Long-Term Combination Therapy Versus Monotherapy With Lithium and Carbamazepine in 46 Bipolar I Patients

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Background: Despite wide clinical use of mood-stabilizer combinations for long-term treatment of patients with bipolar disorder, research on risks and benefits of this practice is limited. We found 14 small, usually brief, clinical trials of maintenance treatment with lithium plus carbamazepine. These trials suggest added benefit of combination treatment over use of either agent alone but also indicate the need for further studies.

Method: In a post hoc analysis, we reviewed the course of 46 patients with DSM-IV–diagnosed bipolar I disorder identified as not improving during long-term monotherapy in a mood disorders clinic, comparing days per year hospitalized in 3 consecutive time periods: before prophylactic treatment, during monotherapy with lithium (N = 31) or carbamazepine (N = 15), and during their combined use (N = 46). Secondary outcome measures were rates of hospitalization, time to first recurrence of an affective episode, use of adjunctive treatments, and adverse effects. We compared outcomes with nonparametric bivariate methods and tested predictive factors by multiple regression.

Results: Subjects showed significant reductions in hospitalized days per year during combination therapy, averaging a decrease of 55.9% (p = .004). Among secondary outcomes, hospitalizations per year fell by 36.1%, and median time to recurrence nearly doubled during combination therapy. Rates of adverse effects increased 2.5-fold, compared with monotherapy, and use of adjunctive psychotropic agents increased by 21.9%.

Conclusion: Combining lithium with carbamazepine yielded substantial benefit but more adverse effects.

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Bipolar disorder is classically considered to have a relatively favorable long-term prognosis.[1] Nevertheless, a considerable proportion of bipolar patients experience unsatisfactory responses to treatment, with high rates of comorbidity and disability.[2–6] Agents with proven mood-stabilizing effects often fail to provide full protection against future affective illness, particularly when employed in monotherapies.[7] Therefore, the combination of agents for long-term treatment of bipolar disorder is common[8,9] and on the rise.[10] Rates of use of various combinations of mood stabilizers and other psychotropic agents in the United States were about 40% to 64% during the 1990s[9,10] and nearly 70% more recently.[11] Similar trends have been observed in other countries as well.[12–14] Although combination treatment is a widely employed clinical practice, scientific data to support the effectiveness and safety of specific combinations of psychotropic medicines are scarce, particularly with regard to long-term prophylaxis.[7,15–18]

Prevalent combinations involve lithium plus an anticonvulsant. Notably, lithium and carbamazepine have been combined to treat bipolar patients since the early 1980s,[19] and this specific combination continues to be widely regarded as a useful option following unsatisfactory results with either agent given alone.[15,17,20] Other anticonvulsants also are combined with lithium, including divalproex,[21] oxcarbazepine,[22,23] and lamotrigine.[24] The evidence on which such practices rest derives almost entirely from uncontrolled or anecdotal case and case series reports, with a probable selection bias toward treatment-resistant cases.

We identified 14 studies[19,25–37] reporting in detail on the combination of lithium plus carbamazepine for maintenance treatment in mainly bipolar patients that are considered in more detail here. Their limitations include small samples, relatively brief observations, and variable control of serum concentrations of the agents employed. The longest systematic study of this combination was for 12 months; it indicated superiority of the combination to either agent given alone.[37]

Given the inconclusive state of evidence for the effects of combining lithium with carbamazepine, we carried out a study aimed at elucidating the long-term effectiveness and tolerability of this combination in patients with DSM-IV–diagnosed bipolar I disorder over many years, following prolonged but unsuccessful monotherapy with either agent.

METHOD

Clinical Setting

The data for this study were ascertained at the Department of Psychiatry of Benjamin Franklin Hospital in Berlin, Germany, a tertiary-care hospital and the teaching facility of Freie Universität Berlin. Subjects were patients of the Berlin Lithium Clinic, an outpatient unit specializing in long-term treatment of patients diagnosed with unipolar, bipolar, or schizoaffective disorders, described in detail previously.[38] Patients entered the clinic either after discharge from the hospital or on referral by community psychiatrists. On admission to the clinic, the subjects provided written informed consent to the anonymous and aggregate scientific use of data from their confidential medical records. The subjects studied represent a small subsample requiring combination treatment of a total of approximately 750 patients followed at the study center over the past 3 decades.

Clinical diagnoses were based on semistructured examinations by a research psychiatrist and a senior supervising psychiatrist and were supported by use of a checklist for DSM-III-R criteria (later updated to meet DSM-IV criteria) for major affective disorders and by consensus secured at a diagnostic conference that considered all available information about each patient. Maintenance treatment usually was initiated as monotherapy, most often with lithium, or in cases involving atypical features (such as mood-incongruent psychotic symptoms), with an anticonvulsant (usually carbamazepine or valproate). If the maintenance monotherapy was considered clinically unsatisfactory by the treating psychiatrist, a combination therapy was proposed to the patient.

Subjects

Patients were included in the present analysis if they met the following criteria: (1) age ≥ 18 years at study entry, (2) a DSM-IV diagnosis of bipolar I disorder, (3) continuous, serum-level–controlled, and closely documented combination therapy with lithium and carbamazepine, following trials of either agent as an equally closely monitored monotherapy.

Clinical Assessments

Information regarding illness history prior to clinic entry was gathered retrospectively from the patients and their families or close friends, together with relevant data from the clinical records. Clinical status during treatment was documented during regular follow-up assessments at intervals of 1 to 12 weeks, on the basis of individual clinical requirements. At each visit, patients underwent clinical psychiatric interviews and laboratory assessments (including serum drug concentrations), with systematic documentation of information about side effects and doses of all psychotropic medications used currently or within the preceding interval. Adverse effects were recorded with a "present/not present" checklist covering 20 frequent symptoms (e.g., tremor, nausea, or drowsiness), as well as additional adverse effects as encountered. The primary outcome parameter was days per year hospitalized for psychiatric illness. Secondary outcome measures included hospital admissions per year, time to first recurrence of an affective episode, and rates of use of other adjunctive medications and of adverse effects. Data on outcome measures were obtained from structured research documentation acquired during long-term follow-up at the Berlin Lithium Clinic; hospitalizations were in readily accessible, publicly supported institutions. Study data had been ascertained prospectively for the periods of the monotherapy and combination therapy; data regarding hospitalization prior to monotherapy were gathered retrospectively and verified in hospital records.

Statistical Analyses

The primary outcome (days hospitalized/year) was compared (1) between the 3 treatment conditions (pretreatment, monotherapy, combination treatment) for the group as a whole, (2) between the 3 treatment conditions for subgroups defined by monotherapy with lithium versus carbamazepine, and (3) between the 3 treatment

Table 1. Characteristics of 46 Bipolar I Patients Treated With Lithium or Carbamazepine Monotherapy and Lithium Plus Carbamazepine Combination Therapy[a]

Measure	All Patients	Started With Lithium	Started With Carbamazepine
Patients, N	46	31	15
Female, N (%)	29 (63.0)	20 (64.5)	9 (66.6)
Age at illness onset, mean ± SD, y[a]	29.9 ± 10.3	27.6 ± 9.34	34.7 ± 11.0
Duration of illness before monotherapy, mean ± SD, y	9.44 ± 8.51	8.67 ± 8.77	11.0 ± 7.99
Duration of monotherapy, mean ± SD, y	9.69 ± 7.53	9.78 ± 7.73	9.50 ± 7.34
Duration of combination therapy, mean ± SD, y	4.62 ± 3.56	4.27 ± 3.31	5.35 ± 4.06

[a]Differences between groups started with lithium and carbamazepine were not statistically significant except for age at illness onset (t = 2.12, p = .040).

conditions for subgroups defined by sex. These comparisons used nonparametric Wilcoxon tests because of non-Gaussian distribution (positive skewing) of the outcome data.

Among secondary measures, we made the same comparisons for hospital admissions per year, rates of adverse effects, and use of other comedications. We counted the number of adverse effects identified and the number of comedications used within each 3-month period (quarter year) in follow-up, divided by the number of quarters at risk (in units of adverse effects/time or adjunctive agents/time). We also compared times to first recurrence during monotherapy versus combination treatment using recurrent event survival analytic methods, on the basis of independent increment counting process, the extension of the Cox proportional hazards model, which is appropriate for use when there are ordered multiple events.

Finally, we carried out a multivariate logistic regression analysis that contrasted the change in hospitalized days per year during combination treatment versus monotherapy as the outcome measure, and lithium or carbamazepine monotherapy as the main explanatory factor. Covariates added sequentially to this regression model were sex, current age, pretreatment hospitalization rate, duration of combination therapy, and percentages of serum levels below agent-specific target ranges during monotherapy and, separately, during combination treatment. Target drug levels were 0.6 to 0.9 mEq/L for lithium and 4 to 12 μg/mL for carbamazepine.

Robust estimation of standard errors was done wherever feasible. Model fits and the time-to-event proportional hazards assumption were examined graphically. Data are reported as mean ± SD or 95% CI; a 2-tailed p value of < .05 was required for statistical significance. Calculations were carried out with commercial microcomputer statistical software (Stata, Stata Corp., College Station, Tex.; SPSS-11.5, SPSS Corp., Chicago, Ill.).

RESULTS

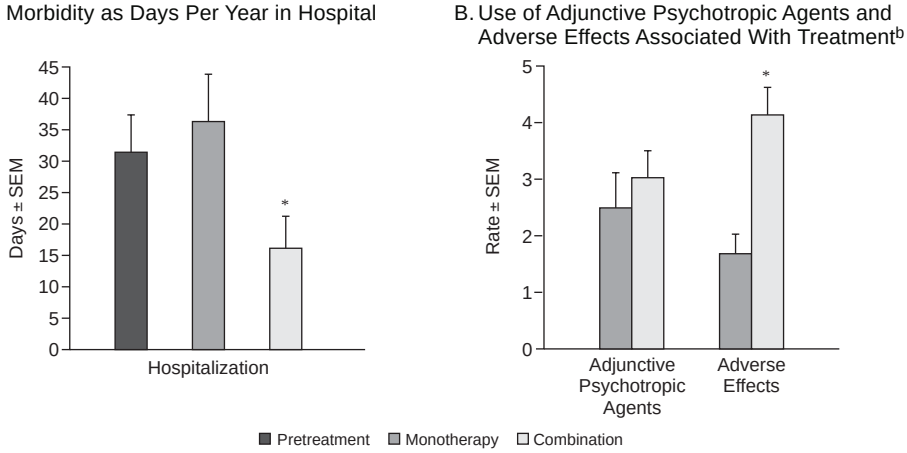
A total of 46 patients with DSM-IV–diagnosed bipolar I disorder (29 women, 17 men) were included. Their estimated mean age at illness onset (defined as first medical contact due to the disorder) was 29.9 ± 10.3 years, followed by a mean latency of 9.44 ± 8.51 years to the start of any long-term maintenance treatment. Initial monotherapy involved lithium salts for 31 subjects (67.0%), and 15 (33.0%) began with carbamazepine alone; monotherapy continued for a mean of 9.69 ± 7.53 years. Lithium and carbamazepine were then combined for another 4.62 ± 3.56 years on average (Table 1). During monotherapy, serum lithium concentrations averaged 0.68 ± 0.10 mEq/L, and levels of carbamazepine averaged 6.7 ± 1.1 μg/mL. Similarly, during combination treatment, serum concentrations averaged 0.69 ± 0.15 mEq/L for lithium and 6.2 ± 1.0 μg/mL for carbamazepine, with no significant differences found within subjects between treatment phases. For monotherapy, 15.7% ± 17.8% of serum levels were < 0.6 mEq/L for lithium or < 4 μg/mL for carbamazepine. This proportion increased to 31.3% ± 27.4% during combination treatment. In both treatment periods, serum drug levels of women were more often below the target range than those of men (during monotherapy: 23.3% ± 18.6% vs. 2.6% ± 3.8% [t = 4.7, df = 1,28; p < .001]; with combination treatment: 37.4% ± 29.8 vs. 21.3% ± 20.1% [t = 2.1, df = 1,40; p = .044]).

Hospitalization and Treatment Course

In this sample of 46 unusually treatment-unresponsive patients with bipolar I disorder (who represent 10% of unselected bipolar patients), the mean hospital days per year did not decrease during monotherapy (31.4 ± 39.8 before vs. 36.3 ± 54.4 days/year during monotherapy; Wilcoxon z = 0.39, p = .93; Figure 1A and Table 2). During monotherapy, compared with pretreatment, 22 (48%) of 46 patients spent fewer days per year in hospital, 2 (4%) were unchanged, and 22 (48%) spent more days per year hospitalized. Patients were hospitalized 0.48 ± 0.59 times per year before long-term treatment and 0.47 ± 0.67 times per year during monotherapy (Wilcoxon z = 0.84, p = .40; Table 2).

After adding lithium or carbamazepine as a second mood stabilizer, the mean hospital days per year fell 55.9%, from 36.3 ± 54.4 during monotherapy to 16.0 ±

Figure 1. Outcomes of 46 Bipolar I Patients Treated With Lithium or Carbamazepine Monotherapy and Lithium Plus Carbamazepine Combination Therapy[a]



[a]Comparisons are for morbidity before treatment (black), long-term monotherapy with lithium or carbamazepine (dark gray), and later combination treatment with both agents (light gray).
[b]Based on mean counts per 3-month exposure times.
*Significantly different, $p < .05$ (for hospitalization from both pretreatment and monotherapy [A] and for adverse effects during combination therapy from adverse effects during monotherapy [B]).

Table 2. Morbidity and Adverse Effects in 46 Bipolar I Patients Before Prophylaxis, During Long-Term Monotherapy With Lithium or Carbamazepine, and During Lithium Plus Carbamazepine Combination Therapy

Measure	A Before Treatment	B Monotherapy	C Combination Therapy	Comparisons (Wilcoxon test)
Days in hospital/y, mean ± SD[a]	31.4 ± 39.8	36.3 ± 54.4	16.0 ± 34.3	A vs C: z = 2.68, p = .007; B vs C: z = 2.88, p = .004
Hospitalizations/y, mean ± SD[a]	0.48 ± 0.59	0.47 ± 0.67	0.30 ± 0.67	A vs C: z = 2.18, p = .019; B vs C: z = 2.18, p = .029
Adverse effects score, mean ± SD[b]	…	1.67 ± 1.96	4.12 ± 3.39	B vs C: z = 3.43, p = .001
Comedication score, mean ± SD[c]	…	2.47 ± 3.37	3.01 ± 2.95	B vs C: z = 1.07, p = .285

[a]Comparisons of A vs. B for hospitalizations/year and days hospitalized/year are not statistically different; see the Results section.
[b]Data available for 34 patients during monotherapy and 46 patients during combination therapy; statistics are based on a comparison of 34 subjects with data from both treatment phases. The adverse effects score is the mean number of adverse events reported per 3-month exposure.
[c]Data available for 30 patients during monotherapy and 40 patients during combination therapy; statistics are based on a comparison of 30 subjects with data from both treatment phases. Comedication score is the mean number of comedications used per 3-month exposure.

34.3 during combination therapy (Wilcoxon z = 2.88, p = .004; Figure 1A and Table 2), and hospitalizations decreased 36.1%, from 0.47 ± 0.67 to 0.30 ± 0.67 admissions per year (Wilcoxon z = 2.18, p = .029). Time in hospital during the combination treatment (16.0 ± 34.3 days/year) also was much lower than the rate of 31.4 ± 39.8 days per year before starting monotherapy (z = 2.68, p = .007; Table 2). Of the 46 patients, 31 (67.4%) experienced fewer hospitalized days per year during combination versus monotherapy, 7 showed virtually no change, and 8 spent more time in hospital with the combination therapy.

It is important to note that we considered possible effects of secular trends in hospitalization across the years represented. Specifically, we tested for the possibility that time per year in hospital may have declined over time, independent of treatment and perhaps due to administrative or economic factors, so as to result in lower levels of hospitalization in the last (combination) treatment phase considered. We examined hospital days per year as a function of year-of-enrollment cohort and found no cohort effect of less hospitalization across the years sampled. Indeed, days per year in hospital increased slightly overall with later years of illness onset during the years before treatment started (linear regression; slope: +1.20 days/year, t = 2.51, p = .018; N = 46). Moreover, hospitalization showed no consistent change in relation to time during the years of monotherapy (slope: +1.35, t = 1.49, p = .15; N = 46) or of combination therapy (slope: –0.28, t = 0.37, p = .72; N = 46). These findings indicate that hospitalization followed no pattern consistent with a cohort effect, and accordingly, the hospitalization rate appears to be a reasonable, objective, and reliable proxy for severity of illness during the observation periods.

A survival analysis comparing the time to first recurrence, including recurrences not leading to hospitalization, revealed an almost 2-fold longer time to the first af-

Table 3. Analysis by Starting Drug (Lithium, N = 31; Carbamazepine, N = 15) Used by Bipolar I Patients Before Prophylaxis, During Long-Term Monotherapy With Lithium or Carbamazepine, and During Their Combined Use[a]

	Before Treatment		Monotherapy		Combination Therapy	
Measure	Lithium	Carbamazepine	Lithium	Carbamazepine	Lithium	Carbamazepine
Days in hospital/y, mean ± SD	38.1[b] ± 45.3	17.6 ± 19.8	31.3 ± 52.6	46.5[c] ± 58.3	16.6[b] ± 29.9	14.7[c] ± 43.1
Hospitalizations/y, mean ± SD	0.55[d] ± 0.64	0.31 ± 0.45	0.45 ± 0.71	0.51[e] ± 0.61	0.29[d] ± 0.53	0.34[e] ± 0.92
Comedication score, mean ± SD[f]	None	None	2.48 ± 3.69	2.47 ± 2.67	2.95 ± 3.04	3.13 ± 2.86
Adverse effect score, mean ± SD[g]	None	None	1.90[h] ± 2.16	1.12[i] ± 1.32	4.15[h] ± 3.51	4.03[i] ± 3.23

[a]Wilcoxon test; significant differences between treatment periods indicated by the same superscript.
[b]z = 2.25, p = .024.
[c]z = 2.73, p = .006.
[d]z = 1.96, p = .050.
[e]z = 1.93, p = .053.
[f]Mean number of adjunctive psychotropic drugs per 3-month assessment interval, averaged across all intervals. Monotherapy: N = 30; combination therapy: N = 40.
[g]Mean number of adverse effects reported per 3-month assessment interval, averaged across all intervals. Monotherapy: N = 34; combination therapy: N = 46.
[h]z = 2.43, p = .015.
[i]z = 2.50, p = .013.

fective episode (manic or depressive) during combination treatment as compared with monotherapy (median time to recurrence: 925 [95% CI = 260 to 1590] vs. 476 [95% CI = 289 to 731] days. This difference, while large and clinically substantial, fell short of statistical significance (z = 1.52, p = .128).

Illness and Treatment Course by Starting Monotherapy

Prior to monotherapy, patients who later would use lithium as the first mood stabilizer experienced 2.2 times more time hospitalized than those patients first treated with carbamazepine (38.1 ± 45.3 vs. 17.6 ± 19.8 days/year, respectively; Table 3). The same subjects experienced a moderate (17.8%) decrease in hospitalized days per year during lithium monotherapy (38.1 ± 45.3 before vs. 31.3 ± 52.6 days/year with lithium; Wilcoxon z = 0.94, p = .35). In contrast, subjects prescribed carbamazepine for monotherapy spent 2.6 times more days per year in hospital (17.6 ± 19.8 before vs. 46.5 ± 58.3 days/year with carbamazepine; Wilcoxon z = 1.29, p = .20).

Adding carbamazepine to lithium for combination treatment was associated with a 47.0% decrease of time hospitalized compared with monotherapy with lithium (from 31.3 ± 52.6 to 16.6 ± 29.9 days/year; Wilcoxon z = 1.57, p = .12). Moreover, adding lithium to carbamazepine yielded a 68.3% decrease of time hospitalized (from 46.5 ± 58.3 to 14.7 ± 43.1 days/year; Wilcoxon z = 2.73, p = .006). Results with respect to hospitalizations per year were similar (Table 3).

Multivariate Analyses

In a sequence of multivariate analyses of factors potentially associated with change in days per year hospitalized during combination treatment versus monotherapy, we incorporated several covariates: lithium versus carbamazepine as the monotherapy agent, sex, age, baseline severity of the illness (as days/year hospitalized before any long-term treatment), duration of combination treatment, and proportion of serum drug levels below the target range during monotherapy and, separately, during combination treatment. None of these factors was significantly related to improvement with combination treatment (all t values: range, 0.13–1.23; p values: range, .13–.88). In particular, the percentage of low serum drug levels during both monotherapy and combination therapy was uncorrelated with change in hospitalization days. A preliminary finding of interest was that women who had started monotherapy with carbamazepine experienced less reduction in time hospitalized during combination therapy than did men. However, women had a significantly higher percentage of below-target serum levels in the combination therapy period; indeed, after including this factor in the multivariate analysis, the sex effect was no longer observed.

Use of Additional Comedication

Use of adjunctive psychotropic agents increased during combination treatment, from a rate of 2.47 to 3.01 drugs per 3-month assessment period, a nonsignificant 21.9% increase (Tables 2 and 4, Figure 1B). Comedication consisted of antidepressants, antipsychotics, benzodiazepines, or thyroxine (in supraphysiologic doses in 6 cases; 3 of those 6 patients were prescribed high-dose thyroxine for more than 1 year). There was no significant association between the use of comedication and the change in days hospitalized per year between monotherapy and combination treatment (by linear regression with robust standard errors: t = 1.33, p = .19). More antidepressants were used during combination therapy than during monotherapy, whereas the use of antipsychotics decreased (Table 4, both changes were nonsignificant). Rates of use of any adjunctive medicines during combination treatment did not differ significantly between subjects starting with lithium or carbamazepine monotherapy (Wilcoxon z = 1.60, p = .28).

