Psychological Medicine, 1997, **27**, 281–289.

Lithium and recurrence in a long-term follow-up of bipolar affective disorder

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ABSTRACT

Background. Though previous studies have clearly shown that lithium affords prophylaxis in bipolar affective disorder, these studies have not demonstrated the persistence of this prophylactic effect beyond the first year of recovery.

Methods. One hundred and eighty-one patients with bipolar affective disorder recovered during 5 years of semi-annual follow-up. After 8 weeks of recovery, 139 were taking lithium prophylaxis and 42 were not. Analyses used drug status (lithium *v.* no-lithium) as a censoring variable to compare these two groups by interval-specific probabilities of recurrence.

Results. Recurrence was initially less likely in the lithium group but interval-specific probabilities of recurrence did not consistently favour either group after the first 32 weeks of recovery.

Conclusions. Biases in treatment decisions may have both reduced the size and altered the specificity of the lithium effects seen here. Nevertheless, the apparent transience of lithium prophylactic effects is unexplained and may reflect important, physiological differences between relapse and recurrence. This possibility invites a controlled lithium discontinuation study, with gradual taper, of patients who have had at least 8 months of sustained euthymia.

INTRODUCTION

A number of carefully executed studies have shown lithium to have prophylactic benefit in bipolar affective disorder (Coppen *et al.* 1971; Prien *et al.* 1974*a*, *b*, 1984; Fieve *et al.* 1976) and lithium prophylaxis has, consequently, become standard in the management of bipolar affective disorder. Important questions nevertheless remain concerning its long-term efficacy outside of formal drug studies (Maj *et al.* 1986; Harrow *et al.* 1990).

Most trials designed to quantify the prophylactic potential of lithium have compared lithium with placebo, or with a tricyclic antidepressant, by the overall affective morbidity during the trial period (Coppen *et al.* 1971), by the number of manic and depressive episodes (Stallone *et al.* 1973; Fieve *et al.* 1976), or by the likelihood of any manic or depressive episode (Prien *et al.* 1974*a*, *b*; Fyro & Petterson, 1977; Mendlewicz, 1984; Markar & Mander, 1989). Only one large, controlled study with random assignment has provided survival analyses to show times to relapse in individual treatment cells (Prien *et al.* 1984). In that 2-year study the difference in the cumulative probability of relapse between a group receiving lithium and a group receiving imipramine was maximal at 9 months and did not increase thereafter.

Recently described, prospective follow-up studies (Harrow *et al.* 1990; Winokur *et al.* 1994) show that the risks for recurrence in bipolar illness persist well beyond the period of 6 months to 1 year encompassed by most maintenance studies. Nine of 10 patients in one such study relapsed eventually despite a symptom-free period of at least 4 months following the index episode (Coryell *et al.* 1995). If lithium effectiveness is also continuous, then survival curves depicting cumulative relapse should continue to diverge.

Discontinuation studies are relevant to the question of how long lithium's prophylactic

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effects extend beyond recovery. However, nearly all placebo controlled discontinuation studies have employed an abrupt cessation of lithium. Data has now accumulated to show that the risk for mania following sudden lithium discontinuation exceeds that which would be predicted by the natural history of the illness (Suppes *et al.* 1991; Baldessarini, 1995). Schou (1993) noted a number of flaws in those studies but his critique was published before Faedda *et al.* (1993) demonstrated this effect directly. In that study, bipolar patients who discontinued lithium over less than a 2-week period had a much higher relapse rate than those who discontinued lithium more gradually.

Of the double-blind, randomized studies listed by Suppes *et al.* (1991) only Mander & Loudon (1988) specified a minimum period of euthymia before discontinuation, but prospective observation in that study extended to only 1 month. With this exception, existing studies do not date the persistence of lithium prophylactic effects from the end of a given episode. Sashidharan & McGuire (1983) implied that a relatively long period of stability had preceded lithium cessation. Patients had taken lithium an average of 7 years before they elected, for unspecified personal reasons, to discontinue the drug. Sixteen developed a recurrence but the likelihood of episodes in each year of follow-up was not significantly higher than in the years preceding lithium prophylaxis.

