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LITHIUM IN AFFECTIVE DISORDERS : A SEVEN YEAR OBSERVATION OF LITHIUM CLINIC

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SUMMARY

Out of 692 patients registered in the lithium clinic, King George's Medical College, Lucknow, 122 patients suffering from affective disorders, receiving lithium for at least 6 months continuously, having had at least 5 serum lithium estimations done and having been evaluated at least once in 6 months while on follow-up, were analysed with a view to study the relapses. About one-third patients suffered no relapse while on lithium. The study revealed that longer the duration of lithium treatment lesser were the frequency, number, intensity and duration of manic/depressive relapses. Majority of patients were maintained on the lower side (0.5-0.8 mEq/L) of the usually recommended therapeutic range (0.6-1.2 mEq/L) for lithium prophylaxis. