patients who were considered resistant to lithium treatment. Completion rates in these 3-week monotherapy trials were 47% and 54%, respectively.

Study Design and Procedures

The last visits of the previous double-blind studies served as the first visits of this 6-month, open-label extension study. To maintain the blind from the previous studies, all subjects were dosed with blinded blister cards during the first 19 days to allow beaded ERC-CBZ titration in subjects previously receiving placebo. Concomitant treatment with lorazepam or psychotherapy was allowed, but investigators were instructed to use as little lorazepam as possible. Assessments were performed every 2 weeks for the first month and monthly thereafter and included adverse event assessments, laboratory evaluations, Young Mania Rating Scale (YMRS),[17] Clinical Global Impressions scale (CGI),[18] and Hamilton Rating Scale for Depression (HAM-D).[19] The primary outcome measure was the time to relapse, as determined by the investigator, in days from the date of enrollment. Relapse was defined by the clinical judgment of the investigator, based on patient symptomatology and the need for intervention. Compliance was measured by pill counts at each study visit.

Table 1. Disposition of Patients

Variable	Prior Treatment Group: Beaded ERC-CBZ	Placebo	Total
Intent-to-treat, N	37	40	77
Early discontinuation, N (%)	26 (70.3)	27 (67.5)	53 (68.8)
Adverse event(s)	8 (21.6)	10 (25.0)	18 (23.4)
Subject choice	7 (18.9)	6 (15.0)	13 (16.9)
Lost to follow-up	2 (5.4)	2 (5.0)	4 (5.2)
Lack of efficacy	6 (16.2)	5 (12.5)	11 (14.3)
Protocol violation	2 (5.4)	3 (7.5)	5 (6.5)
Other	1 (2.7)	1 (2.5)	2 (2.6)

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

Data Analysis

All statistical analyses were performed using SAS Windows (version 8.0; SAS Institute, Cary, N.C.). SAS Type III estimation was utilized, and the significance level was set at .05 for all statistical tests. All efficacy analyses were performed on the intent-to-treat (ITT) population (all enrolled subjects who had a YMRS score from the initial visit and at least 1 subsequent visit). The time to relapse was analyzed using the Kaplan-Meier model. Secondary efficacy variables, including YMRS, CGI-Severity of Illness (CGI-S), and HAM-D scores, were summarized descriptively, and the mean changes from day 1 to endpoint (using the last observation carried forward [LOCF]) were analyzed using analysis of covariance. Subjects whose YMRS mean total score decreased at least 50% from baseline of the double-blind studies were defined as YMRS responders. Vital signs were summarized descriptively. Mean ± SD values are reported, and a significance threshold of $p < .05$ was used.

RESULTS

Subjects

Patient disposition is shown in Table 1. Ninety-two bipolar disorder patients (most recent episode: 67% [N = 62] mixed, 33% [N = 30] manic) were enrolled. Of the 77 subjects in the intent-to-treat sample at 22 sites, 24 (31.2%) completed the study and 53 (68.8%) discontinued early (26/37 received prior treatment with beaded ERC-CBZ and 27/40 received prior treatment with placebo). Only 11 patients (14.3%) withdrew during the study due to lack of efficacy. Eighteen (23.4%) withdrew due to adverse events, 13 (16.9%) withdrew due to patient choice, and 5 (6.5%) withdrew due to protocol violations. Investigators were instructed to be as accurate as possible

in noting the reason for discontinuation, to minimize the possibility that lack of efficacy or adverse event discontinuations were misclassified as subject choice discontinuations. The most commonly reported adverse events leading to discontinuation, occurring in more than 2 subjects, included rash in 4 subjects and manic-depressive reaction in 3 subjects. The mean subject age was 38.3 years; 81.5% (N = 75) of the subjects were white, 58.7% (N = 54) were female, and 67.4% (N = 62) had been diagnosed with mixed episodes.

