Comparative Prophylactic Efficacy of Lithium, Carbamazepine, and the Combination in Bipolar Disorder

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Background: We compared the prophylactic efficacy of lithium, carbamazepine, and the combination and identified possible clinical markers of response.

Method: Fifty-two outpatients who met DSM-III-R criteria for bipolar illness were randomly assigned in a double-blind design for an intended 1 year of treatment with lithium or carbamazepine, a crossover to the opposite drug in the second year, and then a third year on the combination. Patients received monthly detailed evaluations, and daily life chart ratings of the degree of functional incapacity associated with mania or depression were completed.

Results: For evaluable patients: 13 (31.0%) of 42 failed to complete a full year of lithium therapy owing to lack of efficacy, and 2 dropped out because of side effects; 13 (37.1%) of 35 withdrew from carbamazepine within the first year owing to lack of efficacy, and 10 dropped out because of side effects (9 of the 10 had a rash); 7 (24.1%) of 29 withdrew from the combination therapy owing to lack of efficacy. The percentage of the evaluable patients who had marked or moderate improvement on the Clinical Global Impressions scale was 33.3% on lithium, 31.4% on carbamazepine, and 55.2% on the combination treatment, which was not significantly different. By a variety of measures, lithium was more effective than carbamazepine in the prophylaxis of mania. Patients with a past history of rapid cycling did poorly on monotherapy (28.0% responded to lithium; 19.0% responded to carbamazepine), but significantly better on the combination (56.3%, $p < .05$).

Conclusion: These prospective, randomized data suggest a high incidence of inadequate response to either mood stabilizer or their combination despite use of adjunctive agents as needed. Additional novel treatment regimens are needed to better decrease affective morbidity in large numbers of bipolar outpatients.

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Bipolar disorder in its untreated state is a potentially lethal illness characterized by a recurrent, often deteriorating course.[1,2] Lithium has been the drug of choice for the prophylaxis of bipolar disorder, but recent controlled[3–6] and naturalistic[7–9] studies of lithium prophylaxis suggest a generally poorer outcome than often assumed based on the initial studies of Baastrup and Schou[10] and others.[11–13] In fact, a number of studies[3–9,14–17] have reported lithium prophylaxis failure ranging from 26.1% to 70.5% (mean = 41.2%). In addition, given the observations that many bipolar patients have troublesome side effects and are unable to tolerate lithium, clinicians and researchers have sought alternative somatic treatments.

The anticonvulsant carbamazepine has emerged as a well-recognized, second-line treatment option to lithium for refractory bipolar patients.[18–33] Data from 10 controlled or partially controlled studies of carbamazepine prophylaxis in manic depressive illness[4,5,19–26] indicated an approximately 61% marked or excellent response rate to carbamazepine. The cumulative evidence suggests that carbamazepine is an effective drug for the prophylactic treatment of bipolar illness, but the comparative efficacy of carbamazepine and lithium and the identification of possible differential predictors of response remain in need of further clarification.

Several previous double-blind studies have compared the prophylactic efficacy of lithium and carbamazepine.[4–6,22] In two of these studies,[5,22] carbamazepine and lithium were stated to have comparable prophylactic efficacy; in one study,[6] patients taking carbamazepine experienced nonsignificantly less depression, and in another study,[4] lithium, but not carbamazepine, significantly lengthened the time in remission.

Data supporting a potential synergism between carbamazepine and lithium carbonate in the acute and prophylactic treatment of mania have been reported in patients refractory to each agent when used alone.[29–35] In a retrospective chart review, Kishimoto[35] reported that in 7 of 18 patients, the best prophylactic effect was obtained during combination therapy. Up to the present time there have been no published prospective studies that have systematically investigated the prophylactic effects of the combination of lithium and carbamazepine compared with lithium and carbamazepine alone.

In this study, we report on the comparative prophylactic treatment efficacy of lithium, carbamazepine, and the combination of lithium and carbamazepine for 52 bipolar outpatients who entered a double-blind, randomized, crossover study. In addition, we report on potential clinical correlates of response.

