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Is There a Lithium Withdrawal Syndrome?

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Patients who discontinued lithium after a mean of 29±21 months prophylaxis were compared with a similar group who were not taking the drug; all had only been in hospital once, and satisfied DSM–III criteria for mania. During the first three months following withdrawal of lithium, significantly more patients relapsed than in the control group; after this period, the rate was identical. These findings suggest that lithium withdrawal exists as a clinical phenomenon and that a period of lithium treatment does not improve the long-term prognosis, once the drug has been stopped.

Discontinuation studies in the early 1970s were concerned with proving the efficacy of lithium as prophylactic medication, and consequently did not look closely at the possibility of relapse being caused by drug withdrawal. Little attention was paid to the temporal relationship between discontinuation and relapse. It was generally assumed that the pattern of relapse reflected a recrudescence of the natural history of the disease process in a unprotected individual, rather than a drug-induced state. Early relapses were noted in some studies (Melia, 1970), but did not occur in sufficient numbers to arouse comment (Grof *et al*, 1970; Baastrup *et al*, 1970). One of the foremost authorities on lithium therapy has stated that he has never observed withdrawal phenomena or rebound illnesses (Schou, 1980). However, if there is a genuine withdrawal phenomenon it would have important implications both for the method used to discontinue patients from their treatment and also for the management of a rapidly recurring episode after stopping lithium.

Lapierre *et al* (1980) reported 20 cases who had their lithium withdrawn on an open basis, for five days; four patients relapsed within this time and required admission to hospital for mania. This report seems to provide some convincing evidence of a rebound phenomenon, although it has to be interpreted with caution: three of the relapsed patients had experienced a mean of two affective episodes per year in the period between first contact with psychiatric services and the prescription of lithium. Their rapid relapses could therefore be a function of their severe illnesses, rather than a result of lithium withdrawal.

Klein *et al* (1981) switched 21 patients to placebo, but it is not clear whether this was under single-blind conditions; the diagnosis was of affective illness, but no criteria for this are stated. Although 11 patients were reported to have "relapsed into severe psychotic states with paranoid, manic and depressive symptoms within 14 days", it does not appear that any of these were severe enough to warrant admission. All subjects restarted lithium after five weeks.

Christodolou & Lykouras (1982) studied 18 patients (17 of them bipolar) and reported that three relapsed within four days of double-blind placebo subsitution. Two of these relapses were reported as severe and one required ECT, but the severity of symptoms was assessed by rating scales, and none of the patients required admission. Among the assessments made on these patients was a scale measuring side-effects such as anxiety, tremor, restlessness, fatigue, irritability, and other symptoms normally associated with a drug withdrawal state. No increase in these was noted.

King & Hullin (1983) described four patients who suffered minor symptoms of heightened anxiety, irritability, and emotional lability as a result of lithium withdrawal; none of the patients had affective relapses, and none required admission to hospital. Withdrawal symptoms were then studied retrospectively by questionnaire, but usable replies were obtained from only 18% of the patients approached, and such a biased sample means that little reliance can be placed on their stated results.

Sashidharan & McGuire (1983), in a carefully conducted retrospective study of 22 patients satisfying Feighner criteria for primary affective disorder, could find no evidence of a rebound phenomenon: only two patients relapsed during the first two months after discontinuation. In all, 15 patients relapsed, the majority staying well for over one year, and they concluded that there was 'a gradual pattern of relapse over a period of months following discontinuation'.

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Method

The study group was drawn from patients admitted for the first time between 1 January 1970 and 31 December 1981; all satisfied DSM–III criteria for mania (American Psychiatric Association, 1980). Patients with puerperal illness or concurrent organic brain disease, or who were not resident in the UK at the time of their attack, were excluded. Two patients were excluded who committed suicide – one during a first admission and the other on the day of discharge. Also excluded were patients who did not have a clear gap between the stopping of their lithium and the onset of symptoms, as recorded in their case notes.

To be included in the study, patients in both the experimental and control groups had to remain well for at least three months following discharge, to ensure that any subsequent readmission was for a genuine relapse, as opposed to a recurrence of symptoms from the original episode. This excluded a similar number of patients from each group (29% of those on lithium and 22% of those that were not, $\chi^2 = 0.52$, d.f. = 1, NS). The control group therefore consisted of 50 patients, 42 of whom had never been on lithium, and eight who had only taken it for a period of less than three months; the experimental group consisted of 29 patients, established on prophylactic lithium for at least three months following discharge. Any patient who had three successive serum lithium estimations during follow-up of less than 0.4 mmol/litre was to be excluded from the study, but none were found. The patients subsequently took lithium for a mean of 29 ± 21 months.

From the admission notes and nursing records, demographic and clinical factors were recorded including age, sex, previous number of affective episodes requiring treatment but not admission, duration of admission, and family history of affective disorder. The severity of illness was estimated by the Modified Manic Rating Scale (MMRS) (Blackburn, 1977), which was further modified so that it could be used retrospectively on the admission notes. Inter-rater reliability with a rater blind to the purpose of the study gave a correlation of $r = +0.71$, which is in good agreement with the value quoted by Blackburn for the interview situation ($r = +0.68$ to $+0.79$). All patients and their GPs were contacted to provide a full follow-up picture until the close of the study (31 December 1983). The follow-up thus ranged from 2 to 14 years.

The outcome of the two groups was assessed by the life table method, which is the method of choice for analysing longitudinal data (Fleiss *et al*, 1976). Relapses during the course of manic-depressive illness have been shown to be exponential (Grof *et al*, 1970; Schou *et al*, 1970), and when plotted on a semi-logarithmic scale give a straight line, the slope of which is the 'decay constant'. Data from all patients in the study were used. A common starting point (time 0) was defined; at this point, formal follow-up began. For the control group, time 0 was three months after discharge from hospital, when they were considered to have recovered from their first illness. At this point, the experimental group had been established on lithium for three months; time 0 for this group was the point at which they subsequently discontinued their medication. Successive probabilities of remaining well over three month intervals from these points were calculated for both groups, relapse being defined as readmission to hospital.

Accurate information regarding the date of discontinuation of lithium was essential. Out of the 17 cases that were readmitted, seven had discontinued their drug in consultation with the medical staff, and this was clearly recorded; they subsequently developed symptoms and were readmitted. In another five cases, it was recorded at the time of their readmission that they had stopped their lithium, and developed symptoms 5, 7, 9, 14 and 21 days later (in two of these cases the dates of stopping lithium and the subsequent re-emergence of symptoms were corroborated by the patients' wives). In a futher two cases, information regarding discontinuation and subsequent readmission were supplied by other hospitals. Finally, in three cases, it was recorded that the patients stopped their lithium and then developed symptoms, but the exact date of discontinuation was not clear. In these cases the date of the last serum lithium determination was used, as supplied by the lithium office, which records the lithium levels of all patients in the region. These patients were readmitted two months, one year and four years later. This method is unlikely to have introduced any error into the results, since only one patient was involved in the period of significant difference between the groups. Since the analysis of outcome after discontinuation was calculated in three month periods, this patient would, in any event, appear in this first period.

Any retrospective study is dependent on the quality of the case records. This study was greatly facilitated because in Edinburgh all notes are typed before inclusion in the file, and all first admissions have a full and detailed case summary, prepared after discharge.

Results

Although patients were not randomly allocated to experimental or control groups, they did not differ on any factors that have been proposed as predictive of outcome. Thus, mean age was 34 ± 13.5 years (control 37 ± 14.2 years), number of patients with previous episodes was eight (control seven, $\chi^2 = 2.2$, d.f. = 1, NS), family history of affective disorder 11 (control 12, $\chi^2 = 1.9$, d.f. = 1, NS). Length of hospital admission did not differ: 7.1 ± 3.5 weeks (control 5.7 ± 3.5 weeks, $t = 1.67$, d.f. = 77, NS). The diagnostic breakdown of the relapses in the two groups was similar: of the experimental group, 13 (76%) were manic, compared

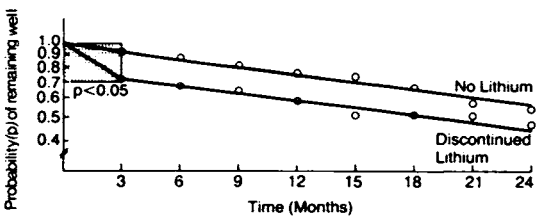


FIG. 1 Semi-logarithmic plot for discontinued lithium ($n = 29$) and control ($n = 50$) groups. Slopes were significantly different over the first 3 months ($P < 0.05$).