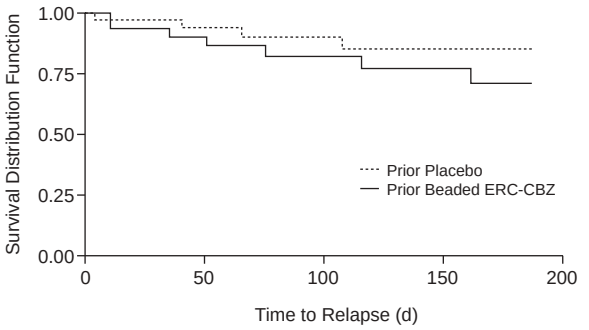
Study medication. Of the 77 subjects in the ITT sample, 37 had received beaded ERC-CBZ and 40 had received placebo in the previous double-blind studies. Both patient disposition and demographics were similar in patients previously taking beaded ERC-CBZ and placebo. The compliance rate during the study was 95.6%. Approximately one third of subjects received at least 6 months of beaded ERC-CBZ treatment, and approximately one third received less than 4 weeks. Patients received beaded ERC-CBZ doses of 200 to 1600 mg/day. At endpoint, approximately 48% (N = 37) of subjects were dosed at 400 to 600 mg/day of ERC-CBZ, while 36% (N = 28) were taking at least 1200 mg/day. The mean final daily dose of beaded ERC-CBZ was 938 mg, with a serum carbamazepine concentration at endpoint of 6.6 μg/mL.

Prior and concomitant medications. Most subjects (91.3% [N = 84]) had received at least 1 treatment for bipolar disorder prior to enrolling in the previous double-blind, placebo-controlled studies, most commonly valproate (28.3% [N = 26]) and lithium (30.4% [N = 28]). Overall, 80.4% (N = 74) of subjects took at least 1 concomitant medication during the study, most frequently ibuprofen (31.5% [N = 29]), lorazepam (28.3% [N = 26]), and paracetamol (22.8% [N = 21]). The mean daily dose of lorazepam was 1.7 ± 0.9 mg based on the 8 of 26 subjects for whom lorazepam dosage was reported.

Efficacy

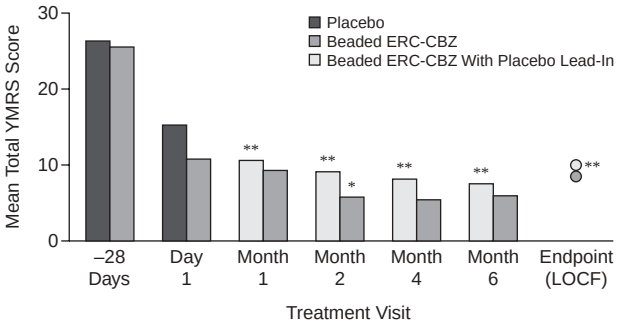
Of the 77 subjects in the ITT population, 11 (14.3%) relapsed during the 6-month study (7 received prior treatment with beaded ERC-CBZ and 4 received prior treatment with placebo). The observed mean time to relapse was 61.1 ± 49.7 days (approximately 2 months). The estimated mean time to relapse based on Kaplan-Meier model was 141.8 ± 5.6 days (4.7 months). A survival function curve is depicted in Figure 1, and mean total YMRS scores are illustrated in Figure 2. In subjects previously treated with placebo, open-label beaded ERC-CBZ led to further decreases in mean total YMRS score, with significant improvements at every visit and at endpoint compared with day 1 ($p < .001$). Additional decreases in mean total YMRS score compared with day 1 in subjects previously treated with beaded ERC-CBZ were not statistically significant, except at month 2 ($p = .0053$). However, at endpoint there was a trend toward further improvement in

Figure 1. Survival Distribution Function Estimate Based on Kaplan-Meier Model for Subjects Previously Treated With Placebo or Beaded ERC-CBZ



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

Figure 2. YMRS Total Scores With Open-Label Beaded ERC-CBZ Treatment[a]

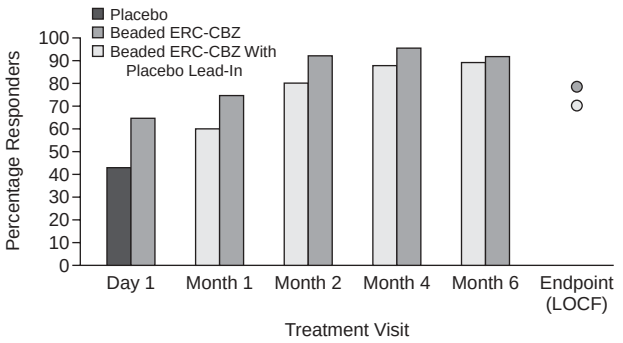


[a]Mean scores at each open-label study visit (observed cases) and at LOCF endpoint are shown, as well as the mean score at the start of the prior double-blind trial, for reference. Patients previously receiving placebo improved with open-label treatment, and those previously receiving double-blind beaded ERC-CBZ maintained improvement on open-label treatment.
*$p < .01$ vs. day 1.
**$p < .001$ vs. day 1.
Abbreviations: ERC-CBZ = extended-release carbamazepine capsules, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

