Carbamazepine extended-release capsules for the treatment of bipolar I disorder

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An extended-release capsule formulation of carbamazepine (Equetro™; Shire, PA, USA) was approved by the US Food and Drug Administration in December 2004 for the treatment of acute manic and mixed episodes associated with bipolar I disorder. Extended-release capsule formulation of carbamazepine offers several advantages to immediate-release carbamazepine formulations such as decreased dosing frequency and lowered plasma carbamazepine fluctuations. These important considerations combine to enhance patient compliance and tolerability, which is essential for the success of any therapeutic treatment regimen. The efficacy, safety, and tolerability of the extended-release capsule formulation of carbamazepine was demonstrated in two randomized, double-blind, placebo-controlled trials and an open-label extension study in patients with bipolar I disorder experiencing either manic or mixed episodes. Although further study is required, the data garnered in these studies, along with the agent's recent approval by the US Food and Drug Administration may eventually lead to increased usage of carbamazepine as a psychotherapeutic agent for the treatment of bipolar disorder.

Keywords: bipolar disorder, carbamazepine extended, mania

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Bipolar disorder is a devastating illness that entails a high risk of suicide in affected individuals [1]. Including all subtypes, the lifetime prevalence of this syndrome is between 3 and 9.8% [2–4]. Although many agents exist to treat specific symptoms of bipolar disorder, these psychotherapeutic agents commonly fail to provide extensive control of the illness, resulting in an expansive change in mood that can be detrimental to a patient and to his or her family. Carbamazepine (CBZ) has been an alternative treatment for bipolar disorder for nearly 30 years. CBZ (5H-dibenz[b,f]azepine carboxamide) was developed by JR Geigy AG in 1953 and was subsequently synthesized by W Schindler in 1960 (**Figure 1**) [5]. It is structurally similar to imipramine, a tricyclic antidepressant.

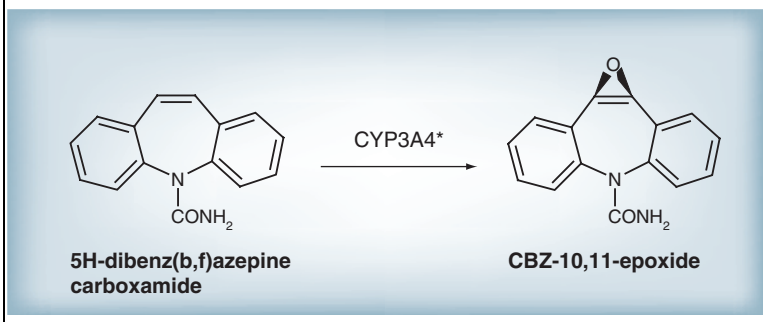
Although CBZ has been used extensively as an antiepileptic agent in Europe since the 1960s, its first approved indication by the US Food and Drug Administration (FDA) was for the treatment of trigeminal neuralgia in 1968. In 1974, an immediate-release (IR)-CBZ formulation was approved by the FDA for the treatment of partial, generalized tonic–clonic, and mixed-pattern seizures. Due to the lack of large, placebo-controlled clinical studies examining the efficacy of CBZ in the treatment of bipolar disorder in the USA, the FDA did not approve this indication until recently (December 2004); however, CBZ has been approved for the treatment of bipolar disorder by agencies in Canada, Japan, Australia and several European countries. Various formulations of CBZ have been developed in addition to conventional tablets; however, only CBZ extended-release capsules (CBZ–ERC) (Equetro™; Shire) have been approved by the FDA for treatment of acute manic and mixed episodes associated with bipolar I disorder.

Overview of market

The first significant experiments implicating CBZ as a possible treatment for bipolar disorder began in Japan in the early 1970s. Takezaki observed improvements in patients with epilepsy who were experiencing manic symptoms after treatment with CBZ [6]. Preliminary findings by Takezaki and Honaoka [7] and Okuma and associates [8] demonstrated its promising efficacy in improving manic and depressive conditions and prophylaxis in small numbers of patients with bipolar disorder.

In the USA during the late 1970s, Post proposed that kindling, a neurologic phenomenon often applied to epilepsy in which repetitive subthreshold electrical stimulation in the limbic system sensitizes to major convulsions and behavioral changes, may explain mood disturbances observed in patients with bipolar disorder [9,10]. Because reports have shown CBZ to diminish neural electrical transmission in the limbic area, in 1978 Ballenger and Post conducted the first double-blind, placebo-controlled study determining the efficacy of CBZ in the treatment of affectively ill patients,

Figure 1. The chemical structure of carbamazapine and its epoxide.