Table 4. Psychotropic Comedication in Bipolar I Patients During Monotherapy (N = 30) and Combination Therapy (N = 40)[a]

Agent	Monotherapy	Combination Therapy
Antidepressants	0.98 ± 1.24	1.43 ± 1.85
Antipsychotics	1.19 ± 1.98	0.89 ± 1.44
Benzodiazepines	0.30 ± 0.96	0.35 ± 0.98
Other[b]	0.00	0.35 ± 1.00
Total	2.47 ± 3.37	3.01 ± 2.95

[a]Data are the mean ± SD number of adjunctive psychotropic medications per 3-month interval.
[b]There were no significant differences (Wilcoxon test) except for "other" comedications (z = 2.02, p = .043).

Adverse Effects

The combined use of 2 mood stabilizers was associated with an increase in reported adverse effects (Tables 2 and 3, Figure 1B). Overall, the mean rate of individual complaints per 3-month assessment period increased by 2.5-fold, from 1.67 ± 1.96 during monotherapy, to 4.12 ± 3.39 during combination therapy (Wilcoxon z = 3.43, p = .001); the increase did not differ significantly among those starting first with lithium or carbamazepine alone (Table 3). Adverse effects most often reported during combination therapy ranked (1) tremor, (2) renal effects (usually polyuria, polydypsia), (3) drowsiness, (4) gastroenterological effects (nausea, diarrhea, loss of appetite), and (5) weight gain.

DISCUSSION

Two interesting findings emerged from this study. First, addition of a second mood stabilizer was associated with a substantial decrease in days per year in hospital in a sample of bipolar I patients who had proved to be unresponsive to prolonged monotherapy with lithium or carbamazepine (Tables 2 and 3, Figure 1A). Second, the combination of lithium and carbamazepine was associated with a substantial increase in adverse effects and minor increase in use of other comedications (Tables 2 and 3, Figure 1B).

Annual hospital admission rates as well as days per year hospitalized were significantly reduced during long-term combination treatment with lithium plus carbamazepine, compared with preceding periods of monotherapy with either agent alone and also compared with the years of latency from illness onset to the start of long-term monotherapy. For example, mean days per year hospitalized during combination therapy fell by 56% compared with monotherapy (Table 2). In fact, hospitalized days per year were reduced during combination treatment versus monotherapy in 31 (67%) of 46 patients. Such reductions are remarkable since the subjects selected had shown no improvement in hospital time during prolonged monotherapy (Figure 1A). Also, the time to first recurrence of an affective episode, including recurrences not leading to hospital admission, was much longer during combination treatment than in monotherapy, although the almost 2-fold difference in median time to recurrence did not reach statistical significance.

A similar lack of response to approximately 4 years of lithium monotherapy compared with pretreatment morbidity was also reported by Bocchetta and colleagues[36] in their study of 22 patients who later improved when carbamazepine was added. These observations and our present findings indicate that even specialized mood disorder clinics may not modify treatment regimens in a small minority of treatment-unresponsive patients for prolonged periods. The lack of reduction of hospitalization during monotherapy in the present sample of 46 unusually treatment-resistant bipolar I subjects contrasts markedly to the overall improvement with monotherapy (mainly with lithium) for a sample of 147 bipolar I patients from the same clinic not selected by treatment response and reported in another study.[39] The broader sample showed a reduction of days per year hospitalized by 86% during monotherapy in a within-subject comparison with the years before the start of prophylactic treatment.

Similar to the present study, we found in an extensive literature review that 13 of 14 previous trials reported superior responses with the combined use of lithium and carbamazepine compared with monotherapy (Table 5). All but 3[32,33,37] of these 14 studies involved bipolar subjects selected for poor initial responses to either lithium or carbamazepine. In these previous trials that varied markedly in methods, about 64% of subjects given lithium plus carbamazepine were considered improved, compared with 67% in the present sample. Interestingly, all 3 previous studies[32,33,37] that included patients not preselected for poor response to monotherapy found that the combination of lithium plus carbamazepine yielded superior benefits to either agent given alone. It is also of interest, that in the studies by Shukla and coworkers[27] and Peselow and colleagues,[35] the combination of lithium and carbamazepine was considered more effective than lithium plus an antipsychotic.

We found that patients selected for initial monotherapy with carbamazepine did considerably less well during monotherapy than those started with lithium (Table 3). This outcome probably reflects the nature of the illnesses of patients assigned to carbamazepine: most had complex or atypical illnesses, with mood-incongruent psychotic features and a relatively chronic course that may be particularly difficult to treat.[40] In addition, carbamazepine may be a somewhat less effective mood stabilizer than lithium.[41,42] Moreover, since patients were not assigned randomly to lithium or carbamazepine in our study, and since relatively few started with carbamazepine, comparisons of results with those

Table 5. Trials of Lithium Plus Carbamazepine Combination Maintenance Treatment in Mainly Bipolar Disorder Patients

