

Safety of Carbamazepine Extended-Release Capsules in Bipolar Disorder Polypharmacy

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Background. This analysis is a retrospective chart review evaluating the safety of carbamazepine (CBZ) extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) when used in combination with other agents as part of a polypharmacy regimen in the treatment of patients with bipolar disorder. The safety of CBZ-ERC was determined by comparing the adverse event profiles of patients on monotherapy versus those of patients on polytherapy.

Methods. The medical records of 300 adult patients (aged 18–70) treated in a private practice setting with CBZ (monotherapy or polytherapy) who met the DSM-IV criteria for bipolar disorder were examined.

Results. We found that patients taking CBZ-ERC together with other agents (antipsychotics, antiepileptics, selective serotonin reuptake inhibitors and other antidepressants, anxiolytics, lithium, and attention-deficit/hyperactivity disorder medications) were no more likely to report gastrointestinal, nervous system, or cutaneous adverse events than patients on CBZ-ERC monotherapy.

Conclusions. These real-world data suggest that the occurrence of adverse events may not differ significantly between patients on CBZ-ERC monotherapy and those on polytherapy with multiple other agents.

Keywords Bipolar disorder, Carbamazepine, Polypharmacy

INTRODUCTION

Bipolar disorder is a serious lifelong illness associated with significant morbidity and mortality. Pharmacotherapy is essential in the treatment of the disorder, although there is no one agent available that has been shown in randomized, placebo-controlled trials to be capable of preventing and/or controlling all facets of the illness, which include mania, hypomania, depression, mixed states (concomitant manic and depressive symptoms), and rapid cycling (1). The complexity of the illness thus often necessitates treatment with a combination of medications (2,3). However, the use of combination therapy introduces additional considerations, such as drug interactions and added side effects.

Carbamazepine (CBZ) is an antiepileptic drug that has also been used to treat bipolar disorder since the 1970s (4). It has been studied in acute mania in at least 17 controlled trials,

demonstrating efficacy and tolerability comparable to lithium (reviewed in Hirschfeld et al. [5]). Recently, a new formulation, CBZ extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) was developed. This formulation consists of three different types of beads—immediate release, extended release, and enteric release—designed to extend release of CBZ to 12 hours. Extended-release CBZ capsules have been shown to be safe and effective in bipolar patients with mixed and manic episodes in three large clinical trials (6–8). A concern regarding the use of CBZ as part of a polypharmacy regimen is its hepatic enzyme-inducing properties; CBZ is an inducer of catabolic enzymes and decreases the plasma levels of many medications, including CBZ itself (9). Conversely, some medications can inhibit CBZ metabolism and cause CBZ toxicity (10,11). Therefore, in this retrospective study, we examined the safety of CBZ-ERC when used in combination with other agents as polypharmacy for the treatment of patients with bipolar disorder. We evaluated the incidence of gastrointestinal (GI), central nervous system (CNS), and cutaneous adverse events associated with CBZ-ERC monotherapy versus polytherapy.

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METHODS

Patient Selection

The study was limited to patients at least 18 years old who met the DSM-IV criteria for bipolar disorder and who had been treated with CBZ-ERC. The medical records of all patients on CBZ-ERC between October 1998 and November 2003 were reviewed, and patients were divided into two groups, one consisting of patients who had taken only CBZ-ERC, and a second group consisting of patients who had taken concomitant medication for at least 7 days. All patients had been treated at Red Oak Psychiatry Associates, Houston, TX.

Study Procedures

Data obtained from patients' medical records included demographic data, diagnosis of both primary and comorbid conditions, dosage of CBZ-ERC, concomitant medications, and adverse events. Primary diagnosis included bipolar subtype—bipolar I (manic, mixed, depressed), bipolar II, or bipolar not otherwise specified. Illness severity and improvement were assessed using the National Institute of Mental Health Clinical Global Impression–Severity (CGI-S) and the Clinical Global Impression–Improvement (CGI-I) scales (12). 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). The severity of illness was established via CGI-S at initiation of CBZ-ERC therapy, and global improvement was measured via CGI-I at subsequent office visits to evaluate response to CBZ-ERC therapy. Clinical response to CBZ-ERC therapy was defined as a score of ≤ 3 on the CGI-I scale. Relapse was defined as a change in CGI-I to ≥ 4 in those subjects who had previously achieved clinical response to CBZ-ERC therapy. The adverse event profiles of patients on CBZ-ERC monotherapy were compared with the profiles of patients on polytherapy. 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 comparisons were performed with one-way analysis of variance or chi-square test.

