Annals of Clinical Psychiatry, 18[S1]:3–7, 2006

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230600653304

Taylor & Francis

Carbamazepine Extended-Release Capsules: A Retrospective Review of Its Use in Children and Adolescents

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Background. *Bipolar disorder occurs in 1% of children and adolescents, but few clinical trials address treatment of this population. This retrospective chart review evaluated the long-term safety and tolerability of carbamazepine extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) in 300 children and adolescent patients who had been treated for bipolar disorder in a private psychiatric practice.*
Methods. *Data were collected from the medical records of all young and adolescent (4–17 years old) patients who met the DSM-IV criteria for a diagnosis of bipolar disorder type I, type II, or bipolar not otherwise specified who had been treated with CBZ-ERC either as add-on or monotherapy between October 1998 and November 2003 at Red Oak Psychiatry Associates, Houston, TX. The severity of illness was assessed using the Clinical Global Impression–Severity scale, and improvement was measured by the Clinical Global Impression–Improvement (CGI-I) scale.*
Results. *A response, defined as a CGI-I score of ≤ 3, was achieved in 76% of patients, 90% of whom were at least markedly ill (CGI-I ≥ 5) at CBZ-ERC initiation. Treatment was well tolerated, with the most common adverse events being somnolence (9.7%), nausea (6.3%), dizziness (5.0%), and rash (4.3%).*
Conclusions. *Carbamazepine extended-release capsules appear safe and efficacious for the treatment of bipolar disorders in children and adolescent patients.*

Keywords Bipolar disorder, Carbamazepine, Children

INTRODUCTION

Bipolar disorder occurs in a significant portion of the U.S. child and adolescent population (1). Although generally considered an adult disease and thought to be rare in younger individuals, a mood episode associated with bipolar disorder occurs before the age of 20 in approximately 25% of patients (2,3). Unfortunately, the disease still remains both underrecognized and undertreated in this population (3).

In part, this lack of appreciation of the problem of pediatric bipolar disorder may stem from a failure to adequately characterize it. Presentation of the illness in this patient group can differ somewhat from that of older individuals, with psychotic symptoms being more prominent in the pediatric population. Additionally, the presence of comorbid conditions such as attention-deficit/hyperactivity disorder (ADHD) can further complicate the differential diagnosis (2,3). Comorbidities are all too frequent in this patient population (2). What must be recognized, however, is that bipolar disorder has a serious impact on the life of the young, placing them at greater risk for suicide, drug abuse, accidents, criminal detention, and sexually transmitted disease (3,4). Moreover, failure to adequately and effectively treat bipolar episodes in children and adolescents can lead to repeated illness and impaired personal, social, educational, and vocational development (3).

Although there are numerous effective agents for bipolar disorder, including neuroleptics, anticonvulsants, benzodiazepines, and lithium, few clinical trials to date have addressed the treatment of this disease in young patients (2,5). Most data used to support treatment recommendations are drawn from clinical trials in adults. Unless supported by corroborating data from studies in children and adolescents, the value of such results in formulating treatment strategies for younger patients is limited. Many of the compounds used to treat bipolar disorder have serious side effects, such as extrapyramidal symptoms, tardive dyskinesia, and diabetes mellitus. Some, such as lithium, have

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narrow therapeutic windows with severe and even lethal toxic effects if blood levels rise too high (5). Pharmacodynamic and pharmacokinetic differences between children and adults make direct comparisons of drug safety and efficacy difficult. For example, metabolic clearance of drugs in newborns is poor, while in children it exceeds that of adults. At puberty, metabolic clearance begins to decline toward adult levels. Children may also experience different or more severe adverse events than adults and, in some cases, even paradoxical ones. It appears, for example, that young children are at greater risk than adults of developing hepatotoxicity during therapy with valproic acid. Of equal importance are the effects of medications on the physical and cognitive development of young patients, particularly for those undergoing long-term therapy.

