Annals of Clinical Psychiatry, 18[S1]:27–30, 2006

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230600653437

Taylor & Francis

Safety and Efficacy of Carbamazepine Extended-Release Capsules in Patients With Bipolar Disorder: QD vs BID

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

Background. *Adherence to prescribed pharmacotherapy is an important factor in the success of a selected treatment regimen. Because the dosing frequency of a particular medication can affect adherence rates, this important aspect of treatment must be taken into account. This report presents results from a retrospective assessment of the charts of 23 patients who received once-daily (qd) carbamazepine extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) for the treatment of bipolar disorder.*
Methods. *The assessment compared qd dosing of CBZ-ERC with twice-daily (bid) dosing by matching the charts of the 23 study subjects to those of 23 similar control patients who had been taking CBZ-ERC dosed bid.*
Results. *In this study, no significant difference was observed in Clinical Global Impression–Improvement (CGI-I) scores between the qd and bid groups. In addition, the percentage of responders (those whose CGI-I score were ≤ 3) was the same (83%) for both groups. Relapse rates and measures of safety and tolerability were also similar in the two treatment groups.*
Conclusions. *These findings suggest that CBZ-ERC dosed qd is comparable in efficacy, safety, and tolerability to CBZ-ERC dosed bid for patients with bipolar disorder.*

Keywords BID, Bipolar disorder, Carbamazepine, QD

INTRODUCTION

Bipolar disorder is a severe, recurrent mood disorder characterized by episodes of mania or hypomania, depression, or mixed episodes (a mixture of manic and depressive symptoms) (1). The pathophysiologic and neuropathophysiologic bases of the disorder are not well understood, but multiple areas of the brain and endocrine system appear to be involved (2,3). A limited understanding of the pathophysiologic processes that underlie bipolar disorder has hampered the development of new treatments tailored to this illness.

The efficacy and safety of once-daily (qd) dosing of medications such as carbamazepine (CBZ) for patients with bipolar disorder are of interest since simpler dosing regimens utilizing other medications have been shown to promote better adherence in this disorder (4). Adherence to a medication regimen is a profound concern in relation to treatment response in patients with bipolar disorder; concomitant administration of two or more psychoactive medications is increasingly prevalent in the management of the illness, especially in refractory cases (5,6). Generally, the fewer daily doses of medication a patient has to take, the better his or her adherence is to that therapeutic regimen (7,8). Many of the medications used to treat bipolar disorder, such as lithium and valproic acid, are frequently dosed twice daily (bid), according to the manufacturers' recommendations (9,10)

Carbamazepine has been a part of the pharmacopoeia for bipolar disorder for decades. Fourteen double-blind, controlled studies have shown CBZ to be effective in the treatment of acute mania (11). Additionally, three recent large clinical trials have demonstrated the safety and efficacy of carbamazepine extended-release capsules (CBZ-ERC) (Equetro™, Shire, Wayne, PA, USA) in bipolar disorder (12–14). These trials have led to the recent U.S. Food and Drug Administration (FDA) approval of CBZ-ERC for use in treating manic and mixed

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

episodes associated with bipolar I disorder. Furthermore, the dosing flexibility and consistency of serum levels afforded by CBZ-ERC may provide a benefit for patients in further reducing frequency of medication.

The purpose of this retrospective chart review was to better determine whether CBZ-ERC can be safely and effectively dosed qd in patients with bipolar disorder.

METHODS

Subjects

The study subjects were adult and pediatric patients with bipolar disorder whose illness had been diagnosed according to DSM-IV criteria. All patients were treated at Red Oak Psychiatry Associates in Houston, TX. Half of the patients had been taking CBZ-ERC dosed qd for their disorder; these patients' charts were matched to those of similar patients who had been taking CBZ-ERC dosed bid.

Demographics for the patients in the qd and bid treatment groups are given in Table 1. More than two thirds of the patients in each group were female; their mean age was approximately 22 years. At the start of CBZ-ERC therapy, nearly 74% of the patients in the qd group were not taking any other psychotropic medications, in contrast to only 30% of patients in the bid group.

