

LITHIUM PROPHYLAXIS IN AFFECTIVE DISORDER

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SUMMARY

Out of 108 patients on the rolls in the Lithium clinic, Madurai Medical College and Govt. Rajaji Hospital, Madurai, India, 47 patients suffering from affective disorders receiving lithium continuously for more than three years were analysed with a view to study the recurrences. Thirteen suffered no relapses while on lithium while nineteen experienced them while on lithium. Four were free from recurrences after lithium was withdrawn. Seven defaulted but suffered recurrences while in four the drug was withdrawn and in both the groups remission was achieved with readministration of lithium. The study reveals that lithium besides averting the recurrences can reduce the frequency, number, duration, intensity of episodes and improve the amenability to drugs. Among the symptoms, suicidal ideas and behaviour and insight were found to be influenced favourably by lithium. Among the factors that help favourable response to lithium were a positive family history of affective disorder, in the first degree relatives and lesser frequency and number of episodes in the pre-lithium period. A reappraisal of the natural history of the illness is called for in the light of lithium prophylaxis of manic depressive psychosis.

In his now historic paper, 'Lithium salts in the treatment of psychotic excitement' Gade (1949) first observed the anti-manic properties of Lithium. It was however Schou's (1954) efforts that led to an extensive clinical application and intensive investigation of the drug. In 1970, the Food and Drug Administration, United States approved Lithium for treating manic illness and for its prophylaxis.

In view of the availability of lithium for prophylaxis of manic depressive psychosis a clearer view of the course of the illness is called for. There have been conflicting reports on this. For example, according to Pollock *et al.* (1939) in the pre-lithium era, 58.1% of patients had only one attack, 26.1% two attacks, 9.3% three attacks and 6.5% more than three attacks. On the other hand, Rennie (1942) found that 70% of all patients had a second

attack, 63.5% third attack and 45% fourth attack. This was especially so in those over forty years. Similarly, Angst *et al.* (1969) after examining the course of endogenous affective psychosis in 979 cases covering 2260 disease cycles concluded that the course of recurrent mood disorders gets progressively more severe. In an earlier work from the first author's unit, 28% of 122 cases had only one attack while recurrence occurred in 63 cases. Chronicity was noticed in 11 patients (Venkoba Rao and Nammalvar, 1977). Surveying 6 major publications on the subject Zis and Goodwin (1979) concluded, that "the vast majority of patients with primary affective disorders experience several episodes during their life time." In this context of severe recurring nature of the disease, the use of lithium becomes relevant. Kraepelinian notion of manic depressive psychosis as a

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benign disorder has lost much of its force (Kraepelin, 1921).

Hartigan (1963) first reported on the prophylactic use of lithium for manic as well as depressive episodes. These beneficial results of lithium were later confirmed both by longitudinal trials that compared frequency of attacks before and after administration of lithium (Baastrup *et al.*, 1970; Coppen *et al.*, 1971; Hullin *et al.*, 1972 and Prien *et al.*, 1973a) and also by matching it against placebo and imipramine (Fieve *et al.*, 1968; Fieve & Mendelewicz, 1972; Prien *et al.*, 1973b; Stallone *et al.*, 1973). It is not clear whether lithium prevents the attacks by normalizing the mood by its normothymotic action as proposed by Schou or it exercises a suppressive action by raising the patient's threshold to stressful life situations (Prien, 1979).

Lithium Clinic :

This communication is from the Lithium clinic functioning from 1975 in the Institute of Psychiatry, Madurai Medical College and Govt. Rajaji Hospital, Madurai, India. The clinic is held once a week. The earlier important publications from this clinic include clinical response to lithium (Venkoba Rao and Hariharasubramanian, 1978a and 1978b); lithium induced E.C.G. changes (Venkoba Rao and Hariharasubramanian, 1980); renal function studies (Venkoba Rao *et al.*, 1979); renal biopsy studies (Venkoba Rao *et al.*, 1981); memory impairment (Sugumar *et al.*, 1980) and the effects of lithium on the adrenal cortex and pineal gland (Parvathi Devi *et al.*, 1973, 1976, 1978 and 1980; Hariharasubramanian *et al.*, 1976). It is felt appropriate at this point to make a critical assessment of the prophylactic benefits to the manic depressive psychosis patients.

Presently, there are 108 patients (M : 70 ; F ; 38) on the rolls of the clinic. Serum lithium was estimated by Amdisen's flame photometric method. The serum levels

were maintained between 0.6 and 1.2 m. mols/lit. Hullin (1979) suggest that the levels from 0.4 to 0.8 m. mols/lit would suffice for prophylaxis though recognising the need for higher levels of 0.6 to 1.2 m. mols/lit for controlling acute manic episodes.