Study	N[a]	Years[b]	Patients and Design	Outcome[c]	Comments[d]
Inoue et al (1981)[19]	2	Approximately 2	Bipolar disorder, lithium nonresponders; retrospective case series	Improved: 2 (100%)	Other comedications allowed
Nolen (1983)[25]	5	Approximately 1	Bipolar disorder, lithium nonresponders; prospective case series	Improved: 3 (60%)	Other comedications allowed, most patients were rapid cyclers, 4/12 patients taking carbamazepine dropped out early
Fawcett and Kravitz (1985)[26]	5	…	Bipolar disorder, lithium nonresponders; retrospective chart review	Improved: 5 (100%)	Poor documentation of nonresponders
Shukla et al (1985)[27]	14	1	Bipolar disorder, lithium nonresponders; prospective vs lithium + antipsychotic drug in previous year	Improved 10 (71%)	Some other comedications allowed, 5/14 early dropouts, more reported adverse drug responses or side effects with higher drug levels and with prior lithium + antipsychotic drug
Lovett et al (1986)[28]	7	2.9	Bipolar disorder, nonresponders to prophylaxis; retrospective chart review	Improved: 5 (71%)	Other comedications allowed, few side effects
Cabrera et al (1987)[29]	3	2.8	Bipolar disorder, lithium nonresponders; prospective case series	Improved: 3 (100%)	Other comedications allowed
Post et al (1990)[30]	13	4.2	Bipolar disorder (91%), lithium nonresponders; prospective case series	Improved: 10 (approximately 77%; unclear denominator)	Other comedications allowed, no serum control, 6/13 dropouts
Strömgren (1990)[31]	1	3	Lithium and carbamazepine nonresponder	Improved: 1 (100%)	Other comedications allowed
Di Costanzo and Schifano (1991)[32]	8	2	Bipolar disorder (rapid cycling), new to lithium or carbamazepine; retrospective chart comparison with no treatment or lithium alone	Improved in year 1: 6 (approximately 75%); combination therapy > lithium alone; less improved in year 2	Poor adherence after year 1
Kishimoto (1992)[33]	18	5.5	Bipolar disorder, unselected for prior treatment response; retrospective, each monotherapy treatment vs combination therapy	Improved: 16 (approximately 89%); combination therapy > monotherapy	Reported adverse drug responses or side effects uncommon (low serum levels)
Fritze et al (1994)[34]	17	Approximately 1.2	Bipolar disorder (90%), lithium nonresponders; retrospective chart review, combination vs prior carbamazepine alone	Improved: 0 (0%); carbamazepine monotherapy > combination therapy	Other comedications allowed, treatment allocation not randomized by rapid-cycling status, no serum control
Peselow et al (1994)[35]	13	Approximately 4.5	Bipolar disorder, lithium nonresponders; retrospective chart review	Improved/stable: 6 (46%)	Other comedications allowed, allocation not randomized, no serum control, 3/13 dropouts
Bocchetta et al (1997)[36]	22	4.6	Bipolar disorder (46%) and schizoaffective disorder, lithium nonresponders; retrospective chart review	Improved: 17 (77%)	≥ 2 years of combination therapy required, few side effects
Denicoff et al (1997)[37]	31	3	Bipolar disorder, unselected for prior treatment response; prospective, double-blind crossover vs monotherapy	Improved: 17 (55%); combination therapy > both monotherapy treatments	Other comedications allowed, combination particularly good in rapid cycling
Baethge et al (present study)	46	4.6	Bipolar disorder, monotherapy nonresponders; prospective, combination therapy after monotherapy	Improved: 31 (67%)	Other comedications and adverse drug responses or side effects increased with combination therapy
Total	205[e]	3.1[f]	Mostly bipolar disorder, lithium nonresponders	Improved: 132/205 (64%)	1/15 trials: treatment-naive subjects; 14/15 trials: open-label; dropouts: approximately 33% (if stated)

[a]Sample: number of cases with combination of lithium + carbamazepine of a total of 639 cases studied.
[b]Mean years of follow-up during combination treatment.
[c]Number and proportion (%) of subjects with substantial clinical improvement during combination therapy; some reports provided no outcome data.
[d]Comedications were typically sedatives but sometimes also antidepressants or antipsychotics and rarely other mood stabilizers.
[e]A total of 112 bipolar patients took the combination and provided outcome data; dropouts not taken into account due to inconsistent documentation.
[f]Mean for all studies except Fawcett and Kravitz[26] and Peselow et al.,[35] who provided insufficient information to include.

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starting with lithium should be made with caution. It is noteworthy that the sequence of the mood stabilizer treatments was not a predictor of outcome in the multivariate analysis.

Many patients in our sample tolerated the combination of lithium and carbamazepine well, but adverse effects were 2.5 times more frequent during the combination treatment compared with monotherapy, with particular excesses of tremor and drowsiness (Table 2). This finding accords with reports by Chaudhry and Waters[43] and by Shukla and coworkers[44] of increased rates of adverse effects referable to the central nervous system during treatment with lithium plus carbamazepine. It is likely that our finding of a high percentage of below-target serum drug levels, particularly among women, is at least in part a consequence of attempts to reduce adverse effects.

Our patients received 21.9% more adjunctive psychotropic medications when undergoing combination therapy than during monotherapy (Table 3). Since one might expect less use of adjunctive medication during combination therapy, this use of multiple treatments may reflect the unusually treatment-unresponsive nature of the sample studied and extra efforts to gain improved responses. Other authors also found little change in the use of adjunctive psychotropic medications during long-term combination treatments with mood stabilizers (Table 5).[33,37] An additional possibility is that the use of adjunctive agents might reflect secular trends toward polytherapy documented in recent years.[8,10] Of note, we found no association of the use of adjunctive agents with outcome during combination therapy.

