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Long-term outcome of lithium prophylaxis in patients initially classified as complete responders

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Abstract. The long-term outcome of lithium prophylaxis was explored in 43 bipolar and 36 unipolar patients who had been classified as complete responders after the first 2 years of treatment. These patients were followed up prospectively for a further period of 5 years (treatment period II), during which their psychopathological state was assessed monthly or bimonthly. Forty-nine patients completed treatment period II, 2 died during this period, 7 did not attend the unit anymore and could not be traced, and 21 definitively interrupted lithium treatment before the end of the period. In 18 cases the decision to stop lithium was taken by the patient. Twenty-five patients relapsed during the treatment period II. Four relapsers had three or more episodes concentrated during the last 2 years of treatment. These results suggest that the predictive value of an initial favourable response to lithium should not be overrated, and that the impact of the drug on the long-term course of major affective disorders in ordinary clinical conditions might be less dramatic than currently believed.

Key words: Lithium – Prophylaxis – Long-term outcome – Late non-response

The efficacy of lithium in preventing recurrences of both bipolar and unipolar affective disorders has been documented by a large number of controlled studies (see Prien 1979 and Schou 1979 for reviews). Nevertheless, the long-term outcome of prophylaxis in patients successfully treated with lithium for 1 or 2 years (which is the usual duration of controlled trials) remains to be established. It has been maintained that lithium does not lose its effect with time (Schou 1986; Page et al. 1987), that response over 6–12 months is a powerful predictor of long-term response (Abou-Saleh and Coppen 1986), and that the chance of a relapse even decreases the longer a patient continues to take lithium (Vinarova and Vinar 1984; Goodnick et al. 1987), but, on the other hand, it has also been stated that most bipolar patients will ultimately have an affective episode during lithium treatment if followed long enough (Dunner and Fieve 1974), and that in some patients, after years of successful treatment, recurrences may reappear with the same frequency than before lithium (Dotti and Bernini 1979). Furthermore, it has been reported that the admission rate for mania to British mental hospitals has recently increased despite the spread of the use of lithium (Symonds and Williams 1981; Dickson and Kendell 1986), which raises doubts about the impact of lithium prophylaxis on the long-term course of bipolar affective disorder in ordinary clinical conditions. It has also been shown that the drop-out rate during long-term lithium treatment is extremely high (Vestergaard and Schou 1988), which may mean that only a minority of patients actually remains on successful lithium prophylaxis for many years.

The present study was designed to explore the long-term outcome of lithium prophylaxis in a sample of bipolar and unipolar patients classified as complete responders after 2 years of treatment. These patients have been followed up prospectively for a further period of 5 years, during which their psychopathological state and plasma lithium levels have been assessed monthly or bi-monthly. All relapses have been recorded, as well as temporary or definitive interruptions of treatment.

Subjects and methods

In a previous paper (Maj et al. 1985) we reported on 43 patients fulfilling DSM III criteria for bipolar affective disorder and 36 patients meeting DSM III criteria for major depression, recurrent, who had completed at 2-year prophylactic treatment with lithium carbonate and had been classified as complete responders, having had no relapse despite a reasonably high risk of recurrence (history of at least one affective episode during the 2-year period preceding the index episode and the start of lithium treatment). They were 33 males and 46 females, with an age range (at the time of the assessment of lithium response) of 26–66 years (mean ± SD 44.5 ± 11.9).

After this first 2-year period (further referred to as treatment period I), lithium prophylaxis has been continued in all these patients, at doses adjusted in order to obtain 12-h plasma lithium levels in the range from 0.5 to 1.0 mEq/l. A conventional preparation of lithium carbonate, given in divided daily doses, has been used. Each patient has been seen monthly or bi-monthly, and his/her psychopathological state has been assessed by means of the Italian version (Perris et al. 1981) of the Comprehensive Psychopathological Rating Scale (CPRS, Åsberg et al. 1978). New episodes (defined as the periods during which the patient fulfilled DSM III criteria for either mania or major depression) have been recorded, as well as temporary or definitive interrup-

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tions of treatment, whose reasons have been ascertained, when possible.

