*Annals of Clinical Psychiatry*, 18[S1]:15–18, 2006

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230600653353

Taylor & Francis

# Outcomes and Length of Treatment With Carbamazepine Extended-Release Capsules in Bipolar Disorder

**LAWRENCE D. GINSBERG, MD**
Red Oak Psychiatry Associates, Houston, TX, USA

***Background.*** *This analysis was a retrospective chart review evaluating the relationship between outcomes and length of treatment with carbamazepine extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) in bipolar disorder.*
***Methods.*** *The medical records of adult patients (≥ 18 years) meeting DSM-IV criteria for bipolar disorder who were treated with CBZ-ERC for 30 days or less, 31 to 180 days, and more than 180 days were reviewed in this study.*
***Results.*** *There were significant differences in mean Clinical Global Impression–Improvement (CGI-I) scores at the best office visit among the three treatment groups. The mean CGI-I scores for the 31- to 180-day (2.3 ± 1.1) and >180-day (1.8 ± 1.0) groups were significantly lower than the mean score for the ≤ 30-day treatment group ($p < 0.0001$), and the mean CGI-I score for the >180-day group was significantly lower than that of the 31- to 180-day group ($p = 0.0027$). Significantly fewer patients in the 31- to 180-day (5.4%; $p = 0.0039$) and >180-day groups reported nausea (4.8%; $p = 0.034$) when compared to the <30 day group.*
***Conclusions.*** *The results of this study indicate that future controlled studies are warranted to further explore the safety and efficacy of CBZ-ERC as a long-term therapy for bipolar disorder.*

**Keywords** Bipolar disorder, Carbamazepine, Maintenance

## *INTRODUCTION*

The chronic nature of bipolar disorder necessitates long-term pharmacological treatment in the majority of patients affected by this disease. Long-term tolerability of these treatments is therefore an important consideration in the choice of drug therapy for bipolar disorder. Only four drugs (lithium, lamotrigine, olanzapine and aripiprazole) are currently approved by the US Food and Drug Administration (FDA) for long-term maintenance therapy in bipolar I disorder, although many other agents are utilized for this purpose. Lithium has been considered the gold standard for maintenance therapy since the 1960s, but several studies have found that up to 50% of patients respond poorly to lithium (1–3). The limitations of current maintenance therapies and lack of additional FDA-approved agents highlight the need for additional options for long-term therapy in bipolar disorder.

Carbamazepine (CBZ) has long been considered a therapeutic option for bipolar disorder. However, previous evaluations of the prophylactic efficacy of CBZ were based on conventional immediate-release formulations (4). Extended-release CBZ formulations have important advantages, including smaller peak-to-trough serum fluctuations, which can potentially yield less peak-related neurotoxicity (5–7). Carbamazepine extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) consist of three different types of beads—immediate release, extended release, and enteric release—designed to extend release of CBZ to 12 hours. This formulation was recently approved by the FDA for acute treatment of patients with bipolar disorder. Here we present the results of a retrospective chart review evaluating the relationship between treatment outcome and duration of CBZ-ERC therapy in an outpatient setting.

Address correspondence to Lawrence D. Ginsberg, MD, Red Oak Psychiatry Associates, 17115 Red Oak Drive, Suite 109, Houston, TX 77090. E-mail: larrydg@earthlink.net

## METHODS

### Patient Selection

The study was limited to adult patients (≥ 18 years old) who met the DSM-IV criteria for bipolar disorder and had been treated with CBZ-ERC either as monotherapy or in combination with other psychotropic agents (Red Oak Psychiatry Associates, Houston, TX, USA) between October 1998 and November 2003.