Limitations of this study include its post hoc approach and relatively small sample size. Still, this is the largest sample of bipolar I patients studied with regard to the combination of lithium and carbamazepine, and the outcome data summarized in this article were ascertained systematically and prospectively over lengthy follow-up periods (Table 5). The possible influence of comorbidity on outcome in this sample remains unclear because we had insufficient operationalized data on other psychiatric disorders in these patients. Another possible confound is that the results may have been influenced by nonspecific clinical factors associated with heightened therapeutic efforts following years of failure of monotherapy. However, such nonspecific factors are unlikely to be effective over the whole follow-up period of 4.6 years. In fact, inclusion of the duration of combination treatment into our multivariate analysis of the treatment outcome revealed that outcome was unrelated to duration of treatment. Also, comedication use and serum levels were not significantly related to outcome. Therefore, although we cannot rule out that factors other than combination treatment might have contributed to outcome, there is no indication that such nonspecific effects had a material impact on clinical outcome.

Our primary outcome criterion is restricted to illness episodes of sufficient severity as to lead to hospitalization. It is therefore reassuring that the secondary parameter, time to first recurrence of any affective episode, showed the same tendency toward a benefit of combination treatment. Moreover, hospitalization data (length of stay and admissions) are relatively reliable for the purpose of this study, covering very long observation periods with risk of inaccurate recollection of illness history by patients. It is important that, in this study, there was no secular trend of the duration of hospitalization that might have interfered with our outcome parameter.

Finally, it may be useful to make several observations about the current status of combination treatments for bipolar disorder. First, it may be feasible to select a prophylactic monotherapy on the basis of clinical characteristics. For example, Grof[45] observed that a family history of bipolar disorder and a fully remitting episodic course favored response to lithium, whereas lamotrigine was more useful in bipolar patients with prominent anxiety and substance use comorbidity. In addition, it seems appropriate clinically to explore the potential of a monotherapy by increasing doses, guided by assays of serum drug concentrations and tolerability, before considering combinations. In choosing a combination treatment for bipolar patients who respond poorly to a vigorous trial of monotherapy, a major limitation is the lack of systematic data supporting the effectiveness and safety of many specific combinations.[16] Additional studies using combinations of lithium, anticonvulsants, and modern antipsychotics, in comparison with parallel, randomly assigned monotherapies, are needed.[46] Comparisons can include subjects of proven poor responsiveness to a monotherapy randomly assigned to an alternative monotherapy as well as to specific combination treatments. In addition, certain combinations might be superior to monotherapies when given from the start of prophylaxis for bipolar disorder; this possibility requires further study, with lithium and carbamazepine or other agents.

In conclusion, this study found that combining lithium and carbamazepine for the treatment of bipolar I patients provided substantial gains over ineffective long-term trials of either agent in monotherapy. These findings and our review of available clinical studies (Table 5) support the clinical value of this specific combination. Nevertheless, more controlled prospective trials of various combination treatments for bipolar I disorder are needed.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), oxcarbazepine (Trileptal).

REFERENCES

1. Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburgh, UK: E&S Livingstone; 1921

