Prophylactic Efficacy of Lithium Versus Carbamazepine in Treatment-Naive Bipolar Patients

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Background: Alternatives to lithium for prophylactic treatment of patients with bipolar affective disorders are increasingly being advocated. However, trials comparing lithium with alternatives are scarce and often biased.

Method: We studied 94 patients with at least 2 episodes of bipolar disorder (DSM-III-R) during the previous 3 years who were in remission at entry into the study. Treatment with lithium or carbamazepine had not exceeded a total of 6 months during their lifetime. Patients were randomly assigned to carbamazepine or lithium at entry into the 2-year double-blind study or during the acute index episode previous to entry into the study. No concurrent antipsychotics or antidepressants were allowed.

Results: On lithium treatment, 12/44 patients developed an episode, compared with 21/50 on carbamazepine treatment. Episodes on lithium treatment occurred almost exclusively during the first 3 months of the trial. Carbamazepine carried a constant risk of an episode of about 40% per year. Efficacy of lithium was superior to that of carbamazepine in patients with a (hypo)manic index episode that had not been treated with study drug during the index episode ($p < .01$) and also in patients with prior hypomanic but no manic episodes ($p < .05$). The proportion of patients who dropped out was slightly higher among those taking lithium (16/44) compared with those taking carbamazepine (13/50), resulting in 16/44 patients (36%) on lithium treatment completing the 2 years with no episode, compared with 16/50 (32%) on carbamazepine treatment.

Conclusion: Lithium appears to be superior in prophylactic efficacy to carbamazepine in bipolar patients not previously treated with mood stabilizers. Our results should reinforce efforts to put and maintain such patients on treatment with lithium.

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Lithium is still considered the first choice in the prevention of episodes in patients with bipolar disorder,[1,2] although efficacy in clinical practice may be less impressive than anticipated from clinical trials.[3] For that reason, alternative treatments are increasingly being advocated.[4] Trials comparing lithium with alternatives are scarce and often preclude an unbiased estimate of the prophylactic efficacy of the 2 drugs because of the inclusion of nonresponders to lithium, the inclusion of patients with diagnoses other than bipolar disorder, and the use of concurrent medications.[5,6] We compared the prophylactic efficacy of lithium and carbamazepine in a 2-year randomized, double-blind trial. To avoid selection bias, only bipolar patients not previously treated prophylactically with either study drug were included, and the study was conducted mainly in normal treatment settings for bipolar patients; also, no significant comedications were allowed.

METHOD

The protocol was approved by the Ethics Committee of the University Medical Center of Leiden (Leiden, the Netherlands) and by ethical review boards of the participating centers and was performed in accordance with the Declaration of Helsinki, 1964, as amended in Tokyo, Japan, 1975; Venice, Italy, 1983; and Hong Kong, 1989.

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Subjects

Patients with bipolar disorder who had at least 2 episodes (symptomatic periods of bipolar disorder: mania, depression, mixed, atypical, psychotic mania, melancholic depression, psychotic depression, etc.) during the previous 3 years, were at least 18 years of age, and spoke Dutch were included at 18 outpatient clinics in the Netherlands. Recruitment of patients with either bipolar or schizoaffective disorder was provided for in the protocol, but since only 6 schizoaffective patients entered the trial, this report is restricted to bipolar patients. At baseline, diagnoses of all patients were assessed by both the local investigator/treating psychiatrist and the central investigator (E.G.Th.M.H.) according to DSM-III-R criteria. Since all patients with bipolar disorder not otherwise specified according to DSM-III-R had an episode history with hypomania but no mania, they were marked as bipolar II, which also corresponds with the current DSM-IV terminology. The central investigator administered the Comprehensive Psychiatric Rating Scale,[7] the Bech Rafaelsen Mania Scale (BRMAS),[8] and the Bech Rafaelsen Melancholia Scale (BRMES)[8] to all patients. At entry into the study, patients were recovered from their last episode, i.e., they did not meet DSM-III-R criteria for a (hypo)manic or major depressive episode. Moreover, they did not receive antidepressants, antipsychotics (depot antipsychotics for the previous 2 months), or benzodiazepines (above allowed dosages, see Treatment). If they had ever received treatment with lithium or carbamazepine, the total of these treatment periods during their lifetime did not exceed 6 months. It is noted that at the time of the study, both drugs were used in the Netherlands mostly for prophylaxis and use for the acute treatment of episodes was rare. Additional exclusion criteria were contraindications for either study medication, clinically significant deviant laboratory values at entry, nonpsychiatric medications that could interfere with the study medication, and pregnant women or women not using proper contraceptive arrangements. Written informed consent was obtained from each patient.

A total of 150 evaluable patients were estimated to be necessary to detect a 20% lower relapse rate on carbamazepine at a relapse rate of 30% for lithium. The sensitivity to detect differences with the survival analyses actually applied was not calculated a priori.

Randomization

Patients were randomly assigned to study medication either at the start of the prophylactic treatment phase, i.e., at actual entry into the study ("prophylactically randomized"), or during an acute episode of (hypo)mania or depression ("acutely randomized"). This was done to comply with the customary strategies of clinicians, who often tend to start with mood stabilizers in patients for whom need of prophylactic treatment is anticipated. In addition, this randomization procedure aimed at avoiding bias from switches from open treatment with a mood stabilizer during the acute phase to a potentially different study drug during the prophylactic phase. These acutely randomized patients entered the actual prophylactic study at a later point in time, i.e., after recovery from the acute episode; after psychotropic medications were stopped, with the exception of the double-blind study medication; and after inclusion and exclusion criteria had been checked again. The restriction of the previous lifetime treatment with lithium or carbamazepine to a total of 6 months included this treatment with double-blind medication during the acute episode prior to entry into the study.

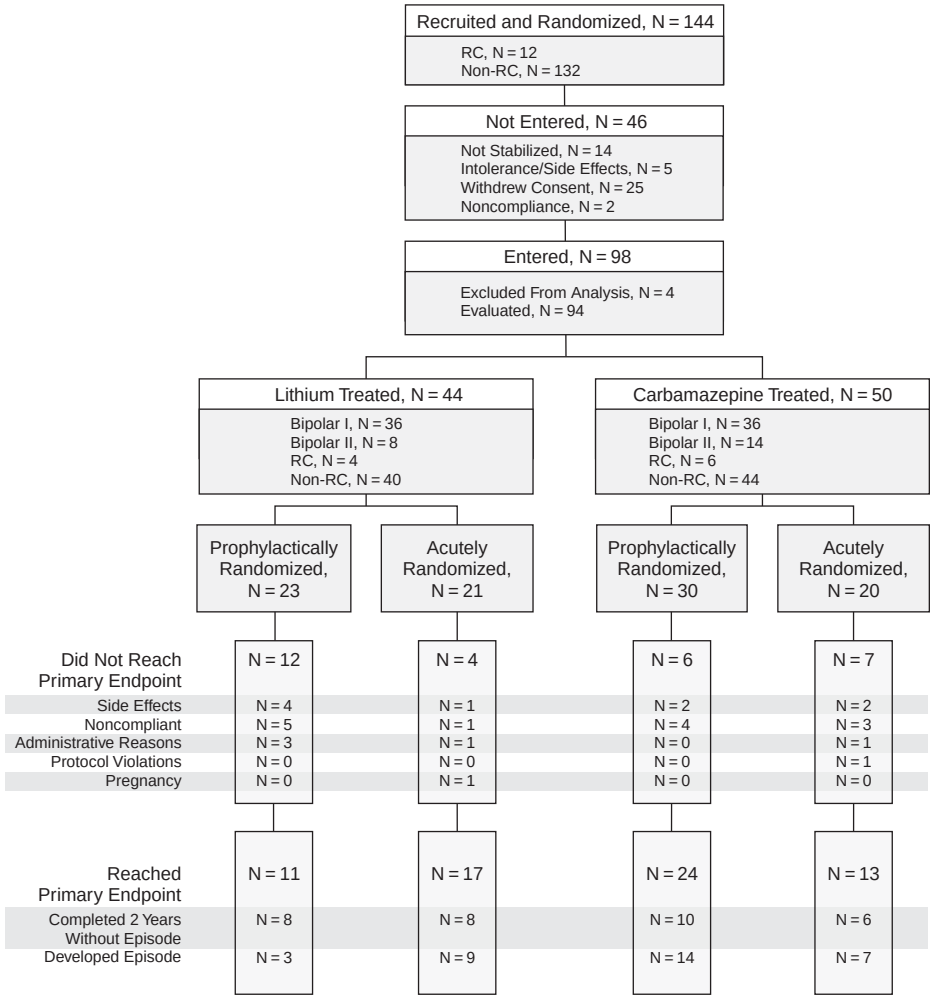
Treatment

Study medication was dispensed by the central pharmacy to local pharmacies for further delivery to patients. Randomization was executed by the central pharmacy on the basis of a list with blocks of 4 or 6. Double dummies were used, and 1 tablet of 400 mg of lithium carbonate or its placebo and 1 tablet of 200 mg of carbamazepine or its placebo were administered in the evening, to be increased after 1 week to 2 tablets each. A week later, 12-hour blood levels were assayed and the dose was adjusted to obtain blood levels between 0.6 and 1.0 mmol/L for lithium and between 6 and 10 mg/L for carbamazepine. Blood drug levels were assayed weekly during the first month, and the frequency declined to once every 3 months after 6 months of treatment. Blood levels of carbamazepine were mainly determined to preserve the double blind with lithium, for which blood drug level assays are mandatory. Blood drug levels were reported to the local investigator for the purpose of dose adjustments as "X units/L," being either 0.X mmol/L of lithium or X mg/L of carbamazepine. The local investigator adjusted the dose to obtain blood levels between 6 and 10 units/L, thus preserving the