*Liver cytochrome P450 3A4 isozyme oxidizes carbamazapine to its active metabolite, CBZ (carbamazapine)-10,11-epoxide.

which included patients with primary affective or schizoaffective illness [11,12]. In their preliminary study, the results showed seven out of ten patients with affective illness (i.e., bipolar disorder, unipolar depression, schizoaffective psychosis) responded (as defined by improvement in the Bunney-Hamburg scales) to CBZ [11]. In another double-blind, placebo-controlled trial in patients primarily with bipolar disorder, seven out of nine patients with a manic episode and five out of 13 patients with depressive symptoms experienced a significant response (as defined by at least a 1 point decrease in the Bunney–Hamburg scale for mania or 1.5 decrease in depression ratings) to CBZ treatment [12].

Treatment guidelines set forth by the American Psychiatric Association in 2002 for patients experiencing severe acute manic or mixed episodes associated with bipolar disorder list lithium (LI) in combination with an antipsychotic or valproate (VPA) in combination with an antipsychotic as first-line therapy [13]. For less severe presentations, monotherapy with LI, VPA, or an antipsychotic such as olanzapine, is recommended. CBZ is suggested as an alternative to LI or VPA in patients with bipolar disorder and, considering the lack of credible placebo-controlled data supporting the efficacy of CBZ at the time these guidelines were published, this is not surprising.

The anticonvulsants CBZ and VPA, together with LI, are loosely classified as mood-stabilizing agents that possess mood-stabilizing properties in either the manic or depressive phase of bipolar illness [14]. Depending on the definition, the atypical antipsychotic olanzapine, as well as a variety of other agents, could also be classified as mood stabilizers. LI and VPA are the most commonly prescribed medicines for treatment of bipolar I disorder [15], due to their long history of effective use in this population of patients. Although LI has been used to treat bipolar disorder successfully for 50 years, there are some distinct drawbacks to this compound. It has a narrow therapeutic index and patients taking this medication must receive regular blood-level monitoring as severe, toxic, or even lethal effects can occur at twice the therapeutic dose [16,17]. This is particularly important in patients with any type of renal impairment which will result in increased blood levels of the drug [16]. Additionally, some studies have shown that LI therapy fails to provide prophylactic efficacy in an average of 40% of patients [18,19,20]

A large meta-analysis of head-to-head comparisons by Macritchie and colleagues found that in trials of VPA versus LI for acute mania, there were no significant differences between the two agents in scores on the Clinical Global Impression-Improvement (CGI-I) or Young Mania Rating Score (YMRS) scales [21]. Similarly, in trials of VPA versus CBZ, there was no significant difference in the number of patients who respond clinically on either of these two medications [21]. Although VPA has proven to be an efficacious agent for the treatment of bipolar disorder, it is associated with certain safety and tolerability concerns. Data from patients with bipolar disorder indicate that up to 58% of patients are overweight and VPA has been shown to cause significant weight gain for some patients [22]. Hepatoxicity, teratogenicity, and pancreatitis are serious complications that have also been associated with VPA therapy [23]. In epileptic [24] and bipolar patients [25], use of VPA has been occasionally associated with polycystic ovaries. Studies in patients with epilepsy have also associated hyperandrogenism [26] and significant reductions in axial and appendicular bone mineral density [27] with VPA treatment in some patients.

The efficacy of VPA and LI in treating patients with bipolar disorder is arguably not dissimilar to that of CBZ, although the usage of CBZ is currently not as widespread as either LI or VPA because of a variety of factors. One of these factors is the fear of rare occurrences of serious hematologic side effects, such as agranulocytosis and aplastic anemia (these are both listed as box warnings) [28]. Another reason for limited use would simply be the previous lack of approval in the USA by the FDA for use in bipolar disorder. Despite the fact that therapeutic

agents are frequently used off-label in practice, the lack of a formal FDA approval results in little knowledge of the utility of a particular agent, reduced reimbursement, legal concerns, and subsequent minimal usage.

Pharmacological profile

Mechanisms of action

The mechanisms of action of CBZ in bipolar disorder have been difficult to delineate since even the pathophysiology has not yet been elucidated. CBZ is extensively oxidized in the liver by the cytochrome component P450 3A4 to the active metabolite, CBZ-10,11-epoxide (CBZ-E) (**Figure 1**) [29]. Both CBZ and CBZ-E possess pharmacologic, psychotropic activity [30,31]. Studies have consistently shown that voltage-gated Na^+ channels are inhibited by CBZ and CBZ-E, especially during depolarization and repetitive neuronal firing [32–35]. Voltage-sensitive Ca^{2+} channels may be inhibited by CBZ, although the evidence is still unclear [36,37]. CBZ has been shown to increase serotonin concentrations [38,39,40], and to inhibit the release of glutamate, presumably by blocking voltage-gated Na^+ channels [34,41,42]. CBZ blocks *N*-methyl-D-aspartate (NMDA)-activated membrane currents and reduces polarization of NMDA receptors [43,44]. CBZ has been reported to inhibit adenyl cyclase activity and decrease cAMP concentrations, which may lead to inhibition of downstream activities with membrane receptors and ion channels, intracellular enzymes, and gene transcription [34,45–47].

