# Carbamazepine extended-release capsules in bipolar disorder

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**Abstract:** Carbamazepine (CBZ) has long been a therapeutic option for bipolar disorder. Carbamazepine extended-release capsules (CBZ-ERC) are a recent formulation of CBZ approved by the US Food and Drug Administration in 2004 for the treatment of acute manic and mixed episodes associated with bipolar I disorder. This new formulation was developed to improve dosing convenience and decrease daily fluctuations in serum CBZ concentration, thereby lowering the incidence of adverse events. Two randomized, double-blind, placebo-controlled trials and an open-label extension study have demonstrated that CBZ-ERC monotherapy is efficacious in patients with bipolar I disorder experiencing either manic or mixed episodes. In these trials, CBZ-ERC was shown to be a safe and well-tolerated therapy. Retrospective chart reviews conducted in private practice settings have shown that clinical response to CBZ-ERC is independent of bipolar subtype, as patients with bipolar I depression and bipolar II disorder responded similarly to patients with bipolar I disorder either manic or mixed episodes. CBZ is currently considered a treatment alternative to lithium and valproate according to the American Psychiatric Association's treatment guidelines for patients with bipolar disorder. Although further study is required, the clinical evidence presented in these studies may change the treatment paradigm.

**Keywords:** bipolar disorder, carbamazepine, mania, extended-release

## Introduction

Bipolar disorder is usually a chronic illness with an episodic and variable course (APA 2002). It is a leading cause of years lived with disability (WHO 2004) and is associated with poor health-related quality of life, high utilization of health care services, work impairment (Dean et al 2004), and significant costs to society (Wyatt et al 1995).

There are many forms of bipolar disorder, ranging from mild depression and brief hypomania to one of severe depression or mania with psychotic features (Muller-Oerlinghausen et al 2002). To help identify the various forms of the illness, 4 subtypes of bipolar disorder have been defined based on patients' clinical characteristics: bipolar I disorder, bipolar II disorder, cyclothymia, and bipolar disorder not otherwise specified (APA 2000). Past estimates of the prevalence of the full spectrum of bipolar disorders have ranged from 3% to 6.5%, with about 1% considered to be the bipolar I subtype (Angst 1998; Stimmel 2004). Furthermore, new data on the prevalence of bipolar spectrum disorders have emerged from the recently completed US National Comorbidity Survey Replication, in which trained professionals interviewed a nationally representative population of 9282 English-speaking US residents aged >18 years. National Comorbidity Survey probands were assessed for the presence of Diagnostic and Statistical Manual of Mental Disorders (4th edition) mental disorders in the 12 months prior to the survey using the World Mental Health Survey Initiative

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version of the World Health Organization Composite International Diagnostic Interview, and it was found that the 12-month prevalence of bipolar disorder (subtype I or II) in the study sample was 2.6% (Kessler 2005).

## Treatment options

Although psychotherapy is a critical component of intervention in bipolar disorder, pharmacotherapy is essential in treating patients who are acutely symptomatic (Suppes et al 2005). The most recent version of the Texas Implementation of Medical Algorithms (TIMA) calls for the treatment of acute manic, depressive, or mixed bipolar symptoms to enable patients to return to normal psychosocial functioning. According to the TIMA recommendations, acute pharmacotherapy should be initiated for mild to severe bipolar symptoms, with decisions on whether to maintain stable treatment dosing, adjust treatment dosing, or select an alternative pharmacotherapeutic strategy being made on the basis of regular follow-up assessments. Upon symptom remission after treatment of acute bipolar mania, a 4- to 6-month course of continuation therapy and subsequent lifetime maintenance therapy with mood stabilizers are recommended for the prevention of recurrences (Suppes et al 2005).