METHOD

Subjects

Subjects included in this report were 52 bipolar patients recruited between September 1988 and June 1992 through the National Institute of Mental Health (NIMH) outpatient clinic. The entire projected 3-year study was designed to compare the therapeutic effects of lithium or carbamazepine in the first year, a crossover to the other drug in the second year, and treatment with the combination of both drugs in the third year. Patients were recruited from the Washington, D.C., metropolitan area and met DSM-III-R diagnostic criteria for bipolar disorder. Informed consent was obtained from the subjects after the nature of the experimental procedures was explained. Patients with other severe medical illnesses or another current Axis I disorder, such as substance abuse, were excluded. Patients ranged in age from 19 to 75 years (mean ± SD = 41.3 ± 11.4) and were about equally divided between women (N = 27) and men (N = 25). In terms of marital status, 25 (48.1%) were married, 14 (26.9%) were single, 12 (23.1%) were divorced, and 1 (1.9%) was widowed. The employment status during the study was as follows: 29 (55.8%) were employed full-time, 8 (15.4%) were employed part-time, 3 (5.8%) were housewives, 3 (5.8%) were students, 5 (9.6%) were retired, and 4 (7.7%) were not working. All except 4 of the patients had at least some college education. Nineteen (36.5%) had bipolar II disorder and 33 (63.5%) had bipolar I (by Research Diagnostic Criteria [RDC] with the stipulation that to meet criteria for bipolar I there must be a full-blown manic episode that led to a hospitalization or its equivalent). Thirty-nine subjects (75.0%) had a history of hospitalization. More than half of the patients (31 [60.8%] of 51) had a past history of rapid cycling (four or more episodes in any 1-year period prior to entering the study), and 1 patient was not assessable. Slightly more than half of the patients (N = 27) had a history of psychosis.

All of the subjects had had previous medication experience: 47 had taken lithium and 10 carbamazepine (6 of the 10 had taken the combination). The 47 patients with previous lithium experience had had varying prophylactic responses, as reported subjectively and rated retrospectively from the life chart data using the Clinical Global Impressions (CGI) scale: 4 (8.5%) had had a marked response; 12 (25.5%), a moderate response; 12 (25.5%), a minimal response; 9 (19.1%), no response; and 10 (21.3%), an insufficient trial to estimate response. For the 4 patients who had had a previous trial on carbamazepine monotherapy, the responses were rated as follows: 1 had had a moderate response; 1, minimal response; and 1, an insufficient trial to estimate response; 1 patient left the study prior to completing his retrospective life chart. For the 6 patients who had had a previous trial on carbamazepine plus lithium therapy, the responses were rated as follows: 1 had had a marked response; 2, a minimal response; and 3, an insufficient trial.

Assessment

After the subjects were accepted into the study, they entered an initial admission phase prior to randomization, which averaged 149.6 ± 104.1 days. All patients had a life chart completed based on their prior course of illness as previously described[36] using the NIMH-Life Chart Method and Manual (NIMH-LCM).[37] At study entry, clinicians rated patients on the prospective daily life charting (LCM-p) scale.[36,37] Each month, patients took home a form able to be scanned by computer on which to rate their mood and functioning twice a day. On the basis of the patients' daily self-ratings and the clinical interview during each outpatient visit, we rated patients' daily mood (manic, depressed, or euthymic) according to the degree of functional incapacity (none, mild, moderate, or severe) experienced, using criteria similar to that in retrospective life charting.

To quantify the number of episodes during the prospective phase based on the LCM-p, a conservative approach to episode quantification was adopted that preserved the ability to describe rapid and ultra rapid cycling.[36] In addition to number of episodes and number of days ill, an average severity score was constructed by multiplying the number of days at each severity level (2.5 for mild, 5.0 for moderate, and 10.0 for severe) and dividing by the number of days in the treatment phase.

In addition to the LCM-p rating, a battery of self- and clinician-administered ratings were performed on a monthly basis: Beck Depression Inventory,[38] Modified Spielberger State-Trait Anxiety Inventory,[39] Hamilton Rating Scale for Depression,[40] Young Mania Rating Scale,[41] and the Raskin Severity of Depression and Mania (RSDM) scale.[42,43] The patients and the research nurses, who administered the clinician ratings, were blind to the medication. In instances when the research nurses were unavailable, ratings were administered by an unblinded physician in order to avoid missing data. The CGI scale[44] was used to assess the overall therapeutic effect of lithium, carbamazepine, or the combination. The patient's clinical response during a treatment phase was compared with that in the year prior to the patient's taking a mood-stabilizing medication or in the worst year when the patient had been taking ineffective medications (if the illness had continued to progress despite treatment intervention).

Treatment

During the admission phase, patients were maintained in an open-label fashion, usually taking the same medication they had been prior to entering the study. At the end of the admission phase, they were randomly assigned to a blind medication (lithium or carbamazepine). When the first 1-year treatment phase was completed, patients were crossed over to the other monotherapy for 1 year. The research nurses were aware that the third treatment phase was the combination, but they were not always aware of when it actually started. For clinical reasons, one patient had the order of treatment Phases 2 and 3 switched. Patients were given a code-numbered package containing lithium, carbamazepine, and/or placebo.