double blind. At the central pharmacy and the local laboratory and/or pharmacy, envelopes with the double-blind code were available for cases of emergency. The double blind was preserved until all patients had completed the trial. Before that time, treatment of individual patients after completion of the trial was either continued on a double-blind basis or treatment with mood stabilizers was open without breaking the code. Other psychotropic drugs were not allowed during the trial except for benzodiazepines at doses equivalent to a maximum of 50 mg/day of oxazepam. At times of impending relapse, doses equivalent to a maximum of 100 mg/day of oxazepam were allowed for no more than 14 days. Medications for somatic diseases were allowed if the medication was judged not to interfere with the study.

Assessments

Regular monthly visits were scheduled with the local investigator, and 6-month visits, with the central investigator. The primary outcome measure was the recurrence

Figure 1. Trial Profile



Abbreviation: RC = rapid cycling.

of an episode of (hypo)mania or major depression according to DSM-III-R criteria as assessed by the local investigator either during the monthly visits or as observed unscheduled. In case of an episode, the central investigator interviewed the patient as soon as possible to confirm the presence of an episode. A 4-point scale for untoward clinical events (adverse effects) was completed by the local investigator at baseline, 2 weeks, and 2, 6, 12, 18, and 24 months. An adverse effect was counted as present if it (1) occurred after the first 2 weeks, (2) was reported at least once during the treatment period, and (3) was at least of moderate severity.

Statistical Analyses

Survival curves were used, and Kaplan-Meier analysis was intended for comparison of the lithium- and carbamazepine-treated groups. Since the proportional hazards assumption did not hold for the lithium treatment group, analysis of subgroups was performed, and Cox regression analysis[9] was applied to estimate differences in survival between the 2 treatments, with time entered as group. Additional variables were selected in a backward stepwise procedure using Wald statistics. Endpoints were (1) completion of the 2-year treatment period without an episode, (2) an episode, (3) treatment-unrelated dropout (administrative reasons, protocol violation, pregnancy), and (4) other dropout, possibly treatment related (adverse effects, noncompliance). Two analyses were performed, 1 with an episode as a terminal event and all cases of dropout censored, and 1 with an episode and treatment-related dropout as a terminal event and only treatment-unrelated dropout censored.