RESULTS

A total of 300 patients who met inclusion criteria for the study were identified. Of these patients, 57 were included in the CBZ-ERC monotherapy group, and 243 patients were included in the polytherapy group (Table 1). There were no statistically significant differences between the percentage of women, mean age, or distribution of bipolar subtypes between the monotherapy and polytherapy groups. The percentage of

Table 1 Baseline Demographics and Clinical Characteristics of Study Population

	Monotherapy	Polytherapy ^a	<i>p</i> -value
Subjects, n	57	243	
Female, n (%)	36 (63.2)	176 (72.4)	
Age, years (Mean \pm SD)	32.6 (10.0)	35.6 (11.5)	0.07
Age range, years	19–66	18–70	
Bipolar I manic/mixed	27	110	0.89
Bipolar I depressed	10	57	0.43
Bipolar II	11	34	0.42
Bipolar NOS	9	42	0.94
Comorbid conditions, n (%)			
Panic disorder	2 (3.5)	36 (14.8)	0.04
Substance abuse	7 (12.3)	36 (14.8)	0.8
Generalized anxiety disorder	4 (7.0)	35 (14.4)	0.2
ADHD	5 (8.8)	24 (9.9)	1.0
Alcohol abuse	2 (3.5)	22 (9.1)	0.3

ADHD = attention-deficit/hyperactivity disorder.

^aConcomitant medications taken by polytherapy patients: antidepressants (n = 102), antiepileptic drugs (n = 83), antipsychotics (n = 81), anxiolytics (n = 79), ADHD drugs (n = 32), selective serotonin reuptake inhibitors (n = 113), lithium (n = 5).

patients with comorbid conditions was higher for patients in the polytherapy group, although the difference only reached statistical significance for panic disorder (monotherapy, 3.5% vs. polytherapy, 14.8%; $p = 0.04$).

Efficacy

The CGI-S score was significantly lower in the monotherapy group than in the polytherapy group (5.0 ± 0.7 vs. 5.3 ± 0.8 ; $p = 0.05$) (Table 2). However, the CGI-I score was significantly lower in the polytherapy versus monotherapy group (2.4 ± 1.2 vs. 2.9 ± 1.3 ; $p = 0.0005$) and the percentage of responders in the polytherapy group was significantly higher than in the monotherapy group (77.8% vs. 52.6%; $p = 0.0002$). The percentage of patients who relapsed was also higher in the polytherapy group than in the monotherapy group (33.9% vs. 16.7%), although this difference did not reach statistical significance. The mean CBZ-ERC dose was significantly higher for

Table 2 Response to Treatment

	Monotherapy	Polytherapy	<i>p</i> -value
CGI-S (mean \pm SD)	5.0 ± 0.7	5.3 ± 0.8	0.04
CGI-I (mean \pm SD)	2.9 ± 1.3	2.4 ± 1.2	0.005
Response, %	52.6	77.8	0.0002
Relapse, %	16.7	33.9	0.09
CBZ-ERC dose (mean \pm SD)	512.3 ± 131.0	576.9 ± 164.1	0.006

CGI-S = Clinical Global Impression–Severity; CGI-I = Clinical Global Impression–Improvement; CBZ-ERC = carbamazepine extended-release capsules.

the polytherapy group than the monotherapy group (576.9 ± 164.1 vs. 512.3 ± 131.0 ; $p = 0.006$).

Adverse Events

Shown in Figure 1 are the percentages of patients in the CBZ-ERC monotherapy versus polytherapy groups experiencing any GI disorder, nausea, vomiting, any CNS disorder, dizziness, somnolence, headache, any cutaneous disorder, or rash. We found that 22.8% of patients on monotherapy and 14.0% of patients on polytherapy experienced a GI adverse event, with 10.5% of patients on monotherapy and 8.6% of polytherapy experiencing nausea, and 3.5% of monotherapy patients and 1.7% of polytherapy patients experiencing vomiting. For CNS adverse events, the percentage of patients experiencing CNS disorders was higher in the monotherapy group (33.3%) than in the polytherapy group (20.6%). The percentage of patients experiencing dizziness was 8.8% in the monotherapy group and 7.4% in the polytherapy group. The incidence of somnolence was higher, with 21.1% of monotherapy patients and 10.7% of polytherapy patients experiencing this adverse event. The percentage of monotherapy patients experiencing headache was significantly higher than in the polytherapy group (12.3% vs. 2.1%; $p = 0.002$).

The percentage of patients experiencing a cutaneous disorder was higher in the monotherapy group (8.8%) than in the polytherapy group (6.6%). The percentage of patients experiencing rash was nearly identical in both groups (monotherapy, 5.3% vs. polytherapy, 5.4%).

We also examined the timing of the above adverse events in the CBZ-ERC polytherapy group. For the polytherapy patients who reported these adverse events, $\geq 75\%$ experienced the adverse events within the first 90 days of starting concomitant medication (Figure 2).