### Study Procedures

In this retrospective study, subjects were divided into three groups according to length of treatment with CBZ-ERC: 30 days or less, 31 to 180 days, and greater than 180 days of treatment. Data obtained from patients' medical records include demographic data, diagnosis of both primary and comorbid conditions, dosage of CBZ-ERC, and adverse events. Primary diagnosis included bipolar subtype—bipolar I, bipolar II, or bipolar not otherwise specified—and most recent episode (manic, mixed, depressed, etc.). Clinical Global Impression–Severity (CGI-S) scale (8) ratings were determined at initiation of CBZ-ERC therapy to document the baseline severity of illness. The CGI-S scale ranges from a score of 1 (no mental illness) to 7 (severe mental illness). The efficacy of CBZ-ERC was measured at the best office visit using ratings on the Clinical Global Impression–Improvement (CGI-I) scale (1 = very much improved to 7 = very much worse), with the best office visit defined as the time point at which the best CGI-I score was recorded after initiation of CBZ-ERC. Clinical response was set at CGI-I scores ≤ 3; clinical relapse was set at a change in CGI-I ≥ 4 after an observed CBZ-ERC response. The CBZ-ERC dose was also recorded at the best office visit. Data on study subjects were drawn exclusively from chart review; patients were not asked to visit the physician's office at any time during the study. Analyses of demographic and adverse event comparison were performed with one-way analysis of variance or chi-square test.

## RESULTS

### Patient Demographics and Disposition

A total of 298 patients who met inclusion criteria for the study were identified. Of these patients, 87 were included in the ≤ 30-day group, 149 in the 31- to 180-day group, and 62 in the >180-day group (Table 1). Baseline demographic and clinical characteristics of the patients indicated that the three groups were comparable. Bipolar I disorder was the most common bipolar subtype in each treatment group, with 46.0% of patients in the ≤ 30-day group, 41.6% of patients in the 31- to 180-day group, and 54.8% of patients in the >180-day group receiving a bipolar I manic/mixed diagnosis. There were no statistically significant differences in the mean age or mean CGI-S score among the three groups.

### Treatment Response

There were significant differences in mean CGI-I scores at the best office visit between the three treatment groups. The mean CGI-I scores for the 31- to 180-day (2.3 ± 1.1) and >180-day (1.8 ± 1.0) groups were significantly lower than the mean score for the ≤ 30-day treatment group ($p < 0.0001$) (Table 2). In addition, the mean CGI-I score for the >180-day group was significantly lower than that of the 31- to 180-day group ($p = 0.0027$). The differences in percentage of responders among the treatment groups were also significant. We found that a significantly higher percentage of patients in the 31- to 180-day (81.9%; $p = 0.0001$) and >180-day (91.9%; $p < 0.0001$) groups responded to CBZ-ERC treatment than in the ≤ 30-day group (46.0%). The percentage of patients relapsing was highest in the >180-day group (47.4%) and lowest in the 31- to 180-day group (24.6%). There was a 46.0% relapse rate in the ≤ 30-day group. The difference in the relapse rates between the 31- to 180-day and >180-day groups reached statistical significance ($p = 0.0096$).

**Table 1** Patient Demographics and Baseline Clinical Characteristics

| | ≤ 30-days | 31- to 180-days | >180-days |
|---|---|---|---|
| Subjects, n | 87 | 149 | 62 |
| Female, n (%) | 61 (70.1) | 106 (71.1) | 44 (71.0) |
| Mean age, years (SD) | 33.6 (11.3) | 35.8 (10.9) | 34.9 (12.3) |
| Age range, years | 18–66 | 18–66 | 18–70 |
| Bipolar I manic/mixed, n (%) | 40 (46) | 62 (41.6) | 34 (54.8) |
| Bipolar I depressed, n (%) | 19 (21.8) | 33 (22.1) | 15 (24.2) |
| Bipolar II, n (%) | 13 (14.9) | 24 (16.1) | 8 (12.9) |
| Bipolar NOS, n (%) | 15 (17.2) | 30 (20.1) | 5 (8.1) |
| Mean CGI-S (SD) | 5.1 (0.8) | 5.3 (0.8) | 5.2 (0.8) |
| *p*-value vs. ≤ 30-day group | N/A | 0.085 | 0.54 |
| *p*-value vs. 31- to 180-day group | N/A | N/A | 0.39 |

NOS = not otherwise specified; CGI-S = Clinical Global Impression–Severity.