At the end of a 5-year follow-up period (further referred to as treatment period II), the following information has been available: 1) number of patients who definitively interrupted lithium before the end of treatment period II, and the reasons for this interruption; 2) number of patients who reported having temporarily interrupted lithium during treatment period II, and the reasons for this interruption; 3) number of patients who relapsed, number of relapses and patients' mean total morbidity (expressed in months) during each year of treatment period II; 4) mean number per visit of CPRS manic and depressive symptoms during interepisodic intervals in each year of treatment period II (we used the list of 9 manic and 15 depressive CPRS items proposed by Maj and Perris 1985, omitting from the calculations the last visit before and the first visit after the one in which DSM III criteria for mania or major depression were met).

Statistical analysis was performed by Student's t test for paired and unpaired data, χ^2 test with Yates' correction and Pearson's test, as indicated.

Results

Of the 79 patients (43 bipolars and 36 unipolars) who had been classified as responders at the end of the treatment period I, 49 (25 bipolars and 24 unipolars) completed the treatment period II, two died (both of cancer) during this period, 7 no longer attended the unit and could not be traced, and 21 definitively interrupted lithium treatment before the end of the period. In three cases, interruption of treatment was decided by the physician, due to severe persistent impairment of renal concentrating ability. In 18 cases, the decision was taken by the patient, who reported the following reason(s) for discontinuation: conviction of being cured and of needing no more drugs in nine cases; trouble related to somatic side effects in 8; relapse during treatment in 6; hassle to take medicines in 3; loss of energy, creativity or productivity in 2. Interruption of treatment was followed by a relapse within 3 months in 6 of the 15 patients in whom reliable information could be obtained.

Of the 49 patients who completed the treatment period II, two temporarily interrupted lithium during this period following medical advice as they underwent major surgery, and eight reported having temporarily interrupted lithium against medical advice. The reason(s) for discontinuation of treatment mentioned by these last patients were: hassle to take medications in five cases; trouble related to somatic side effects in four; travels, intercurrent diseases or other situations in which taking lithium had become more difficult in three; missing the highs of hypomania in two. Of the ten patients who admitted temporary interruption of lithium during treatment period II, four relapsed during this period.

Within the total sample of 79 patients, 25 (10 bipolars and 15 unipolars) relapsed during treatment period II: 10 had one relapse, 5 two relapses, 4 three relapses and 6 more than three relapses. Overall, bipolar patients had 25 relapses (10 manic and 15 depressive), of which 15 required hospitalization, and unipolars 38 relapses (all depressive), of which 23 required hospitalization. The relapse rate and the patients' mean total morbidity were fairly steady from one year to another (Table 1). Patients' mean number of morbid episodes per year and mean total morbidity per year during treatment period II were significantly lower than during the 2-year period preceding the index episode and the start of lithium prophylaxis ($t=3.45$, $P<0.001$, Student's paired t-test).

Table 1. Drop-outs, relapses and patients' mean total morbidity during each year of treatment period II

Year	No. patients on prophylaxis	No. dropouts	No. patients relapsed	No. relapses	Patients' total morbidity (months, mean ± SD)
1	79	8	10	15	0.53 ± 0.21
2	71	5	9	12	0.46 ± 0.19
3	66	4	8	12	0.49 ± 0.22
4	62	7	9	14	0.51 ± 0.20
5	55	6	7	10	0.49 ± 0.12

Table 2. Mean number per visit of interepisodic CPRS depressive and manic symptoms during each year of treatment period II

Year	No. depressive symptoms (mean ± SD)	No. manic symptoms (mean ± SD)
1	1.87 ± 0.90	0.19 ± 0.17
2	2.07 ± 0.85	0.22 ± 0.16
3	2.10 ± 0.81	0.24 ± 0.16
4	1.94 ± 0.96	0.25 ± 0.18
5	1.97 ± 1.00	0.23 ± 0.17

Of the 49 patients who completed the treatment period II, 14 had relapsed and 35 had not relapsed. Relapsers did not differ significantly from non-relapsers with respect to the ratio between bipolars and unipolars, the frequency of morbid episodes before lithium, the frequency of a family history of bipolar affective disorder and the mean plasma lithium levels during treatment period II. Four relapsers had three or more episodes concentrated during the last 2 years of treatment period II, after having been relapse-free for 5 years (treatment period I plus the first 3 years of treatment period II): this late non-response to lithium did not appear to be a consequence of non-compliance, in view of the stability not only of plasma lithium levels but also of red blood cell/plasma lithium ratio throughout treatment period II.

