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Lithium Carbonate Prophylaxis Failure

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Summary. Data from non-rapid-cycling bipolar (manic-depressive) patients who were receiving long-term treatment with lithium carbonate were analysed by the life table method to determine when lithium carbonate prophylaxis failures occurred. Forty-four of 96 patients failed to keep well in spite of maintenance lithium therapy. The analysis revealed an early, rapid failure rate during the first six months of treatment, which was followed by a slower rate of failure. Several clinical factors were assessed to determine if any of them predicted which patients would experience their initial failure in the early or late interval, but none of these factors, which included age, sex, age of onset, rate of affective attacks, family history, and the nature of the preceding episode, were found to have any predictive value regarding lithium prophylaxis failure. We found, however, that patients who had early failures tended to have a subsequent early failure in spite of continued maintenance with lithium carbonate.

Introduction

The long-term administration of lithium carbonate to bipolar (manic-depressive) patients in order to achieve a reduction in future attacks of mania and/or depression is now an accepted mode of therapy. However, the 'prophylactic' effect of lithium carbonate is not complete, and a significant percentage of bipolar patients continue to have affective episodes in spite of treatment. In a study of lithium carbonate prophylaxis failure reported earlier from this clinic, we found that a high frequency of affective attacks (rapid cycling) predicted a poor prophylactic response to lithium carbonate (Dunner and Fieve, 1974).

The purpose of the present study is to examine further those clinical factors which might predict lithium carbonate prophylaxis failure in non-rapid-cycling bipolar patients. The sample under study is considerably larger than in our earlier report because we now include patients who were treated in our clinic on an 'open' basis as well as those who participated in our double-blind studies (Stallone *et al*, 1973). Further, the data have been analysed by the life table method in order to take account of the varying lengths of time patients were followed (Greenwood, 1926; Fleiss *et al*, 1976).

Methods

The records were examined of all the patients who had ever attended the Lithium Clinic at the New York State Psychiatric Institute. In order to be included in this report, patients had to meet the following criteria: (1) diagnosis of primary affective disorder based on the criteria of Feighner *et al* (1972); (2) a history of previous admission to hospital for mania (Dunner *et al*, 1970); (3) normal mood at some time during their clinic follow-up of at least four weeks; and (4) treated for at least four weeks with lithium carbonate on an open or double-blind basis, or with placebo or with no medication. Patients were excluded who met the above criteria but were rapid cyclers in that they had four or more episodes of depression and/or mania per year during the two-year period previous to their attending the clinic (Dunner and Fieve, 1974).

At each clinic visit data were recorded as to mood state and prescription of antidepressants or antipsychotic medication. All but fifteen patients received their initial lithium treatment in the clinic. However, the lithium trial was considered to begin whenever the patient first received lithium carbonate, here or elsewhere.

In addition to the course of illness while the

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patient was in the clinic, data were systematically recorded regarding the prior course of illness. The data recorded during lithium carbonate or control treatment included the duration of treatment; the nature of the initial affective failure (if any) and, when this occurred, its treatment; and, where possible, data regarding further failures. For patients who were discharged from the clinic, it was noted whether they were of normal mood or otherwise. Formal statistical follow-up began four weeks after the patient was judged to have recovered from the index episode. Data were analysed up to 1 March 1974.

Ninety-six patients had lithium treatment and 38 patients had control (either placebo or nothing) treatment; 31 patients contributed data to both the lithium and the control groups. Table I presents various background characteristics of the two groups. The greater mean age and lower mean number of episodes in the control group are attributable to most of these patients having been maintained on lithium for periods ranging from a few months to over four years before being switched to the control group, and to a reduction in episode frequency while on lithium.

TABLE I

Characteristics of lithium and control samples

Characteristic	Lithium (n = 96)	Control (n = 38)
Age at start of treatment (mean±sd) ..	44·0±12·9	48·5±11·1
Percent female ..	46%	63%
Number of episodes in two years before treatment (mean±sd) ..	2·8±1·5	2·1±1·4
Age at first symptoms (mean±sd) ..	27·2±11·0	27·4±12·7

The data were analysed statistically by the life table, a technique which controls for varying lengths of patient follow-up and provides probabilities of remaining well from the start of follow-up through each of any number of consecutive time intervals (Fleiss *et al*, 1976). A summary chi square test with one degree of freedom is available for comparing entire sequences of probabilities (Mantel, 1966), and critical ratio tests are available for comparing probabilities associated with single points in time (Greenwood, 1926).