Carbamazepine (CBZ), a novel anticonvulsant, has been used to treat mania in adults for over two decades. A number of studies have evaluated the immediate-release CBZ formulations over extended periods, but less is known about the long-term tolerability and efficacy of the more recently introduced beaded CBZ extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) in the treatment of bipolar disorder, especially in the young population. The newer formulation offers the promise of reduction in side effects and daily fluctuations of CBZ serum concentrations, as well as greater dosing convenience. However, its use has been investigated in adults with bipolar disorder. Two randomized, double-blind, placebo-controlled, multicenter studies using nearly identical protocols determined that a 3-week course of CBZ-ERC monotherapy was effective in treating acute mania or mixed episodes in adult patients diagnosed with bipolar I disorder. Pooling the data from both trials created a population of 443 patients. By the end of the 3-week trial, twice as many patients in the CBZ-ERC arm had responded as in the placebo arm. The mean change from baseline as measured by the Young Mania Rating Scale was 6.1 points better in the CBZ-ERC group than in the placebo group at day 21. Subgroup analysis showed that CBZ-ERC was equally effective for acute mania regardless of age, race, or gender, and this effect was significant in patients experiencing manic and mixed episodes. Treatment with CBZ-ERC was also associated with improvement in Hamilton Depression Rating Scale scores and significant decreases in the severity of depressive symptoms in patients experiencing a mixed episode. This particular effect of CBZ-ERC is very promising, as few medications treat both the depressive and manic symptoms typical of a mixed presentation. Adverse events in the CBZ-ERC cohort were mild to moderate; although the early discontinuation rate (42%) was high, it is comparable to dropout rates reported with other medications in acute mania trials. The investigators concluded that the trial results confirmed the efficacy of CBZ-ERC in the treatment of acute mania (6,7).

Despite findings of efficacy in adults, however, it is essential to investigate use of this compound in the pediatric population to determine its safety and efficacy in younger patients. To aid in achieving this goal, a retrospective chart review of children and adolescent patients with a DSM-IV diagnosis of bipolar disorder was initiated in a private practice setting in Houston, TX. The primary objective of this chart review was to evaluate the long-term safety and tolerability of extended-release CBZ therapy in children and adolescents with bipolar disorder.

METHODS

Data were collected from the medical records of all young patients who met the DSM-IV criteria for a diagnosis of bipolar disorder type I, type II, or bipolar not otherwise specified (NOS) who had been treated with CBZ-ERC either as add-on or monotherapy between October 1998 and November 2003 at Red Oak Psychiatry Associates, a private psychiatric practice in Houston, TX. Data included gender, age, diagnosis, comorbidities, concomitant medications, dosages of CBZ-ERC, adverse effects, and response to treatment.

The severity of disease was assessed using the Clinical Global Impression–Severity (CGI-S) scale. Scale scores range from 1, which indicates no presence of mental illness, to 7, which signifies severe mental illness. Improvement was measured by the Clinical Global Impression–Improvement (CGI-I) scale (1 = very much improved to 7 = very much worse). A CGI-I score of ≤ 3 was considered a response to treatment, while a CGI-I score of ≥ 4 after a response constituted a relapse.

Similar data had been gathered on a large cohort of adult bipolar patients treated with CBZ-ERC therapy. These data were then compared with that of the pediatric population. Subgroup analyses were done by diagnoses: manic/mixed, bipolar I depressed, and bipolar II.

Statistical Analysis

The primary outcome measures were improvement in psychiatric symptoms as measured by the CGI-I and treatment-emergent adverse events. Mean scores and standard deviations were determined for descriptive data and for the CGI-S and CGI-I. A secondary comparison was done of outcome measures from this pediatric cohort with those of a similar adult population of bipolar patients. Chi-square tests were done on descriptive data, including age and diagnosis, as well as on percentage of response in each group and adverse events. Gender distribution, CGI-S, CGI-I, and medication dose were analyzed using one-way between subject analysis of variance for diagnostic subgroups.

RESULTS

A total of 300 child and adolescent patient charts were reviewed and included in the study (300 adult charts were reviewed for comparison). The mean age of the young patients was 12.3 ($\pm$ 3.2) years, with a range of 4 to 17 years; 40.7% of patients were female. Bipolar I was the diagnosis in 108 patients (36%), bipolar II in 66 (22%), and bipolar NOS in 126 (42%). Within each

Table 1 Bipolar Subtype of Patient Population

Diagnosis	Adult	Child and Adolescent	*p*-Value[a]
Bipolar I	68%	36%	<0.0001
Depressed	22.3%	9.3%	<0.0001
Manic	10.0%	7.0%	0.24
Mixed	35.3%	19.7%	<0.0001
Bipolar II	15%	22%	0.04
Bipolar NOS	17%	42%	N/A

NOS = not otherwise specified; N/A = not available.
[a]*p*-value based on chi-square test.

