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Predictors of Response to Carbamazepine Extended-Release Capsules Treatment in Bipolar Disorder

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Background. *Predictors of response to psychoactive drugs are valuable in providing practical guidance and in optimizing a treatment regimen. Here we used linear regression analysis to identify treatment-specific predictors of response to therapy with beaded extended-release carbamazepine capsules (CBZ-ERC) (Shire, Wayne, PA, USA) in 600 outpatients with bipolar disorder.*
Methods. *Data were obtained from medical charts of subjects who received CBZ-ERC in a private practice setting. Illness severity and improvement were assessed using the Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I) scales.*
Results. *We found that increasing baseline CGI-S scores correlated with lower CGI-I scores (R^2 = 0.01, p = 0.009); that is, the higher the baseline CGI-S score, the greater the expected degree of improvement. There was also a correlation between increasing CBZ-ERC dose and improvement in CGI-I scores (R^2 = 0.02; p = 0.0004). Moreover, we found that increasing carbamazepine (CBZ) blood concentration correlated with decreases in CGI-I scores (R^2 = 0.12; p = 0.025), and that there was a correlation between higher total daily CBZ-ERC dose in mg/kg of body weight and decreases in CGI-I scores (R^2 = 0.01; p = 0.038).*
Conclusions. *These findings suggest that bipolar patients with more severe baseline symptoms, on higher CBZ-ERC doses, and with higher CBZ blood levels were more likely to respond to CBZ-ERC treatment.*

Keywords Bipolar disorder, Carbamazepine, Predictors to response

INTRODUCTION

According to the World Health Organization, bipolar disorder is ranked as the sixth leading cause of disability in the world for persons aged 15 to 44 years (1). In addition to impairments in psychological performance and increased risk of suicide in individuals with the disorder, it has significant negative effects on social functioning. These consequences may include loss of employment or employment difficulties and stress on relationships (1). Furthermore, average annual U.S. health care costs in a managed care plan for an adult patient with bipolar disorder 1 year following diagnosis are $19,116, which is four times the cost accrued by an average member (2). Thus, a priority for clinicians who treat patients with bipolar disorder is to assist patients in achieving and maintaining a euthymic condition and preventing recurrence of mania, hypomania, or depression, thereby improving patients' social relations and reducing hospital care costs.

In clinical studies, evaluating predictors of response to a drug will improve treatment by identifying patient characteristics and variables associated with positive or negative outcomes. Since there are many drugs for treatment of bipolar disorder, these predictors can be used to better match drugs to patients for optimal response. Several reports have indicated comorbid substance abuse, mixed episode, and rapid cycling to be associated with lithium unresponsiveness, whereas those same variables have been associated with responsiveness to valproic acid (3–8). Limited studies, however, have focused on predictors of response to carbamazepine (CBZ) therapy in patients with bipolar disorder. In a placebo-controlled study of 19 patients with acute mania

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who were predominantly unresponsive to lithium, good response to CBZ treatment (as defined by an improvement of 2 or more points on the global Bunney-Hamburg scale) was more likely to be achieved by patients who had mixed episodes or rapid cycling, increased severity of mania, and negative family history of bipolar disorder (9).

In this retrospective analysis of 600 outpatients with bipolar disorder, we searched for predictors of response to treatment with beaded CBZ extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA), which were recently approved by the United States Food and Drug Administration (FDA) for the treatment of acute manic and mixed episodes associated with bipolar I disorder.

METHODS

Medical records were reviewed for 600 patients with bipolar disorder (as defined by DSM-IV criteria) who were treated with CBZ-ERC as monotherapy or polytherapy at a single private practice setting (Red Oak Psychiatry Associates, Houston, TX) between October 1998 and November 2003. Baseline data gathered included gender, age, bipolar presentation, and body weight at initiation of CBZ-ERC therapy. In addition, available information on starting date and dates of office visits, CBZ-ERC dose, CBZ blood concentration, and white blood cell (WBC) count were collected.