RESULTS

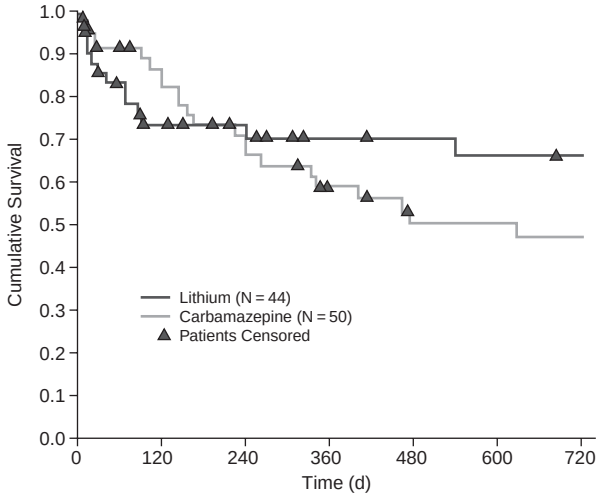
Patients were recruited beginning in 1989, and the last patient evaluation was in 1996. Of the 144 patients who were recruited, 46 acutely randomized patients did not

Table 1. Patient Characteristics

Characteristic	Value
Female, %	54.3
Age, mean (SD), y	41.89 (13.92)
Age at onset, mean (SD), y[a]	31.57 (11.24)
Years from first episode, mean (SD)[a]	9.2 (9.7)
No. of prior episodes, median (range)[b]	5 (2–19)
No manias (bipolar II diagnosis in DSM-IV), N (%)	22 (23.4)
Marital status, N (%)	
Married	52 (55.3)
Divorced	9 (9.6)
Widowed	2 (2.1)
Never married	31 (33.0)
Rating scale total scores, mean (SD)	
BRMAS	1.80 (2.62)
BRMES	5.23 (4.51)
CPRS[c]	18.21 (13.24)

[a]N = 81.
[b]N = 62.
[c]N = 86.
Abbreviations: BRMAS = Bech Rafaelsen Mania Scale, BRMES = Bech Rafaelsen Melancholia Scale, CPRS = Comprehensive Psychiatric Rating Scale.

Figure 2. Cumulative Survival on Carbamazepine or Lithium Treatment With Episodes as Terminal Events



enter the study (Figure 1). Of the 98 patients entered, 3 were excluded from analyses because post hoc inclusion criteria were found not to be met, and 1 was excluded because of missing essential baseline data. Thus, 94 patients were available for analysis. No statistically significant imbalances in general demographic characteristics between the groups were found (Table 1). Data were missing for some of these variables due to imprecision of patients' recall or to inability to make clear distinctions between episodes.

The mean ± SD blood drug levels for the treatment period (excluding the samples at week 1) were 6.8 ± 1.2 mg/L for carbamazepine (N = 49) and 0.75 ± 0.18 mmol/L for lithium (N = 41). Blood carbamazepine levels were not in the predefined range within 30 days in 16 cases and within 60 days in 13 cases. For lithium, these figures were 6 cases and 2 cases, respectively. The mean blood drug levels per patient for the entire treatment period were not in the predefined range for 8 patients taking carbamazepine and for 3 patients taking lithium.