RESULTS

Eighty-four patients were followed on open lithium and 24 were followed on double blind lithium; 12 patients were followed under both conditions. Differences in course on lithium were small between the groups followed openly and double blind ($\chi^2 = 0{\cdot}85$, df 1, ns), permitting the two groups to be combined into a single 'lithium group' consisting of 96 patients.

Twenty-three patients were followed on placebo after having been maintained on lithium, and six were followed on placebo with no prior lithium treatment. The courses on placebo for these two groups of patients were similar ($\chi^2 = 0{\cdot}34$, df 1, ns). Nine other patients were followed in the clinic on no medication, eight after having been maintained on lithium. The course of these nine patients was similar to the course of the 29 on placebo ($\chi^2 = 0{\cdot}13$, df 1, ns), permitting the two groups to be combined into a single 'control group' consisting of 38 patients.

The overall clinical courses of the lithium and control groups are illustrated in Fig. 1. Both groups showed a rapid rate of failure for the initial six months of treatment, followed by a slower failure rate thereafter. The courses for the lithium and control groups until the time of initial failure were significantly different ($\chi^2 = 19{\cdot}86$, df 1, $P < 0{\cdot}001$).

The curves permit the following kinds of probabilities to be estimated; given that a patient has remained well for a specified length of time (e.g. for 26 weeks), what is the likelihood of his remaining well for a further specified length of time (e.g. for a further 26 weeks)? The likelihood is calculated simply as the ratio of the probability associated with the latter time point to the probability associated with the former. For the control group, the chances that a patient who has already remained well 26 weeks will still be well at 52 weeks are $0{\cdot}19/0{\cdot}31 = 0{\cdot}61$, or about 3 : 2. For the lithium group, the corresponding chances are $0{\cdot}55/0{\cdot}62 = 0{\cdot}89$, or about 8 : 1.

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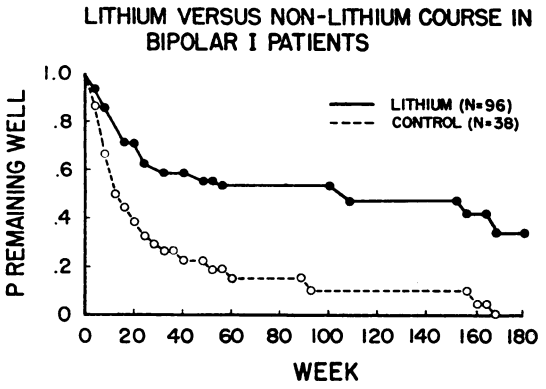


FIG. 1.—The probability of remaining well over time is illustrated for patients who received lithium carbonate versus control treatment. Treatment with lithium carbonate is clearly superior to control. In both instances there is a rapid, early rate of failure followed by a slower rate of failure.

With respect to each of a number of parameters of treatment course, the lithium group was superior to the control group. Attention was next directed at identifying any characteristics of the lithium-treated patients that might be associated with the early, relatively fast failure rate or with the later and slower failure rate. The characteristics studied are tabulated in Table II. Not a single one of the factors analysed even approached being significantly associated with the course of maintenance lithium. The nature of the immediately preceding episode was found not to be associated with the *time* until the first lithium failure. Likewise, no association at all was found between the previous episode and the *nature* of the first lithium failure. Furthermore, an analysis of lithium blood levels failed to demonstrate any relationship between failure and low blood lithium concentration.

A total of 44 patients failed on maintenance lithium. They were divided into those who failed within the first three months ('early failures', n = 20) and those who failed after the first three months ('late failures', n = 24). Seventeen of the early failures and 14 of the late failures were continued on lithium in the clinic after having recovered from their first lithium failure. The time to a second lithium failure was analysed by the life table method for the two groups, starting four weeks after recovery from the first failure (Fig. 2). The

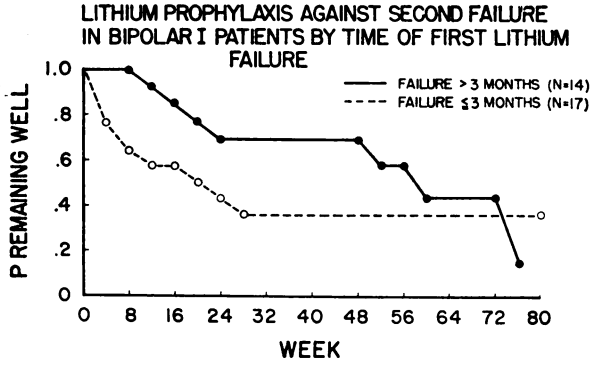


FIG. 2.—The probability of remaining well with continued lithium treatment after recovery from the initial failure episode, which occurred in spite of lithium treatment, is illustrated. Patients who had an early initial failure had an early second failure episode, whereas patients whose initial failure was late had a delayed second failure.

early failure group again tended to experience a second lithium failure earlier than the late failure group, especially within the first eight weeks of the second follow-up. Although the sample sizes are small, the difference is statistically significant ($\chi^2 = 4{\cdot}07$, df 1, $P < 0{\cdot}05$).