Table 2 Comorbid Axis I Conditions Among Patient Population (≤18 years old)

Diagnosis	Number of Patients (%) (n = 300)
Attention-deficit/hyperactivity disorder	47
Substance abuse	7
Obsessive-compulsive disorder	6
Oppositional defiant disorder	3
Generalized anxiety disorder	3
Posttraumatic stress disorder	3
Abuse or neglect	2
Panic disorder	2
Tourette syndrome	2

of these subgroups, further classification was performed, and these diagnostic bipolar subtypes are presented in Table 1.

Almost two thirds (n = 197) of patients treated with CBZ-ERC had ≥ 1 comorbid Axis I condition (Table 2). Forty-seven percent of patients had ADHD, 7% had substance abuse, 6% had obsessive-compulsive disorder, and 3.3% had oppositional defiant disorder. Generalized anxiety disorder and posttraumatic stress disorder were each found in 2.7% of patients. Physical, sexual, or emotional abuse or neglect had occurred in 2.3% of patients, while 2.3% suffered from panic disorder. Tourette's disorder was reported in 2% of patients.

At initiation of therapy, 10% of patients were diagnosed as moderately ill, 53% as markedly ill, 31% as severely ill, and 6% as extremely ill. The mean baseline CGI-S was 5.32 ± 0.75, with a range of 4 to 7. The mean dose of CBZ-ERC (determined at the best CGI-I visit) was 541.4 ± 238.1 mg/day with a range of 200 mg/day to 2100 mg/day, and the mean CGI-I was 2.3 ± 1.3. Among patients who were treated with CBZ-ERC, 76% demonstrated clinical improvement. Of those who improved, only 29% eventually suffered a relapse (CGI-I score of ≥ 4 after a response).

As there is no placebo group with which to compare, all adverse events that occurred in 2% of patients are listed as treatment emergent. Somnolence was reported in 9.7% of patients, nausea in 6.3%, dizziness in 5.0%, rash in 4.3%, headaches in 4%, vomiting in 3.3%, and decreased white blood cell (WBC) count in 2.3%. A total of 119 patients either discontinued the study drug or were lost to follow-up. Most of these patients (n = 66) discontinued because of adverse events, though 11 did so through noncompliance and 19 for unspecified reasons. Table 3 presents the reasons noted for discontinuation of the study medication.

Table 3 Reasons for Patient Discontinuation of Extended-Release Carbamazepine Capsules

Reason for Discontinuation	Number of Patients (%) (n = 119)
Allergic reaction	1 (0.3)
Parental request	4 (1.3)
Adverse event	66 (22)
Suicide	1 (0.3)
Difficulty obtaining the medication	1 (0.3)
Lab work (need to draw blood, etc.)	3 (1)
Change in mood symptoms	3 (1)
Increased comorbidities	3 (1)
Lack of efficacy	11 (3.6)
Noncompliance	7 (2.3)
Pregnancy	1 (0.3)
Unknown, unspecified	19 (6.3)

Serious adverse events occurred in several patients. One patient had an allergic reaction to the drug and nearly developed Stevens-Johnson syndrome, and 6 other patients developed rashes. Eight patients attempted suicide, including one whose suicide attempt resulted in death.

Results from the young patient group were compared with those from an adult group of 300 patients treated with CBZ-ERC (Table 1). The mean age of this group was 35.1 ± 11.3 years, with a range of 18 to 70 years, and the percentage of patients who were female—70.6%—was much higher in the adult group ($p < 0.0001$). However, in both patient cohorts, the percentage of patients on CBZ-ERC monotherapy was the same—31.3%. Bipolar subtypes varied significantly between the two groups. Nearly twice as many adults as young patients had been diagnosed with bipolar I (68% vs. 36% respectively), and younger patients were more likely than adults to receive a diagnosis of bipolar NOS.