AIMS

The principal aims of the study are—

- (a) to compare the pre and post lithium pattern of recurrences in bipolar affective disorder ;
- (b) to ascertain whether lithium affects the features of the recurrences like their frequency, the duration, the number and intensity ;
- (c) to study how the factors like family history of affective illness in the first degree relatives, pre-lithium recurrence pattern, clinical diagnosis, duration of the illness, age and sex of the patient, age at onset of illness and polarity of first and index episodes affect the response to lithium ; and
- (d) to observe the effect of lithium on suicide ideation and suicide behaviour and insight.

MATERIAL AND METHOD

Forty seven (M : 28 ; F : 19) among 108 lithium clinic patients, lent themselves for study on the basis of the criterion of having been on lithium therapy for a *minimum* period of three years. The duration of therapy varied from three to six years. The age of the patients ranged from 21 to 63 years (mean 39.5). The diagnoses were : Bipolar depression (MDP) (ICD 296.1) (N—40) ; Recurrent Mania (ICD 296.2 ; N—3) ; Unipolar depression (ICD 296.3 ; N—4). The duration of illness varied from two to fifteen years preceding lithium administration. The material (N—47) was divisible into five groups, based on the pattern of response.

Group I (N=13) : Total remission without recurrences ; continuously on lithium (Total duration of treatment 3—5.5 years) ;

Group II (N=4) : Remission for 2 years while on lithium. Drug withdrawn ; No recurrences for 2 years following cessation of lithium.

Group III (N=4) : Remission without recurrences for 2.5 years while on lithium ; lithium was then withdrawn. Recurrences within a mean period of 8 months. Lithium restarted and maintained with remission and no further recurrence for 1.5 years.

Group IV (N=7) : Recurrences after de-faulting. Remitted after resuming

lithium. No recurrences while on lithium for 3 years.

Group V (N=19) : Recurrences occurred while on continuous lithium therapy. (Duration of treatment 3-6 years).

Tables I and II offer data on the patients in all the groups.

This is an open and single blind study without involving control or a comparison with other drugs or placebo. Each patient served as his own control and the comparison has been between pre- and post-lithium characteristics of recurrences. Such open and single blind studies have been reported (Schou, 1959 ; Wharton & Fieve, 1966 ; Blinder, 1968 ; and Vander Velde, 1970) and found to be quite valid on reappraisal

TABLE I—*Details of episodes (Pre-lithium period)*

Factors	G1	GII	GIII	GIV	GV
Total No. of episodes ..—Manic ..	30	3	3	18	48
—Depressive ..	32	4	3	8	45
No. of episode per patient —Manic ..	2.3	0.75	0.75	2.6	2.55
—Depressive ..	2.5	1.00	0.75	1.1	2.35
Frequency/year ..	0.8	0.5	0.5	0.8	1.7
Duration of each episode ..	3	2.5	2.5	3	3
	months	months	months	months	months
Intensity of each episode ..	Moderate/ severe	Mild/ Moderate	Moderate	Severe	Moderate severe
Interval of remission between episode.	10 months.	1 year.	3 years	1.4 years.	8 months.

TABLE II—*Duration of follow-up*

Duration in years	G1	G2	G3	G4	G5
Duration of continuous therapy —Mean	3.4	3	3	3.2	4.4
—Range	3—5.5	3	3	3—3.5	3—6
Duration of drug-free period	2	0.6	1.5	..
				weeks	
Duration of therapy after restart- ing	1.5	3	..
Total duration of follow-up ..	3.4	5	5.3	6.2	4.4

following the controlled studies referred to earlier.

The criteria for recurrences were the persistence of disturbed mood and biological symptoms like insomnia, anorexia and alteration of psychomotor activity for more than 72 hours.

OBSERVATIONS

(a) *Recurrences* : The recurrences occurring in Group V (supra) notwithstanding the continuous administration of lithium revealed the following features. The frequency and the number of recurrences, the duration and intensity of each of them were all significantly less when compared with the pre-lithium period. While there were 48 pre-lithium manic episodes, they fell to 27 in the post-lithium period. For the depressive episodes, the corresponding pre-lithium and post-lithium figures were 45 and 28. The average number of episodes in the pre-lithium period was 4.9 per patient but it was 2.9 in the post-lithium stage. The frequency of episodes per year came down from 1.73 in the pre-lithium to 1.01 in the post-lithium period. The mean duration of each episode which was 12 weeks prior to lithium fell to 3.8 weeks. While the intensity of the pre-lithium episodes was rated as moderate to severe, in the post-lithium it was mild to moderate. The inter

episodal period of 8 months during pre-lithium period lengthened to 11.5 months during lithium administration (Table III).