Formulation & pharmacokinetics

The ER technology of CBZ–ERC utilizes the Microtrol® delivery system. This capsule formulation is made up of three different types of beads in order to extend delivery beyond what can be achieved with conventional immediate-release formulations. A total of 25% of these beads are designed to release the drug immediately after dissolution of the capsule; 40% of the beads are polymer-coated for an ER profile, and the remaining 35% are coated with a pH-sensitive coating to allow for the enteric release of CBZ. The timed release of these beads is unaffected by variations in gastrointestinal transit time. In addition, the capsule does not have to be taken with food. For patients with difficulty swallowing, the capsules can also be opened and their contents sprinkled onto soft food such as apple sauce, as long as the contents of the capsules are not crushed or chewed [48].

Minimizing plasma CBZ fluctuations inherent to IR formulations was an important factor in the development of ER formulations of CBZ, including CBZ–ERC. In studies of CBZ in patients with epilepsy, large plasma CBZ fluctuations led to side effects at peak concentrations and breakthrough seizures at trough concentrations [49–52]. Most studies examining plasma CBZ fluctuations were conducted in patients with epilepsy. Ghose and colleagues showed serum CBZ and CBZ-E fluctuations in a 24-h period in patients dosed daily, twice daily, and three-times daily to be 73 and 46%; 59 and 34%; and 33 and 41%, respectively [53]. Furthermore, IR-CBZ dosed twice daily produced diurnal plasma CBZ fluctuations in which greater plasma CBZ concentrations and CBZ-E:CBZ ratio variation occurred during the day than at night (CBZ, day vs. night: 64 vs. 48%; CBZ-E/CBZ ratio, day vs. night: 64 vs. 48%, respectively) [54].

Disconcerting findings of high patient noncompliance to pharmacotherapy in bipolar disorder are likely linked to the aforementioned plasma drug fluctuations and high incidence of adverse events at peak concentrations. Keck and associates reported noncompliance rates ranging from 51 to 64% in patients with bipolar disorder treated with various mood stabilizers [55,56]. Noncompliance has frequently been attributed to the dosing regimen: Cramer and associates reported compliance rates of 87% for drugs dosed daily; 81% twice daily; 77% three-times daily; and 39% four-times daily [57]. Since CBZ is rapidly eliminated from the body [58], IR-CBZ is dosed three- or four-times daily; however, this increased frequency of dosing may result in poor patient compliance [53,59].

CBZ–ERC, in contrast to IR-CBZ, produces smoother plasma CBZ and CBZ-E profiles (39 and 35%, respectively) [60]. Miller and colleagues reported minimal inter- and intravariability in the absorption constant in patients with epilepsy who switched from IR-CBZ to CBZ–ERC compared with the high variations in the immediate-release formulation [61]. Furthermore, incidence of CNS side effects decreased from 49 to 20% following conversion from IR-CBZ to CBZ–ERC [62]. These clinical observations, in addition to the twice daily dosing regimen with CBZ–ERC, would improve patient compliance by providing less frequent dosing and better tolerance as a result of fewer side effects from decreased peak plasma CBZ concentrations.

The pharmacokinetics of CBZ–ERC are linear over a single dose range of 200 to 800 mg. In previous studies, a single 200-mg dose of CBZ–ERC produced a peak plasma CBZ concentration of 1.9 ± 0.3 µg/ml in 19 ± 7 h [28]. For CBZ-E, it took 36 ± 6 h to reach a peak concentration of 0.11 ± 0.012 µg/ml [28]. After repeated dosing of 800 mg every 12 h, the peak plasma CBZ concentration was 11.0 ± 2.5 µg/ml in 5.9 ± 1.8 h, and for CBZ-E, 2.2 ± 0.9 µg/ml in 14 ± 8 h [28]. The average half-life of CBZ and CBZ-E following repeated dosing with CBZ–ERC is estimated to be 12 to 17 h and 25 to 43 h, respectively [28].

Efficacy of carbamazepine–extended-release capsules in bipolar disorder

Three out of four clinical trials (rwo randomized, 3-week, double-blind, placebo-controlled studies [63,64] and a 6-month extension study [65]) were essential in demonstrating the efficacy of CBZ–ERC for the treatment of manic or mixed episodes in bipolar I disorder. In all short-term studies, concomitant treatment with lorazepam or psychotherapy was allowed, but investigators were instructed to use as little lorazepam as possible, and no use of lorazepam was permitted after week 2. Lorazepam was permitted for the duration of the 6-month extension study. Each 3-week trial was a 21-day, randomized, double-blind, placebo-controlled Phase 3 study that utilized a 5- to 7-day, placebo lead-in period. Treatment with ERC-CBZ was initiated at 200 mg twice daily and titrated (up or down) rapidly by increments of 200 mg/day to a final dose of between 200 mg/day and 1600 mg/day. All patients were hospitalized during the lead-in period and for at least the first 7 days of double-blind treatment. After day 7 of double-blind treatment, patients displaying sufficient improvement could be discharged at the discretion of the treating physician. Each week, adverse events and adherence were recorded and efficacy assessments were carried out. The primary outcome measure was the change from baseline to last observation in the YMRS total score. Secondary efficacy assessments included mean change from baseline to last observation in CGI-Severity (CGI-S) [66] and CGI-Improvement (CGI-I) scores [66] and Hamilton Depression Rating Scale (HDRS) [67] total scores.