An analysis of efficacy in three bipolar subtypes—manic/mixed patients, bipolar I depressed patients, and bipolar II patients—demonstrates comparable efficacy in adults and in children and adolescents for all groups (Table 4). In manic/mixed bipolar disorder, mean CGI-S and CGI-I scores were identical for both age groups. Response rates differed only slightly, with adults demonstrating a 75% response and children and adolescents a 71% response. Adult patients had a slightly higher mean dose than the child and adolescent cohort (626.2 mg/day vs. 557.9 mg/day, respectively). None of the differences were significant.

Findings in the bipolar I depressed group were similar, with nearly identical mean CGI-S and CGI-I scores in both groups of patients. The adult response rate was 72%, while the child and adolescent rate was 68%. The mean child and adolescent dose of medication was slightly higher than the adult (594.7

Table 4 Treatment Outcomes for Patients Taking CBZ-ERC

	Adult (n = 300)	Child and Adolescent (n = 300)	*p*-Value
Manic/Mixed			
CGI-S (SD)	5.3 (0.8)	5.3 (0.8)	.55[a]
CGI-I (SD)	2.4 (1.2)	2.4 (1.3)	.84[a]
Responders[b]	75%	71%	.63[c]
Dose (SD)[d]	626.2 (264.6)	557.9 (200.0)	.09[a]
Depressed			
CGI-S (SD)	5.2 (0.9)	5.3 (1.0)	.82[a]
CGI-I (SD)	2.5 (1.2)	2.7 (1.3)	.57[a]
Responders[b]	72%	68%	.90[c]
Dose (SD)[d]	575.0 (194.1)	594.7 (177.9)	.70[a]
Bipolar II			
CGI-S (SD)	5.0 (0.7)	5.2 (0.7)	.13[a]
CGI-I (SD)	2.4 (1.2)	2.3 (1.3)	.82[a]
Responders[b]	72%	68%	.86[c]
Dose (SD)[d]	609.7 (213.5)	564.7 (268.2)	.43[a]

[a]*p*-value based on 1-way between subjects ANOVA.

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

[c]*p*-value based on chi-square test.

[d]Dose at date of CGI-I in responders.

Table 5 Treatment-Emergent Adverse Events in Adult and Child and Adolescent Patients Treated with Extended-Release Carbamazepine Capsules by Bipolar Subtype

Diagnosis and Adverse Events	Adult (n = 300)	Child and Adolescent (n = 300)	*p*-Value[a]
Bipolar I Manic/Mixed			
Somnolence	11.0%	7.5%	0.55
Nausea	7.3%	5.0%	0.70
Rash	5.8%	3.8%	0.72
Dizziness	3.7%	6.3%	0.59
Bipolar I Depressed			
Somnolence	4.5%	7.1%	0.98
Nausea	7.5%	14.3%	0.52
Rash	7.5%	7.1%	0.71
Dizziness	7.5%	7.1%	0.71
Vomiting	3.0%	7.1%	0.72
Headache	4.5%	14.3%	0.22
Bipolar II			
Somnolence	14.3%	12.1%	0.97
Nausea	14.3%	6.1%	0.27
Dizziness	9.5%	10.6%	0.88

[a]*p*-value based on chi-square test.

mg/day vs 575.0 mg/day, respectively). Again, none of these differences were statistically significant.

Efficacy was also comparable in bipolar II patients, with 72% of adults achieving a response and 68% of children and adolescents doing so. Mean CGI-S and CGI-I scores were again nearly identical, and the mean dose in the adult group was slightly higher than in the young group (609.7 mg/day vs. 564.7 mg/day, respectively). No significant differences were noted in any of these parameters.

Treatment-emergent adverse events were similar between adults, and children and adolescents in all three bipolar subtypes (Table 5). Although there were some differences between the two age groups, none were significant and no consistent patterns emerged; similarly, no significant differences were noted in relapse rates between adults and children and adolescents. Among manic/mixed patients, 35.0% of adults and 35.1% of young patients experienced a relapse; among bipolar I depressed patients, 39.6% of adults and 42.1% of the children and adolescents relapsed; and in the bipolar II group, 29.0% of adults and 37.3% of children and adolescents relapsed.

DISCUSSION

The results of this study indicate that CBZ-ERC is a safe and effective treatment for young patients with a variety of bipolar disorder subtypes. The response rate among these patients was 76%, and less than one third of those who demonstrated improvement with CBZ-ERC therapy eventually relapsed. This result is especially noteworthy considering that 90% of these patients were at least markedly ill at the time CBZ-ERC was initiated, and 37% were severely or extremely ill. The mean CGI-I score of 2.3 indicates that there was a marked improvement in many patients.

