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A Retrospective Analysis of Changing From Alternative Agents to Carbamazepine Extended-Release Capsules in Bipolar Disorder

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

Background. *Patients with bipolar disorder do not respond to the same therapy in the same way. This potentially necessitates the trial of various treatment modalities in a patient until the illness can be successfully controlled.*
Methods. *Medical histories from 187 patients were reviewed to obtain information on efficacy when patients were switched from their initial drug therapy—immediate-release (IR) or extended-release (ER) carbamazepine (CBZ) tablets, valproic acid, lamotrigine, lithium, olanzapine, and oxcarbazepine—to beaded CBZ extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA). Clinical Global Impression–Severity and Clinical Global Impression–Improvement scores were used to assess severity of illness, and response and relapse rates, respectively.*
Results. *The overall response rate was 79.7%. The greatest percentage of responders to CBZ-ERC treatment was seen in patients originally on lithium (90.5%), followed by those initially treated with oxcarbazepine (84.8%), olanzapine (81.5%), lamotrigine (77.8%), valproic acid (75.4%), and IR or ER CBZ tablets (74.2%). The overall relapse rate was 38.2%. Patients on lithium had the highest relapse rate (52.6%), followed by those on olanzapine (50.0%), valproic acid (34.9%), IR or ER CBZ tablets (34.8%), oxcarbazepine (32.1%), and lamotrigine (28.6%). Adverse events were minimal, with nausea, dizziness, and somnolence being the most frequent.*
Conclusions. *The encouraging treatment response and adverse event profile observed in this retrospective analysis suggest that CBZ-ERC is an efficacious agent for the treatment of patients with bipolar disorder switched from other psychotropic agents.*

Keywords Bipolar disorder, Carbamazepine, Switching

INTRODUCTION

The prevalence of bipolar I and II disorders is approaching 4% of the population in the United States (1). Even today, the etiology and pathology of bipolar disorder remain largely unknown. While no cure is available, myriad pharmacotherapeutics have been observed to relieve particular symptoms associated with the mania and depression seen in patients with bipolar disorders (2–4). In prescribing a psychotherapeutic drug, there is no guarantee that the treatment will be effective given, among other factors, the uniqueness of every patient in his/her response to a given therapy and additional drug therapy that may affect the efficacy of the drug (5,6). If a patient is unresponsive to a therapeutic agent, the physician can and typically does resort to switching from one drug to another in order to find the best medication for a particular patient's symptoms.

Carbamazepine (CBZ) has been an alternative therapeutic agent for treatment of bipolar disorder for nearly two decades (2,7,8). Beaded CBZ extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) are the newest CBZ formulation; the capsules are filled with three different types of beads: 25% immediate release, 40% extended release, and 35% enteric release, designed to extend time of delivery of the drug beyond 12 hours. This beaded formulation minimizes plasma CBZ fluctuations, which may decrease the incidence and severity of adverse events and increase patient compliance (9).

In this retrospective analysis, the aim was to determine the efficacy of switching to CBZ-ERC in patients with bipolar

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

disorder who were previously receiving other agents for the treatment of their illness.

METHODS

Medical records were reviewed for 187 subjects with bipolar disorder (as defined by DSM-IV criteria) who were treated at a single private practice setting (Red Oak Psychiatry Associates, Houston, TX) between October 1998 and November 2003. Subjects were allocated into six groups according to baseline drug therapy. Demographic data gathered included gender, age, and bipolar presentation.

Study Assessments

At initiation of CBZ-ERC, Clinical Global Impression–Severity (CGI-S) scale ratings were documented for baseline severity of illness. The efficacy of CBZ-ERC 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 ≤ 3; clinical relapse was set at a change in CGI-I scores ≥ 4, after an observed CBZ-ERC response. In addition, CBZ-ERC dose was recorded at best office visit.

RESULTS

Baseline Characteristics and CBZ-ERC Dose

Valproic acid (n = 57) was the most common drug taken before switching to CBZ-ERC among the 187 patients, followed by oxcarbazepine (n = 33), CBZ (namely, immediate-release [IR] and extended-release [ER] tablets; n = 31), olanzapine (n = 27), lithium (n = 21), and lamotrigine (n = 18). Mean age ranged from 19.6 to 39.0 years among the six groups. Bipolar subtype varied among the six groups, with bipolar I (manic/mixed) being most common in those patients who were initially treated with CBZ, lithium, olanzapine, or valproic acid (demographic information can be seen in Table 1). At baseline in each subgroup, more than 81% of the patients were at least markedly ill (CGI-S score ≥ 5), with the exception of those in the CBZ and olanzapine groups, in which only 52% and 56% were markedly ill, respectively (Figure 1). Daily average CBZ-ERC dose among all groups ranged from 584.2 to 687.9 mg.