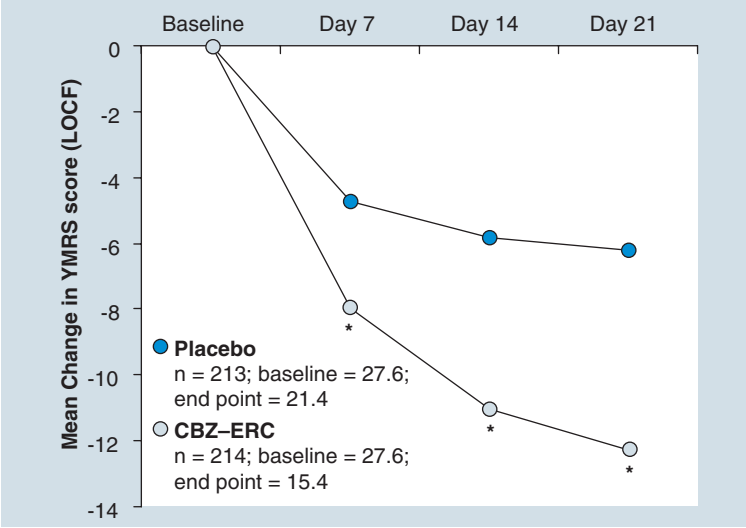
The last visits of the previous 3-week studies served as the first visits of the 6-month, open-label extension study. All patients in the intent-to-treat population (n = 77) were given CBZ–ERC (200–1600 mg/day) [65]. To maintain the blind from previous studies, those previously on placebo were noted and dosed with blind blister cards for the first 19 days to allow CBZ–ERC titration. Assessments were performed every 2 weeks for the first month of the study and monthly thereafter. The primary outcome measure was the time to relapse, although other assessments included tallying of adverse events, laboratory evaluations, YMRS scores, CGI scores, and HDRS scores.

Efficacy of carbamazepine–extended-release capsules in mania

Analysis of pooled patient data from 40 study sites (34 in the USA and six in India) participating in the aforementioned 3-week studies yielded a total of 443 patients who were randomized to double-blind treatment: 223 patients to the CBZ–ERC treatment group and 220 patients to the placebo group. Of these randomized patients, a total of 240 (54.2%) completed the trials, which were conducted between December 1999 and April 2003. Average daily CBZ–ERC intake in the acute trials before the full effects of enzyme induction was 707 mg (data on file). Lack of efficacy led to discontinuation of 10% of patients on CBZ–ERC therapy and 22% on placebo [68].

Mean change in YMRS total scores were statistically significant at all time points in patients on CBZ–ERC versus those on placebo (last observation carried forward [LOCF]; $p < 0.0001$ at all time points) (**Figure 2**) [69]. At day 21, patients on CBZ–ERC therapy had a 44% reduction from baseline YMRS total scores [69]. At end point, 52% of patients on CBZ–ERC responded to treatment (defined as ≥ 50% decrease in YMRS score) compared with 26% in patients given placebo (LOCF; $p < 0.0001$) [69]. A significant decrease in CGI-S total score was observed in the CBZ–ERC-treated group compared with the placebo-treated group (mean change: -1.19 vs. -0.51, respectively; $p < 0.0001$), indicating improvements in severity of illness with CBZ–ERC therapy [69]. In accordance, the percentage of patients who improved in illness (defined by CGI-I) with CBZ–ERC treatment was 56 vs. 28% in the placebo group ($p < 0.0001$) [69]. An interesting result from the pooled analysis was that at end point, patients treated with CBZ–ERC had a mean change in HDRS total score that was significantly greater than those of the placebo group (LOCF: -2.9 vs. -1.3, respectively; $p = 0.01$) [69].

Figure 2. Mean change in YMRS total scores in pooled analysis of 3-week studies. Data represent the change in mean total YMRS scores of the pooled study population in the 3-week trials.



*p < 0.0001 compared with placebo following analysis of covariance with baseline score as covariate.
ERC–CBZ: Carbamazepine extended-release capsules; LOCF: Last observation carried forward;YMRS: Young Mania Rating Scale.

Efficacy of carbamazepine–extended-release capsules in mixed episodes

Patients with mixed episodes have been shown to be difficult to treat due to the coexistence of both mood poles [70]. This subgroup has been shown to have a poor response to LI monotherapy [71]. Studies in treatment with CBZ have indicated that it may be more effective in improving manic symptoms rather than depressive symptoms in mixed episodes [72,73].

