Eur Arch Psychiatry Clin Neurosci (1999) 249 : 227–230

ORIGINAL PAPER

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Early onset of lithium prophylaxis as a predictor of good long-term outcome

Received: 3 August 1998 / Accepted: 23 June 1999

Abstract The recurrence rates during lithium preventive treatment were investigated in a sample of 270 Mood Disorder subjects subdivided according to their onset time for lithium prophylaxis as very early (within 5 years from the onset of illness), early (6–10 years), late (11–20 years) and very late (more than 21 years). 131 subjects of the sample followed for 4 years prolonged the observation for a further period of 8 years. Results indicated that beginning lithium therapy within the first ten years of illness predicts better preventive outcomes than beginning prophylaxis later, both in major depression, recurrent and bipolar patients.

Key words Prophylactic treatment · Lithium salts · Recurrence index

Introduction

The preventive mood-stabilizing property of lithium is clearly established. Lithium has been confirmed to be the first-line preventive treatment for bipolar disorders (Price and Heninger 1994). As reviewed by Souza and Goodwin (1991) and Montgomery and Rouillon (1992), lithium has also demonstrated good efficacy in the prophylaxis of unipolar depressive illness.

Several studies and reviews have identified clinical predictors of preventive efficacy of lithium salts (Goodwin and Jamison 1990, Schou 1989).

Among all the clinical features related to lithium response, some reports suggested that having three or four previous episodes could predict a poor response (Gelember 1989, Post et al. 1990). In this sense, a crucial issue for the clinician is to decide which is the best moment for beginning prophylactic lithium. According to the APA guidelines (1994), it should be started after the third episode in unipolars and after the second episode in bipolars, also considering the clinical characteristics which predict a more severe course of illness such as early onset, secondary cases of bipolar and recurrent unipolar forms and high recurrence rates.

The prevention of recurrence is the goal of long-term treatment: according to the available data, lithium prophylaxis should reduce the number of episodes and/or their clinical severity, preventing the natural worsening of mood illness.

It is a common clinical observation that the prophylactic action of lithium tends to gradually increase during the course of the treatment (Schou 1985). Although remissions and recoveries are more likely to occur with an earlier started acute treatment, (Kupfer et al. 1989, Barbini et al. 1996), it is presently unknown whether there is a relation between the early (or late) lithium prophylaxis and the long-term outcome pattern. Assuming that a good preventive effect of lithium could be predicted by its early beginning, the aim of this study was to test this hypothesis comparing the outcome on treatment of four groups of patients who received lithium at different times of their illness course, also taking into account the other clinical variables possibly related to lithium response.

Material and methods

Sample

The cohort included 298 subjects (111 males, 187 females) recruited from the patients who had been referred to the Outpatient Lithium Clinic for Mood Disorders of S. Raffaele Hospital in Milan since January 1990.

All subjects were diagnosed according to DSM-IV criteria (APA, 1994) as having Major Depression, Recurrent (N = 119) and Bipolar Disorder (N = 179). Information about clinical onset and course of the disease was collected from the DIS Affective Disorders Section.

Patients with Axis I co-diagnoses were excluded.

Thirty-one major depression, recurrent and fifty-five bipolar patients were part of the group of 213 patients previously studied

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(Gasperini et al. 1993) and still coming to our Lithium Clinic. Among the 298 subjects, 28 patients interrupted lithium therapy: in 10 patients lithium was interrupted by their clinician for the occurrence of serious side effects (hypotyroidism N = 3; several ponderal increase N = 5; myocardial stroke N = 1; pregnancy N = 1). Nine patients themselves discontinued the treatment and 9 patients dropped out or were referred to other care centers. All these cases were excluded from the analyses.

Drop-out patients excluded, the present study included 270 subjects who had a minimum lithium prophylaxis period of 48 months without discontinuation.

For each of 270 patients included, we registered the onset time of lithium prophylaxis in the clinical course of illness, according to which we subdivided the sample into four groups:

- "very early" group including patients who initiated lithium within the 5th year from the onset of illness (N = 119);
- "early" group including patients who initiated lithium between the 6th and 10th year from the onset of illness (N = 54);
- "late" group including patients who initiated lithium between the 11th and 20th year from the onset of illness (N = 52);
- "very late" group including patients who initiated lithium after the 21th year from the onset of illness (N = 45).

Follow-up

The duration of follow-up period ranged from a minimum 4-year to a maximum 8-year period. Among the sample of 270 patients followed on lithium treatment for at least 4 years, 131 patients prolonged follow-up until the 8th year of treatment.

All patients enrolled received lithium as maintenance therapy with doses adjusted for obtaining 12-hour plasma levels within standard therapeutic range. The mean values ranged between 0.5 and 0.9 mEq/l for plasma levels and between 0.2 and 0.5 mEq/l for red blood cell levels. During the follow-up, determination of lithium levels was obtained for each patient every two months. At the same time, clinical conditions of patients were evaluated by their own clinicians and also by another psychiatrist (L.F.) who administered the 21-Hamilton Rating Scale for Depression (Hamilton 1964) and the Young Scale for Mania (Young 1978).

At the time of control, patients who met DSM-IV criteria for a major depressive or a manic episode, after having been euthymic for the previous eight weeks, were recognized as having a new recurrence. In those cases, they received additional care and treatment according to clinical therapeutical standards (for details see Gasperini et al. 1993).

Recurrence rate assessment

As the cycle pattern of mood illness has high quotes of interindividual variability (Angst 1981), the recurrence rates of patients were measured as indices and not as number of acute episodes during their life course. The recurrence rates before and during prophylaxis were calculated as the ratio between the number of episodes over the time (in months) between the onset of the illness and the beginning of lithium prophylaxis, for the former, and between the number of episodes over the length (in months) of prophylaxis, for the latter: Recurrence indices were defined as the recurrence rates X 100.

The gradient between recurrence index before and after the beginning of lithium treatment was assumed as a measure of the outcome.

Statistical analyses

Clinical and demographic variables in the sample subdivided according to onset time of lithium prophylaxis were compared by Chi-square, t-tests and one-way Anova.

The good/bad outcome, measured as recurrence rate gradient, was processed as a dependent variable against the other variables of interest such as polarity, sex, current age, duration of illness, age of onset of illness, duration of lithium treatment and onset time of prophylaxis ("very early", "early", "late" and "very late") by stepwise multivariate logistic regressions.

We carried out different logistic analyses: the first in the whole group of 270 patients treated for 4 years, the second in the subgroup of 131 patients treated for 8 years.

Results

Table 1 shows the distribution of clinical and demographic characteristics of the sample subdivided according to the onset time of lithium prophylaxis.

In the whole sample of 270 patients treated for 4 years, the outcome on lithium treatment, measured as the gradient between recurrence indices before and after lithium treatment, was analyzed by logistic analyses taking into account polarity, sex, age, onset, duration of illness, duration of lithium prophylaxis and onset time of lithium prophylaxis. On stepwise multivariate logistic regression the "onset time of lithium prophylaxis" was the only variable significantly associated to the outcome on lithium treatment ($t = -6.01$ $P \leq 0.00001$).

Also processing the subgroup of 131 patients who prolonged prophylaxis for 4 more years, the same variable was the only significant one ($t = -6.11$ $P \leq 0.00001$). In fact, good outcomes on lithium treatment (high gradient values) were significantly more related to "very early" and "early" onset time of prophylaxis than to "late" and "very late" ones. Table 2 shows the percentages of improvement among patients who completed the period of 4-year follow-up on lithium (A) and among patients who completed the observation of 8-year follow-up on lithium (B). In both groups an earlier lithium treatment was related to a better prophylaxis outcome as shown by higher percentages of improvements among "very early" (within 5 years from the illness onset) and "early" (within the tenth year of illness) onset of lithium treated patients.

The polarity of the illness did not condition the outcome on lithium treatment. That was confirmed also by separately processing the gradient against the independent variables in major depression, recurrent (N = 99) and bipolar (N = 171) samples. The logistic analyses carried out in major depression, recurrent and bipolar subjects confirmed the predictive role of "onset time of lithium prophylaxis" as shown by significant values from stepwise analyses in major depression, recurrent ($t = -4.45$ $P \leq 0.00001$) and in bipolar groups ($t = -4.87$ $P \leq 0.00001$).

Considering that, as shown in Table 1, the four subgroups are different in their previous course of the illness (current age, age of onset and duration of illness), we performed regression analysis matching the sample by current age and age at onset. In both cases analysis provided the same role of "onset time of lithium prophylaxis" as shown by significant values from stepwise analyses in the sample matched by current age (N = 52) ($P \leq 0.005$) and by age at onset (N = 82) ($P \leq 0.0003$).