Efficacy

The overall response rate of the study group to CBZ-ERC based on CGI-I was 79.7%, suggesting that CBZ-ERC was able to improve symptoms not successfully treated using the other psychotherapeutic drugs. The greatest percentage of responders to CBZ-ERC treatment was seen in patients originally on lithium (90.5%), followed by those on oxcarbazepine (84.8%), olanzapine (81.5%), lamotrigine (77.8%), valproic acid (75.4%), and IR or ER CBZ tablets (74.2%) (Figure 2). It is noteworthy that switching from one CBZ formulation to another can favorably affect treatment outcome as shown by the improvement achieved in patients who switched from IR or ER CBZ tablets to CBZ-ERC.

The overall relapse rate was 37.6%. The greatest relapse rate occurred in patients who were originally on lithium (52.6%), followed by those previously treated with olanzapine (50.0%), valproic acid (34.9%), IR or ER CBZ tablets (34.8%), oxcarbazepine (32.1%), and lamotrigine (21.4%) (Figure 2). Patients who were formerly on lithium had the earliest average days to relapse (103.5 ± 102.5) (Table 2), followed by those previously treated with lamotrigine (179.0 ± 171.6), oxcarbazepine (209.2 ± 206.9), olanzapine (232.2 ± 149.0), valproic acid (239.7 ± 252.8), and IR or ER CBZ tablets (341.7 ± 496.9). The subgroup of patients who relapsed on CBZ-ERC after lithium

Table 1 Patient Demographic Information

Previous agent	VPA	CBZ	Li	OXC	OLZ	LTG
Subjects (n)	57	31	21	33	27	18
Gender (% female)	35.1	29.0	57.1	57.6	55.6	88.9
Mean age (y) (SD)	17.0 (10.5)	19.6 (16.8)	27.0 (18.2)	19.8 (11.7)	34.3 (10.0)	39.0 (14.8)
Age range (y)	5–51	5–63	7–70	7–46	19–55	15–66
Mean dose (mg) (SD)	584.2 (240.4)	674.2 (317.3)	590.5 (172.9)	687.9 (319.9)	607.4 (197.9)	600.0 (223.6)
Bipolar type						
Bipolar I (%) (manic/mixed)	31.6	16.7	76.2	35.5	27.3	51.9
Bipolar I (%) (depressed)	19.3	33.3	4.8	19.4	12.1	29.6
Bipolar II (%)	26.3	33.3	9.5	12.9	15.2	7.4
Bipolar NOS (%)	22.8	16.7	9.5	32.3	45.5	11.1

VPA = valproic acid; CBZ = carbamazepine tablets (immediate- and extended-release); Li = lithium; OXC = oxcarbazepine; OLZ = olanzapine; LTG = lamotrigine; NOS = not otherwise specified, SD = standard deviation.

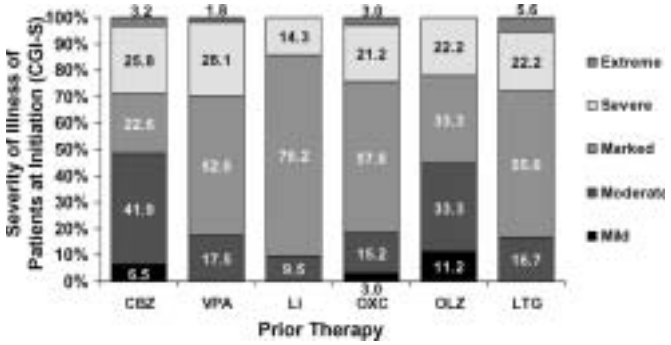

Figure 1 Severity of illness (CGI-S) at CBZ-ERC initiation. CBZ-ERC = carbamazepine extended-release capsules; CGI-S = Clinical Global Impression–Severity; CBZ = carbamazepine (immediate- and extended-release tablets); VPA = valproic acid; Li = lithium; OXC = oxcarbazepine; OLZ = olanzapine; LTG = lamotrigine.