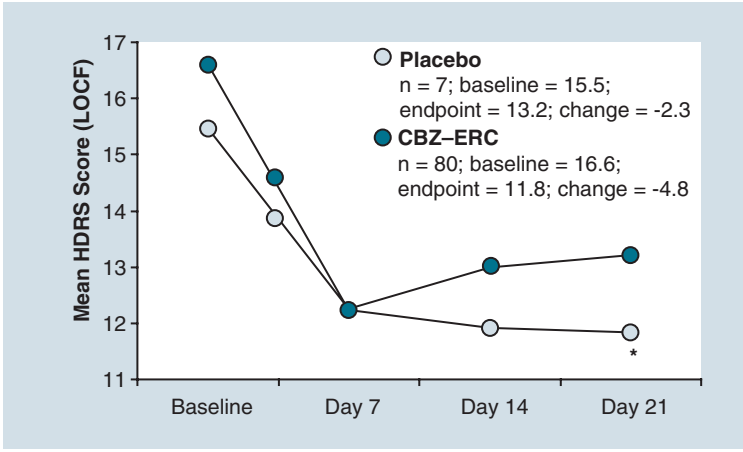
CBZ–ERC has demonstrated its efficacy in the treatment of mania symptoms in patients with mixed episodes. Pooled analysis of YMRS total scores in patients experiencing mixed episodes on CBZ–ERC therapy (n = 80) in the 3-week studies showed significant improvements in YMRS total scores at days 14 and 21, compared with those on placebo (n = 67; LOCF: both $p < 0.01$) [74]. At day 21, there was a 47% reduction from baseline YMRS total scores in patients on CBZ–ERC therapy.

CBZ–ERC has also shown promising results in improving depressive symptoms in patients with mixed episodes. A noteworthy finding in the 3-week studies was that, at day 21, patients with mixed episodes who were treated with CBZ–ERC had significant improvements in depressive symptoms as shown by mean change in HDRS score (LOCF; $p < 0.05$), suggesting that CBZ–ERC may have antidepressant effects, as well antimanic effects in this particular patient population (**Figure 3**) [74]. Subanalysis of HDRS items indicated improvements from baseline at day 21 in insomnia-middle (n = 0.0168); insomnia-late (p = 0.0076); agitation (n = 0.0081); and anxiety (psychic) (p = 0.0064) [74]. After 6 months of continued CBZ–ERC therapy, the HDRS total score at end point remained significantly reduced compared with baseline scores in the pooled analysis of the 3-week studies (n = 54; LOCF: 18.0 vs. 13.5, respectively; p = 0.0003). Although the mean HDRS score indicated that, as a whole, the population was not in remission, the population included manic patients and was not seriously depressed at initiation.

Long-term efficacy

In the 6-month, open-label extension study [65] in which patients from 3-week studies were given CBZ–ERC, the average daily dose was 938 mg following enzyme induction. Only 11 (14.3%) patients discontinued due to lack of efficacy during the study. Of the 11 patients who relapsed (14.3%), estimated mean time to relapse by the Kaplan–Meier model was 142 ± 6 days. At each monthly time point inpatients previously taking placebo in the short-term trials who were started on CBZ–ERC in the open-label extention study, mean change in YMRS total score was significantly greater, compared with the mean change in YMRS total score from day 1, which supported the efficacy of CBZ–ERC in improving manic symptoms demonstrated in the short-term studies (LOCF month 1, 2 and 6: $p < 0.0001$; month 4: $p < 0.001$) (**Figure 4**) [74]. Mean change in YMRS total scores in patients who continued CBZ–ERC treatment from the previous 3-week trials was statistically significant only at month 2 vs. day 1 of the long-term study (LOCF: -17.2 vs. -14.7; $p < 0.01$) (**Figure 4**) [74]. This result was expected and suggested that improvements in manic symptoms from the previous 3-week CBZ–ERC treatment were maintained. Percentage of YMRS responders to CBZ–ERC treatment (defined as ≥50% decrease from baseline of the first day of the prior 3-week studies in YMRS total scores to study end point) was 78.4% in patients previously on CBZ–ERC and 72.5% in those previously on placebo. Mean CGI-S and CGI-I scores significantly improved from baseline at each time point in patients who were formerly on placebo (both $p < 0.05$); however, no

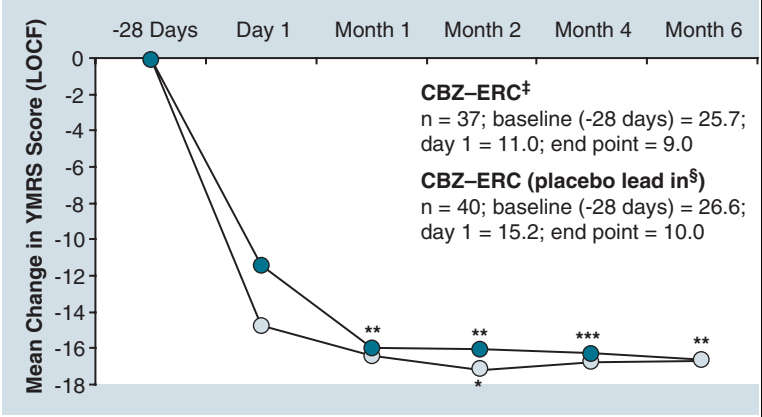
Figure 3. Mean HDRS total scores in patients with mixed episodes in the pooled analysis of 3-week trials. Data represent the mean total HDRS scores for the pooled 3-week study population.