**Table 2** Response to CBZ-ERC Treatment

| | ≤30-days | 31- to 180-days | >180-days |
|---|---|---|---|
| Mean CGI-I (SD) | 3.2 (1.2) | 2.3 (1.2) | 1.8 (1.0) |
| *p*-value vs. ≤ 30-day group | N/A | <0.0001 | <.0001 |
| *p*-value vs. 31- to 180-day group | N/A | N/A | 0.0027 |
| Responders, n (%) | 40 (46.0) | 122 (81.9) | 57 (91.9) |
| *p*-value vs. ≤ 30-day group | N/A | 0.0001 | <.0001 |
| *p*-value vs. 31- to 180-day group | N/A | N/A | 0.3987 |
| Relapse, n (%) | 16 (40.0) | 30 (24.6) | 27 (47.4) |
| *p*-value vs. ≤ 30-day group | N/A | 0.13 | 0.67 |
| *p*-value vs. 31- to 180-day group | N/A | N/A | 0.01 |
| Mean dose at best CGI-I, mg (SD) | 527.5 (156.9) | 595.9 (230.8) | 678.9 (244.0) |
| *p*-value vs. ≤ 30-day group | N/A | 0.083 | 0.0008 |
| *p*-value vs. 31- to 180-day group | N/A | N/A | 0.029 |

CBZ-ERC = carbamazepine extended-release capsules; CGI-I = Clinical Global Impression–Improvement; SD = standard deviation.

The mean CBZ-ERC dose for responders at best CGI-I increased with length of treatment; the mean dose for the ≤ 30-day group was 527.5 ± 156.9 mg, while the mean dose for the 31- to 180-day group was 595.9 ± 230.8 mg, and for the >180-day group it was 678.9 ± 244.0 mg. The dosage for the >180-day group was significantly higher than the ≤ 30-day ($p$ = 0.0008) and 31- to 180-day ($p$ = 0.029) groups.

### *Tolerability*

The incidence of the most common treatment-emergent adverse events (dizziness, nausea, somnolence, vomiting, and rash) in each group is shown in Figure 1. We found that the incidence of these adverse events was highest in the ≤ 30-day group, although there were no significant differences in the incidence of somnolence and nausea among the three treatment groups. There were, however, significantly fewer patients in the 31- to 180-day group (3.4%) reporting dizziness than in the ≤ 30-day group (16.1%; $p$ = 0.002). Significantly fewer patients in the 31- to 180-day group (5.4%; $p$ = 0.0039) and > 180-day (4.8%; $p$ = 0.0341) groups experienced nausea than in the ≤ 30-day group. In addition, significantly fewer patients in the 31- to 180-day group reported rash than in the ≤ 30-day group ($p$ = 0.0308). There were no reports of any serious rashes or blood dyscrasias. We found a significantly higher incidence of patients in the ≤ 30-day group (65.5%) reporting any adverse event than the 31- to 180-day (35.6%; $p$ = 0.0003) and >180-day groups (38.7%; $p$ = 0.015) (Table 3). Furthermore, the number of days to any adverse event was significantly lower for the ≤ 30-day treatment group (11.4 ± 7.1 days) than for both the 31- to 180-day (55.3 ± 44.2; $p$ < 0.0001) and >180-day (254.5 ± 341.3; $p$ < 0.0001) treatment groups.

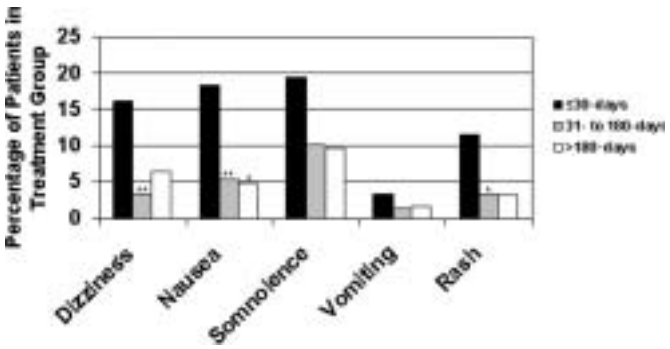


**Figure 1** Incidence of dizziness, nausea, somnolence, vomiting, and rash in ≤ 30, 31 to 180, and >180-day treatment groups. The percentage of patients in each treatment group reporting the selected adverse events is shown. *$p$ < 0.05; **$p$ < 0.01 vs ≤ 30-day treatment group.