Study Outcomes

During the 2-year study period, 12/44 patients (27%) on lithium treatment and 21/50 patients (42%) on carbamazepine treatment developed an episode. The survival curves with episodes as the terminal event suggest different outcomes for lithium and carbamazepine (Figure 2). However, it is apparent that almost all episodes on lithium treatment occurred during the first 3 months, while episodes on carbamazepine treatment were more evenly distributed over the 2-year study period (see Figure 2). Analysis of the hazard function showed a cumulative hazard for lithium of about 0.3 at 100 days with no further increase, which means that the proportional hazard assumption does not hold. Therefore, instead of the intended Kaplan-Meier analysis, a more detailed analysis was performed that differentiated between acutely randomized and prophylactically randomized patients. In terms of episode ratios, only 3/23 prophylactically randomized patients had an episode on lithium treatment compared with 9/21 acutely randomized patients. In contrast, ratios for carbamazepine were 14/30 and 7/20, respectively. In Figure 3, the same differences are illustrated in terms of survival with episodes as the terminal events. From Figure 3, the differences in survival between lithium and carbamazepine in relation to patients being acutely randomized or prophylactically randomized are apparent, as is the difference in survival between patients treated with lithium and being acutely randomized or prophylactically randomized. Subsequently, a Cox regression analysis was performed with treatment (lithium or carbamazepine), randomization status, time, and all second-order and third-order interactions as covariates. The result of the backward stepwise procedure shows no main effects and the following significant interaction effects (Table 2). The significant randomization-by-group interaction indicates a difference in efficacy between lithium and carbamazepine across the groups of acutely randomized patients compared with prophylactically randomized patients. The time-by-group interaction indicates a difference in efficacy between lithium and carbamazepine that is different at the beginning of the 2-year trial period compared with the end of this period. The third-order randomization-by-time-by-group interaction indicates that this difference between lithium and carbamazepine over the trial period is, additionally, different between the groups of acutely randomized patients compared with prophylactically randomized patients. Although the interaction of time by group was not significant ($p = .06$), it was not removed, because this resulted in a significant loss in variance ex-

Figure 3. Cumulative Survival on Carbamazepine or Lithium Treatment According to Randomization Status With Episodes as Terminal Events

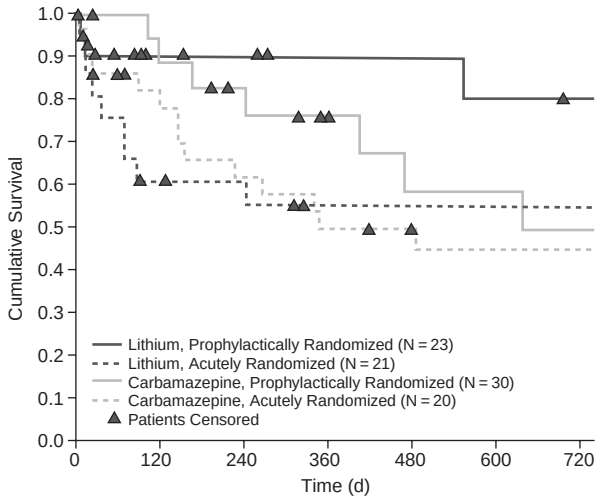


Figure 4. Cumulative Survival on Carbamazepine or Lithium Treatment According to Randomization Status With Episodes and Treatment-Related Dropout as Terminal Events

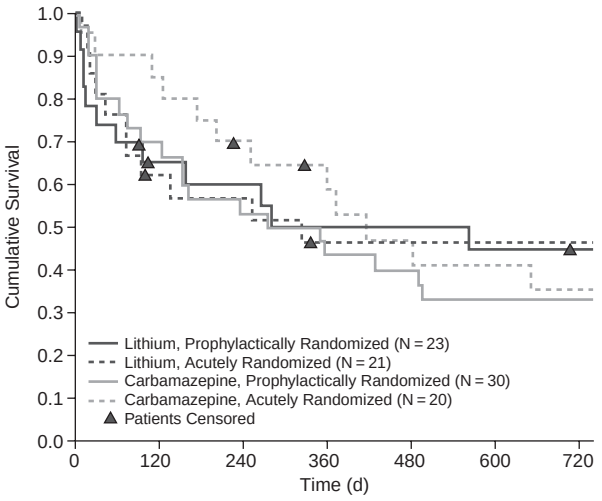


Table 2. Results of the Backward Stepwise Cox Regression Analysis With Episodes as Terminal Events[a]