The data showed a lack of any preferential prophylactic property of lithium either for manic or depressive episodes in the bipolar patients. Both responded identically. In respect of the unipolar depression it is difficult to draw any conclusion since there were only four such patients in the series though three responded with no recurrences (Two each in Group I and II).

Thus pre and post-lithium recurrences reveal the mitigating effects of lithium although recurrences could not be totally averted in this group. Additionally the relapses were easily controlled by increasing the dose of lithium or by combining it with phenothiazines or anti-depressants depending upon the episode. None of the patients required hospitalisation. On the other hand, before the institution of lithium the relapses were treated by ECT and hospitalization in addition to anti-depressants and phenothiazines. There were six instances of recurrence in the post-lithium phase where they were preceded by stressful life events. It is likely that contrary to the claim, lithium did not lessen the vulnerability of the patients to life's stresses.

(b) *Clinical features of the recurrences* : Clinical features were studied with special

TABLE III

Factors	Pre-lithium	Post-lithium	% Change
No. of episodes			
.. .. . —Manic ..	48	27	36.25
.. .. . Depressive ..	45	28	62.2
Average number per patient	4.9	2.9	59.2
Frequency per year	1.73	1.01	38.4
Mean duration of episode (in weeks)	12	3.8	63.2
Intensity of episodes	Moderate/ severe	Mild/ moderate	
Mean interval of remission (in months)	8	11.5	66.6

reference to the occurrence of suicidal thoughts and attempts and preservation of insight, both before and in post-lithium stages. Though eight patients had suicidal ideas and two attempted suicide in the series during pre-lithium period, none experienced them nor made attempt during lithium treatment. The receding of suicidal ideas and absence of suicidal attempts while under lithium even during recurrences adds a new dimension in suicide prevention programme. This also brings a fresh look at the course and natural history of the illness. In an earlier study on the course and outcome of depression from the department 45% experienced suicidal ideas, 25% attempted suicide with one ending in suicide (Venkoba Rao and Nammalvar, 1977). There have been no suicidal death or attempt among the patients in all the five groups in the post lithium period.

It is interesting to note that several patients who reported to the clinic during the recurrences were aware of a change in their mental and physical well being. While before the starting of lithium therapy, the insight was poor, but when under lithium the patients were able to sense the oncoming recurrence and seek relief in the clinic. This adds considerably to the early management of relapses and may explain the shorter duration of episodes under lithium. This was not so in those with non-drug compliance (Group IV).

Time taken for remission :

The period required for remission after restarting lithium was highest (6 weeks) in Group IV (defaulters) indicating the unfavourable effects of irregular adminis-

tration on their own. The time taken in all the groups for induction of remission is indicated in Table IV.

Factors affecting the responses :

Age, and sex of the patients, the age at the onset of illness, the duration of the illness and the polarity of the first or index episodes did *not influence* the successful lithium prophylaxis either in Group I or the not so successful response in other groups (Table V). On the other hand, the occurrence of affective illness in the first degree relatives was more frequent in Group I than in the other groups. It was nearly five times more frequent than in the Group V patients. Affective illness in the second degree relatives did not bear such relation (Table VI). Attention was drawn to this by Fieve (1976) while summarising the available literature.

DISCUSSION

Our data offer strong support for the lithium prophylaxis in Bipolar affective disorder. Out of 47 probands receiving lithium for more than three years, 28 patients responded to lithium either with no recurrences at all while on drug (N-13) ; or after its withdrawal (N-4) or after re-administration following voluntary withdrawal (N-4) and defaulting (N-7). Nineteen patients experienced recurrences while on continuous treatment but they were marked by lessened frequency, number, intensity and duration and a higher susceptibility to drug treatment without hospitalisation or ECT. Such observations have been referred to by Fieve (1976). There have been numerous favourable reports on

TABLE IV—*Time taken for remission after starting lithium therapy*

Duration in weeks	G1	G2	G3	G4	G5
Period for remission ..	2.5	3.5	3.5	6	3.8
Period for second remission	2	8	..

The earlier onset of remission in G1, G2, and G3 patients was statistically significant.

