Carbamazepine and Valproate in the Maintenance Treatment of Bipolar Disorder

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Background: Carbamazepine and valproate are used in the treatment of acute bipolar mania and as maintenance treatments for bipolar disorder. We reviewed the available data from randomized clinical trials of these agents in bipolar disorder to assess their efficacy and tolerability in the maintenance phase of illness management. ***Data Sources:*** We conducted a MEDLINE search augmented by a manual search of bibliographies, textbooks, and abstracts from recent scientific meetings to identify studies of carbamazepine and valproate in the maintenance treatment of bipolar disorder. ***Data Synthesis:*** Although a paucity of data exists from randomized, placebo-controlled trials, carbamazepine and valproate appear to prevent relapse as monotherapy in patients with bipolar disorder. Preliminary evidence of predictors of response to each respective agent has been identified. Combinations of carbamazepine and lithium and of valproate and olanzapine may have greater efficacy than monotherapy. ***Conclusion:*** Although carbamazepine and valproate have been less well studied in maintenance treatment than lithium, each agent appears to have efficacy in this phase of illness management. However, for many patients, combination therapy may provide better long-term prevention of illness relapse and recurrence.

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The long-term treatment of bipolar disorder includes a number of important goals, such as the prevention of episode relapse and recurrence; elimination of subsyndromal symptoms; prevention of suicide; facilitation of compliance; and optimization of interpersonal, social, and vocational functioning.[1] Although lithium has been the most thoroughly studied medication in the prophylaxis of bipolar disorder,[2] a number of clinical trials of carbamazepine and valproate have also been conducted to assess the efficacy of these agents in the prevention of morbidity in bipolar disorder. We conducted a MEDLINE search augmented by a manual search of bibliographies, textbooks, and abstracts from recent scientific meetings to identify studies of carbamazepine and valproate in the maintenance treatment of bipolar disorder. We review below the randomized controlled trials of the efficacy and safety of carbamazepine and valproate in bipolar disorder.

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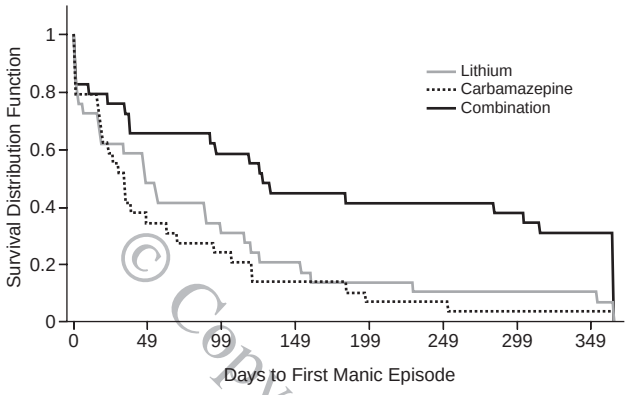
CARBAMAZEPINE

Five randomized, controlled trials of carbamazepine prophylaxis in bipolar disorder were reported in the 1980s and early 1990s.[3–7] Four of these studies were comparisons with lithium,[3–6] and 1 was a comparison with placebo.[7] In 3 of the 4 lithium comparison trials,[3–5] there were no significant differences in efficacy between carbamazepine and lithium. In the fourth study, lithium was superior to carbamazepine on the primary outcome measure, which was time in remission from randomization.[6] The one study that compared carbamazepine with placebo is difficult to interpret because of the potential confounding effects of adjunctive medications for manic and depressive symptoms during the trial.[7] Dardennes et al.[8] conducted a meta-analysis of the 4 trials comparing lithium and carbamazepine. These investigators found that conclusive evidence of carbamazepine's efficacy as a prophylactic agent was lacking from these trials because of heterogeneity in design and differences in statistical power and sensitivity of outcome measures.