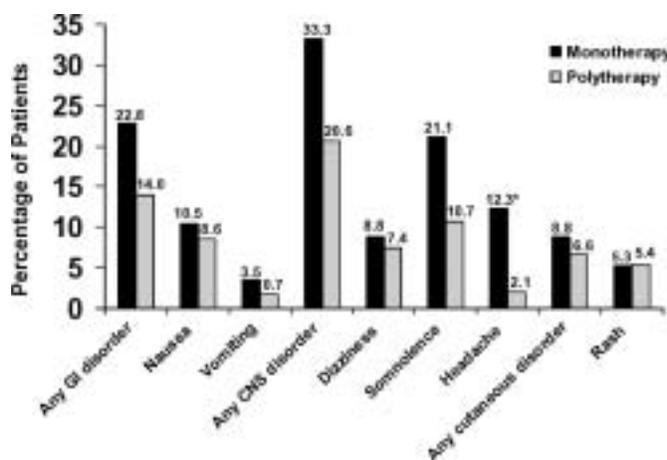


Figure 1 Percentages of patients on CBZ-ERC monotherapy versus polytherapy experiencing adverse events. * $p = 0.002$. GI = gastrointestinal; CNS = central nervous system.

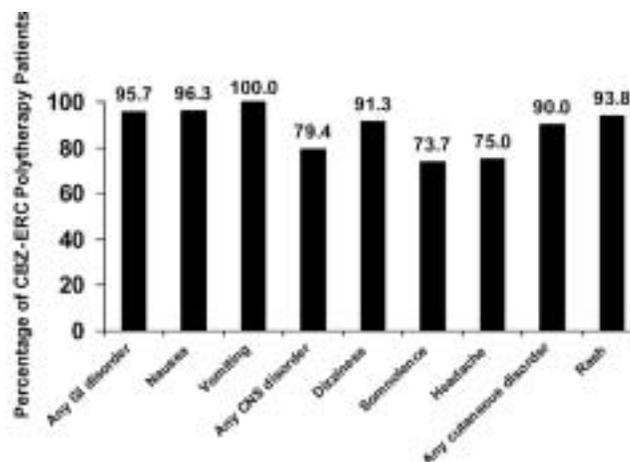


Figure 2 Timing of adverse events in the CBZ-ERC polytherapy group. For CBZ-ERC polytherapy patients who reported any GI disorder, nausea, vomiting, any CNS disorder, dizziness, somnolence, any skin disorder, rash, or headache, the percentages of patients who experienced the adverse events within the first 90 days of starting concomitant medication are shown. GI = gastrointestinal; CNS = central nervous system; CBZ-ERC = carbamazepine extended-release capsules.

DISCUSSION

The results from this retrospective study indicate that CBZ-ERC can be safely used in combination with other medications as part of a polypharmacy treatment regimen for bipolar disorder. Somewhat surprisingly, the incidence of all adverse events examined was higher in patients on monotherapy than on polytherapy, but none of these differences reached statistical significance. The differences could be attributable to the smaller sample size of the monotherapy ($n = 57$) versus polytherapy ($n = 243$) group. It is also possible that there was higher vigilance for adverse events with monotherapy than with polytherapy.

The use of >1 mood stabilizer in combination has become common in the treatment of refractory cases of bipolar disorder (13,14). In this study both the mean CGI-S score and mean CBZ-ERC dose were significantly higher in polytherapy patients, suggesting a greater degree of illness severity in this group that may have necessitated combination therapy. Furthermore, although the percentage of responders was higher in the polytherapy group, the percentage of polytherapy patients who relapsed was twice as high as in the monotherapy group, indicating that these cases may have been more refractory.

Comorbid conditions such as substance abuse and anxiety disorders are commonly associated with bipolar disorder (15). We found that 57.6% of patients (including patients in both the monotherapy and polytherapy groups) in this study had comorbid conditions, including panic disorder, substance abuse, generalized anxiety disorder, attention-deficit/hyperactivity disorder, and alcohol abuse. These conditions frequently require treatment with pharmacologic agents, and it is therefore

important to have a bipolar disorder therapy that can be safely used with these medications. In this study, comorbid conditions were indeed higher in the polytherapy group than in the monotherapy group. In particular, we found that the incidence of panic disorder was significantly higher in the polytherapy group.

The pharmacokinetic properties of CBZ can present a challenge in using it with other medications. The most commonly encountered problems involve CBZ inducing metabolism of other drugs (such as lamotrigine, valproate, etc.), thereby decreasing their efficacy, and other drugs inhibiting CBZ metabolism, causing CBZ toxicity. Concurrent use of CBZ and clozapine is not recommended, however, due to an increased risk of blood dyscrasia. Results from this study indicate, however, that the incidence of adverse events was not significantly different in patients on CBZ-ERC polytherapy versus monotherapy, suggesting that the CBZ-ERC formulation may be used safely as part of a polytherapy regimen with a variety of pharmacologic agents.

CONCLUSIONS

These findings must be viewed against the study's methodological limitations, which include its retrospective nature and lack of randomized, controlled design. However, the private practice setting provides us with valuable real-world data for evaluating the use of CBZ-ERC in a naturalistic setting. Future prospective trials evaluating the safety of CBZ-ERC in polypharmacy are warranted.

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