Study Design

This study was a retrospective review and analysis of the medical charts of 23 patients who had been taking CBZ-ERC qd for bipolar disorder. The charts of all patients on CBZ-ERC from October 1998 to November 2003 were reviewed to identify patients on CBZ-ERC dosed qd. These patients were matched to a control group of 23 similar patients who had been taking CBZ-ERC bid. Patients in the two treatment groups were matched according to age, gender, bipolar subtype diagnosis, score on the Clinical Global Impression–Severity (CGI-S) scale at the time of CBZ-ERC initiation (reconstructed from chart notes), and mean dose of CBZ-ERC being administered when the Clinical Global Impression–Improvement (CGI-I) score was measured. 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). If more than 1 match was found for a given patient, a record was selected at random to serve as a control. No significant differences in selection criteria were noted between the two treatment populations (*p*-value vs. bid control; chi-square statistic).

Table 1 Patient Demographics

	CBZ-ERC (qd)	CBZ-ERC (Control; bid)	*p*-Value
Subjects	23	23	
Gender (% female)	69.6%	69.6%	0.75[a]
Mean age (SD)	21.9 (16.2)	21.5 (14.5)	0.93[b]
Age range	4–70	5–56	
CBZ-ERC monotherapy at Initiation	73.9%	30.4%	0.01[b]

[a]*p*-value vs. bid control (chi-square test).

[b]*p*-value vs. bid control (one-way between subjects analysis of variance).

RESULTS

Characteristics of Subjects

Table 2 indicates the percentage of patients in the qd group who had each of the three main bipolar subtypes: 43.1% with bipolar I, 21.7% with bipolar II, and 34.7% with bipolar not otherwise specified. At the start of treatment, 91% of study subjects were at least markedly ill ($p = 0.66$ vs bid control; one-way between subjects analysis of variance). Differences in the frequency with which patients in the qd and bid groups used any specific concomitant medications and discontinued any specific medications were not statistically significant.

Efficacy

The CGI-I scores for the two treatment groups are given in Table 3. No significant differences were observed in CGI-I

Table 2 Bipolar Subtypes in CBZ-ERC Groups

	Dosed qd	Dosed bid
Bipolar I	(n = 10; 43.4%)	(n = 10; 43.4%)
Depressed	8.7%	8.7%
Manic	4.3%	4.3%
Mixed	26.1%	26.1%
Mixed, psychotic	4.3%	4.3%
Bipolar II	(n = 5; 21.7%)	(n = 5; 21.7%)
II	17.4%	21.7%
II, RC	4.3%	0.0%
Bipolar NOS	(n = 8; 34.7%)	(n = 8; 34.7%)
NOS	30.4%	34.7%
NOS, RC	4.3%	0.0%

RC = rapid cycling; NOS = not otherwise specified.

Table 3 CGI-I Scores of Study Subjects

	Dosed qd	Dosed bid (control)	*p*-Value
CGI-I	1.9	2.4	0.20[a]
Dose (SD)	413.0 (168.7)	469.6 (176.9)	0.27[a]
% Response[b]	83%	83%	0.70[c]

CGI-I = Clinical Global Impression–Improvement.

[a]*p* value vs. bid control (one-way between subjects analysis of variance).

[b]Response is defined as achieving a CGI-I ≤ 3.

[c]*p* value vs. bid control (chi-square test).

Table 4 Treatment-Emergent Adverse Events

	Dosed qd	Dosed bid (Control)	*p*-Value[a]
Dizziness	13.0%	13.0%	1.00
Somnolence	13.0%	8.7%	0.66
Nausea	13.0%	4.3%	0.60
Rash	4.3%	13.0%	0.60
Headaches	8.7%	4.3%	0.65
Relapse[b]	11%	11%	1.00

Adverse events occurring in ≥ 5% for either group listed.
[a]*p*-value vs. bid control (chi-square test).
[b]Relapse is defined as a CGI-I score ≥ 4 after documentation of a CGI-I ≤ 3.

scores between the qd and bid groups. In addition, the percentage of responders, defined as those who obtained a CGI-I score of ≤ 3, was the same (83%) in each group.

Safety and Tolerability

Table 4 lists the treatment-emergent adverse events that occurred in ≥ 5% of patients in either group. No significant difference was observed in the frequency of treatment-emergent adverse events between patients in the qd and bid groups. Also, the relapse rate, defined as a change in CGI-I to ≥ 4 after an observed CBZ-ERC response, was the same (11%) in both groups.