YMRS score, even in patients who had received beaded ERC-CBZ in the prior double-blind studies ($p = .1098$). There was no significant correlation between serum carbamazepine concentration and YMRS total score at any timepoint. The percentages of YMRS responders (≥ 50% decrease from baseline of the double-blind studies) over time and at endpoint for the ITT population (observed cases and LOCF) are depicted in Figure 3. At study endpoint, 78.4% (29/37) of prior beaded ERC-CBZ subjects and 72.5% (29/40) of prior placebo subjects were considered responders.

For subjects previously treated with placebo, the mean CGI-S score was significantly improved at each visit and at endpoint when compared with day 1 ($p < .05$). Addi-

Figure 3. YMRS Response Rates With Open-Label Beaded ERC-CBZ Treatment at Each Study Visit (observed cases) and at Endpoint (LOCF)[a]



[a]Subjects whose YMRS total scores decreased by 50% or more from baseline of double-blind treatment (day 28) were considered responders. At endpoint, 78.4% of subjects previously treated with beaded ERC-CBZ and 72.5% of subjects previously treated with placebo were considered responders.

Abbreviations: ERC-CBZ = extended-release carbamazepine capsules, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

tional decreases in CGI-S scores in subjects previously treated with beaded ERC-CBZ were not statistically significant at endpoint compared with day 1 ($p = .55$). For subjects treated with placebo in the previous double-blind studies, CGI-Improvement (CGI-I) scores improved significantly at each study visit versus day 1 of beaded ERC-CBZ treatment (all $p < .05$). Prior increases in CGI-I scores in subjects previously treated with beaded ERC-CBZ were maintained during the study. Overall, HAM-D total score showed no significant difference from day 1 to month 6. In the previous double-blind studies, there was a nonsignificant improvement in HAM-D scores that was maintained in the present study. However, the 54 patients with mixed states (but not the 23 patients with mania) had a significant decrease in HAM-D score from baseline of the double-blind studies (18.0) to day 1 (12.6, $p < .0001$) that remained decreased at endpoint (13.5, $p = .0003$) compared with baseline of the double-blind studies. Importantly, no worsening of depressive symptoms was noted during this study.

Safety

Adverse events. Of 351 treatment-emergent adverse events reported during the study, 200 (56.9%) were reported to be related or possibly related to study drug by the investigator and 17 (4.8%) were designated severe. The most frequently reported adverse events included headache (21.7% [N = 20]), dizziness (16.3% [N = 15]), and rash (13.0% [N = 12]). A total of 19 patients (20.7%) discontinued treatment due to a treatment-emergent adverse event, most commonly worsening of bipolar symptoms (in 7 patients [7.6%]) and rash (in 4 patients [4.3%]). There was a total of 12 serious adverse events, all judged to be unrelated to study drug by investigators. There were no deaths during the study or within 30 days after study termination.

Laboratory evaluations and vital signs. No cases of aplastic anemia or agranulocytosis were reported during the study. No patient had clinically significant weight gain (i.e., more than a 7% increase from baseline). Mean percentage change in weight from day 1 to endpoint was –0.4%, and the mean change from day 1 to month 6, and for completers, was +0.7%. No meaningful change in blood glucose was noted, no subject had severe electrocardiogram (ECG) changes or ECG changes leading to discontinuation, and no significant change in QTc was noted. The magnitude of the differences between prior treatment groups in the mean change from baseline to endpoint for laboratory tests was small and not clinically relevant, except for the differences between prior treatment groups for alkaline phosphatase (mean change = 5.5 IU/L for those who received prior treatment with placebo) and cholesterol (mean change = –1.1 mg/dL for those who received prior treatment with beaded ERC-CBZ vs. 18.2 mg/dL for those who received prior treatment with placebo).