Despite systematic guidelines for the treatment of bipolar disorder, the selection of appropriate therapeutic agents for use in conjunction with these guidelines can be challenging, because the symptoms of bipolar disorder may be very different in different phases of the illness. Several agents are currently available for the treatment of bipolar disorder, and the initial treatment depends on the type of episode the patient is experiencing at presentation. Lithium has been extensively studied in the treatment of acute mania and as maintenance therapy since the discovery of its mood-stabilizing properties more than 50 years ago (Goodwin et al 1969; Belmaker 2004), and it is currently considered to be a first-line treatment option in acute mania and prophylaxis in bipolar disorder. Nonetheless, despite its first-line status and its demonstrated overall efficacy in these settings, lithium therapy has been shown to be ineffective or poorly tolerated in a significant proportion of patients (Bowden et al 1994). In addition, it has a narrow therapeutic range and requires regular blood level monitoring, as severe or toxic effects can occur at twice the therapeutic dose. Its narrow therapeutic range is an especially important consideration in older patients as their renal excretion becomes less efficient, resulting in an increased risk of lithium-associated toxic effects (Goodwin 2003; Belmaker 2004).

Although lithium is widely used globally, the anticonvulsants valproate and carbamazepine (CBZ) have also become established therapeutic options in the treatment of bipolar disorder (Mitchell et al 2002; Suppes et al 2005). Extensive clinical research has shown that these agents have mood-stabilizing properties and are therefore effective treatments in the management of bipolar disorder (Mitchell et al 2002). The current review will examine data for a twice-daily extended-release capsule formulation of CBZ (CBZ-ERC) (Shire Pharmaceuticals, Wayne, PA, USA) that contains three different types of beads (immediate release, extended release, and enteric release). This particular formulation has been approved by the US Food and Drug Administration (FDA) for the treatment of acute manic and mixed episodes associated with bipolar I disorder.

## Rationale for development of CBZ-ERC

Clinical evidence of the efficacy of CBZ in the treatment of bipolar disorder emerged in the early 1970s. At this time, several small studies reported the antimanic effects of CBZ as well as its prophylactic effects against the recurrence of manic and depressive episodes in patients with bipolar disorder (Okuma et al 1973). Over the next several decades, many double-blind, controlled trials demonstrated the efficacy of CBZ in the treatment of acute mania in bipolar disorder, with response rates similar to those of lithium (McElroy et al 2000). Until recently, all controlled evaluations of CBZ in bipolar disorder have used immediate-release formulations of CBZ that require dosing 3 or 4 times daily to avoid potentially problematic serum drug fluctuations. Studies have shown that the large fluctuations in serum CBZ levels observed with immediate-release CBZ formulations are associated with intermittent adverse effects such as diplopia, drowsiness, and headache in patients with epilepsy (Hoppener et al 1980; Riva et al 1984). The established correlation between fluctuations in serum CBZ levels and intermittent side effects helped prompt the development of extended-release formulations of CBZ for use in epilepsy. The subsequent use of extended-release CBZ in patients with epilepsy provided clinical evidence that, compared with immediate-release formulations, extended-release CBZ was associated with lower peak serum CBZ concentrations, decreased circadian

toxicity, and decreased central nervous system (CNS) side effects (Canger et al 1990; Haefeli et al 1994).

Non-adherence to medication is common among patients with bipolar disorder (Keck et al 1996; Svarstad et al 2001). Potential factors affecting compliance with medication include adverse effects and the demands of treatment, including frequent dosing regimens (Jamison et al 1983; Greenberg 1984). Since extended-release formulations of CBZ have been developed to decrease daily fluctuations in serum CBZ concentrations and improve dosing convenience, several large clinical trials have recently been conducted to assess the efficacy and tolerability of a novel, beaded, extended-release capsule formulation of CBZ in bipolar disorder (Weisler et al 2004c, 2005; Ketter et al 2004).

## Pharmacology

### Pharmacodynamics

Although recent neurochemical and neuroimaging studies have been promising, a specific pathophysiological abnormality in bipolar disorder has not been discovered (Belmaker 2004). Clinical and preclinical evidence suggests that second messenger systems and molecular "switches" known as G-proteins are involved in the underlying mechanisms that result in bipolar disorder (Gould et al 2002). A variety of medications used to treat bipolar disorder have widely varying mechanisms of action (MOA), which in many cases are also still not well understood. Alterations in postreceptor pathways, intracellular signaling, neural plasticity, and changes in gene expression are believed to play important roles in the therapeutic effects of these agents (Gould et al 2002).