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TABLE I
Life table for discontinued lithium group (n=29)

Interval: months	*No. starting interval well (=a)*	*No. failing in interval (=b)*	*Interval-specific probability of failure (=c=b/a)*	*Interval-specific probability of remaining well (=1−c)*	*Cumulative probability of remaining well*
0–3	29	8	0.28	0.72	0.72
4–6	21	1	0.05	0.95	0.68
7–9	20	1	0.05	0.95	0.65
10–12	19	2	0.11	0.89	0.58
13–15	17	2	0.12	0.88	0.51
16–18	15	0	0.00	1.00	0.51
19–21	15	0	0.00	1.00	0.51
22–24	15	1	0.07	0.93	0.47

TABLE II
Life table for control group (n=50)

Interval: months	*No. starting interval well (=a)*	*No. failing in interval (=b)*	*Interval-specific probability of failure (=c=b/a)*	*Interval-specific probability of remaining well (=1−c)*	*Cumulative probability of remaining well*
0–3	50	4	0.08	0.92	0.92
4–6	46	2	0.04	0.96	0.88
7–9	44	3	0.07	0.93	0.82
10–12	41	3	0.07	0.93	0.76
13–15	38	1	0.03	0.97	0.74
16–18	37	4	0.11	0.89	0.66
19–21	33	4	0.12	0.88	0.57
22–44	29	2	0.07	0.93	0.54

with 17 (68%) of the controls. The only criterion on which they did differ was severity of initial illness as rated by the MMRS (experimental group 28.0 ± 7; control group 22.4 ± 8; $t=2.67$, d.f.$=76$, $P<0.01$). All chi-squared analyses included Yates' correction factor for continuity; *t*-tests were 2-tailed for independent samples.

The life tables (Tables I and II, Fig.1) show that there is an increased risk of relapse over the first three months following the discontinuation of lithium, compared with the first three months for the control group after recovery from their initial illness ($z=2.17$, $P<0.05$). After this period, the decay constants (rates of relapse) for the two groups are identical.

Discussion

This is the first study to report on a group of bipolar I patients after a first illness, with a similar group as a control. Readmission rather than the recurrence of symptoms was chosen as the outcome measure, since it is much more accurate in a retrospective study.

The increased risk of relapse over the first three months following the discontinuation of lithium lends support to the hypothesis that a withdrawal state does exist. As documented above, symptoms tended to recur rapidly, most patients being re-admitted within this first follow-up period. It is not possible retrospectively to be certain that the patients were well at the time they stopped their lithium, although great care was taken to exclude any patients where there was any doubt. Independent confirmation of lack of symptoms was obtained for five out of the eight patients that relapsed during this first period (three from medical staff, two from spouses).

The slopes of the graphs after the first three months are identical, indicating that a period of lithium treatment (in this case, a mean of $2\frac{1}{2}$ years) dose not improve the prognosis once it has been stopped. There is therefore no justification for short periods of prophylaxis.

Patients were not randomly allocated to treatment

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or no-treatment, but differed only on the severity of their initial illness, as rated by the MMRS. This is not surprising, since it is reasonable to assume that patients were put on lithium after their first admission because the clinicians believed (for whatever reason) that they were at an increased risk of future relapse. An alternative explanation for the results then seems possible, but if this group had an increased risk of relapse as a result of having had a more severe initial illness, a straight-line decay graph of a steeper slope than the control group would be expected. This is not the case, however, and no other studies have shown severity of symptoms to be predictive of future prognosis.

The results of this study are in contrast to that of Sashidharan & McGuire (1983), which is the only other one of comparable size. However, the latter shows important differences, with a mix of unipolar and bipolar patients, and it is not clear whether the bipolar patients are I or II; in the present study all patients were bipolar I, and it may be this group that is at high risk of a rebound state developing. This difference might go some way towards explaining the contradictory findings in the literature. Such a possibility is further supported by the fact that seven of the eight relapses in this study in the first three months were for mania (the other being for a mixed affective state), whereas in the earlier study there were an equal number of manic and depressive relapses.

Comparison with the study of Baastrup *et al* (1970) is also interesting: although he states that "there was no indication of rebound or abstinence effects", the investigation was completed in five months. During that time, 12 out of 22 manic depressive patients who had been switched to placebo relapsed; these also were equally divided between mania and depression, which might be a reflection of the ratio of bipolar to unipolar and bipolar I to bipolar II patients in the study. Although it is stated that "the relapses were spread over this period in a manner subjected to analysis elsewhere", these data are apparently unpublished, and no further conclusions can be drawn about them.

The possibility of a lithium withdrawal state has obvious implications for clinical practice. Early relapses might, in the absence of the phenomenon being recognised, lead to the patient being persuaded to restart lithium, and then to take it for a much longer period than necessary, perhaps for life. However, had the relapse been treated without lithium, the future prognosis might have been good and further prophylaxis unnecessary.

This is a retrospective study, and its data suggest that a prospective double-blind discontinuation study is needed of bipolar I patients, concentrating particularly on the temporal relationship between stopping the drug and the recurrence of symptoms. If the increased risk of relapse during the initial withdrawal period is confirmed, identification of types of individuals prone to this type of reaction would be helpful.

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