A Long-term Retrospective Follow-up Study of Patients Treated with Prophylactic Lithium Carbonate

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Patients suffering from unipolar and bipolar affective illness, who began treatment with prophylactic lithium carbonate during a 5-year period, were followed up and 59 out of 101 interviewed. Most had been taking lithium for at least 13 years: 49% had a complete remission, 41% a partial but significant response, and 10% no response. No specific individual or illness factor was found to correlate with favourable outcome, and no correlation between average serum lithium level and outcome. No side-effects could be associated specifically with the long-term use of lithium, but there was a surprisingly high incidence of clinical hypothyroidism.

This paper presents the results of a long-term retrospective follow-up study of a sample of patients given lithium carbonate as prophylaxis against recurrent affective disorders. Since the first classical papers of Baastrup & Schou (1967, 1968a,b; Schou, 1968) there have been a number of similar studies, using the so-called 'mirror-image' technique to assess the efficacy of prophylactic lithium. In addition, several controlled, random-assignment, double-blind studies have clearly established the efficacy of prophylactic lithium in both unipolar and bipolar patients (Coppen et al., 1963, 1971; Baastrup et al., 1970; Prien et al., 1971, 1973a,b, 1974; Cundall et al., 1972; Persson, 1972; Mendlewicz et al., 1973; Stallone et al., 1973; Dunner et al., 1982; Kane et al., 1982; Peselow et al., 1982).

The limitations of this type of retrospective study have been described (Blackwell & Shepherd, 1968; Blackwell, 1969), but this particular study is the first to follow a large cohort of patients over a period of 17 years, with detailed follow-up data being established first in 1971 and then 12 years later, in 1983. Thus, useful information has been obtained regarding long-term efficacy and side-effects, despite the fact that the data could not be subjected to a rigorous 'mirror-image' analysis.

Method

The sample

The subjects were a consecutive series of 101 patients, the first to be treated with prophylactic lithium by one consultant psychiatrist working in north London; all began lithium therapy between 1966 and 1971. Prior to that time, all had suffered from several episodes of depression and/or hypomania. The criteria for defining these episodes were that specific symptoms of depressive or hypomanic mood were elicited by the clinician, which were of at least 2 weeks duration and of sufficient severity as to impair the subject's usual functioning, though not necessarily requiring admission to hospital. There were distinct intervals between these episodes when the subject's mood state was normal for at least 4 weeks.

Assessments of the patients

Initial status

A detailed examination of their hospital and clinic case notes was carried out to identify characteristics of this group at the time of initial lithium prescription. This included:

(a) demographic details (age, sex, socioeconomic and marital status, employment record);
(b) family history of physical and psychiatric illness;
(c) initial diagnosis and detailed psychiatric history prior to commencing lithium treatment, including age of onset, length and pattern of illness, previous treatment, characteristics of illness including the presence or absence of specific symptoms, frequency of relapses, suicide attempts.

Follow-up status

In 1971, the entire cohort of patients who had been taking lithium for up to 5 years was reviewed (Benaim & Lappin, 1973). They were assigned to one of three outcome groups, depending on whether their response to lithium was complete, partial or insignificant. These outcome groups were defined as follows:

(a) complete response, i.e. there had been no episodes of hypomania or depression requiring treatment whilst the patient was taking lithium;
(b) partial response, i.e. some episodes of illness occurred whilst the patient was taking lithium, but these were less often and produced less handicap (in terms of need for additional medication, admission to hospital, duration of episode, time away from work) than those prior to lithium treatment;
(c) insignificant response, i.e. there was no detectable change in frequency or severity of relapses after lithium treatment was begun.

In 1983, attempts were made to trace these patients again via out-patient clinics, general practitioners, family
practitioner committees and informal sources. All were asked to attend for interview, with the option of being interviewed in their home if unable to travel. The interview included collection of the following data: demographic details, psychiatric and physical morbidity since beginning lithium treatment, details of lithium therapy (average dose, length of time for which the drug was taken, individual patterns of taking treatment, compliance, reasons for discontinuation), employment history, marital history and social functioning since commencing treatment.