Analysis	β	SE	Wald χ^2	p Value[b]
Randomization by group	0.80	0.32	6.42	.01
Time by group	–0.0018	0.0009	3.58	.06
Randomization by time by group	–0.0025	0.0012	4.42	.04

[a]Patients were randomized acutely (during an episode of [hypo]mania or depression) or prophylactically (at the time of actual entry into the study). Groups received carbamazepine or lithium.
[b]df = 1.

plained ($\chi^2 = 4.8$, df = 1, p = .03). It is apparent from Figures 2 and 3 that carbamazepine carries a proportional risk of an episode of about 40% per year, while the risk of an episode on lithium treatment is larger in acutely randomized patients as compared with prophylactically randomized patients and is larger early in the 2-year study period (Figures 2 and 3).

If, in addition to an episode, treatment-related dropout was counted as a failure, much of the difference between lithium and carbamazepine and between the 2 randomization groups taking lithium vanished, since, especially in the prophylactically randomized lithium group, many patients dropped out due to adverse effects or refusal to comply (Figures 1 and 4).

Several possible explanations for the observation that episodes on lithium treatment occurred mainly shortly after entry into the study were evaluated. The most obvious explanation would be a relapse of the index episode, in which case the episode would be expected to be of the same polarity as the index episode. However, episodes in acutely randomized patients on lithium treatment were not more often of the same polarity as the index episode than those in prophylactically randomized patients on lithium treatment or those in acutely randomized patients on carbamazepine treatment (Table 3). The data do suggest that lithium may be more effective than carbamazepine in prophylactically randomized patients with a (hypo)manic index episode, since none of the 12 patients taking lithium developed an episode, compared with 8 of 13 taking carbamazepine (p < .01, Fisher test).

Severity of residual symptomatology at entry could also be related to early episodes. However, acutely randomized patients with a depressive index episode had a mean ± SD score on the BRMES of 6.4 ± 5.3 (N = 23) at baseline compared with 5.7 ± 4.0 (N = 28) in prophylactically randomized patients. Acutely randomized patients with a (hypo)manic index episode had a mean BRMAS score of 0.8 ± 0.8 (N = 18) at baseline, compared with 2.6 ± 3.8 (N = 24) in prophylactically randomized patients. Therefore, acutely randomized patients were not more symptomatic at study entry than prophylactically randomized patients. Rapid cycling does not appear to be of importance either, because a total of only 10 patients (4 on lithium treatment, 6 on carbamazepine treatment) met criteria for rapid cycling. Of these patients, only 1 (on carbamazepine treatment) had an episode within the first 90 days. The data are suggestive of a difference between lithium and carbamazepine in bipolar II patients, since none of the 8 patients with bipolar II disorder had an episode on lithium treatment, compared with 7/14 on carbamazepine treatment (p < .05, Fisher test). However, only 3 bipolar II patients in each treatment group were acutely randomized, and bipolar II patients were unequally distributed between treatments (8 on lithium treatment, 14

Table 3. Relation Between the Index Episode and Outcome Episode (during prophylactic treatment) for the Lithium Treatment Group and the Carbamazepine Treatment Group According to Randomization Status

	Outcome					
	Lithium[a]			Carbamazepine		
Randomization Group	None	(Hypo)manic	Depressed	None	(Hypo)manic	Depressed
Acutely randomized						
(Hypo)manic index episode	5	2	2	6	3	0
Depressed index episode	6	1	3	7	2	2
Prophylactically randomized						
(Hypo)manic index episode	12	0	0	5	4	4
Depressed index episode	7	1	2	11	1	5

[a]One patient's index episode data were missing, and 2 patients had mixed index episodes (1 developed an episode [depressed], 1 did not develop an episode).

on carbamazepine treatment). Other patient variables such as age, age at first episode, and illness duration did not appear to have explanatory power. There was some indication that the number of previous episodes was positively correlated with relapses, but data from only 61 patients were available, and information bias could have affected this result, because data were missing due to inability to make clear distinctions between episodes.