ERC–CBZ: Carbamazepine extended-release capsules; HDRS: Hamilton Depression Rating Scale; LOCF: Last observation carried forward.

further improvements were observed in those previously on CBZ–ERC treatment in the 3-week studies, indicating that improvements in overall illness were also maintained.

Figure 4. Mean change in YMRS total scores with long-term CBZ–ERC treatment. Data represent the mean change in YMRS scores among the population of patients in a 6-month extension trial of CBZ–ERC (-28 days is equivalent to the beginning of the preceding 3-week trial).



‡p < 0.05 compared with placebo following analysis of covariance with baseline score as covariate. §Patients who were previously placebo in the acute 3-week trials before entrance into the 6-month study.
*p < 0.01; **p < 0.001; ***p < 0.0001 vs. baseline (one-sample *t*-test of mean change from day 1).
ERC–CBZ: Carbamazepine extended-release capsules; HDRS: Hamilton Depression Rating Scale; LOCF: Last observation carried forward.

When compared with the mean HDRS scores at baseline from the previous 3-week studies, mean change in HDRS scores were statistically significant (**Figure 5**).

Study in patients who failed therapy with LI

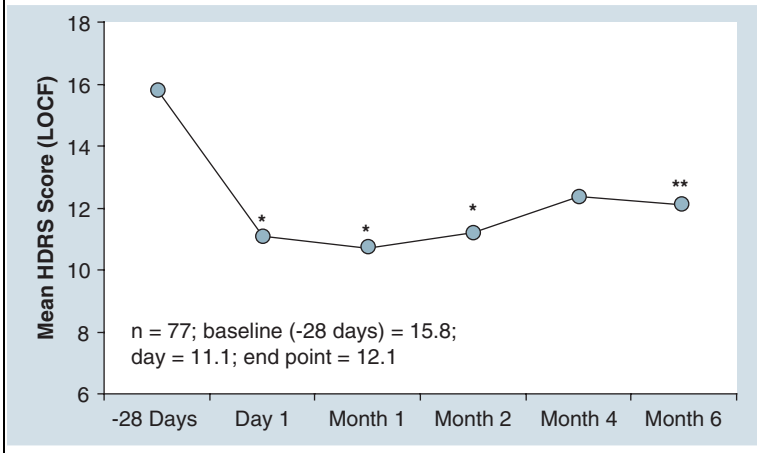
A 3-week, multicenter, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of CBZ–ERC in patients with manic or mixed episodes who had previously failed or could not tolerate therapy with LI was conducted. The mean change in YMRS total scores from baseline to end point was statistically significant in both patients on CBZ–ERC and placebo (both $p < 0.001$); however, there was no statistical significance between groups [74]. Furthermore, no differences in mean CGI-S and CGI-I scores between CBZ–ERC and placebo treatment groups were observed [74]. This trial was underpowered (CBZ–ERC: n = 27; placebo: n = 30) and thus further studies with larger study populations are warranted. Furthermore, these patients may have been generally more resistant to treatment, intolerant of adverse events or may have been more ill and not able be successfully treated with any agent in monotherapy in clinical trials.

Safety

In the pooled analysis of the two 3-week trials, the most frequently reported treatment emergent adverse events with CBZ–ERC were dizziness, somnolence, and nausea (**Table 1**) [68]. A decrease in the incidence of treatment-emergent adverse events was observed after initiation, indicating that the aggressive CBZ–ERC titration schedule led to adverse events early in treatment (**Table 1**). Adverse events with the more aggressive dosing strategy led to the discontinuation of 11% of patients in the intent-to-treat CBZ–ERC treatment group compared with 5% in the placebo group. The most common adverse events observed with long-term CBZ–ERC therapy were headache (22%), dizziness (16%), and mild rash (13%). Overall, treatment-emergent adverse events led to a discontinuation of 21% of patients in the open-label extension study.

To this date, there have been no cases of aplastic anemia, or agranulocytosis in any clinical studies of CBZ–ERC for the treatment of bipolar disorder, although no cases would be expected, given the extremely low incidence rate of such. No statistically significant alterations in electrocardiogram variables (i.e., corrected QT, QT, QRS, PR and ventricular rate) were

Figure 5. HDRS total scores from the 6-month CBZ–ERC study. The data represent the mean total HDRS score among the study population on CBZ–ERC in the 6-month extension open-label extension trial.