The MOA of CBZ in the treatment of bipolar disorder has not been clarified. It has been well established that CBZ exerts its antiepileptic effects by inhibiting the high-frequency firing of sodium channels. This effect produces a functional blockage of voltage-gated sodium channels that could be associated with its mood-stabilizing properties (Gould et al 2004). In experimental studies, CBZ acts as an antagonist at adenosine receptors, which are generally G-protein-coupled receptors that modulate neurotransmitter release and numerous behavioral and cognitive functions. Carbamazepine has also been reported to inhibit the enzyme adenylyl cyclase, which attenuates cyclic AMP-mediated signaling and may lead to inhibition of downstream activities with ion channels and transcription factors (Gould et al 2004). Additional findings on the MOA of CBZ include reports of its effects on the voltage-gated ion channels in neurons where at therapeutic concentrations it acts as a calcium ion channel blocker (Ulrich et al 2003), and it exerts regulatory effects on receptor-mediated excitatory and inhibitory neurotransmission (Li et al 2002).

## Pharmacokinetics

The extended-release formulation CBZ-ERC utilizes a drug delivery system consisting of a fixed ratio of specialized beads to extend the release of CBZ beyond what can be achieved with conventional immediate-release formulations. Twenty-five percent of these beads are designed to release drug immediately after swallowing for rapid absorption, 40% of the beads are polymer-coated to dissolve gradually over 8–12 hours to achieve steady-state serum CBZ levels, and the remaining 35% are enteric-release beads with a pH-sensitive coating that releases CBZ slowly in the gut to maintain optimal blood levels. The timed release of CBZ is unaffected by variations in gastrointestinal (GI) transit time. Additionally, the capsule does not have to be taken with food; it can be opened and its contents sprinkled onto soft foods (McLean et al 2001).

The pharmacokinetics of CBZ-ERC have been determined following single and repeat dose administration. Following a single 200-mg dose of CBZ-ERC, peak plasma CBZ concentration was found to be $1.9 \pm 0.3$ μg/mL, and time to reach peak was $19 \pm 7$ hours. After repeated dose administration of CBZ-ERC 800 mg every 12 hours, the peak plasma CBZ concentration was $11.0 \pm 2.5$ μg/mL and time to reach peak was $5.9 \pm 1.8$ hours. The pharmacokinetics of CBZ-ERC are linear over a single-dose range of 200–800 mg (Shire 2005).

CBZ is 76% bound to plasma proteins and is primarily metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for metabolizing CBZ to its active metabolite CBZ-10,11-epoxide. Since CBZ induces its own metabolism, the half-life is variable. The average half-life can range from 35 to 40 hours following a single dose of CBZ-ERC and 12 to 17 hours following repeated dosing of CBZ-ERC.

In a pharmacokinetic study conducted in patients with epilepsy, twice-daily CBZ-ERC was shown to be bioequivalent to immediate-release formulations of CBZ given four times daily (Garnett et al 1998). Minimizing the fluctuations in serum CBZ concentrations inherent in immediate-release formulations was an important factor in the development of CBZ-ERC. Low peak-to-trough blood level variability ensures that blood CBZ levels remain

relatively stable (Stevens et al 1998). In studies of CBZ in patients with epilepsy, conversion from immediate- to extended-release CBZ resulted in marked reductions in common dose-related CNS side effects. Pharmacokinetic analysis showed marked variability in absorption and blood drug concentrations with immediate-release formulations of CBZ compared with CBZ-ERC. These findings suggest that the improved CNS tolerability observed in patients treated with CBZ-ERC is a result of smoother drug delivery and reduced variability in absorption provided by the extended-release formulation (Miller et al 2004b). These clinical findings, in addition to twice daily dosing with CBZ-ERC, should improve patient compliance by providing a more convenient dosing regimen and improved tolerance with fewer side effects.