The mean number per visit of CPRS manic and depressive symptoms during interepisodic intervals remained steady from one year to another of treatment period II (Table 2). Nevertheless, the mean number of depressive symptoms per visit during the treatment period II was significantly higher than during treatment period I ($t=2.04$, $p<0.05$, Student's paired t-test). Patients' mean number of interepisodic symptoms during treatment period II did not correlate significantly with their mean plasma lithium levels.

Discussion

The first evidence provided by the present study is a confirmation of the previously reported (Vestergaard and Schou 1988) high drop-out rate during long-term lithium prophylaxis. In fact, although our investigation was carried out

in a sample of patients who had got a considerable advantage out of the first 2 years of lithium treatment, the percentage of drop-outs during the following 5 years was found to be as high as 38%. Indeed, the initial success of treatment not only did not prevent patients from dropping out, but in some cases seemed paradoxically to encourage discontinuation, since the conviction of being cured and of needing no more drugs was the most frequently reported reason for interruption of prophylaxis. This may mean that in clinical practice a particular effort should be devoted to convincing initial complete responders of the necessity to continue treatment, especially in view of the fact that lithium discontinuation appears to be frequently followed by a relapse within a few months, as our data confirmed.

It is interesting to notice that in the present study missing highs of hypomania was only seldom reported as a reason for interruption of lithium treatment, which is in line with the recent report by the Danish group of the Aarhus hospital (Maarbjerg et al. 1988), but in disagreement with the findings obtained in most American investigations (Polatin and Fieve 1971; Van Putten 1975; Jamison et al. 1979). It cannot be excluded that sociocultural factors played a role in such divergence of results: the greater emphasis laid in American society on effectiveness and productivity might enhance the social advantage related to periods of hypomania, so that patients might be more likely to miss these periods during lithium treatment. Another point on which our data are in agreement with those of the Aarhus group and at variance with those of American authors (in particular, Jamison et al. 1979) is the nature of the side effects which are most frequently reported as reasons for lithium discontinuation: in the present study, as well as in that by Maarbjerg et al. (1988), only somatic side effects (in particular, weight gain and polyuria) were mentioned by the patients, whereas in American studies patients found cognitive side effects (memory and concentration disturbances) more important. This divergence may be in part related to the different methods of data collection.

Overall, the results of the present investigation confirm that lithium retains its prophylactic efficacy in the long term. In fact, there was a highly significant difference, with respect to the mean number of morbid episodes per year and the mean total morbidity per year, between treatment period II and the pre-lithium period. Nevertheless, the relapse rate was somewhat higher than that reported in some other recent follow-up studies (Bouman et al. 1986; Page et al. 1987). Moreover, we were able to confirm the anecdotic report by Dotti and Bernini (1979) that in some patients recurrences may reappear, after years of successful treatment, with the same frequency than before lithium: this happened in four patients of our sample, despite an apparent good adherence to treatment regimen. This late non-response to lithium prophylaxis may represent an important target for future research, from both the clinical and the biological viewpoint. It is also interesting to notice that the mean number per visit of interepisodic CPRS depressive symptoms was significantly higher in the treatment period II as compared to the first 2 years of prophylaxis: this confirms the clinical impression that in some patients on lithium treatment a sort of persistent mild dysphoria may develop as treatment goes on.

As a consequence of the high drop-out rate, and of the relapses occurring in some patients, only 44.3% of the subjects who had been classified as complete responders after the first 2 years of lithium treatment were found to be still on completely successful lithium prophylaxis at the end of the following 5 years. This means that the predictive value of an initial favourable response to lithium should not be overrated, and that the impact of the drug on the long-term course of major affective disorders in ordinary clinical conditions may be less dramatic than currently believed. The reports by Symonds and Williams (1981) and Dickson and Kendell (1986) that the admission rate for mania to British mental hospitals has not decreased, in spite of the spread of the use of lithium, could be explained in this light, especially if one considers that, according to the results of several discontinuation studies (Cordess 1982) and to the trend observed in the present investigation, the risk of a relapse in particularly high during the months following lithium withdrawal.

In conclusion, the efficacy of lithium in preventing recurrences of both bipolar and unipolar affective disorders remains unquestionable. However, the drug is clearly not a panacea, and problems related to patients' compliance seem to damp considerably its long-term morbidity suppressive effect in an ordinary clinical setting.

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