DISCUSSION

The completion rate in this study was low (26.1%), as is often the case in monotherapy maintenance trials.[20,21] Indeed, combination therapy is typically needed in bipolar disorder,[22,23] and lower relapse rates are reported with combination therapy versus monotherapy.[24,25]

The relapse rate of 14.3% over 6 months in the current study compares favorably with previously reported relapse rates for placebo (74%) and lithium (29%).[3] Supporting the findings of the previous double-blind studies, our results indicated that subjects previously receiving placebo who then received beaded ERC-CBZ in this open-label trial had significant YMRS and CGI score improvements beginning at the first visit (month 1), compared with the baseline visit (before beaded ERC-CBZ treatment). These improvements from baseline after 1 month of open-label treatment were comparable in magnitude (60% YMRS score decrease) to those seen with blind beaded ERC-CBZ (51% YMRS score decrease). In addition, patients who received beaded ERC-CBZ in the prior double-blind studies tended to show further improvement with open continuation treatment, perhaps related to additional efficacy and/or spontaneous remissions that were not captured in the brief 3-week controlled trials.

Treatment-emergent adverse events in this study were typical of carbamazepine and included headache, dizziness, and rash. Rash was a frequent adverse event leading to discontinuation (4.3%), as in previous carbamazepine

studies.[4,24,26] No patient had serious rash, aplastic anemia, or agranulocytosis. This study would not be expected to detect rare events such as aplastic anemia or agranulocytosis, which occur with an incidence of 1.4 and 5.1 per million patients treated per year, respectively.[27] Importantly, weight gain was not seen in this study, consistent with previous long-term carbamazepine studies.[26] Weight gain and associated health risks are major concerns in treating bipolar patients.[28] As many widely used bipolar therapies such as lithium, valproate, and olanzapine are associated with substantial weight gain,[29] carbamazepine may be an important treatment option in patients at risk for obesity-related problems.

This study has several important limitations. First, the open design does not allow comparison of efficacy of treatment and natural course of illness as is possible with double-blind, placebo-controlled designs. In addition, the relatively brief (6-month) duration does not allow as much opportunity to capture relapses as longer (typically 12- to 24-month) trials. The high early discontinuation rate and the common practice of not continuing to collect data after early discontinuations are important confounding influences. "Censoring" or using only data points at which patients were protocol compliant is another important limitation, particularly in view of the high early discontinuation rate. In addition, although only 11 patients (14.3%) were classified as relapsing, an additional 7 patients discontinued early due to worsening of bipolar symptoms classified as a treatment-emergent adverse event. It is possible that such cases actually represented relapses, in which case the relapse rate would be 18/77 (23.4%). Although the latter rate is substantially higher than our reported rate of 14.3%, it is still comparable with that observed with other agents such as lithium.[3] Finally, contemporary maintenance studies utilize "enriched" designs in which patients are openly stabilized on treatment with study medication prior to randomization, allowing assessment of maintenance utility without the confound of early discontinuations due to acute adverse effects. Curiously, allowing acute initiation of beaded ERC-CBZ within the current study does not appear to have yielded a substantial confound of this type, as early discontinuation rates were similar for patients receiving beaded ERC-CBZ and placebo in the prior double-blind studies.

CONCLUSION

Up to 6 months of open-label treatment with beaded ERC-CBZ twice daily, at doses of up to 1600 mg/day, was associated with a low rate of relapse in patients with manic or mixed bipolar disorder. YMRS and CGI-S score improvements demonstrated in 2 previous 3-week double-blind studies were replicated with open-label treatment in patients previously receiving placebo and maintained in patients previously receiving blinded treatment with beaded ERC-CBZ. Adverse events were generally mild to moderate and were typical of carbamazepine. Controlled studies are warranted to further explore the efficacy of beaded ERC-CBZ in preventing relapse in bipolar disorder. These results, taken together with the findings of the double-blind acute trial and the tolerability limitations of other agents, suggest that carbamazepine use as described in the current guideline for the treatment of bipolar disorder may reflect underutilization of an important treatment option.[30] Double-blind, placebo-controlled carbamazepine maintenance trials in bipolar disorder are warranted to explore this issue in a systematic fashion.

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

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