The dosage for lithium was increased until the patient was rated euthymic or as having a mild degree of impairment for at least 4 weeks, or dose-limiting side effects supervened. The dosage for carbamazepine was increased until clinical response occurred, side effects intervened, or a dose limit of 1600 mg/day was achieved. Blood levels were targeted for 0.5 to 1.2 mmol/L for lithium and 4 to 12 mg/L for carbamazepine. When patients were taking lithium or carbamazepine and randomly assigned to the other medication, then the first drug was tapered over at least a 1-month period after the new medication was in the therapeutic range.

A patient was not considered to have started a prophylactic treatment phase until a therapeutic dose was achieved and one of the following conditions was met: (1) the patient was taking no adjuvant medication and either had switched polarity or had become euthymic for at least 2 weeks; (2) the patient was taking adjuvant medication and became euthymic for more than 2 weeks and then relapsed before the adjuvant medication was tapered; (3) the patient was taking no adjuvant medication and had been out of an affective episode of moderate or greater severity for at least 4 weeks; or (4) the patient was on effective adjunct treatment and was only mildly ill for at least 4 weeks, but withdrawal of the adjuvant medication caused worsening of symptoms. In this fashion, patients who could not achieve complete mood stabilization were retained in the trial, so that the study sample would most closely represent patients in actual clinical practice.

If a patient was unable to be stabilized on lithium or carbamazepine in addition to adjuvant treatment for at least 4 months, then the patient was considered to have a treatment failure and was moved to the next arm of the treatment trial. During the trial, adjuvant medications (not blinded) were used acutely for breakthrough episodes of mania or depression in an attempt to keep the patient in the given phase of the study. If the patient was manic with psychotic features or experienced moderate to severe dysfunction, then haloperidol or perphenazine was usually prescribed. Clonazepam or thioridazine was usually prescribed if a patient became hypomanic and insomniac. If an antidepressant was required for breakthrough depressive symptoms, nortriptyline was the treating physician's (K.D.D.) first drug of choice. If the patient did not respond to nortriptyline or had treatment-limiting side effects, then the second antidepressant was usually fluoxetine. If a patient had a past history of a good clinical response to a specific adjuvant medication, then that medication could be substituted. Patients were tapered off adjuvant antidepressants if they remained euthymic for at least 1 month or if they switched to hypomania.

A patient was considered to have relapsed if hospitalization was required or if the patient became severely incapacitated for at least several days; in either case, the patient was advanced prematurely to the next treatment phase.

Patients were usually seen and evaluated in the outpatient clinic every 2 weeks but no less than monthly. Blood medication levels were examined on at least a monthly basis as well. If the blood level suggested the possibility that the patient was not compliant, this issue was raised with the patient. Noncompliance was infrequent, presumably because patient education fostering medication compliance was performed on an ongoing basis.

Statistics

The data for treatment efficacy were analyzed with the following tests: analyses of variance with repeated measures using post hoc Bonferroni t tests, Cochran's Q test, McNemar chi-square, and generalized Wilcoxon (Breslow) test for the survival analyses. The data were analyzed for the 29 patients who were evaluable in all three treatment phases.

To examine the power of the various life history variables to predict a positive response to each treatment, logistic regression analyses were performed separately for all evaluable cases within each treatment phase (N = 42

Table 1. Entry and Completion Status for Three Treatment Phases*

	Lithium (Phase 1 or 2)		Carbamazepine (Phase 1 or 2)		Lithium and Carbamazepine (Phase 3)	
Status	N	%	N	%	N	%
Entered treatment phase[a]	50	100.0	46	100.0	31	100.0
Evaluable for prophylactic treatment response[b]	42	84.0	35	76.1	29	93.5
Completed full year of treatment	29	58.0	22	47.8	22	71.0
Stopped early due to treatment failure	13	26.0	13	28.3	7	22.6
Not evaluable for prophylactic treatment response[b]	8	16.0	11	23.9	2	6.5
Stopped early due to side effects	2	4.0	10	21.7	0	0.0
Noncompliant with treatment	1	2.0	0	0.0	1	3.2
Dropped out or moved during treatment	4	8.0	1	2.2	1	3.2
Confounding substance abuse	1	2.0	0	0.0	0	0.0

*Fifty-two patients entered the study; 33 patients completed both trials of monotherapy; 29 patients completed all three treatment phases.
[a]Patients unable to tolerate lithium or carbamazepine in Phase 1 or 2 were ineligible for the combination treatment (N = 12).
[b]Percentages are based on number of cases entering the treatment phase.