Low-dose studies also speak to the issue of sustained prophylactic benefit. Most of these, though, have likewise failed to specify the duration of symptom-free periods preceding dose reassignment (Coppen *et al.* 1983; Maj *et al.* 1986) or they have observed patients for a relatively brief period after dose reassignment (Waters *et al.* 1982). Gelenberg *et al.* (1989) both described a minimum period of clinical stability preceding reassignment, and followed patients for a substantial period afterward. The survival curves which describe lengths of time to relapse by dose group diverged during the first year but then became largely parallel, indicating little further accumulation of drug effect.

Thus, there is currently little direct evidence with which to quantify the further benefits of lithium prophylaxis in patients who have been symptom-free, on lithium, for 1 year or more. Moreover, some authors have questioned whether lithium's prophylactic effects are as robust in typical clinical settings as they are in formal drug studies where inclusion criteria and special attention to compliance may serve to maximize apparent drug effects (Dickson & Kendell, 1986; Harrow *et al.* 1990; Maj *et al.* 1991; Peselow *et al.* 1994).

The probands described below participated in the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression – Clinical Studies, a long-term, high-intensity follow-up of patients with manic disorder, major depressive disorder or schizoaffective disorder (Keller *et al.* 1986). Though they were recruited through in-patient units and out-patient clinics, and were therefore seeking treatment at the time, the protocol did not influence treatment selection. Treatment assignment was, therefore, non-random. Some bipolar patients were prescribed, and chose to take, lithium prophylaxis while a substantial number were observed prospectively without lithium prophylaxis. The sample sizes, combined with the length of follow-up, afford an opportunity to show whether lithium effects accumulate beyond 1 year in a naturalistic setting. The following analyses consider evidence that among the subset of patients with bipolar I or schizoaffective disorder, manic type, lithium offered protection from recurrence even after a sustained episode-free period.

METHODS

The following analyses concern only subjects who entered the study in an episode of Research Diagnostic Criteria manic disorder, schizoaffective disorder, manic type (mainly affective or 'other' subtype) or major depressive disorder with a history of mania or schizoaffective mania (Spitzer *et al.* 1978) (Table 1). The RDC definitions for mainly affective or 'other' subtypes of schizoaffective mania closely resemble DSM-III-R and DSM-IV criteria for manic disorder with mood-incongruent psychotic features. The criteria used to select this study group therefore corresponded closely to the DSM-III-R and DSM-IV definitions of bipolar disorder.

Subjects entered the study shortly after hospital admission or within 2 months of their first out-patient visit. The five centres involved

Table 1. *Characteristics of lithium and no-lithium prophylaxis groups*

	No-lithium prophylaxis $N = 42$	Lithium prophylaxis $N = 139$
Sex, number (%) female	20 (47·6)	77 (55·4)
Age, mean (S.D.)		
At intake	37·3 (14·0)	37·3 (12·7)
At first manic episode	29·8 (13·2)	29·7 (11·7)
Family history, number (%) positive for mania or SA-mania*	4 (9·5)	38 (27·3)
Substance abuse, number (%) with		
Alcoholism	3 (7·1)	13 (9·4)
Drug abuse	2 (4·8)	3 (2·2)
Alcoholism or drug abuse	5 (11·9)	14 (10·1)
Previous episode, number (%)	34 (80·9)	119 (85·6)
Number (%) in-patient†	35 (83·3)	132 (95·0)
Duration of index episode, onset to recovery in weeks, mean (S.D.)	75·5 (99·1)	50·5 (102·5)
Number (%) with RDC schizoaffective disorder	3 (7·1)	5 (3·6)
Polarity of index episode, number (%) with		
Mania/SA-mania only‡	6 (14·3)	65 (46·8)
Major depression/SA-depression only	11 (26·2)	15 (10·8)
Both manic and depressive phases	25 (59·5)	59 (42·4)
Polarity of previous episode, number§ (%) with		
Mania/SA-mania only	5 (17·9)	33 (33·0)
Major depression/SA-depression only	17 (60·7)	41 (41·0)
Both manic and depressive phases	6 (21·4)	26 (26·0)
Phase sequence of index episode, number (%) with		
Mania, then depression	4 (9·5)	15 (10·8)
Depression, then mania	2 (4·8)	16 (11·5)
A mixed state	3 (7·1)	5 (3·6)
Treatment after 8 weeks of recovery, number (%) with		
Any tricyclic antidepressant	13 (31·0)	40 (28·8)
Any MAOI	1 (2·4)	5 (3·6)
Any antipsychotic‖	10 (23·8)	60 (43·2)
Any combination of antidepressant and antipsychotic	20 (47·6)	82 (59·0)
Antipsychotic alone	6 (14·3)	38 (27·3)
Antidepressant alone	10 (23·8)	22 (15·8)