DISCUSSION

Lithium carbonate is clearly superior to placebo as a treatment to reduce further affective episodes in bipolar patients. It is also clear that if patients receiving lithium carbonate are followed long enough a considerable portion will have a recurrence of an affective episode. The phenomenon of failure of lithium carbonate prophylaxis appears to have two components: a high percentage (25 per cent in our data) of patients failing early (within the first three months of treatment), and a persistent yet low rate of failure thereafter. Clinically, it would be helpful to be able to predict which patients will fail early, since our data suggest that such patients are also more prone to a second affective episode earlier than patients whose initial failure is delayed; but even with the aid of statistical method as sensitive as the life table we are unable at this time to demonstrate that

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TABLE II

Association between various characteristics and course on lithium carbonate

Characteristic	Probability of remaining well at week			Summary chi square
	16	52	104	
Sex				
Male (n = 52)	0·74	0·55	0·47	
Female (n = 44)	0·67	0·56	0·56	0·01
Age at treatment				
<45 (n = 51)	0·69	0·51	0·43	
≥45 (n = 45)	0·73	0·61	0·53	0·94
No. episodes in 2 prior years				
0–2 (n = 47)	0·71	0·57	0·53	
3 (n = 18)	0·72	0·61	0·46	0·01
4–7 (n = 31)	0·70	0·50	0·50	
Nature of prior episode				
Mania (n = 53)	0·75	0·57	0·48	
Depression (n = 25)	0·62	0·52	0·41	0·07
Cyclic (n = 13)	0·69	0·48	0·48	
Age of first symptoms				
<25 (n = 44)	0·70	0·52	0·45	
≥25 (n = 45)	0·72	0·64	0·55	0·88
Age of first hosp.				
<30 (n = 48)	0·69	0·57	0·49	
≥30 (n = 46)	0·74	0·55	0·47	0·01
Family history (first degree relatives)				
Bipolar illness (n = 31)	0·71	0·64	0·59	
Unipolar illness (n = 19)	0·58	0·42	0·42	0·18
None (n = 40)	0·79	0·58	0·53	
Onset of mania				
Gradual (n = 39)	0·69	0·53	0·46	
Abrupt (n = 26)	0·71	0·53	0·53	0·04

any of the clinical factors we studied predict early, or for that matter late, failure of lithium carbonate prophylaxis.

Some of these factors may be of particular interest. For example, the data from our earlier study suggested that rapid cycling (8 or more affective episodes in the two preceding years) predicted quick lithium failure (Dunner and Fieve, 1974). Nevertheless, patients who had an episode frequency almost as high (say, 4 to 7 in the preceding two years) had comparable rates of lithium failure to patients with lower episode frequency.

A second finding of interest is the lack of association between family history and failure of lithium carbonate prophylaxis. Mendlewicz *et al* (1973), reporting on a subgroup of the same patients studied here, found that those with a history of mania in their first-degree relatives tended to remain well during double-blind treatment with lithium, whereas those without a family history of mania were more likely to be lithium prophylaxis failures. There are, however, two important methodological differences between this study and that of Mendlewicz *et al.* The family history data reported here were mainly based on the patients' reports, whereas Mendlewicz *et al* used a family study method, which results in greater accuracy of data (Mendlewicz *et al*, 1975).

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However, in contrast to Mendlewicz *et al* (1973) we analysed data for failure over the complete course of lithium administration, whereas they confined their lithium failure data to the duration of the double-blind trial. Many patients in our clinic received lithium carbonate on an open basis before double-blind administration was started. Since the failure rate is highest in the first six months of lithium treatment, some of the patients who were recorded by Mendlewicz *et al* (1973) as having had a prophylactic response to lithium had in fact failed on open lithium before the double blind trial.

Conclusion

In relation to clinical practice, our data suggest that lithium carbonate treatment of bipolar patients should be maintained even if patients should have a recurrence of illness. Many patients expect that long-term treatment with lithium carbonate will prevent their ever becoming ill, and we feel it is important that such patients should be made aware of the possibility of relapse and should know to what extent their overall course of illness may be influenced by the treatment.

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