Study Assessments

At initiation of CBZ-ERC treatment, Clinical Global Impression–Severity (CGI-S) scale ratings were recorded in order to document the baseline severity of illness. Response to CBZ-ERC treatment was measured at the best office visit using ratings on the Clinical Global Impression–Improvement (CGI-I) scale. (Best office visit was defined as the time point at which the best CGI-I score was recorded after initiation of CBZ-ERC.) The CGI-S scale ranges from a score of 1 (no mental illness) to 7 (severe mental illness), and the CGI-I scale ranges from 1 (very much improved) to 7 (very much worse). Clinical response was set at CGI-I scores lower than or equal to 3, and clinical relapse was defined as the occurence of a CGI-I score ≥ 4 in a patient who had previously experienced a clinical response.

Statistical Analysis

Using Analyse-it® software (Analyse-it Software, Ltd, Leeds, UK), multiple linear regression was performed to estimate the association between CGI-I score (the primary dependent variable) and the following covariates: CGI-S score, age, total daily CBZ-ERC dose (in milligrams), total daily CBZ-ERC dose (in mg/kg of body weight), CBZ blood concentration in patients receiving CBZ-ERC monotherapy, and CBZ blood concentration in patients receiving CBZ-ERC in combination with other therapies. The magnitude of significant ($p < 0.05$) linear associations is represented by R^2, the proportion of the variability in response accounted for by the covariate. Also explored were associations among CBZ blood concentrations, CBZ-ERC total daily dose, and WBC count.

RESULTS

Baseline Characteristics and CBZ-ERC Dose

Of the 600 subjects, 55.7% were female and mean age was 23.7 ± 14.2 (Table 1). Each bipolar subtype was represented in the study group, with bipolar I manic/mixed being the most common (36.2%) (Table 1). At baseline, 87% of the patients were at least markedly ill (CGI-S ≥ 5). Response to CBZ-ERC treatment was noted in 74.3% of patients and subsequent relapse was observed in 32.3% of patients who initially responded. The average daily CBZ-ERC dose taken by responders (recorded at best office visit) was 585.8 ± 207.2 mg.

Association Between CGI-I Scores and Covariates

There was a negative association between baseline severity of illness and CGI-I scores ($R^2 = 0.01$; $p = 0.009$), such that patients with more severe symptoms at baseline tended to improve to a greater degree when treated with CBZ-ERC. There was no association between response to CBZ-ERC and patient age ($R^2 = 0.00$; $p = 0.5674$) (Table 2).

Total daily CBZ-ERC dose in milligrams and total daily CBZ-ERC dose in mg/kg of body weight were negatively correlated with CGI-I scores ($R^2 = 0.02$; $p = 0.004$ and $R^2 = 0.01$; $p = 0.0379$, respectively); that is, the greater the dose of CBZ-ERC, the lower the expected CGI-I score (Table 2).

In patients on CBZ-ERC monotherapy, there was a negative correlation between CBZ blood concentration and CGI-I scores ($R^2 = 0.12$; $p = 0.0248$); in other words, patients on CBZ monotherapy who had higher CBZ blood concentrations tended to improve to a greater degree (Table 2). There was no

Table 1 Baseline Demographics

Number of subjects	600
Gender (% female)	55.7
Age range (y)	4–70
Mean age (y [SD])	23.7 (14.2)
Bipolar type (%)	
Bipolar I manic/mixed	36.2
Bipolar I depressed	15.8
Bipolar II	18.5
Bipolar NOS	29.5

NOS = not otherwise specified.

Table 2 Association Between CGI-I Scores and Covariates

Variables	N (No. of patients)	R^2	*p*
Negative association			
CGI-S	600	0.01	0.009
CBZ-ERC dose[a]	592	0.02	0.0004
CBZ-ERC dose[a]/body weight	327	0.01	0.0379
CBZ blood concentration[b] (monotherapy)	41	0.12	0.0248
No association			
Age	600	0.00	0.5674
CBZ blood concentration[b] (polytherapy)	143	0.00	0.3227

CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; CBZ-ERC = extended-release carbamazepine capsules; CBZ = carbamazepine.
[a]Dose at best office visit.
[b]Measured at or near best.