* $\chi^2 = 5{\cdot}7$, df = 1, $P = 0{\cdot}017$.
† $P = 0{\cdot}021$, Fisher's exact test.
‡ $\chi^2 = 16{\cdot}0$, df = 1, $P = 0{\cdot}0001$.
§ Numbers with adequate description of previous episode were 28 for 'no-lithium' and 100 for 'lithium' groups.
‖ $\chi^2 = 5{\cdot}1$, df = 1, $P = 0{\cdot}024$.

were the Brockton VA Hospital and the Massachusetts General Hospital in Boston, Rush-Presbyterian at St. Lukes Medical Center in Chicago, University of Iowa College of Medicine in Iowa City, New York State Psychiatric Institute, Columbia University in New York, and Washington University School of Medicine in St. Louis.

Baseline assessments included the Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978). Follow-up evaluations occurred at 6-month intervals for the first 5 years and at yearly intervals for the next 5 years. Whenever possible the rater who completed baseline assessments for a given subject also followed that patient. Study participation did not influence treatment. Treatment was determined by each patient's personal physician according to that physician's judgement and patients were followed regardless of their compliance with this treatment.

These analyses describe the first 5 years of follow-up. Beyond this point, other thymoleptics such as carbamazepine came into wide use and this would have complicated data analysis. Moreover, most first recurrences took place within the first 5 years of follow-up. Of the 146 initial recurrences observed in the 10 years of follow-up, 134 (91·0%) occurred in the first 5 years.

Raters used the Longitudinal Interval Follow-up Evaluation (LIFE) (Keller *et al.* 1987) to structure follow-up interviews. They identified times at which significant improvement or worsening had occurred and then quantified those symptoms present in the intervals. 'Recovery' required at least 8 contiguous weeks during which symptoms of that disorder were absent or limited to one or two of a mild degree. The beginning of recovery was the first of these weeks. 'Recurrence' presumed recovery and, in the following analyses, the appearance of symptoms sufficient to meet RDC at the definite level for major depression, mania or schizoaffective disorder following recovery was designated a recurrence. The LIFE also tracked, on a week-by-week basis, the types and amounts of all psychotropic medications taken in the interval (Keller *et al.* 1986). Medical records were sought in all cases and were used to supplement histories provided by the patients. Lithium levels contained in these records were systematically recorded.

To assess the effects of lithium prophylaxis on recurrence risk, we adapted life-table methods (Kaplan & Meier, 1958; Kalbfleisch & Prentice, 1980) to include medication status as a censoring

https://doi.org/10.1017/S0033291796004461 Published online by Cambridge University Press

variable. Patients in the lithium prophylaxis group were depicted in the survival analysis (were considered 'at risk' for relapse) as long as they continued to take lithium and remained in the follow-up. Drug changes provoked by recurrences did not result in lost data, however, because the recurrence necessarily preceded the change in treatment. If a patient relapsed while taking lithium, he or she was classified as a 'failure' in survival analytic terminology and was registered in the 'cumulative percent with recurrence'. If a patient discontinued lithium before relapse, he or she was classified as a 'censored case'.

The cumulative probability of relapse over the course of 5 years was estimated separately for the two treatment groups using life-table analyses. Because 'recovery' required 8 symptom-free weeks, the life-table comparisons between patients taking lithium and those not taking lithium began 2 months after the end of the index episode. The survival curves were compared using log-rank tests. Logistic regression analyses were then conducted to control for the effects of those potentially meaningful baseline variables which differed significantly across the two groups.