Tolerability

Adverse effects were recorded as the reason for discontinuation of treatment in a total of 9 patients; 5 on lithium treatment and 4 on carbamazepine treatment. The adverse effects involved with lithium were psoriasis (N = 1), ataxia (N = 1), severe sleep disturbance (N = 1), problems with contraception (N = 1), and unknown (N = 1), and with carbamazepine, rash (N = 2), weight loss and decreased sodium levels (N = 1), and severe general malaise with increased γ-glutamyltransferase level (N = 1).

The following adverse effects had a difference in incidence of at least 10% in the 88 patients still in the trial 2 weeks after study entry. Most adverse effects occurred more often in lithium-treated patients than in carbamazepine-treated patients: blurred vision, 11/42 (26%) on lithium and 5/46 (11%) on carbamazepine; difficulties concentrating: 19/42 (45%) on lithium and 15/46 (33%) on carbamazepine; feeling thirsty: 17/42 (41%) on lithium and 10/46 (22%) on carbamazepine; decreased appetite: 9/42 (21%) on lithium and 4/46 (9%) on carbamazepine; hand tremor: 13/42 (31%) on lithium and 2/46 (4%) on carbamazepine; and muscular weakness: 6/42 (14%) on lithium and 2/46 (4%) on carbamazepine, respectively. Only increased appetite occurred more often with carbamazepine than with lithium: carbamazepine, 15/46 (33%); lithium, 7/42 (17%).

DISCUSSION

The results indicate significant differences between lithium and carbamazepine that can be summarized as follows. Prophylactic treatment with carbamazepine resulted in a constant risk of an episode of about 40% per year during the 2-year trial period. The risk with lithium treatment is more complex. In prophylactically randomized patients, lithium was very effective, with few patients experiencing an episode during the 2-year study. On the other hand, the efficacy of lithium was poor in the first 3 months in acutely randomized patients, that is, in patients who had started lithium during an acute episode and had entered the study after remission of the episode and after stopping possible concurrent psychotropic medication. About 40% of these patients experienced an episode within the first 3 months. However, for patients surviving this period, lithium was very effective, with few patients experiencing an episode.

What can explain these differences in efficacy of lithium? The subdivision of the sample into "acutely randomized" and "prophylactically randomized" patients was the result of the clinical decision of the local investigator/treating psychiatrist regarding whether the patient needed a mood stabilizer during the acute episode. We have not been able to pinpoint any specific disease characteristics related to this division, except for the fact that most bipolar II patients were included in the prophylactically randomized group. This finding may point to greater effectiveness of lithium in bipolar II patients, as suggested before.[10] However, the difference in efficacy between acutely randomized and prophylactically randomized patients also applies to bipolar I patients. This finding is in line with studies[10,11] reporting that lithium may be especially effective in less severely ill bipolar patients, as signified in our study by being recruited after the acute episode remitted and concurrent psychotropic medications were stopped, apparently without problems. In another study, Greil et al.[12] found lithium to be more effective than carbamazepine in "classic" bipolar I patients, i.e., those patients without mood-incongruent delusions or comorbidity.

Another possible explanation could be that stopping of psychoactive medication, e.g., antipsychotics or antidepressants, in acutely randomized patients shortly before entry into the study could have induced withdrawal phenomena, resulting in early episodes. If this is true, carbamazepine would have to protect better against this effect than lithium. We are not aware of data supporting such a difference. Relapse of the acute index episode due to stop-