for lithium, N = 35 for carbamazepine, and N = 29 for the combined treatment). Using the SAS LOGISTIC procedure,[45] two series of logistic regression analyses were run. First, all life history variables were treated as candidate predictors, and variables were identified for which the chi-square value associated with improvement in prediction of response had a probability value of .05 or less for any of the three treatment phases. Next, each such variable was forced to enter a separate predictive model, so that the standardized estimate of the maximum likelihood parameter could be computed as an indicator of the direction and magnitude of relationship between the predictor variable and positive response for each treatment. Variables that were identified as significant predictors of good treatment response were further examined to see whether any particular cut-point, or threshold value, captured most of the predictive power of the variable.

RESULTS

Entry and Completion Studies

Although 52 patients entered the study, not all patients started each treatment phase due to dropouts and side effects on monotherapy. The number of patients who were evaluable for each prophylactic treatment phase, completed a full year, dropped out of the phase owing to a lack of efficacy, or dropped out because of side effects is shown in Table 1. Of the 2 patients who dropped out of the lithium phase because of side effects, 1 developed cystic acne and one psoriasis. Of the 10 patients who dropped out of the carbamazepine phase because of side effects, 9 developed a rash and one had a significant drop in white blood cell and platelet counts. There were no dropouts because of side effects on the combination as those who were drug-intolerant were not reexposed.

The mean ± SD plasma concentration during the lithium phase was 0.84 ± 0.13 mmol/L; during the carbamazepine phase, it was 7.67 ± 1.34 mg/L; and during the combination phase, it was 0.84 ± 0.17 mmol/L for lithium and 7.69 ± 1.29 mg/L for carbamazepine. The number of patients with two or more occurrences of low levels (for lithium, less than 0.5 mmol/L; for carbamazepine, less than 4 mg/L) was as follows: lithium, N = 7; carbamazepine, N = 1; combination phase—carbamazepine, N = 1; lithium, N = 4 (1 patient on lithium monotherapy and 1 patient on lithium in the combination phase had more than two low levels).

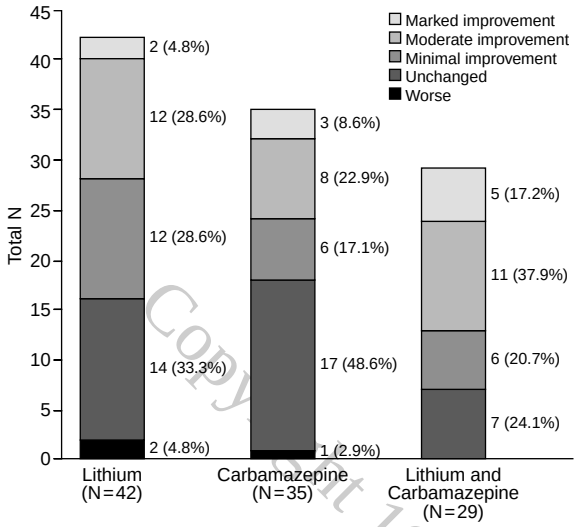
Data were recorded on patients who had an early treatment failure (dropped out of the treatment phase before 1 year owing to a lack of efficacy). While time to failure varied between the carbamazepine phase (mean = 254.6 days) and the lithium or combination phases (mean = 306.8 and 331.4 days, respectively), this survival result was not significant. In the lithium phase, 4 treatment failures were ascribed to mania and 9 to depression. In the carbamazepine phase, 7 treatment failures were ascribed to mania and 6 to depression. In the case of the combination phase, 3 failures were attributed to mania and 4 to depression. The number of patients in each treatment phase who required hospitalization due to a lack of efficacy was as follows: lithium, N = 8; carbamazepine, N = 2; combination, N = 4.

Treatment Efficacy

Clinical outcome as rated by the CGI scale for the evaluable data set is shown in Figure 1. The percentage of patients with a good treatment response (marked or moderate improvement) was comparable for the monotherapies (33.3% on lithium compared with 31.4% on carbamazepine) and was 55.2% for the patients on the combination. The differences across the three treatment phases were not significant.

There was some suggestion of differential response between the two drugs. Four patients with a poor response to lithium showed marked or moderate improvement on carbamazepine. Conversely, 4 patients with a poor response

Figure 1. Clinical Outcome as Rated by the Clinical Global Impressions Scale (Evaluable Data Set)



to carbamazepine showed a moderate or better response to lithium. Of the 15 patients who had a poor response to both monotherapies, 4 had a good treatment response on the combination. In addition, 2 patients with moderate improvement on monotherapy showed a marked improvement on the combination, yielding a total of 6 of 16 patients showing a distinct benefit from combination treatment compared with either monotherapy.