In addition, interval-specific probabilities, the cumulative probabilities of relapse within each 8-week interval, were computed. Again, only individuals who continued in the same treatment group and who had had no recurrence were considered 'at risk' in each interval. The effective sample size in each interval was the number entering the interval minus one-half of those withdrawn during the interval. These procedures were repeated while confining failures to episodes of major depression or schizoaffective depression and, again, while confining failures to episodes of mania or schizoaffective mania.

RESULTS

Of 198 patients who began follow-up in an episode of mania or schizoaffective mania, or who began follow-up with major depressive disorder and had a lifetime history of mania or schizoaffective mania, 181 (91·4%) were observed to recover within the first 5 years of follow-up. At the beginning of recovery, 145 of these 181 patients were taking lithium. At the end of the ninth week this number had fallen to 139. No one began lithium therapy within the first 8 weeks of recovery.

Table 1 compares the 139 who were taking lithium in the ninth week of recovery to the 42 who were not. These groups did not differ significantly by demographics, episode duration, proportion with previous episodes or the presence of substance abuse. The no-lithium and lithium groups also had nearly identical global severity ratings; mean (S.D.) Global Assessment Scale Scores (Endicott *et al.* 1976) were 37·7 (12·6) and 37·4 (11·2), respectively. Illness duration, the time from the first-ever manic episode to intake into the study, were likewise nearly identical – 7·5 (9·5) years and 7·6 (9·3) years, respectively. Those in the lithium group were significantly more likely to have in-patient status at intake, a family history of mania, an index episode which included a manic phase, and treatment with an antipsychotic at the ninth week of recovery.

Recurrence was most likely in the first three, eight-week intervals (Table 2). The effective sample size in the first interval was reduced by censoring within the interval. Recurrence was at least somewhat more likely in the no-lithium group in each of these intervals. Beyond this point, recurrence rates did not consistently favour either group. The numbers of individuals at risk and remaining within their baseline drug categories grew progressively smaller, making group comparisons less meaningful. In light of this, we chose a multiple of the first 32 weeks (96 weeks) and limited subsequent analyses to this time period.

In the no-lithium group, 23 developed a recurrence between weeks 9 and 96 and four were lost to follow-up leaving, at that point, 15 who remained recurrence-free and under observation. Of those taking lithium at week 9, 58 developed a recurrence, 35 discontinued lithium while symptom-free and six others were lost to follow-up, leaving 40 who remained in follow-up without recurrence. Those who discontinued while symptom-free did not differ from the remaining lithium patients by any of the variables listed in Table 1.

Figs. 1 and 2 illustrate the cumulative recurrence rates for the members of the two groups. Survival curves in Fig. 1 begin with the ninth week of recovery following index episode

Table 2. *Interval-specific probabilities of recurrence by the absence or presence of lithium prophylaxis*

Interval, weeks	No-lithium prophylaxis		Lithium prophylaxis			
	Effective sample size in interval	Number (%) with recurrence in interval	Effective sample size in interval	Number (%) with recurrence in interval	Number with measured lithium level	Mean (S.D.) mean lithium level
9–16	41	5 (12·2)	136	14 (10·3)	43	0·84 (0·23)
17–24	35	6 (17·1)	113	12 (10·6)	33	0·84 (0·28)
25–32*	28·5	6 (21·1)	92·5	4 (4·3)	24	0·83 (0·22)
33–40	21·5	1 (4·7)	85	8 (9·4)	20	0·88 (0·20)
41–48	20	1 (5·0)	74·5	6 (8·1)	21	0·65 (0·26)
49–56	19	0 (0·0)	65·5	3 (4·6)	17	0·85 (0·26)
57–64	19	1 (5·3)	60	1 (1·7)	20	0·88 (0·24)
65–72	18	1 (5·6)	56	4 (7·1)	18	0·81 (0·27)
73–80	17	1 (5·9)	48·5	2 (4·1)	11	0·89 (0·26)
81–88	16	0 (0·0)	45	3 (6·7)	12	0·79 (0·24)
89–96	16	1 (6·3)	41·5	1 (2·4)	13	0·86 (0·29)

* Log-rank $\chi^2 = 7{\cdot}5$, df = 1, $P = 0{\cdot}0236$.