ping of these medications is a less plausible explanation, since in the study the episodes were not predominantly of the same polarity as the acute (index) episodes. Also, neither the polarity of the index episode per se (mania or depression) nor the severity of residual symptoms at entry appeared to be related to early recurrence/relapse. Nevertheless, we may have missed predictive characteristics, since the analysis of the subgroups was post hoc and, unfortunately, we did not record detailed information on illness history or on treatment during the acute index episode, which especially applies for the acutely randomized patients. Clearly, that information might have contained clues to understanding the high relapse rate in the lithium group during the first 3 months. A final explanation may be found in differences in dropout rate, which was higher with lithium, especially during the first months of treatment. This finding may suggest that lithium is less well tolerated than carbamazepine. Since lithium appeared to be particularly effective after these first months had passed, it would be important to know whether patients who dropped out early in treatment would have had similarly good protection against future episodes had they remained in treatment. The same holds true for patients who experienced an episode early in treatment. In other words, should every effort be made to keep patients on lithium, even when troublesome adverse effects or early episodes occur?

The clinical relevance of this study may be questioned as a possible limitation, since the role of carbamazepine in the prophylactic treatment of bipolar disorder has declined, whereas the use of valproate has increased.[13] However, in the current Dutch guidelines on the pharmacologic treatment of bipolar disorder, as in many other European countries, lithium is still considered the first choice, with both carbamazepine and valproate as the second-step alternatives.[14] Moreover, if the choice of an alternative to lithium is based on results from randomized controlled trials, carbamazepine still holds the better record for prophylaxis compared with valproate.[15]

In addition, the methodology of prophylactic studies in bipolar disorder has evolved over the years, especially with regard to outcome measures.[16] Although full episodes according to DSM-III-R (the main outcome criterion in our study) are a robust measure of outcome,[17] recent studies have used other outcome measures as well, e.g., scores on symptom rating scales, Global Assessment Scale scores, the need for concurrent psychotropic medication, or time to intervention for emerging mood episodes.[12,18,19] Our study design did not incorporate these secondary outcome measures a priori, and of course possibilities for a post hoc analysis were restricted. For instance, although we used symptom rating scales (BRMAS and BRMES), patients were rated only at 6-month intervals (to check for mood stability during the study) or when a full episode was present.

We investigated bipolar patients not previously treated for prophylaxis. From the only study on comparable patients—not a blinded study—it was concluded that lithium is slightly superior to carbamazepine.[12] Recurrence rates in both our study and the study by Greil et al.[12] were on the order of 30% in 2 years. In other studies, these rates were between 46% in 2 years and more than 90% in 1 year,[6] probably signifying the inclusion in these studies of patients previously unsuccessfully treated with lithium. In addition, antipsychotics and antidepressants were not allowed at any time in the present study, making the differences in recurrence rates with other trials even more significant. Our trial helps to clarify some choices available for the prophylactic treatment of patients with bipolar disorder. In patients not previously treated prophylactically, lithium is to be preferred over carbamazepine. The main reason is that if a patient survives the first 3 months of prophylactic treatment, the risk of a recurrence appears to be very low, less than 10% per year in our study. If one of the disadvantages of lithium, i.e., an early episode or troublesome adverse effects, takes effect, carbamazepine may be a valuable alternative, but with the drawback of a large risk of recurrence, about 40% per year in our study. Trials to assess the efficacy of continued lithium treatment despite an early episode or troublesome adverse effects are of utmost clinical importance, since a risk of recurrence of less than 10% per year would be an as yet unmatched advantage, if also valid for other patients not previously treated. Whether the high efficacy of lithium found in this trial will again turn out to be more than can be expected in clinical practice remains to be established. Indeed, after 2 years, fewer than 50% of the patients were still in treatment. On the other hand, our results are consistent with the suggestion that recent disappointment with the efficacy of lithium may be related to broadening of its indications and inclusion of lithium nonresponders, while it continues to work well for patients with typical bipolar disorder.[1,12,20–22]

In conclusion, our results should reinforce efforts to put and maintain on lithium treatment bipolar patients who have not previously been treated with mood stabilizers, because the possible prophylactic effect is impressive and superior to that of carbamazepine and because these bipolar patients are the ones who may be most effectively protected from the progressive course of the illness.[2]

Drug names: carbamazepine (Tegretol, Epitol, and others), oxazepam (Serax and others).

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