Two recent studies of carbamazepine prophylaxis in bipolar disorder attempted to overcome some of the methodological limitations of earlier trials and provide more definitive data.[9,10] In the first study, Denicoff et al.[9] compared the prophylactic effectiveness of carbamazepine, lithium, and the combination in 52 patients who met DSM-III-R criteria for bipolar I disorder. Patients received randomized, double-blind treatment with carbamazepine

Figure 1. Carbamazepine, Lithium, and Combination Therapy: Mean Survival Time to a First Manic Episode[a]



[a]Reprinted with permission from Denicoff et al.[9] Lithium and carbamazepine mean survival time = 179.3 days, lithium mean survival time = 89.8 days, and carbamazepine mean survival time = 66.2 days. Generalized Wilcoxon (Breslow): $\chi^2 = 7.50$, df = 2, p = .024.

(mean ± SD plasma concentration = 7.7 ± 1.3 mg/L) or lithium (mean ± SD plasma concentration = 0.8 ± 0.1 mmol/L) for the first year, the alternate treatment for the second year, and then combination therapy (mean ± SD plasma concentration of carbamazepine, 7.7 ± 1.3 mg/L; lithium, 0.8 ± 0.2 mmol/L) for the third year. Patients were evaluated monthly using daily mood ratings. Adjunctive treatment with antidepressants, antipsychotics, and benzodiazepines was permitted for breakthrough episodes throughout the 3-year trial.

Mean survival time to a first manic episode was significantly longer in the combination treatment phase (179 days) compared with the lithium monotherapy phase (90 days) and the carbamazepine monotherapy phase (66 days) (Figure 1).[9] Patients receiving combination therapy were significantly less likely to have a manic episode (33%) compared with lithium (11%) or carbamazepine monotherapy (4%). Patients spent significantly less time manic during the lithium and combination phases compared with the carbamazepine monotherapy phase of the trial. There were no significant differences among the treatment groups in prevention of depressive episodes. Although the proportion of patients who displayed moderate or marked improvement on the Clinical Global Impressions scale derived from Life Chart data was not significantly different among the 3 treatment phases, there was a trend in favor of combination treatment (55%) compared with lithium (33%) and carbamazepine (31%). The majority of patients in each treatment phase required adjunctive medications (lithium phase, 74%; carbamazepine phase, 77%; combination phase, 72%), although there were no significant differences among groups. Overall, this study found a high incidence of inadequate response among all 3 treatment groups despite liberal use of adjunctive medications.

The investigators[9] conducted a post hoc analysis of correlates of response to each treatment. Patients with rapid cycling did poorly on monotherapy with carbamazepine (19% responders) or lithium (28% responders), but did significantly better on combination therapy (56% responders). A prior history of rapid cycling and more than 10 years between onset of illness and entry into the study were associated with poor carbamazepine response. There was no significant difference in mean carbamazepine plasma concentrations between carbamazepine responders and nonresponders.

In the second recently reported randomized controlled trial, Greil et al.[10] compared carbamazepine (mean ± SD dose = 621 ± 186 mg/day) with lithium (mean ± SD plasma concentration = 0.6 ± 0.1 mmol/L) in an open-label, randomized, parallel-group 2.5-year trial involving 144 patients with bipolar I, II, and not otherwise specified (NOS) disorders. Outcome measures were hospitalization, episode recurrence, need for additional psychotropic medications, and adverse events requiring treatment discontinuation. There were no significant differences between treatment groups based on survival analysis in time to hospitalization or episode recurrence. However, patients in the lithium group had significantly longer survival time in the study when recurrences were combined with need for additional medication and/or adverse events compared with patients in the carbamazepine group. Recurrences occurred significantly more frequently in the carbamazepine group (47%) compared with the lithium group (28%). Numerically (but not significantly) more carbamazepine-treated (N = 9) than lithium-treated (N = 4) patients discontinued due to severe adverse events. In contrast, significantly more patients reported mild or moderately bothersome side effects on lithium (61%) compared with carbamazepine (21%).

Two interesting post hoc analyses addressed correlates of response[11,12] and nonresponse in the subgroup of patients with bipolar II and NOS disorders.[13] In the overall sample of 171 patients with bipolar I, II, and NOS disorders, patients with classical bipolar I disorder (with mood-congruent delusions and absence of comorbidity, N = 104) had significantly lower hospitalization rates with lithium compared with carbamazepine.[11,12] For the nonclassical group (bipolar II or NOS, or bipolar I with mood-incongruent delusions or comorbid psychiatric diagnoses), there was a trend in favor of carbamazepine.[11,12] Greil and Kleindienst[13] also compared separately the response of 57 bipolar II and NOS patients to carbamazepine and lithium.[13] There were no significant differences between treatment groups on any of the 4 outcome measures; however, the power to detect such differences was small.