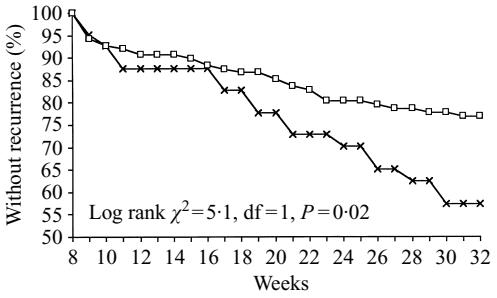

FIG. 1. Cumulative probabilities by presence (□, $N = 139$) or absence (×, $N = 42$) of lithium prophylaxis: weeks 8–32.

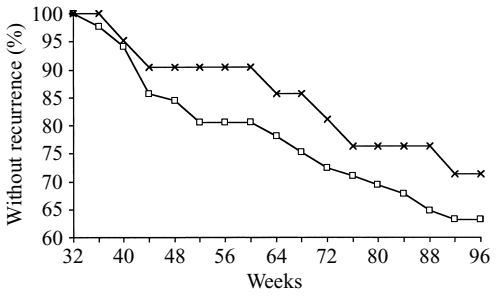

FIG. 2. Cumulative probabilities by presence (□, $N = 86$) or absence (×, $N = 22$) of lithium prophylaxis: weeks 32–96.

and end at 32 weeks; Fig. 2 begins in week 33. A significant difference favoured the lithium group in the first, but not the second, interval.

Logistic regression analyses were done to control for a family history of mania and for polarity difference in the index episode. After control for these variables, a significant relationship remained between lithium and recurrence risk in the first 32 weeks (Table 3); those taking lithium were one-half as likely to suffer a recurrence than those not taking lithium (odds ratio = 0·47). In weeks 33–96, though, lithium treatment was not associated with the likelihood of recurrence.

Table 3. *Logistic regression of early and late recurrence by lithium status, family history and index episode polarity*

	Wald χ^2 (df = 1)	*P*	Odds ratio
Weeks 9–32			
Lithium prophylaxis	3·73	0·05	0·47
Family history of mania	0·07	0·80	0·89
Index episode polarity	2·12	0·15	0·75
Weeks 33–96			
Lithium prophylaxis	0·39	0·53	1·41
Family history of mania	0·89	0·35	1·58
Index episode polarity	2·08	0·15	0·72

Patients receiving lithium prophylaxis at week 9 were twice as likely as those not receiving lithium to be taking antipsychotics. Survival analyses for weeks 9–32 and for weeks 33–96 were repeated with the exclusion of those taking antipsychotics at week 9. This yielded a cumulative recurrence rate of 0·248 for the remaining lithium patients, a rate nearly identical to that for patients in the overall group inclusive of those taking antipsychotics (0·232). With the smaller number occasioned by this exclusion, the comparison between lithium and no-lithium

https://doi.org/10.1017/S0033291796004461 Published online by Cambridge University Press

groups was not quite statistically significant (log-rank $\chi^2 = 3{\cdot}06$, df = 1, $P = 0{\cdot}080$). Recurrence rates during the 33–96 week intervals were 0·250 and 0·307 for no-lithium and lithium groups, respectively (log-rank $\chi^2 = 0{\cdot}31$).

Mean lithium levels for the lithium group exceeded 0·8 meq/l for all but 2 of the 11 intervals listed in Table 2. While this indicates generally good compliance, lithium levels fell below 0·6 meq/l on at least one occasion for 22 patients. The exclusion of these subjects did little to change results. The cumulative recurrence rate in the first 32 weeks was 0·238 (*v.* 0·428 for the 42 not on lithium). The difference between lithium and no-lithium groups remained statistically significant (log-rank $\chi^2 = 4{\cdot}096$, df = 1, $P = 0{\cdot}043$). Cumulative recovery rates for the later interval were 0·2857 and 0·3853 for the no-lithium and lithium groups, respectively.