## Clinical studies

### Efficacy

For more than 30 years, CBZ has been used to treat bipolar disorder. Early controlled trials of CBZ in the treatment of acute mania were conducted with conventional immediate-release formulations and confounded by coadministration with lithium or standard antipsychotics. In the first double-blind, placebo-controlled study of CBZ in affectively ill patients (ie, bipolar, unipolar depression, schizoaffective illness), preliminary results showed that 7 of the first 10 patients treated with immediate-release CBZ responded favorably with an antimanic, an antidepressant, or a prophylactic response (Ballenger et al 1978). In comparative studies, immediate-release CBZ was found to be as efficacious as lithium in the treatment of acute mania in bipolar disorder (Okuma et al 1990; Small et al 1991; Emilien et al 1996). In one study, a 4-week, double-blind, multicenter trial involving 105 patients aged 13–65 years with manic or mixed bipolar disorder, 62% of patients in the immediate-release CBZ group showed moderate to marked amelioration of manic symptoms (as judged by the treating physician) at final assessment, compared with 59% in the lithium group (not significant) (Okuma et al 1990). In a separate 4-week, comparative, double-blind study, immediate-release CBZ monotherapy (n = 15) and valproate monotherapy (n = 15) were found to be comparably effective in the treatment of acute mania in patients hospitalized with bipolar disorder (Vasudev et al 2000). The primary efficacy analysis in that study revealed that the mean Young Mania Rating Scale (YMRS) score in the valproate group decreased significantly more than in the immediate-release CBZ group, although rates of response ($\geq$50% decrease in total YMRS score from baseline) were not significantly different between the two groups, as favorable clinical responses were attained by 53% of patients in the immediate-release CBZ group and 73% of patients in the valproate group.

While the efficacy of CBZ in treating acute mania associated with bipolar I disorder has been well characterized, evidence suggests that clinical responses to this agent are independent of symptomatology or bipolar subtype. In particular, a 21-day, open-label study involving 36 patients with bipolar disorder revealed that immediate-release CBZ reduced Hamilton Depression Rating Scale (HDRS) scores by an average of 72.7% (from 32.6 to 8.9; $p < 0.0001$ for change relative to baseline) between baseline and end point in the subset of patients with bipolar depression (n = 27) and by an average of 50.4% (from 35.1 to 17.4; $p = 0.0009$ for change relative to baseline) in the subset of patients with depressive mania (n = 9) (Dilsaver et al 1996). More recently, a retrospective chart review of patients treated in a private practice setting found that CBZ-ERC also appears to be effective in reducing the symptoms of bipolar II disorder (Ginsberg 2004a). Of the 111 patients treated with CBZ-ERC in that review (85% of whom were classified as being "markedly ill", "severely ill", or "extremely ill" at the time of treatment initiation), 82 (74%) experienced a response to treatment as indicated by the achievement of a Clinical Global Impression-Improvement (CGI-I) score $\leq$3.

Aside from exhibiting efficacy in the acute treatment of bipolar disorder, CBZ has also been found to be effective as maintenance therapy in $\geq$10 controlled or partially controlled studies, with a cumulative "marked or excellent" response rate of approximately 61% (Denicoff et al 1997). Several studies have compared the prophylactic efficacy of immediate-release CBZ with that of lithium, which, in a pooled analysis of maintenance studies averaging 1.5 years in length, was found to reduce the likelihood of manic recurrence by a factor of 2.5 and the likelihood of depressive recurrence by a factor of 1.8 (Goodwin and Jamison 1990; Baldessarini et al 1996). Comparison studies involving immediate-release CBZ and lithium have found overall response rates to be similar, with no trends indicating one agent's superiority to the other in the maintenance setting. A meta-analysis of clinical data from 10 double-blind, randomized, comparative trials of immediate-release CBZ vs lithium as maintenance therapy found a relapse rate of 60% in lithium-treated patients vs 55% of CBZ-treated patients; the difference

between the groups was not significant (Davis et al 1999). In one recent randomized, double-blind study comparing the prophylactic efficacy of immediate-release CBZ and lithium in bipolar disorder, lithium was superior to immediate-release CBZ in terms of 2.5-year hospitalization rates (lithium, 26%; immediate-release CBZ, 62%; $p = 0.012$) in patients with "classical" bipolar I disorder (without mood-incongruent features and psychiatric comorbidity and without mixed states; n = 67), while immediate-release CBZ showed a trend toward being more effective (2.5-year hospitalization rates: lithium, 44%; immediate-release CBZ, 31%; $p = 0.34$) in the more heterogeneous "nonclassical" subgroup of patients (n = 104).These findings suggest that patients with classical features benefit more from prophylactic therapy with lithium, while those with nonclassical features may benefit more from prophylaxis with CBZ, which appears to provide a broader spectrum of activity (Greil et al 1998; Kleindienst et al 2000).