When scores were based on one sample t-test of mean change from baseline values at day 1in 6-month study, no statistical significance was detected.
*p < 0.0001; **n = 0.05 based on one sample t-test of mean change from baseline scores of pooled analysis from the 3-week studies.
ERC–CBZ: Carbamazepine extended-release capsules; HDRS: Hamilton Depression Rating Scale; LOCF: Last observation carried forward.

observed in the 3-week or long-term trials. Most importantly, no deaths have occurred as a result of CBZ–ERC therapy.

In the pooled 3-week studies, CBZ–ERC treatment led to a low incidence (~5%) of clinically significant weight gain (≥7% increase from baseline) [74]. Mean weight change in patients on CBZ–ERC was +2.3 lb in the pooled 3-week studies [74] and -0.9 lb in the 6-month trial [65]. Long-term CBZ–ERC therapy has not been shown to alter blood-glucose concentrations [65].

Table 1. Treatment-emergent adverse events reported weekly in pooled 3-week trials.

	Adverse events	%
Week 1		
	Dizziness	38
	Somnolence	28
	Nausea	27
	Vomiting	15
	Ataxia	11
	Pruritus	5
Week 2		
	Constipation	6
	Vomiting	5
Week 3		
	None	

Note: Adverse events have an incidence ≥5% and at least twice the rate observed in placebo patients.

Total plasma cholesterol concentrations have been shown to increase approximately 20 mg/dl in patients with bipolar disorder treated with CBZ–ERC [74,65]. In one of the 3-week studies, total cholesterol ($p < 0.0001$), low-density lipoprotein-cholesterol ($p< 0.0001$), and high-density lipoprotein-cholesterol (HDL-C) ($p < 0.01$) increased significantly from baseline measurements in patients on CBZ–ERC [64]. Despite these increases in cholesterol, there was no meaningful change in total cholesterol to HDL-C ratio (4.0:1 at baseline and 4.2:1 at end point). Results from the 6-month CBZ–ERC open-label study showed no further increase in plasma cholesterol concentrations in patients who were previously on CBZ–ERC in the 3-week studies [65]. This finding suggests that the increase in total plasma cholesterol levels is not continuous. However, in the 3-week and 6-month studies, blood was collected at nonfasting states since these studies were not specifically designed to measure this parameter. Thus, no definitive conclusions can be made on the effects of CBZ–ERC on blood glucose and cholesterol concentrations without further studies.

Since CBZ is metabolized by, and induces the cytochrome P450 isoform CYP3A4, the possibility of interaction with a number of other medications, including CBZ itself, does exist. Although a new formulation, CBZ–ERC still contains CBZ and, as such, offers no advantage over immediate-release CBZ with respect to drug interactions. Agents that are either metabolized by CYP3A4, or those that play a role in the activity of CYP3A4 can potentially interact. Although the exact reductions or increases in dosage of these agents need to be empirically determined, having knowledge of these interactions can help guide the appropriate selection of medications. As seen in **Table 2**, drugs that have been shown to, or that would be expected to increase plasma CBZ levels include, but are not limited to, the following drugs: cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketaconazole, itraconazole, verapamil and valproic acid (increases CBZ-10,11-epoxide). Drugs that have been shown

Table 2. Selected drug interactions with carbamazepine [28].

Selected other agents affecting CBZ level
Decrease CBZ
Phenobarbital
Carbamazepine
Cisplatin
Doxorubicin
Felbamate
Rifampin
Primidone
Increase CBZ
Fluoxetine
Valproate
Azoles
Cimetidine
Macrolides
Grapefruit juice
Loratadine
Nicotinamide
Verapamil
Selected psychiatric agents affected by CBZ
Decreased by CBZ
Bupropion
Clonazepam
Citalopram
Clozapine*
Quetiapine
Risperidone
Haloperidol
Lamotrigine
Valproate
Acetaminophen
Cyclosporin
Glucocorticoids
Methadone
Oral contraceptives‡
Oxcarbazepine
Warfarin
Increased by CBZ
Clomipramine
Phenytoin
Primidone

**Combination therapy with clozapine and CBZ is not recommended.*

‡Increase effective dose of estrogen in contraceptive to 50 µg. CBZ: Carbamazepine.

to, or would be expected to, decrease plasma CBZ levels include but are not limited to the following: cisplatin, doxorubicin HCl, felbamate (also increases CBZ-10,11-epoxide), rifampin, phenobarbital, phenytoin, primidone and theophylline. These lists are not all inclusive, but represent a general list of the commonly known interactions.