DISCUSSION

The results from this retrospective chart review indicate that qd dosing of CBZ-ERC has efficacy, safety, and tolerability comparable to bid dosing. All degrees of illness severity, the three main subtypes of bipolar disorder, and a wide range of ages (from young children to elderly patients) were represented in the group of patients included in the analysis. No statistically significant differences were found in CGI-I scores and the frequency of treatment-emergent adverse events between patients in the qd and bid groups. The relapse rate was also the same in both groups.

Once-daily dosing of CBZ-ERC is likely a more convenient treatment option than a bid regimen for patients who are taking other medications. A high rate of patient adherence is essential to achieving maximum therapeutic efficacy. As adherence to drug therapy increases when daily dosing frequency decreases, the interval between medication doses should be as long as is practical (15). The amount of drug administered and the dosing interval should represent a compromise that achieves the longest possible duration of effective serum concentration with minimal toxicity. A number of drugs used to treat bipolar disorder are approved for qd dosing by the FDA. Olanzapine qd monotherapy is approved for acute mixed or manic episodes, as well as for maintenance, in bipolar I disorder. In addition, olanzapine qd, in combination with lithium or valproate, is approved for acute manic episodes in patients with bipolar I disorder (16). Risperidone is also approved for qd dosing in acute or mixed manic episodes in bipolar I disorder (17), and lamotrigine is approved for qd dosing in maintenance treatment of bipolar I disorder (18).

CONCLUSIONS

In light of the results from this retrospective study and the greater adherence, convenience, and patient satisfaction likely associated with qd therapy, clinicians who choose CBZ-ERC to treat bipolar disorder may want to consider prescribing it for qd use especially in patients who find it hard to adhere to therapy.

ACKNOWLEDGMENTS

Editorial support for the preparation of this article was provided by Precept Educational Sciences, Berkeley Heights, NJ, USA. This study was sponsored by an educational grant from Shire, Wayne, PA, USA.

REFERENCES

1. Belmaker RH: Bipolar disorder. *N Engl J Med* 2004; 351:476–486
2. Berns GS, Nemeroff CB: The neurobiology of bipolar disorder. *Am J Med Genet* 2003; 123C(1):76–84
3. Post RM, Speer AM, Hough CJ, Xing G: Neurobiology of bipolar illness: Implications for future study and therapeutics. *Ann Clin Psychiatry* 2003; 15:85–94
4. Gupta S, Al-Samarrai S, Masand PS, Lentz BJ, Keller PJ, Droney TM: Real-world outcomes of once daily risperidone dosing. *Prim Care Companion J Clin Psych* 2000; 2:55–57
5. Zarate CA Jr, Quiroz JA: Combination treatment in bipolar disorder: a review of controlled trials. *Bipolar Disord* 2003; 5:217–225
6. Freeman MP, Stoll AL: Mood stabilizer combinations: a review of safety and efficacy. *Am J Psychiatry* 1998; 155:12–21
7. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL: How often is medication taken as prescribed? A novel assessment technique. *JAMA* 1989; 261:3273–3277
8. Greenberg RN: Overview of patient compliance with medication dosing: a literature review. *Clin Ther* 1984; 6:592–599
9. Lithobid® [package insert]. Marietta, GA: Solvay Pharmaceuticals, Inc; December 2002
10. Depakote® [package insert]. North Chicago, IL: Abbott Laboratories; November 2003
11. Keck PE Jr, McElroy SL, Nemeroff CB: Anticonvulsants in the treatment of bipolar disorder. *J Neuropsychiatry Clin Neurosci* 1992; 4:395–405
12. Weisler RH, Kalali AH, Ketter TA, and the SPD417 Study Group: A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry* 2004; 65:478–484
13. Weisler RH, Hirschfeld R, Cutler AJ, Gazda T, Ketter T, Keck P, Swann A, Kalali A: Efficacy of extended-release carbamazepine

in bipolar disorder: results of two pooled clinical trials. Presented at the US Psychiatric and Mental Health Congress; November 18–21, 2004; San Diego, CA

14. Weisler RH, Keck PE Jr, Swann AC, Cutler AJ, Ketter TA, Kalali AH, for the SPD417 Study Group: Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2005; 66:323–330
15. Browne TR: Pharmacokinetics of antiepileptic drugs. *Neurology* 1998; 51(5 suppl 4):S2–S7
16. Zyprexa® [package insert]. Indianopolis, IN: Eli Lilly and Company; May 2004
17. Risperdal® [package insert]. Titusville, NJ. Janssen Pharmaceutica Products LP; December 2003
18. Lamictal® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; June 2004