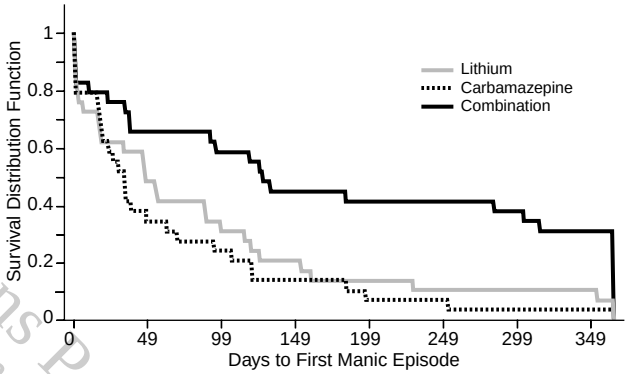
The mean percentage of time ill for the 29 patients evaluable in all three treatment phases is shown in Table 2. The percentage of time ill for the different mood states across the three treatment phases differed for the duration of mania ($F = 7.41$, $df = 2,56$; $p < .01$), but not for depression or total time euthymic. Post hoc analyses showed significantly less percentage of time manic during the lithium and the combination treatment phases compared with the carbamazepine treatment phase. Moreover, the number of patients who experienced no mania in each phase was as follows: lithium, N = 3 (11.1%); carbamazepine, N = 1 (3.7%); combination, N = 9 (33.3%). This was significantly different across the three drug phases (Cochran's $Q = 11.56$, $df = 2$, $p < .01$).

The average severity of illness for the 29 patients is shown in Table 3. No significant difference was found in the average severity across the three drug phases. However, when separated by polarity, the average severity of mania was found to differ significantly across the three drug states. The post hoc analyses demonstrated less average severity of mania while patients were on lithium treatment or the combination compared with carbamazepine. The number of total episodes was significantly fewer in the combination phase compared with the carbamazepine and lithium phases. The number of manic episodes was significantly fewer in the combination phase compared

Table 2. Percentage of Time Ill for 29 Patients Who Were Evaluable in the Three Treatment Phases

	Retrospective Year		Lithium		Carbamazepine		Lithium and Carbamazepine	
Illness State	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Euthymia	42.7	26.9	60.3	25.9	54.7	28.5	62.5	27.7
Mania								
Mild	11.4	15.8	8.3	6.5	13.3	12.1	6.8	7.7
Moderate	7.2	10.1	0.5	1.0	5.4	10.5	1.5	4.1
Severe	6.5	9.6	0.2	0.9	0.3	0.8	0.1	0.3
Total	25.1	20.3	9.1	6.8	19.0	19.5	8.4	10.6
Depression								
Mild	14.6	15.8	18.2	14.8	17.0	14.3	18.6	18.1
Moderate	14.5	18.5	10.9	16.0	8.3	11.0	9.4	14.2
Severe	3.1	6.5	1.5	4.5	0.9	2.1	1.2	3.5
Total	32.2	25.1	30.6	25.3	26.3	22.8	29.1	27.5

Figure 2. Mean Survival Time to First Manic Episode Was Greater on the Combination of Lithium and Carbamazepine Compared With Either Monotherapy (N = 29)*



*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): $\chi^2 = 7.50$, $df = 2$, $p = .024$.

with the carbamazepine phase. Using survival analysis, a significant difference was found for the number of days to the first manic episode (Figure 2). Other mean ratings were not significantly different across the three phases (Table 3).

The number of patients requiring adjunctive medication and the mean and median percentage of time on adjunctive medication are shown in Table 4. No significant difference was found in the number of patients or the percentage of time on adjuncts across the three treatment phases. We also examined the use of adjunctive medication during the three drug-treatment phases for CGI responders compared with the nonresponders to see if adjunct medications could account for differences in efficacy. Compared with responders, the nonresponders were more likely to have received adjunctive medication when on lithium (Fisher's exact test, $p < .05$) or on the combination therapy (Fisher's exact test, $p < .01$), but not on carbamazepine treatment. Since nonresponders tended to receive more antidepressants and neuroleptics/benzodiazepines and to continue

Table 3. Summary Outcome Variables for the 29 Patients Evaluable for Prophylactic Treatment Response*