Conclusions

Owing to the success of CBZ–ERC in the treatment of bipolar disorder and its tolerability and safety profiles in patients, it was approved by the FDA for the treatment of acute manic and mixed episodes associated with bipolar I disorder. Currently, it is the only CBZ formulation approved by the FDA for the treatment of bipolar disorder. Results from short-term (3-week) studies showed improvement in manic symptoms within 1 week of CBZ–ERC therapy, which was the first day that ratings were performed after baseline. Observations from the long-term (6-month) study suggest continued efficacy in reducing manic symptoms. Adverse events in all trials were typically mild to moderate and transient in nature. As would be expected, there were no reports of aplastic anemia or agranulocytosis in these clinical trials. Also, unlike VPA [75] and most antipsychotics [76–78], CBZ–ERC was associated with a low incidence of clinically significant weight gain and no hyperglycemia. Although statistically significant, the amount of mean weight change seen in the pooled analysis of these trials was not considered clinically significant (≥7%). Even though increases in total plasma cholesterol concentrations were observed in CBZ–ERC-treated patients, the concentrations did not increase further with continued therapy. Due to the increase in HDL-C, the total cholesterol to HDL-C ratio did not demonstrate a meaningful change. Since patients were not fasting during blood withdrawal, more strictly designed trials are warranted to validate the significance of the blood glucose and cholesterol observations.

Expert opinion

CBZ–ERC has been widely prescribed for decades by clinicians for the treatment of bipolar disorder, even before this drug formulation was approved by the FDA for this indication. Since CBZ has been a therapeutic agent for trigeminal neuralgia, epilepsy and bipolar disorder for nearly 30 years, its safety and tolerability profiles are well-characterized. The trials mentioned in this review are the first double-blind, placebo-controlled and long-term studies on CBZ–ERC for the treatment of bipolar disorder. From the results of these trials, CBZ–ERC demonstrated response rates comparable to other placebo-controlled studies of LI, VPA and atypical antipsychotics [79]. It is effective in improving manic symptoms in patients with mixed episodes, a difficult subgroup to treat. Also, the extended-release formulation may optimize patient compliance by providing less plasma CBZ fluctuations and side effects. CBZ is currently an

Highlights

- Based on two pivotal randomized clinical trials that are presented in this paper as pooled clinical trial data demonstrating the safety and efficacy of carbamazepine extended-release capsules (CBZ-ERC) in the treatment of mania associated with bipolar disorder, CBZ-ERC has been approved by the US Food and Drug Administration (FDA) for use in patients with bipolar disorder who are experiencing acute manic or mixed episodes.
- Side effects and the need for frequent dosing are major deterrents to treatment compliance; CBZ-ERC, with its extended-release formulation, minimizes fluctuations in plasma carbamazepine (CBZ) levels and consequently reduces the incidence of side effects, in addition to allowing less frequent (twice-a-day) dosing.
- Short-term, randomized, placebo-controlled trials have shown that CBZ-ERC 200-1600 mg/day results in significant improvement in manic symptoms of bipolar disorder within 1 week of treatment initiation, and preliminary long-term data suggest that for some patients, this beneficial effect persists over the course of 6 months with continued CBZ-ERC monotherapy; these trials also revealed significant improvement in depressive symptoms by 3 weeks in many patients.
- In these same clinical trials, adverse events were generally mild to moderate in severity and typically occurred early in treatment, during dose titration; furthermore, no reports of aplastic anemia or agranulocytosis were documented in these studies, although none would be expected, as patient numbers were not large enough given the rarity of these events.
- Weight gain frequently arises as a key consideration in the selection of a treatment option for bipolar disorder, and unlike many other psychotropic agents, CBZ-ERC is associated with a low incidence of clinically significant (≥7%) weight gain; in addition, blood sugar changes are very uncommon in patients treated with CBZ-ERC.

alternative treatment to LI and VPA according to the American Psychiatric Association's treatment guidelines for patients with bipolar disorder [13]. However, based on the efficacy and mild long-term safety and tolerability profile of CBZ–ERC in patients with bipolar disorder, along with its FDA approval and ample medical education, this paradigm may change.

Safety and tolerability issues are major factors that determine the success of a drug. Dosage and titration regimens are important variables that influence patient tolerability. In the studies mentioned in this review, the titration approach of CBZ–ERC was aggressive at 200 mg/day in the 3-week studies and 200 mg/3 days in the long-term study. Yet, the slower-titration approach in the long-term study did lead to decreases in common adverse events versus those in the 3-week studies. In clinical settings, titration is expected to be slower, which will presumably decrease the frequency of the common CNS and gastrointestinal side effects. Some clinicians may have misconceptions about the frequency of aplastic anemia and agranulocytosis in patients on CBZ, which have a low incidence of occurence. An important observation in the studies of CBZ–ERC in the treatment of bipolar disorder was that no reports of aplastic anemia or agranulocytosis were evident, although none would be expected since the patient populations were small in these trials and the incidences are very low. With obesity an epidemic in the USA [80] and the importance of body image in some patients, minimizing drug-induced weight gain is commonly an issue in choosing a particular drug for patients. From the findings of these trials utilizing CBZ–ERC in patients with bipolar disorder, CBZ–ERC appears to be relatively benign in this respect.

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