The demographics of this population were typical of bipolar child and adolescent patients. Nearly two thirds of the individuals in this group presented with ≥ 1 comorbid Axis I condition, a result consistent with the high level of comorbidity frequently found in young bipolar patients (2). Attention-deficit hyperactivity disorder was the most common comorbidity and was found in almost half of these patients. Substance abuse is the second most common comorbidity observed in bipolar children and adolescents, which is consistent with the findings of this study (2).

Given the high percentage of patients with multiple disorders, it is not surprising that 68% were taking ≥ 1 medication in addition to CBZ-ERC. The very high proportion of children and adolescents taking agents such as dextroamphetamine/amphetamine (35.3%), atomoxetine (15.1%), methylphenidate extended release (13%), methylphenidate immediate release (10.1%), and dextroamphetamine (4.3%) is a reflection of the importance of ADHD as a comorbidity of bipolar disorder in this age group.

The adverse events experienced by these patients were generally mild to moderate, and the extended-release formulation was well tolerated in this pediatric population. At 4.3%, the rate of rash in these patients is somewhat lower than that noted elsewhere (6). However, 5 patients (1.6%) did discontinue the medication because of a decline in WBC. Benign leukopenia has been commonly reported with CBZ therapy, and the much more serious blood disorders, agranulocytosis and aplastic anemia, have been observed, though rarely (6). Perhaps most serious, 8 patients attempted suicide, 1 successfully. However, both the attempts and the completed suicide must be considered in light of the high inherent risk for suicide in this group (8).

Although 39.6% of patients discontinued CBZ-ERC, this result is consistent with therapeutic experience in bipolar patients (6). Most discontinuations were the result of adverse events or a failure to comply with the regimen. However, only 7 patients (2.3%) failed to adhere to their medication schedule, whereas adherence can generally be as low as 40% in bipolar patients (6). The adverse events observed in this group must also be considered in light of the large number of other medications being used and their potential for confounding these results. Furthermore, the adverse events experienced here must be weighed against those known to occur with many therapies typically used to treat bipolar patients. Agents such as risperidone and olanzapine have been utilized to treat bipolar disorder, but are known to cause serious adverse events, including tardive dyskinesia, extrapyramidal symptoms, and hepatotoxicity (risperidone), as well as significant weight gain (olanzapine) (9). As previously noted, lithium, which is commonly used to treat bipolar disorder, has a narrow therapeutic index, and blood monitoring is necessary to avoid toxic effects (5). Comparisons with the adult bipolar group receiving CBZ therapy indicate that there are few if any differences, and none of them are of statistical or clinical significance. Based on these results, it is reasonable to suggest that the safety and efficacy data reported elsewhere on the use of CBZ-ERC in adults may adequately reflect likely results in younger patients.

The limitations of this study are those inherent to a retrospective chart review. Although every attempt has been made to provide robust data, chart reviews frequently offer incomplete data and may fail to answer some questions of interest. Since large numbers of patients are still taking CBZ-ERC, it was not possible to determine the mean duration of treatment. The large number of concomitant medications taken by these patients and the fact that some were added or discontinued over the course of the study period precludes making a definitive determination of causality in the case of adverse events. The lack of a control group is another limitation. Nonetheless, retrospective chart reviews offer valuable insights into potential therapies when more robust data are not available. With the lack of well-designed clinical trials of therapeutic interventions for bipolar disorder, particularly in the young population, data from studies such as these make an important contribution to the medical literature.

CONCLUSIONS

Carbamazepine extended-release capsules were found to be a safe, well-tolerated, and efficacious medication for the treatment of bipolar disorder, including bipolar I, bipolar II, and bipolar NOS in child and adolescent patients. Response was robust, and less than one third of those who responded experienced a subsequent relapse. These results are similar to those observed in adult populations and corroborate earlier findings. Extended-release formulations of medication offer more convenient dosing, which may encourage better adherence and improved response rates. Convenient dosing and increased adherence are particularly important in the young population, which is at risk for the complications of this disorder, including impaired personal, social, educational, and vocational development.

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.

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