Outcome	Lithium Mean	Lithium SD	Carbamazepine Mean	Carbamazepine SD	Lithium and Carbamazapine Mean	Lithium and Carbamazapine SD	ANOVA With Repeated Measures F (df = 2,56)	p
Average severity								
Mania	0.26	0.19	0.63	0.74	0.25	0.36	7.55	.004
Depression	1.15	1.12	0.93	0.89	1.05	1.17	1.17	.315
Total	1.41	1.14	1.57	1.08	1.30	1.18	1.44	.246
Number of episodes/year								
Mania	3.66	2.93	4.55	3.69	2.90	3.40	3.37	.041
Depression	2.59	3.57	2.16	3.31	1.74	2.18	1.23	.297
Total	6.25	5.04	6.71	6.06	4.64	4.26	3.27	.045
Depression rating scales (range)								
HAM-D (0–64)	7.1	4.6	7.8	4.6	7.1	4.1	0.78	.426
RSDM (depression) (3–15)	4.7	1.4	4.9	1.5	5.0	1.4	1.03	.347
BDI (0–63)	6.9	5.2	7.2	4.8	7.2	5.1	0.09	.889
Mania rating scales (range)								
YMRS (0–60)	3.3	2.3	5.2	4.8	4.4	2.5	3.12	.067
RSDM (mania) (3–15)	3.8	0.7	4.3	1.5	3.9	0.7	2.43	.119
Anxiety rating scale (range)								
STAI (20–80)	40.2	9.5	40.3	10.1	41.1	9.9	0.31	.678

*Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, RSDM = Raskin Severity of Depression and Mania scale, STAI = Spielberger State-Trait Anxiety Inventory, YMRS = Young Mania Rating Scale.

Table 4. Patients Requiring Adjunct Medications and Time on Medications During the Drug Treatment Phases (Evaluable Data Set)

Variable	Lithium (N = 42)	Carbamazepine (N = 35)	Lithium and Carbamazepine (N = 29)
Any adjunctive medication, N (%)	31 (73.8)	27 (77.1)	21 (72.4)
Antidepressants, N (%)	19 (45.2)	13 (37.1)	9 (31.0)
Percentage of time in each phase (mean ± SD)	47.2 ± 23.4	44.5 ± 37.7	54.7 ± 35.2
Median percentage	45.4	26.6	60.3
Neuroleptics/benzodiazepines, N (%)	23 (54.8)	22 (62.9)	16 (55.2)
Percentage of time in each phase (mean ± SD)	20.9 ± 30.5	27.9 ± 24.1	22.5 ± 31.9
Median percentage	12.5	20.6	7.8

taking them for a longer period of time, these data suggest that differential use of adjuncts did not lead to the better prophylactic antimanic response on lithium or the combination compared with carbamazepine.

We also analyzed the percentage of time ill and the average severity of illness in the three prospectively rated treatment phases and the retrospective year most representative of the patient's illness (prior to the patient's taking a mood-stabilizing medication or the worst year on ineffective medications) (Table 2). The percentage of time manic was found to differ significantly across the four phases ($F = 10.26$, $df = 3,84$; $p < .001$), and the post hoc analyses showed more time manic in the retrospective year compared with all three prospectively rated treatment phases. The percentage of time euthymic also differed significantly across the four phases ($F = 6.67$, $df = 3,84$; $p < .01$), and the post hoc analyses showed more time euthymic in the lithium, carbamazepine, and combination phases compared with the retrospective year. No significant reduction was found for the percentage of time depressed across the four phases.

The average severity was found to differ significantly across the four phases ($F = 16.88$, $df = 3,84$; $p < .001$). The post hoc analyses showed significantly less average severity of illness for each of the three prospective treatment phases compared with the retrospective year. The average severity for mania was found to differ significantly across the four phases ($F = 19.80$, $df = 3,84$; $p < .001$), and the post hoc analyses demonstrated significantly less average severity for mania in all three treatment phases compared with the retrospective year. Again, no significant difference was found for the average severity for depression across the four phases.

Correlates of Response

Logistic regression analysis suggested that a positive response to lithium was associated with a constellation of variables, including being younger at the time of study entry (mean ± SD age for responders = 35.7 ± 13.1 years, for nonresponders = 44.5 ± 10.7 years; $p < .05$), having a first treatment by age 20 or earlier ($p < .01$), and having had fewer years elapse since the onset of the first bipolar symptoms (responders = 15.2 ± 8.0 years, nonresponders = 23.9 ± 13.3 years; $p < .05$). In addition, having no more than one lifetime hospitalization for mania ($p < .05$) and having manifested the first bipolar symptoms with depression rather than mania ($p = .05$) were significant predictors of a positive response to lithium.