The results of these 2 large randomized trials present rather discouraging findings regarding the efficacy of monotherapy maintenance treatment with carbamazepine or lithium. Regardless of the different outcome measures

used in each study, there were high rates of treatment failure and need for adjunctive treatment with antidepressants, antipsychotics, and benzodiazepines for breakthrough symptoms or episodes. Although combination therapy with carbamazepine and lithium was superior to monotherapy on several outcome measures in the study by Denicoff et al.,[9] approximately 75% of patients still required treatment with other agents. Among clinical correlates of response, carbamazepine appeared to be most efficacious in nonclassical bipolar I disorder and bipolar II and NOS disorders. Several methodological differences and limitations should also be mentioned about these 2 large studies. Neither trial utilized a placebo control group, making it difficult to parse out true drug effects on spontaneous recurrence and relapse rates. In the study by Greil et al.,[10] only 1 patient of 10 patients screened for possible participation in the study was actually enrolled, underscoring the difficulty in conducting such trials and in extrapolating the results more generally to broader populations of patients with bipolar disorder.[14] Mean plasma concentrations of carbamazepine and lithium were higher in the study by Denicoff et al.,[9] although this did not seem to significantly improve response rates. Alternatively, it is possible that response rates to carbamazepine and lithium might have been higher in the study by Greil et al.[10] if higher maintenance concentrations had been achieved.

VALPROATE

Valproate monotherapy has been studied in 1 placebo-controlled, double-blind, randomized controlled prophylaxis trial,[15] 2 randomized, open-label comparison trials with lithium,[16,17] and 1 double-blind comparison extension trial with olanzapine.[18] Lambert and Venaud[16] conducted an 18-month open-label comparison of valpromide (a prodrug converted to valproic acid) and lithium and reported a 20% lower rate of relapse among patients receiving valpromide compared with lithium. In addition, patients treated with lithium were more likely to discontinue treatment due to side effects or lack of efficacy. Hirschfeld et al.[17] compared the effectiveness of lithium and divalproex in a 1-year open-label, naturalistic pharmacoeconomic trial. Adjunctive medications were allowed as needed. There were no significant differences in recurrence and relapse rates between the 2 groups.

Bowden et al.[15] conducted a rigorous randomized, double-blind, placebo-controlled, parallel-group prophylaxis trial comparing divalproex with lithium in bipolar I disorder. To enroll in this trial, patients were required to have experienced a manic episode within 3 months and to have had at least 1 prior manic episode within 3 years. Prior to randomization, patients received divalproex or lithium during an initial open-label stabilization phase. Divalproex and lithium were titrated to target plasma trough concentrations of 71–125 mg/L or 0.8–1.2 mmol/L, respectively. There was no significant difference among the 3 treatment groups on the primary measure of outcome, time to relapse for any mood episode. The lack of a significant difference between the treatment and placebo groups was likely due to the inclusion of a substantial proportion of mildly ill patients and the choice of outcome measure.[19,20] Nevertheless, there were a number of important findings on secondary outcome measures. For example, among patients who responded to divalproex for acute mania and who were randomized to divalproex, response was superior to placebo in proportion of patients not terminating for relapse (71% vs. 50%), proportion of patients who maintained a complete response during the 1-year trial (41% vs. 13%), and mean number of days in treatment (209 vs. 143 days). Divalproex was also superior to placebo on rate of termination for any mood episode (24% vs. 38%), early termination for depression (6% vs. 16%), and termination for failure to adhere to protocol, intercurrent illness, or administrative reasons (16% vs. 25%). Patients who received divalproex were significantly less likely to experience depression or terminate from the study due to intolerance or noncompliance than patients receiving lithium. Correlates of response to valproate in these studies included mixed mania, rapid cycling, and absence of co-occurring personality disorder.[21–23]