2. Gitlin MJ, Swendson J, Heller TL, et al. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995;152:1635–1640
3. Müller-Oerlinghausen B. Does effective lithium prophylaxis result in a symptom-free state of manic-depressive illness? some thoughts on the fine-tuning of mood stabilization. Compr Psychiatry 2000;41 (suppl 1):26–31
4. Judd LL, Akiskal HS, Schettler PJ. The long-term natural history of a weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;39:530–537
5. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 2003;64:680–690
6. Joffe RT, MacQueen GM, Marriott M, et al. A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. Bipolar Disord 2004;6:62–66
7. Baldessarini RJ, Tarazi FI. Drugs and the treatment of psychiatric disorders: antipsychotic and antimanic agents. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York, NY: McGraw-Hill Press; 2005. In press
8. Fenn HH, Robinson D, Luby V, et al. Trends in pharmacotherapy of schizoaffective and bipolar affective disorders: 5-year naturalistic study. Am J Psychiatry 1996;153:711–713
9. Tohen M, Zarate CA Jr, Hennen J, et al. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 2003;160:2099–2107
10. Frye MA, Ketter TA, Leverich GS, et al. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. J Clin Psychiatry 2000;61:9–15
11. Kupfer DJ, Frank E, Grochocinski VJ, et al. Demographic and clinical characteristics of individuals in a bipolar disorder case registry. J Clin Psychiatry 2002;63:120–125
12. al-Ghamdy YS, Qureshi NA, Abdelghadir MH, et al. Psychotropic drugs prescriptions in Al-Qassim region, Saudi Arabia. East Mediterr Health J 1999;5:27–34
13. Rittmannsberger H, Meise U, Schauflinger K, et al. Polypharmacy in psychiatric treatment: patterns of psychotropic drug use in Austrian psychiatric clinics. Eur Psychiatry 1999;14:33–40
14. Lloyd AJ, Harrison CL, Ferrier IN, et al. The pharmacological treatment of bipolar disorder: practice is improving but could still be better. J Psychopharmacol (Oxf) 2003;17:230–233
15. Freeman MP, Stoll AL. Mood stabilizer combinations: review of safety and efficacy. Am J Psychiatry 1998;155:12–21
16. Ghaemi SN. Polypharmacy of bipolar disorder. In: Ghaemi SN, ed. Polypharmacy in Psychiatry. New York, NY: Marcel Dekker; 2002: 35–77
17. Goodwin FK. Rationale for using lithium in combination with other mood stabilizers in the management of bipolar disorder. J Clin Psychiatry 2003;64(suppl 5):18–24
18. Zarate CA Jr, Quiroz JA. Combination treatment in bipolar disorder: review of controlled trials. Bipolar Disord 2003;5:217–225
19. Inoue K, Arima S, Tanaka K, et al. A lithium and carbamazepine combination in the treatment of bipolar disorder: preliminary report. Folia Psychiatr Neurol Jpn 1981;35:465–475
20. Pies R. Combining lithium and anticonvulsants in bipolar disorder: a review. Ann Clin Psychiatry 2002;14:223–232
21. Solomon DA, Keitner GI, Ryan CE, et al. Lithium plus valproate as maintenance polypharmacy for patients with bipolar disorder: a review. J Clin Psychopharmacol 1998;18:38–49
22. Centorrino F, Albert MJ, Berry JM, et al. Oxcarbazepine: clinical experience with hospitalized psychiatric patients. Bipolar Disord 2003;5:370–374
23. Ghaemi SN, Berv DA, Klugman J, et al. Oxcarbazepine treatment of bipolar disorder. J Clin Psychiatry 2003;64:943–945
24. Evins AE. Efficacy of newer anticonvulsant medications in bipolar spectrum mood disorders. J Clin Psychiatry 2003;64(suppl 8):9–14
25. Nolen WA. Carbamazepine, a possible adjunct or alternative to lithium in bipolar disorder. Acta Psychiatr Scand 1983;67:218–225
26. Fawcett J, Kravitz HM. The long-term management of bipolar disorders with lithium, carbamazepine, and antidepressants. J Clin Psychiatry 1985;46:58–60
27. Shukla S, Cook BL, Miller MG. Lithium-carbamazepine vs lithium-neuroleptic prophylaxis in bipolar illness. J Affect Disord 1985;9:219–222
28. Lovett L, Watkins SE, Shaw DM. The use of alternative drug therapy in nine patients with recurrent affective disorder resistant to conventional prophylaxis. Biol Psychiatry 1986;21:1344–1347
29. Cabrera J, Albrecht J, Müller-Oerlinghausen B. Kombinierte rezidiv-prophylaktische Behandlung der manisch-depressiven Erkrankung mit Lithium und Carbamazepin oder Oxcarbazepin. [Combined preventive treatment of recurrent manic-depressive disease with lithium and carbamazepine or oxcarbazepine.] Nervenarzt 1987;58:245–249
30. Post RM, Leverich GL, Rosoff AS, et al. Carbamazepine prophylaxis in refractory affective disorders: a focus on long-term follow-up. J Clin Psychopharmacol 1990;10:318–327
31. Strömgren LS. The combination of lithium and carbamazepine in treatment and prevention of manic-depressive disorder: review and case report. Compr Psychiatry 1990;31:261–265
32. Di Costanzo E, Schifano F. Lithium alone or in combination with carbamazepine for the treatment of rapid cycling bipolar disorder. Acta Psychiatr Scand 1991;83:456–459
33. Kishimoto A. The treatment of affective disorder with carbamazepine: prophylactic synergism of lithium and carbamazepine combination. Prog Neuropsychopharmacol Biol Psychiatry 1992;16:483–493
34. Fritze J, Beneke M, Lanczik M, et al. Carbamazepine as adjunct or alternative to lithium in the prophylaxis of recurrent affective disorders. Pharmacopsychiatry 1994;27:181–185
35. Peselow ED, Fieve RR, Difilia C, et al. Lithium prophylaxis of bipolar illness: value of combination treatment. Br J Psychiatry 1994;164: 208–214
36. Bocchetta A, Chillotti C, Severino G, et al. Carbamazepine augmentation in lithium-refractory bipolar patients: a prospective study on long-term prophylactic effectiveness. J Clin Psychopharmacol 1997;17:92–96
37. Denicoff KD, Smith-Jackson EE, Disney ER, et al. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry 1997;58:470–478
38. Berghöfer A, Kossmann B, Müller-Oerlinghausen B. Course of illness and pattern of recurrences in patients with affective disorders during long-term lithium prophylaxis: a retrospective analysis over 15 years. Acta Psychiatr Scand 1996;93:349–354
39. Baethge C, Smolka MN, Gruschka P, et al. Does prophylaxis-delay in bipolar disorder influence outcome? results from a long-term study of 147 patients. Acta Psychiatr Scand 2003;107:260–267
40. Grof P, Alda M, Grof E, et al. The challenge of predicting response to stabilising lithium treatment: the importance of patient selection. Br J Psychiatry 1993;163(suppl 21):16–19
41. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorders: results of the MAP study. Neuropsychobiology 2000;42(suppl 1):2–10
42. Hartong EGTM, Moleman P, Hoogduin CAL, et al, and the LitCar Group. Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. J Clin Psychiatry 2003;64:144–151
43. Chaudhry RP, Waters BGH. Lithium and carbamazepine interaction: possible neurotoxicity. J Clin Psychiatry 1983;44:30–31
44. Shukla S, Godwin CD, Long LEB, et al. Lithium-carbamazepine neurotoxicity and risk factors. Am J Psychiatry 1984;141:1604–1606
45. Grof P. Selecting effective long-term treatment for bipolar patients: monotherapy and combinations. J Clin Psychiatry 2003;64(suppl 5): 53–61
46. Tohen M, Chengappa KNR, Suppes T, et al. Relapse prevention in bipolar I disorder: 18 month comparison of olanzapine plus mood stabilizer vs mood stabilizer alone. Br J Psychiatry 2004;184:337–345