A poor response to carbamazepine was associated with having more than 10 years elapse between the onset of the first bipolar symptoms and entry into the study and a past

history of rapid cycling (4 [19.0%] of 21 rapid cyclers responded, 7 [53.8%] of 13 non–rapid cyclers responded [$p < .05$]). Rapid-cycling patients also responded better on the combination therapy (9 [56.3%] of 16) than on either monotherapy (7 [28.0%] of 25 for lithium and 19.0% for carbamazepine [Cochran's $Q = 7.00$, $df = 2$, $p < .05$]). Four of the 9 rapid-cycling patients who responded to the combination did not respond to either monotherapy.

Prior course of illness variables reflecting less severity of illness predicted good response to the combination of lithium and carbamazepine. A greater number of hospitalizations for mania predicted a poor response to the combination (mean ± SD hospitalizations for responders = 1.4 ± 2.0, for nonresponders = 3.6 ± 2.8; $p < .05$). In fact, having had more than one hospitalization for mania was associated with a poor response to the combination ($p < .05$). A greater mean number of weeks hospitalized per year (mean ± SD weeks for responders = 0.88 ± 0.85, for nonresponders = 2.84 ± 2.77; $p < .05$) predicted a poor response to the combination. The following list of pertinent demographic and course of illness variables did not significantly contribute to the prediction of a positive response to the three treatments: gender, marital status, education, diagnosis (bipolar I compared with bipolar II), age at onset, number of times hospitalized for depression, and number of depressed, manic, or total episodes.

The previous lithium response (assessed retrospectively from the life chart) did not strongly predict the response in any of the prospective treatment phases. A prospectively observed good treatment response on one monotherapy phase did not predict a good treatment response on the other monotherapy phase. The treatment response during the first treatment phase (lithium or carbamazepine) did not predict the treatment response during the second treatment phase.

During the monotherapy treatment phases, the blood level of lithium and carbamazepine was not associated with treatment response. In the combination phase, the lithium level (0.76 ± 0.14 mmol/L) for responders was lower than in nonresponders (0.93 ± 0.16 mmol/L; $t = 2.94$, $df = 23.80$, $p < .01$); there was no difference for the carbamazepine level, however.

The weight at the end of the lithium compared with the carbamazepine treatment phase was significantly higher for 30 patients evaluable in both phases: (mean end weight on lithium = 185.4 ± 43.5 lb; on carbamazepine = 182.0 ± 38.5 lb; paired t test = 2.24, $df = 27$, $p < .05$).

DISCUSSION

The results obtained in this clinical trial suggest that lithium is more effective than carbamazepine in the prophylaxis of mania but not depression, and that the combination of lithium and carbamazepine is better than either monotherapy in several respects. However, the results were obtained in many patients who were not naive to these drugs, so they are potentially susceptible to selection bias. When on lithium compared with carbamazepine therapy, the patients experienced significantly less time manic, a significantly lower average severity for mania, and fewer manic episodes per year. These findings are similar to the results in the study completed by Watkins et al.[4] who found that lithium was more effective than carbamazepine in the maintenance of bipolar illness. Patients spent nonsignificantly less time depressed and had lower average severity for depression when on carbamazepine than on lithium therapy, similar to the study of Lusznat et al.[6] None of our analyses looking at total illness (combining mania and depression) when patients were administered lithium compared with carbamazepine showed any significant difference. In this respect, our trial is consistent with several previous studies[5,22,46] reporting a lack of difference between the two drugs.

Evidence suggesting an increased efficacy on the combination includes the findings that rapid cyclers did better on the combination compared with either monotherapy, a higher percentage of patients succeeded in finishing the treatment phase, a higher percentage of patients on the combination rated as responders on the CGI scale, and a significantly higher number of patients experienced no mania during the combination phase. In addition, patients experienced significantly fewer total number of episodes on the combination compared with lithium therapy, and the mean number of days to the first manic episode was significantly higher during the combination phase (Figure 2). Having the combination phase occur in Year 3 may have biased the data, but it is unclear in which direction. Some dropouts may have been treatment resistant, thus leaving a more responsive group to survive in the third phase. However, of the 21 patients who did not enter the combination phase, 12 were ineligible due to side effects to either lithium or carbamazepine and 4 moved from the geographic area.