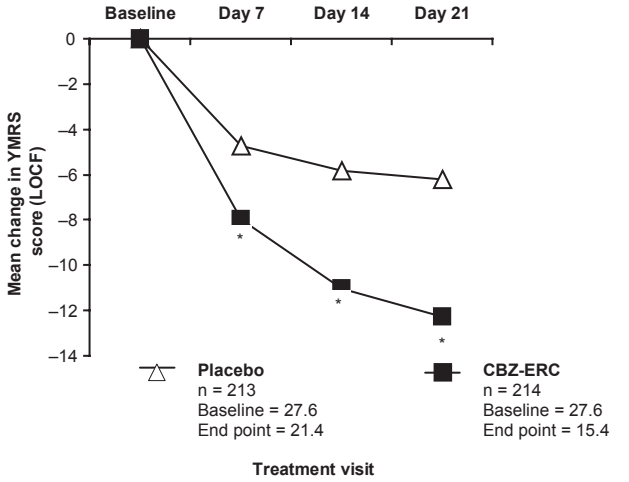


**Figure 1** Mean change in YMRS total scores in pooled analysis of 3-week studies of CBZ-ERC in acute mania.
*$p < 0.0001$ compared with placebo following analysis of covariance with baseline score as covariate.
**Abbreviations:** YMRS, Young Mania Rating Scale; LOCF, last observation carried forward; CBZ-ERC, carbamazepine extended-release capsules.

## Efficacy of CBZ-ERC in acute mania

Recently, two large 3-week, double-blind, randomized, placebo-controlled, multicenter trials demonstrated that monotherapy with twice-daily CBZ-ERC was effective in the treatment of acute mania in patients with bipolar I disorder experiencing manic or mixed episodes (Weisler et al 2004c, 2005). To be eligible for enrollment in these studies, patients had to be ≥18 years old and meet DSM-IV criteria for bipolar I disorder with current episode manic or mixed and with manic symptoms severe enough to necessitate hospitalization. A history of ≥1 previous manic or mixed episode and a minimum baseline total score of 20 on the YMRS were required. The initial 400-mg dose of CBZ-ERC or placebo could be titrated by the investigators between 200 mg and 1600 mg in daily increments of 200 mg. Efficacy assessments were carried out weekly and included the YMRS, the Clinical Global Impression (CGI) scale, and the HDRS.

To better elucidate the results from these two similar trials, the data were combined and the efficacy and safety of CBZ-ERC were evaluated based on the combined study population. Pooled data from these two pivotal studies (which took place across a total of 40 study sites – 34 in the United States and 6 in India) included a total of 443 patients, 223 of whom were randomized to double-blind treatment with CBZ-ERC and 220 of whom were randomized to receive placebo. A total of 240 randomized patients (54%) in the pooled analysis completed the 21-day study period, and the rate of discontinuation due to lack of efficacy was found to be higher in the placebo group (22%) than in the CBZ-ERC group (10%).

The primary efficacy endpoint was the YMRS total score at the end of the double-blind treatment period. As shown in Figure 1, using the last observation carried forward analysis, CBZ-ERC-treated patients in the combined patient population had significantly greater decreases in mean YMRS scores from baseline than those in the placebo group at day 7, 14, and day 21, the primary endpoint ($p < 0.0001$ at all time points). By the end of the trial, 52% of CBZ-ERC-treated patients in the combined population had responded (≥50% reduction in YMRS score) vs 26% of placebo-treated patients ($p < 0.0001$). Patients receiving CBZ-ERC also experienced significantly greater improvements in symptoms ratings on both CGI-Improvement (CGI-I) and CGI-Severity (CGI-S) scales than those treated with placebo ($p < 0.0001$) (Weisler et al 2004a).

Subgroup analyses of the pooled data from these two pivotal studies showed that CBZ-ERC reduced both manic and depressive symptoms. At endpoint, there were significant reductions in mean YMRS total scores in both manic ($p < 0.0001$) and mixed ($p < 0.01$) bipolar patients treated with CBZ-ERC. Importantly, CBZ-ERC treatment led to significant improvement in the severity of depressive symptoms in mixed bipolar I patients ($p < 0.05$) and in the combined patient population ($p = 0.01$) as evidenced by significant

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