In order to assess their mental state at the time of interview, the ninth edition of the Present State Examination (PSE) was administered (Wing et al, 1974).

Analysis

The course of each individual's illness whilst on lithium was thus examined in terms of episodes of depression or hypomania, number of admissions, severity of the recorded episodes, frequency of episodes, suicide attempts and ability to function adequately at work and at home. A comparison was then made with the pre-lithium data for each individual and with the data obtained in 1971, the latter to assess the stability of the response. These comparisons were analysed using the chi-squared test.

Results

Of the 101 patients, 59 were interviewed in 1983: 20 were dead (detailed information regarding this group was sought from case notes, general practitioners and relatives), two were living abroad, four refused to be interviewed and 16 were never traced.

Characteristic of the initial sample

Sociodemographic details

The original group comprised 47 men and 54 women, their ages ranging from 19 to 75 years, the mean age at commencing lithium treatment being 45 years. A total of 74 were married, nine divorced, 15 single and three widowed. According to the Registrar General's classification, 22% were social class I, 49% social class II, 20% social class III non-manual, 7% social class III manual and 2% social class IV.

Diagnosis

At the time of starting lithium, 35 patients were classed by one of the authors (S. B.) as having unipolar affective disorder, 65 bipolar affective disorder and one a schizophrenic illness.

Family history of psychiatric illness

A positive family history of bipolar illness was found in 61 subjects, and in all but one of these, their own diagnosis was also that of bipolar illness. There was a family history of unipolar illness in 46, which was evenly distributed amongst subjects with both diagnoses. There was a family history of completed suicide in 18, of which 14 were bipolar subjects. Nine had a family history of alcoholism; all of these were bipolar subjects.

Age of onset of illness

In 30, the age of onset of illness was less than 25 years, in 34 it was between 26 and 35 years, in 22 it was between 36 and 45 years, and in 15 it was over 45 years. There was no significant difference in age of onset of illness between those subjects with bipolar and those with unipolar disorders.

Characteristics of illness prior to lithium

The characteristics of illness before treatment with lithium included on average 8.5 depressive episodes (range 0–80), 3.8 admissions for depression (range 0–30), 2.7 hypomanic episodes (range 0–16), 2.1 admission for hypomania (range 0–9). The average frequency of episodes was 19 months.

The length of illness prior to lithium treatment varied from 1 month to 30 years, with a mean of 5 years. The frequency of occurrence of episodes was no different between unipolar and bipolar subjects.

Analysis of preliminary data

All the preliminary data were examined to see whether the original population could be defined by distinct subgroups, clustering in terms of sex, age of onset of illness, symptoms or family history. Using the chi-squared test to compare subgroups, it was not possible to demonstrate any significant clusters.

Follow-up data (1983)

Patients not available

No follow-up data were available for 22 patients. This group was not significantly different from the remainder of the original population in terms of any initial variables, as determined from their case notes.

Patients who had died

Twenty patients had died by 1983. The causes of death were: suicide (6), cancer (5), myocardial infarction (4), accident (2), cerebrovascular accident (1), respiratory failure (1) and pulmonary embolus (1). At the time of death, eight of these were known to still be taking lithium. In comparing the 20 dead subjects with the rest of the original population, there was no major differentiating characteristic of statistical significance. All six who committed suicide had been diagnosed as having bipolar illness, in each case characterised by severe depressions which prevented them from working or functioning socially; five had shown a partial response to lithium and one had shown no response. The average age at time of death was 47 years (range 30–56).

Patients who were interviewed

A total of 59 patients were re-interviewed in 1983. On examination of their mental state, including use of the PSE, none of these were found to have clinically significant psychiatric signs or symptoms, either at the time of interview or in the preceding 4 weeks. It was therefore presumed that the data which they provided at those interviews were valid.