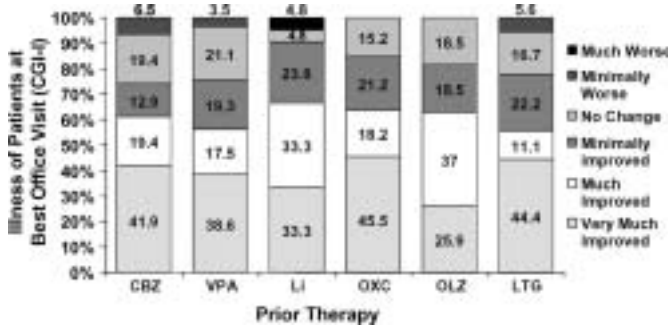

Figure 2 Improvement (CGI-I) at best office visit. CGI-I = Clinical Global Impression–Improvement; CBZ = carbamazepine (immediate- and extended-release tablets); VPA = valproic acid; Li = lithium; OXC = oxcarbazepine; OLZ = olanzapine; LTG = lamotrigine.

Table 2 Days to Relapse for Patients on Previous Agents

Previous Agent	Days to Relapse (mean ± SD)
Lithium	103.5 ± 102.5
Lamotrigine	179.0 ± 171.6
Oxcarbazepine	209.2 ± 206.9
Olanzapine	232.2 ± 149.0
Valproic acid	239.7 ± 252.8
Carbamazepine	341.7 ± 496.9

therapy may represent treatment-resistant patients, since lithium is widely regarded as a highly effective first-line drug for mania and prophylaxis for mania and depression (10).

Safety and Tolerability

The most common side effects that occurred during treatment with CBZ-ERC in all patients were nausea (9.6%), dizziness (8.0%), somnolence (4.8%), vomiting (3.7%), and rash (3.2%) (Table 3). Results from other trials using CBZ-ERC also reported similar adverse events, which were usually mild and transient in nature; however, percentages in this retrospective analysis were lower (11–13).

Table 3 CBZ-ERC Treatment Emergent Adverse Events

Adverse event[a]	Percentage
Nausea	9.6
Dizziness	8.0
Somnolence	4.8
Vomiting	3.7
Rash	3.2

CBZ-ERC = carbamazepine extended-release capsules.
[a]Adverse events occurring in greater than 2% of the population are listed.

DISCUSSION

Overall, the percentage of patients who were switched from other psychotropic agents to CBZ-ERC for treatment of bipolar disorder and responded was 79.7%, as measured by CGI-I, with the highest percentage of responders among individuals previously on lithium (90.5%). Adverse events were mild and infrequent, and were similar to those observed in other CBZ-ERC trials; however, the low adverse event occurrence may be because of slow titration of CBZ.

Patients who were switched from IR or ER CBZ tablets to CBZ-ERC showed improvement in their psychiatric condition, which may reflect better patient compliance with or tolerability of the beaded CBZ-ERC formulation, although the latter issues were not studied.

There remains controversy over the similarities and differences between CBZ and oxcarbazepine. The high response rate (84.8%) in patients who were switched from oxcarbazepine to CBZ-ERC demonstrates that although the former agent is structurally similar to CBZ, those subtle differences can result in an increase in efficacy as measured by CGI-I.

Recently, the efficacy of CBZ-ERC in bipolar disorder was demonstrated in two large, well-controlled, 3-week, randomized, double-blind, placebo-controlled trials that found CBZ-ERC monotherapy to be effective in the treatment of manic and mixed episodes. In a pooled analysis of the two trials, 52.3% of patients on CBZ-ERC (n = 214) responded to treatment, defined as a ≥50% decrease in the Young Mania Rating Scale score versus 25.8% on placebo (n = 213) at endpoint (14). Furthermore, statistically significant improvements were found in both CGI-I and CGI-S scores in the CBZ-ERC–treated group.

The considerable methodological limitations of this retrospective analysis should be weighed when considering the findings. The patient population evaluated was from a single center, and the retrospective design can lead to observation and assessment bias. Many variables could not be evaluated and/or controlled. Among others, these factors included the patients' past medical/psychiatric history, extent of prior treatment, specific reasons for switching from the baseline therapeutic agent to

CBZ-ERC (treatment failure, adverse events, tolerability issues, noncompliance, etc.), frequency of clinic visits, laboratory parameters, duration of CBZ-ERC treatment, concomitant medications used during the treatment period, and treatment washout periods prior to initiation of CBZ-ERC treatment.

CONCLUSIONS

This retrospective review confirms the findings of previous placebo-controlled trials that demonstrated the efficacy of CBZ-ERC for the treatment of bipolar disorder, but extends those results to patients in a real-world clinical setting. Well-controlled, prospective clinical trials are warranted to confirm these observations and to provide further guidance on switching from another bipolar disorder therapeutic agent to CBZ-ERC.

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