Table 1 Clinical and demographic characteristics of the sample subdivided according to the onset time of lithium prophylaxis

Variables	Very early (n = 119)	Early (n = 54)	Late (n = 52)	Very late (n = 45)
Sex (M/F)	48/71	15/39	18/34	17/28
MDR/BP	46/73	20/34	16/36	17/28
Age (M ± SD)	42.5 ± 14.5*	47.5 ± 11.7*	50.7 ± 10.3*	59.5 ± 8.5*
Onset (M ± SD)	35.6 ± 13.4**	35.1 ± 12.2**	30.1 ± 10.1**	26.5 ± 8.3**
Years of illness (M ± SD)	6.9 ± 4.8***	12.4 ± 3.5***	20.6 ± 5.3***	32.9 ± 6.9***
Months of lithium treatment (M ± SD)	57.5 ± 53.1	51 ± 26	65.8 ± 50.9	51.3 ± 25
Recurrence	15.4 ± 15.9[a]	7.1 ± 10.7[a]	3.7 ± 3.0[a]	2.6 ± 2.9[a]
Index before lithium (M ± SD) recurrence	2.9 ± 6.3	2.9 ± 3.9	2.9 ± 3.2	2.7 ± 4.2
Index during lithium (M ± SD)				

* F = 21.68 3DF $P \leq 0.0001$
** F = 8.03 3DF $P \leq 0.0001$
*** F = 311.46 3DF $P \leq 0.0001$;
[a] F = 20.13 3DF; $P \leq 0.0001$

Table 2 Percentage of improvement* in the four onset time of lithium prophylaxis group patients observed for (A) 4-year follow-up (N = 270) and (B) 8-year follow-up (N = 131)

Groups of onset	(A) Improved	Not improved	(B) Improved	Not improved
Time of lithium				
"Very early"	95.5%	4.5%	93.1%	6.9%
"Early"	83.3%	16.6%	84%	16%
"Late"	48.7%	51.3%	57.7%	42.3%
"Very late"	55.8%	44.1%	54.5%	45.5%

* Improvement was rated by positive gradients between recurrence indices before and after lithium treatment

Discussion

In the present study the most striking result was that an earlier lithium prophylaxis could condition a better outcome pattern.

According to our results, beginning lithium prophylaxis early during the course of the illness and especially within the first five years seemed to predict the best outcomes for recurrence course both for major depression, recurrent and bipolar patients. A possible explanation of this finding could simply be that the recurrence rates of illness in the early years are lower than the rates of the following ones. In this sense, as recurrence of both major depression, recurrent and bipolar forms tends to become more and more frequent with each successive episode (Prien and Kocsis 1995) the outcome on lithium prophylaxis could be affected by the natural course of the illness. Maj and colleagues (1996) recently reported the finding that longer duration of illness could explain the phenomenon of late-poor response of subjects who in the first five years of lithium prophylaxis had showed a good response (Maj et al. 1989, Post et al. 1993, Koukopoulos et al. 1995).

According to our previous data (Gasperini et al. 1993) the recurrence indices of the period before lithium prophylaxis did not prove to affect the outcome on lithium: this very findings has been replicated in the present study in which, on the other hand, the worst recurrence indices before lithium clustered among the best lithium responders. Indeed, the best responders of our sample, i.e., the group of patients who initiated lithium prophylaxis within their first five years of illness (N = 119), were the same who had significantly higher recurrence rates before beginning prophylaxis.

In this sense, patients with the worst recurrence rates and illness courses before prophylaxis could be considered as more severe than and not comparable to the other ones. In fact, a very high frequency of episodes per se could determine the worsening of the course of the illness with increasing new recurrences and shortening cycle-length. Moreover, a high recurrence rate early in the course of the illness could identify biologically more severe subgroups of mood patients with a more homogeneous and better outcome to lithium (Smeraldi et al. 1984).

In addition, a very high recurrence rate is always one of the main clinical criteria of choice for starting lithium treatment. Therefore, one possible methodological limit of our study could be the selection of a priori lithium responder group.

Nevertheless, the fact that the "very early lithium onset" subjects dramatically decreased the number of their recurrences after lithium treatment appeared of great clinical importance in prophylactic treatment of Mood Disorders.

Dealing with our results, we would like to emphasize the importance of the outcome criterion definition: since prophylactic usefullness of lithium gradually increase in the course of treatment and since the high interindividual variability in recurrence rate, the evaluation of good outcomes should not simply include the occurrence/not occurrence of new episodes. That is the reason why we considered the decrease of specific recurrence patterns between the periods before and after the beginning of lithium treatment prophylaxis as a suitable predictor of a good outcome. To our knowledge, the results of our study are the first ones in literature and therefore need to be confirmed.

From the clinical practice there is a general agreement of not treating long-term patients who only had one single episode of major depression or more than one with a lengthy interval between the episodes. Moreover, accord-

ing to standard guidelines, the presence of a minimum of at least three episodes for unipolars and two for bipolars as also the occurrence of other factors of severity (very early age of onset of illness, high recurrence rates and/or very severe episodes plus familial aggregation) strongly recommends the beginning of preventive treatment (APA 1994). In this sense, the preventive efficacy of early treatment with lithium just after recovery from the first affective episode might be of crucial importance for the life course of mood illness.

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