Patients with lithium prophylaxis did not differ from those without it by the overall likelihood of manic/schizoaffective-manic recurrences (log-rank $\chi^2 = 0{\cdot}51$, df = 1, $P = 0{\cdot}82$). In contrast, a significant difference favouring the lithium group emerged for the likelihood of major depression recurrence (log-rank $\chi^2 = 7{\cdot}70$, df = 1, $P = 0{\cdot}005$). The interval-specific probabilities of depressive recurrence for the no-lithium group in the first three, 2-month periods at risk were 10·0%, 13·9% and 10·0%. Corresponding rates for the lithium group were two to three-fold smaller – 5·2%, 3·4% and 4·8%. After 32 weeks there was no consistent difference favouring lithium prophylaxis in interval-specific probabilities of depressive recurrence. Interval-specific probabilities of manic recurrence were 2·5%, 5·1% and 13·7% for the first three intervals in the no-lithium group. Corresponding values were 5·2%, 7·7% and 1·0% for the lithium group. Probabilities of manic recurrence were insignificant for all intervals.

DISCUSSION

Treatment assignments in this sample were naturalistic and non-random. Various biases, to be discussed, probably operated to lessen apparent drug effects. These biases, however, would not have produced the time limits on drug effects seen here. These limits were striking and invite at least two interpretations. Episodes which occur within 8 months of an earlier one may differ in their physiological origins from episodes which occur after longer symptom-free periods. We are not aware of attempts to contrast early and late recurrences, either from phenomenological or physiological perspectives. If such differences were shown it would be appropriate to distinguish the timing of new episodes by the terms 'relapse' and 'recurrence' as suggested by Frank *et al.* (1991) for major depressive disorder. Lithium may be effective in the prevention of relapses but not in the prevention of recurrences. Such a view is, at this point, highly speculative but would concur with the findings of Markar & Mander (1989). These authors began survival curves 6 months after recovery and, in a lengthy comparison of those taking lithium with those not taking lithium, they found no significant difference in the likelihood of rehospitalization.

Alternatively, patients who need lithium may simply relapse quickly without it, leaving patients whose course would otherwise be unaffected by prophylaxis. If this is so, the proportion of patients in the no-lithium group who would have benefited from lithium appears to have been a minority. Of those at risk in the first 32 weeks, 50·4% of the no lithium group and 25·2% of the lithium group relapsed. Presumably, then, one quarter of the no lithium group would have benefited prophylactically from lithium had they been taking it.

These two possibilities have very different ramifications. If lithium is only effective during the early 'risk for relapse' period following an episode, and not in the subsequent 'risk for recurrence' period, then further lithium therapy may be unnecessary and, in light of the expense and side effects involved, undesirable. If the second explanation holds, then an important, albeit small, subgroup of all patients given lithium prophylaxis may be at risk if lithium is withdrawn, even after lengthy periods without symptoms. A clinically relevant conclusion, consistent with both interpretations, is that patients who survive for 8 months after an episode with neither lithium or a relapse will probably not benefit from lithium begun at that point.

The treatment effects seen here were unexpectedly phase specific; patients taking lithium differed significantly from those not taking lithium by recurrence risks for major depressive

episodes. Risks for new manic episodes did not differ by treatment group. Lithium was associated with a more substantial reduction of depressive episodes than of manic episodes in several mirror-image prophylaxis studies (Poole *et al.* 1978; Rybakowski *et al.* 1980). However, a review of those lithium prophylaxis studies which were placebo controlled concluded that placebo/lithium differences were not larger for depressive relapses than for manic/hypomanic relapses (Goodwin & Jamison, 1990, p. 689). None of the eight studies reviewed found that lithium was significantly more protective for depressive relapses.

A possible explanation supposes that patients whose prior course had been predominantly depressive were over-represented among those not given lithium. In fact, nearly all those whose index episode involved only mania (65 of 71, or 91·5%), but only half of those who had been depressed only (15 of 26, or 57·7%), were in the lithium prophylaxis group. If lithium is at least as effective in the prevention of depressive episodes as in the prevention of manic episodes, and if patients tend to persist in their polar predominance, then such a treatment assignment bias would produce the differential seen here.