Lithium usage

Their average age at starting lithium was 45 years (range 19–75). Figure 1 shows the length of time for which these patients had regularly taken lithium; most had taken it for more than 13 years.
LONG-TERM STUDY OF PROPHYLACTIC LITHIUM CARBONATE

The mean daily dose was 800 mg (range 250–1600 mg), mostly as single daily dose preparations. The mean recorded serum level, approximately 12 h post-dose, was 0.7 mmol/litre (range 0.3–1.2 mmol/litre). Since lithium was first prescribed for them, 61% had taken the drug continuously. The reasons given by the others for stopping lithium were: unwillingness to take long-term treatment (12), unacceptable side-effects (11), the treatment considered ineffective by the doctor (4), concomitant physical illness (3) and in order to become pregnant (1). Twenty-nine of the total 31 who stopped taking lithium suffered relapses, and 19 subsequently recommenced their treatment. Two subjects (both with a unipolar illness) have remained free of recurrence since stopping lithium and have now been well, without medication, for over 6 years.

Outcome

As described above, the subjects were all assigned to one of three outcome groups, both in 1971 and in 1983. In 1971, (when 101 subjects were included), 48% had shown a complete response, 42% a partial response and 10% an insignificant response. In 1983, (when 59 subjects were re-examined), 49% had shown a complete, 41% a partial and 10% an insignificant response. In the 12 years since these patients had been reviewed, the proportions in each group had not changed and there was no movement between outcome groups of the 59 patients followed up in 1983.

Having categorised the patients in terms of their response to lithium, all the preliminary and follow-up data were examined to see whether there were any variables which correlated with outcome (using the chi-squared test). No association was found between outcome and any of the variables examined, which included: age, sex, family history, age of onset of illness, diagnosis, previous treatment, previous physical history, nature and severity of their pre-lithium illness, dose of lithium, average serum level and concurrent treatment or side-effects.

During the period of lithium treatment, the marital and socioeconomic status of these patients had remained similar to that pre-lithium, but a higher proportion were able to work fulltime (36 compared with 12 before lithium).

At the same time of follow-up, four subjects were found to be living in institutions (one in a long-stay ward of a psychiatric hospital, three in old people’s homes).

Additional treatment was given concurrently to 43 (73¾%) of these patients at some point during their lithium treatment. In the case of patients who had no further episodes of affective illness after starting lithium, the additional treatment given was either hypnotic drugs or psychotherapy. The percentages receiving other forms of treatment, compared with the pre-lithium figures, are shown in Table 1.

Side-effects

The side-effects recorded in the case notes, or reported on detailed questioning at interview of the 59 patients, were as follows: tremor (23 subjects), subjective memory loss (23), weight gain (21), polyuria or polydipsia (21), loss of creativity (11), diarrhoea (10), hypothyroidism (10), goitre (7), nausea (5), impotence (5), gastric pain (4) and psoriasis (4). Hypothyroidism was diagnosed biochemically by routine measurement of plasma T3 and T4 and of TSH. Eleven subjects stopped taking lithium because of side-effects. None of the 59 patients seen in 1983 had any known renal disease and no other side-effects which might be specifically associated with prolonged use of lithium were detected.

<table>
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<th>Other treatment given</th>
<th>Prevalence</th>
<th>Concurrent</th>
<th>P value</th>
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<td>Prior to</td>
<td>Concurrent</td>
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<td>lithium treatment</td>
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<td>(mean 5 years)</td>
<td>(mean 11 years)</td>
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<td>Psychotherapy/analysis</td>
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Discussion
This study presents retrospective data from a large cohort of patients taking prophylactic lithium over a period of up to 17 years. Potential bias was introduced, in that 22 patients were either not traced or would not be interviewed. It is possible that these subjects were those in whom lithium had not produced a favourable response, and that they were therefore unwilling to cooperate with the study. This group of patients is also unusual in the marked bias towards social classes I and II, which is thought to be due to the inclusion of patients referred from outside London and even from other countries, at a time when lithium was not widely used or available. These latter patients were predominantly from the higher social classes.