## *DISCUSSION*

We found that there was a significantly higher incidence of adverse events in the ≤ 30-day group than in the 31- to 180-day and >180-day treatment groups. We also found that significantly more patients in the 31- to 180-day and >180-day groups responded to treatment than in the ≤ 30-day group. Both of these results suggest that a combination of inadequate response to CBZ-ERC therapy and adverse events associated with CBZ-ERC contributed to the early withdrawal of patients from CBZ-ERC therapy in the ≤ 30-day treatment group.

**Table 3** Timing and Incidence of Any Adverse Event

| | ≤30-days | 31- to 180-days | >180-days |
|---|---|---|---|
| Any AE (%) | 57 (65.5) | 53 (35.6) | 24 (38.7) |
| *p*-value vs. ≤ 30-day group | N/A | 0.0003 | 0.015 |
| Mean time to any AE, days (SD) | 11.4 (7.1) | 55.3 (44.2) | 254.5 (341.3) |
| *p*-value vs. ≤ 30-day group | N/A | <0.0001 | <0.0001 |
| *p*-value vs. 31- to 180-day group | N/A | N/A | <0.0001 |

AE = adverse event; SD = standard deviation.

Higher relapse rates in the longer treatment groups can be attributed to the relapsing nature of the disorder overall.

The incidence of any adverse event in the ≤ 30-day treatment group of 65.5% was similar to the 56.9% incidence reported in a previous 6-month open-label study of CBZ-ERC in patients with bipolar disorder by Ketter and colleagues (4). Ketter also reported that 16.3% of patients suffered dizziness and 13.0% of patients suffered rash during CBZ-ERC treatment, similar to what we found in the ≤ 30-day treatment group in the current study. However, we did find the incidence of dizziness and rash in the 31- to 180-day and >180-day treatment groups to be much lower, suggesting that these two groups of patients tolerated CBZ-ERC therapy particularly well. This tolerability was also evidenced by the significantly longer time to onset of any adverse event in these treatment groups. It would be interesting to determine what the underlying basis for the greater tolerability in these patients is.

## *CONCLUSIONS*

The findings of this study must be viewed in the light of its methodological limitations. Due to the lack of randomization and the retrospective nature of the study, we could not control for potentially confounding factors, such as concomitant medications. Information may also have been missed or incorrect as the result of improper or absent documentation in patients' medical records. However, naturalistic studies such as this one do offer meaningful insights into everyday clinical practice that are not readily obtained from the highly selected patient groups included in clinical trials (9), and the results of this study indicate that future controlled studies are warranted to further explore the safety and efficacy of CBZ-ERC as a long-term therapy for bipolar disorder.

## *ACKNOWLEDGMENTS*

Editorial assistance for the preparation of this manuscript was provided by Precept Educational Sciences, Berkeley Heights, NJ, USA. This study was supported by a grant from Shire, Wayne, PA, USA.

## *REFERENCES*

1. Harrow M, Goldberg JF, Grossman LS, Meltzer HY: Outcome in manic disorders. a naturalistic follow-up study. *Arch Gen Psychiatry* 1990; 47:665–671
2. O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE: Outcome of bipolar disorder on long-term treatment with lithium. *Br J Psychiatry* 1991; 159:123–129
3. Keck PE Jr, McElroy SL: Outcome in the pharmacologic treatment of bipolar disorder. *J Clin Psychopharmacol* 1996; 16(2 suppl 1):15S–23S
4. Ketter TA, Kalali AH, Weisler RH, for the SPD417 Study Group: A 6-month, multicenter, open-label evaluation of extended-release carbamazepine capsule monotherapy in bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry* 2004; 65:668–673
5. Hoppener RJ, Kuyer A, Meijer JW, Hulsman J: Correlation between daily fluctuations of carbamazepine serum levels and intermittent side effects. *Epilepsia* 1980; 21:341–350
6. Tomson T: Interdosage fluctuations in plasma carbamazepine concentration determine intermittent side effects. *Arch Neurol* 1984; 41:830–834
7. Riva R, Albani F, Ambrosetto G, et al: Diurnal fluctuations in free and total steady-state plasma levels of carbamazepine and correlation with intermittent side effects. *Epilepsia* 1984; 25:476–481
8. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W: Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res* 1997; 73:159–171
9. Baldessarini RJ, Tohen M, Tondo L: Maintenance treatment in bipolar disorder. *Arch Gen Psychiatry* 2000; 57:490–492