Treatment effect sizes overall were also smaller than the results of controlled studies would predict. As Guscott & Taylor (1994) have noted, naturalistic studies regularly show poorer results than do controlled studies. In this study, differences in recurrence likelihood between those taking and those not taking lithium might have been larger had patients been randomly assigned to treatment conditions. If factors which made lithium use less likely also made recurrence less likely, then such a bias may have limited lithium's apparent prophylactic effects. Family history may have been such a factor (Table 1). Many studies have suggested that a family history of mania is associated with a good response to lithium (reviewed in Goodwin & Jamison, 1990, p. 700) and this fact may have influenced clinicians to prescribe it. However, a negative family history may be associated with a lower episode frequency (Winokur *et al.* 1994). Therefore, the lower proportion of patients with a positive family history in the no-lithium group may have acted to diminish the apparent effects of lithium. Index episode polarity may have comprised another confounder in that Keller *et al.* (1994) described a lower recurrence rate among patients whose index episode was solely manic. Notably, though, significant lithium effects on recurrence risks remained after logistic regression analyses controlled for these two variables.

Another, more global, bias may have operated as well. These patients were all recruited from tertiary care centres and patients who have failed conventional treatment are over-represented in such places. Those who received lithium may have been relatively poor candidates and this too would have limited outcome differences between groups.

However, this population may be no less representative of the individuals typically seen by contemporary psychiatrists than are those described in formally controlled studies of prophylaxis. Eliminated from the latter groups were patients with co-morbidity or diagnostic ambiguity, patients unwilling to participate in a trial in which they might have been assigned to ineffective treatment, and patients unwilling or unable to comply with research protocols. The most recent, large-scale study of lithium prophylaxis serves as an example. Gelenberg *et al.* (1989) screened 1200 patients to find 255 (21·2%) who seemed to meet study criteria. Of these, 157 (13·1%) agreed to an interview and 94 (7·8%) were randomly assigned in the project. Fifty-nine completed protocol or relapsed. This was only 4·9% of those screened and 23·1% of those thought to be eligible.

For these reasons, naturalistic studies such as the one described here offer an extremely important compliment to randomized controlled trials (RTCs) (Lavori *et al.* 1994*a*, *b*). Both have clear, but different, advantages and disadvantages. The RCT avoids the inherent, and often obscure, biases arising from clinically determined treatment assignment. Naturalistic studies must attempt to control for these confounds statistically but have the advantage of a much more inclusive, and therefore generalizable, sample.

While recruitment bias may have lessened the apparent importance of lithium in preventing relapse, there is no clear way in which such biases would have produced the temporal effects seen here. Differences between lithium and no-lithium were present during the first three intervals of observation (weeks 9–32) but were

absent thereafter. The implications of this observation are clinically important and can best be explored in future lithium discontinuation studies. They should differ from earlier studies in two ways. They should restrict subjects to those who have been episode-free for at least 8 months and they should execute discontinuation gradually. Molnar *et al.* (1988) and Molnar & Fava (1989) have shown that this might be done with acceptable clinical consequences. Six bipolar patients who had been clinically stable on lithium for at least 12 months underwent gradual lithium discontinuation. Analyses revealed a mean survival time of 16 months after lithium discontinuation. Interventions were prompt and neither of the two individuals who relapsed developed a full syndrome or required hospitalization.

Such studies, of course, should also randomly assign patients to the continuation and discontinuation arms of the protocol and thereby avoid the biases that may have produced the differential effects for depressive and manic recurrences seen here. If the results indicate that a distinction between relapse and recurrence is indeed important to lithium effects, it would remain to locate the optimal boundary between the two types of events. Current results, and a review of other relevant studies, suggest that that boundary would lie between 8 and 12 months.

From the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression – Clinical Studies, conducted with the participation of the following investigators: M. B. Keller (Chairperson, Providence); W. Coryell (Co-Chairperson, Iowa City); H. S. Akiskal (San Diego); J. D. Maser (Washington, D.C.); P. W. Lavori, T. I. Mueller, M. T. Shea (Providence); J. Fawcett, W. A. Scheftner (Chicago); G. Winokur, J. Haley (Iowa City); J. Endicott, A. Leon, J. Loth (New York); J. Rice, T. Reich (St. Louis). Other contributors include: N. C. Andreasen, P. J. Clayton, J. Croughan, G. L. Klerman (deceased), R. M. A. Hirschfeld, M. M. Katz, E. Robins (deceased), R. W. Shapiro (deceased), R. L. Spitzer and M. A. Young.

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This manuscript has been reviewed by the Publication Committee of the Collaborative Depression Study, and has its endorsement.

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