Despite these methodological shortcomings, the results obtained do reveal several interesting points. First, 50% of patients showed a complete remission whilst on prophylactic lithium, 40% showed a partial but significant response and 10% a negligible response. This response was true of both unipolar and bipolar patients, and the prophylactic effect of lithium carbonate did not diminish with time in the patients who showed a good response.

The percentage of patients who show no apparent response to prophylactic lithium varies considerably in published studies. However, all studies agree that there is a significant proportion of both unipolar and bipolar patients who will relapse whilst taking lithium carbonate. This study has followed subjects over a long period of time, and has indicated that the subjects can be categorised according to response within the first 5 years of treatment. On examining the same subjects 12 years later, none had moved from one outcome group to another. It has previously been suggested by Dunner & Fieve (1974) that if patients are followed for long enough, they will all ultimately have a further affective episode, but this study did not confirm that hypothesis.

Secondly, in the bipolar group of patients, lithium was equally effective in preventing hypomanic and depressive episodes. This has been a subject of debate for some years, since Prien et al (1971, 1973a,b, 1974) found that lithium had a greater effect in preventing the manic phase of illness rather than the depressive phase. However, Baasrup et al (1970) and Coppen et al (1963) have found essentially similar prophylactic effects against the manic and depressive phases in their bipolar patients, and the results of this study, with a larger number of patients, confirm that finding.

Thirdly, these results do not show that a positive family history of bipolar illness indicates a more favourable response to prophylactic lithium; nor were we able to isolate any other specific factor which was correlated significantly with outcome. This conflicts with the strong correlation found by Mendlewicz et al (1973) between positive family history of bipolar illness and good response to prophylactic treatment. However, using a life-table method of analysis on a cohort of 120 patients, Dunner et al (1976a) found no association between negative family history and failure of lithium prophylaxis. In addition, on analysis of the relationship between sex, age at treatment, diagnosis, number of previous episodes, age of onset of illness and outcome of treatment, they concluded that there was no significant association between any of these factors and outcome. Our long-term study substantiated this evidence and also demonstrated no correlation between eventual outcome and certain other factors, including previous physical history, previous treatment, severity of illness before treatment, symptoms before treatment, dose, serum level and occurrence of side-effects.

Fourthly, only three of our subjects could be defined as 'rapid cyclers' (four or more affective episodes per year), and all of these seemed to derive considerable benefit from prophylactic lithium. Dunner & Fieve (1974) described this subgroup of manic-depressive patients and noted that they seemed not to respond to prophylactic lithium. However, in a later paper, Dunner et al (1976b) re-analysed the data from their sample of 'rapid cyclers' and concluded that lithium carbonate was effective in preventing hypomanic episodes in these patients.

Fifthly, the mean serum level, measured 12 h post-dose, was 0.7 mmol/litre in all three outcome groups, with no correlation between mean serum level and outcome. The guidelines concerning desirable plasma lithium levels for prophylaxis are still conflicting. A number of studies have indicated a higher rate of relapse among subgroups of patients maintained with average serum levels below 0.4 mmol/litre (Hullin, 1980) and 0.8 mmol/litre (Prien & Caffey, 1976). Recently, however, Peselow et al (1982) examined a large cohort of patients maintained on prophylactic lithium alone and found that they were unable to demonstrate a minimum level of lithium below which prophylaxis
against depression is ineffective. Sashidaran et al (1982) followed a cohort of 53 patients on lithium therapy and retrospectively detailed their serum level and mental state over a period of 3 years. They found that those who did not relapse during the trial had spent significantly less time with serum levels over 0.9 mmol/litre than had those who relapsed.

Finally, the side-effects found in our subjects have all been previously well documented. There was a surprisingly high incidence of clinical hypothyroidism, and further work is in progress to examine this group in more detail. We were not able to demonstrate any side-effects specifically associated with long-term lithium treatment, but in view of the association of tardive dyskinesia and long-term neuroleptic treatment, it is essential to continue to monitor closely those patients who have taken lithium for extended periods, in case of similar developments.

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**References**


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