Divalproex was compared with olanzapine in a 47-week trial[18] of patients who responded to either agent at the completion of a 3-week inpatient double-blind trial for acute mania.[24] Responders were maintained on double-blind treatment and received flexible-dose divalproex (500–2500 mg/day) or olanzapine (5–20 mg/day). There were no significant differences in rates of manic relapse between the divalproex (50%) and olanzapine (41%) groups or in the median time to manic relapse (74 days, divalproex; 270 days, olanzapine). Approximately 85% of patients in each group discontinued the study before completion. Significantly more patients receiving divalproex experienced nausea, nervousness, and low platelet counts; somnolence, increased appetite and weight gain, akathisia, dry mouth, and elevated hepatic transaminase levels were significantly more common in olanzapine-treated patients.

As with response in monotherapy maintenance studies of lithium and carbamazepine, overall maintenance response rates to valproate monotherapy, while clinically important, are not sufficient for many patients. In this context, 2 randomized controlled trials evaluated divalproex combination therapy in comparison to mood-stabilizer monotherapy.[25,26] Solomon et al.[25] compared the efficacy of the combination of divalproex and lithium with lithium monotherapy for continuation and maintenance treatment in a pilot study of 12 patients with bipolar I disorder. Patients receiving the combination were significantly less likely to experience a relapse or recurrence, but were significantly more likely to experience 1 or more moderate or

severe side effects. There was no significant difference between the 2 groups in need for adjunctive medications.

In a second, larger combination therapy trial, Tohen et al.[26] compared the efficacy of olanzapine cotherapy with lithium or valproate versus placebo with lithium or valproate in an 18-month maintenance trial. Patients entered this long-term study after achieving syndromic remission in a 6-week randomized, controlled, double-blind study of acute mania.[27] Patients receiving the combination of olanzapine plus valproate or lithium had significantly longer time to recurrence of mania (362 days) compared with the patients receiving placebo plus valproate or lithium (63 days). The combination therapy group also had a significantly lower mania recurrence rate (15% vs. 35%). There were no significant differences in time to or rates of depressive recurrence. Insomnia occurred significantly more commonly in the placebo group; mean weight change (2 kg vs. –2 kg) and clinically significant weight gain (> 10% change from baseline) (20% vs. 2%) were significantly more common in the combination therapy group.

UNANSWERED QUESTIONS AND CLINICAL IMPLICATIONS

From the studies reviewed above, highly suggestive evidence exists to support the efficacy of carbamazepine and valproate as maintenance therapy options for bipolar disorders. However, the type of conclusive evidence that exists for lithium (i.e., double-blind, placebo-controlled trials with positive findings on primary efficacy measures) is still lacking. Nonetheless, several impressions emerge from the available maintenance trials of carbamazepine and valproate. First, although monotherapy with carbamazepine or valproate is an efficacious maintenance approach for some patients, no more than 25% of patients maintained euthymia on monotherapy on either agent by 1 year. Second, combination therapy appears to provide greater benefit in preventing episode recurrence for both agents, although there are few such studies. These findings are consistent with naturalistic studies in large clinical populations.[28–30] Not surprisingly, the price of combination therapy is often a greater cumulative side effect burden.

The available literature to date leaves a number of unanswered, but highly clinically relevant questions. Which combinations provide the most prophylactic benefit? Are certain combinations more efficacious for certain illness subtypes (e.g., bipolar I, II, NOS, with or without psychosis, with or without rapid cycling)? Which combinations provide the best overall tolerability? Is it possible to use lower therapeutic doses of combinations than would otherwise be required in monotherapy? What is the dose–relapse prevention relationship for carbamazepine and valproate? Is the risk of antidepressant-associated switching lower when antidepressants are added to mood-stabilizer combinations rather than monotherapy? The answers to these questions await much needed further study.

Drug names: carbamazepine (Tegretol and others), divalproex (Depakote), olanzapine (Zyprexa).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, carbamazepine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder; and divalproex, olanzapine, and valproate are not approved for the maintenance treatment of bipolar disorder.

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