Table 3 Associations Between Variables

Variables	N (No. of data points)[a]	R^2	*p*
Positive association			
CBZ blood level vs. CBZ-ERC dose (monotherapy)	41	0.11	0.021
CBZ blood level vs. CBZ-ERC dose (polytherapy)	143	0.18	<0.0001
Negative association			
WBC count vs. days on CBZ-ERC	893	0.01	0.0161
No association			
WBC count vs. CBZ-ERC dose	893	0.00	0.7787

CBZ = carbamazepine; CBZ-ERC = extended-release carbamazepine capsules; WBC = white blood cell.
[a]Data points may contain data from more than one office visit per patient or when both variables were available at the same office visit.

association between response and CBZ blood concentration in patients receiving CBZ-ERC in combination with other therapeutic agents ($R^2 = 0.01$; $p = 0.3227$) (Table 2).

Associations Between Variables

As expected, there was a positive correlation between CBZ blood concentration and total daily CBZ-ERC dose in patients on CBZ-ERC monotherapy and in patients on CBZ-ERC in combination with other therapies ($R^2 = 0.13$; $p = 0.0210$ and $R^2 = 0.18$; $p < 0.001$, respectively) (Table 3).

There was a negative association between time on CBZ-ERC and WBC count ($R^2 = 0.01$; $p = 0.0161$). However, no association was observed between WBC count and total daily CBZ-ERC dose ($R^2 = 0.00$; $p = 0.7787$) (Table 3).

DISCUSSION

The intention of this retrospective analysis was to identify variables and characteristics (pretreatment and during treatment) of patients with bipolar disorder that lead to good response as defined by improvement in CGI-I score with CBZ-ERC therapy. Our findings indicate that greater severity of illness at initiation, higher CBZ-ERC dose, and higher CBZ blood concentrations were associated with patient improvement. In addition, higher CBZ-ERC dose correlated with increasing CBZ blood concentration, and duration of treatment was negatively associated with WBC count.

Reports on correlates of nonresponse and response to CBZ are sparse. One post hoc analysis showed that a history of rapid cycling in patients with more than 10 years from onset of illness to initiation of study was associated with poor CBZ response (10). However, Post and colleagues found that rapid cyclers did respond better to CBZ treatment (9). Likewise, Okuma and colleagues showed that 78% of patients who responded to CBZ treatment were rapid cyclers.

This analysis showed no association between age of patients and response to CBZ-ERC therapy. The finding that greater severity at initiation of CBZ-ERC treatment was correlated with more favorable CGI-I scores during treatment was similar to the results from a previous study; although response in that study was measured using a different scale and the formulation of CBZ was not extended release (9).

To date, CBZ blood concentrations have not been shown to correlate with clinical response. Results from this analysis suggest that a higher CBZ-ERC dose and CBZ blood concentration may potentiate good clinical response. An interesting observation in this study was that the negative relationship between CBZ blood concentration and CGI-I scores was statistically significant in patients on CBZ-ERC monotherapy, but not polytherapy. One explanation could be that patients are dosed less aggressively with CBZ-ERC when it is used in combination with other therapies.

In addition to associations between baseline characteristics and clinical improvement, WBC count, which tends to decrease with CBZ treatment, was negatively associated with days on CBZ-ERC. This occurrence was also observed in a study by Joffe and colleagues in which significant reductions in WBC count were observed within 1 week of treatment with CBZ; however, WBC count did not decrease any further by the fourth week of treatment (11). No aplastic anemia or agranulocytosis was reported in a 6-month maintenance study of 77 patients with bipolar disorder who were on CBZ-ERC (12).

Drawing conclusions from retrospective data can be problematic given the methodological and clinical limitations. However, this information is beneficial because patients were in a naturalistic setting, and the outcomes may be more realistic than those found in clinical studies.

CONCLUSIONS

This analysis of predictors of improvement with CBZ-ERC therapy indicates that increased severity of illness, higher CBZ-ERC dose, and higher CBZ blood concentration may be

associated with good outcomes in patients with bipolar disorder. Despite the limitations of this study, the information presented here will be of use for future prospective, randomized, placebo-controlled studies to further explore and confirm clinical correlates of response to CBZ treatment.

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