TABLE V

Factors			G1	G2	G3	G4	G5
			(N=13)	(N=4)	(N=4)	(N=7)	(N=19)
Age	Range	..	30—63	22—55	45—50	35—55	25—60
	Mean	..	45.5	38.8	46.2	42.5	41.5
Sex :	Male	..	9	4	2	6	10
	Female	..	4	..	2	1	9
Total duration of illness (years)		..	7.5	2	5.1	15	5.3
Age at onset of illness (years)	—Range	..	22—50	20—45	35—40	25—35	20—55
	Mean	..	38.5	32.5	37.5	29.3	32.5
Polarity of first episode	—Manic	..	9	1	1	3	9
	—Depression	..	4	3	3	4	10
Polarity of index episode	—Manic	..	10	1	3	6	11
	—Depressive	..	3	3	1	1	8

TABLE VI—Family History of Mental Illness

Nature of illness		Degree of relatives	G1 (N=13)	G2 (N=4)	G3 (N=4)	G4 (N=7)	G5 (N=19)
Affective Illness	I Degree relatives	..	3 (23%)	1 (25%)	1 (25%)	..	1 (5%)
	II Degree relatives.	..	2	2	1	..	2

lithium prophylaxis in bipolar illness (Hartigan, 1963 ; Baastrup & Schou, 1967 ; Prien *et al.*, 1979 ; and Narayanan *et al.*, 1979). The placebo control studies have revealed that about 30% of manic-depressives on lithium experienced a relapse during a two-year follow-up period (Baastrup *et al.*, 1970 ; Prien *et al.*, 1973 ; Stallone *et al.*, 1973 ; Coppen *et al.*, 1971). The relapse rate by contrast was 90% among those receiving placebo.

The effectiveness of the prophylactic effect in unipolar depressives has been advanced by Schou (1979) and Prien (1979) amongst others. However, in our series the number of unipolar depressives is too small to help draw any firm conclusion.

It is intriguing that the Group I patients (N=13) experienced no relapse while those Group V suffered relapses though miti-

gated although both groups were receiving lithium continuously. A higher incidence of affective disorder in the first degree relatives, lesser frequency of episodes, and lesser time required for inducing remission were associated with the absence of relapses in Groups I and II and their easy control in Group III. This state of affair did not prevail in Group V. Thus the type of response calls for further study over the possibility whether one is dealing with different types of affective disorders within the bipolar group in relation to lithium response. Spitzer *et al.* (1978) have stated that the illness lasting for over 2 years becomes treatment resistant. Rapid cyclers (four or more episodes per year) do not fare well with lithium as was pointed out by Dunner and Fieve (1974).

With the advent of prophylaxis, a

critical reappraisal of the natural history of the disease and course becomes necessary. The episodes of either mania or depression get modified under the influence of continuous lithium therapy in regard to frequency, number, duration as well as symptom content. From the present study two other important findings have emerged. One is the complete absence of suicidal ideation and suicidal attempt during recurrences. One should not overlook those in Group I who enjoyed total absence of recurrences while assessing the risk of suicide. Barraclough (1972) has calculated that one-fifth of the suicides in MDP patients was preventable by lithium treatment. Sainsbury (1980) by extrapolating this figure, claimed that in England the total suicides would have been less by 750 per year.

The other clinical feature, the retention of insight in a large majority of patients enabled them to sense that the recurrence was around the corner and report at the clinic earlier thereby facilitating early treatment and a quicker control of symptoms. In years to come there is a likelihood of a change in the symptomatology of the manic-depressive episodes when it is claimed that lithium specifically alters the core symptoms viz. the affective and ideational features of the illness (Goodwin and Zis 1979). One should therefore be prepared to recognize the "truncated" or "metamorphosed" episodes of effective illness in patients already on lithium. This situation is analogous to the treated long term illnesses like Tubercular disease.

One other major index of prophylactic benefits from lithium apart from the lowering the number of recurrences and suicide control is the reduction in cost involved in the management of the patient. None of the patients in the present series needed hospitalization for treatment of recurrences, nor were the ECTs resorted to avoiding thereby the fear that they generate. They were

all effectively controlled with drugs. It has been estimated that around 4 billion dollars have been saved in the United States during the decade following the approval of lithium by FDA for use in mania and as prophylaxis for bipolar illness (Reifman and Wyatt, 1980). This was arrived by assessing the economy in the psychiatric care and increased production by MDP patients treated with lithium.

It is not possible with the present data to state categorically as to when the lithium therapy should be stopped. For instance, in Group II, only four responded with a remission after a cessation of lithium for two years. The Group I patients (N=13) were enjoying remission but were on lithium. On the other hand, the Group V patients (N=19) suffered recurrences even while on lithium. However, it is clear that in a certain group of patients lithium could be withdrawn without the risk of recurrences. Further studies are awaited in this regard.

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