Patients appeared to experience less mania in all three of the prospectively assessed treatment phases compared with the retrospective year most representative of their illness. This finding is especially important considering the tendency for untreated affective illness to show a pattern of illness progression.[2] Although comparing retrospective and prospective data raises methodological issues, one would expect that more illness would be detected in the prospective phase since it was intensively monitored and charted (on a daily basis). In addition, patients might be less likely to recall or report manic periods retrospectively. The finding that the prospective phases were not significantly better than the retrospective year in terms of depression plus the large degree of depression remaining during the prospective phases highlights the greater dif-

ficulty in treating the depressed versus manic phases of bipolar illness. This diminished impact of treatment on bipolar depression occurred despite use of adjunctive antidepressants as needed. Although the use of adjuncts may have clouded some of the interpretations of this study, the design more closely follows clinical practice and may have helped allow patients to stay in this extended, 3-year outpatient study with a low dropout rate.

Ten patients dropped out of the carbamazepine phase because of side effects compared with only 2 in the lithium phase. Twenty percent (9 of 45) of the patients had a rash while on carbamazepine treatment. This percentage is much higher than the frequently cited figure of 3% for carbamazepine-produced rash[47] and somewhat higher than the 12% incidence of rash observed in our clinical experience in the treatment of inpatients at the National Institute of Mental Health.[48]

Although the patients did better in the prospective phases compared with the pretreatment or most representative retrospective year, the amount of morbidity was still very high. The substantial morbidity and low response rates found despite vigorous pharmacologic treatment with lithium or carbamazepine with adjunctive treatment as necessary are consistent with previous studies demonstrating high rates of lithium[3–9,14–17] and carbamazepine prophylaxis failures.[22,23] While there was a high percentage of rapid cyclers in our sample, we attempted to recruit and study a representative spectrum of bipolar outpatients, and this was reflected in the low total disability rate: 92.3% were working, going to school, or were retired. The patient recruitment and selection process was derived from those who were already being treated on an outpatient basis (with one exception) and was not based on an index hospitalization. On the other hand, 21 (56.8%) of 37 patients with a previous evaluable trial of lithium were rated as having a poor response to lithium prior to entering the study, which may have contributed to the low response rate.

Overall, the patients were compliant in taking their medication, and they achieved what most consider to be therapeutic blood levels. The mean level in this study for carbamazepine was 7.7 mg/L, which is comparable to the mean serum carbamazepine level (7.2 ± 2.7 mg/L) for good responders in the study by Okuma et al.[49] The finding that the mean plasma level of carbamazepine was not significantly different in responders compared with nonresponders agrees with an earlier study by our group[50] that found that carbamazepine levels in plasma or CSF were not related to the degree of acute antidepressant or antimanic response and with the study by Simhandl et al.[46] that found no difference in efficacy on high versus low plasma level of carbamazepine for bipolar patients. The mean plasma level for lithium of 0.84 mmol/L is within the standard range of levels that Gelenberg et al.[51] found to be more effective in treating bipolar disorder than those with a lower serum lithium concentration (0.4 to 0.6 mmol/L).

The finding that a past history of rapid cycling predicted carbamazepine nonresponse is consistent with the results of Okuma[28] and the report by Joyce[52] who found that among 18 rapid-cycling patients only 4 had a marked response to carbamazepine. Our study also identified preliminary evidence of clinical markers of positive treatment response; lithium-responsive patients compared with nonresponsive patients had no more than one prior hospitalization for mania, a shorter duration of illness, and a younger age at study entry. Responders to the combination also had a history of fewer prior hospitalizations for mania and shorter durations of hospitalization.

In conclusion, the results suggest that (1) lithium and carbamazepine have a roughly equal but less than adequate prophylactic efficacy in overall bipolar illness; (2) lithium is superior to carbamazepine in the prophylaxis of mania; and (3) the combination of lithium and carbamazepine is better than either monotherapy, especially in rapid cyclers. Further, despite the use of adjunctive antidepressants, none of the treatments were found to have a significant impact on depression. The uniformity of relatively poor response in rapid-cycling patients on monotherapy with either lithium or carbamazepine in this study and in the literature[28,52,53] and the findings of better response on the combination (this study and reference 54) suggest that one might consider combination treatment in rapid-cycling patients from the outset or in those who fail lithium monotherapy. However, even with the combination of carbamazepine and lithium and the use of adjunctive antidepressant and antimanic treatment as necessary, substantial illness-related morbidity remained in this highly motivated and highly functional outpatient bipolar population. These data further highlight the need for exploration of new effective treatment options such as gabapentin, lamotrigine, or other combinations for the long-term prophylaxis of bipolar illness, particularly in the large percentage of patients who are poorly responsive to the more standard agents.

Drug names: carbamazepine (Tegretol and others), clonazepam (Klonopin), fluoxetine (Prozac), haloperidol (Haldol and others), nortriptyline (Pamelor and others), perphenazine (Trilafon), thioridazine (Mellaril and others).

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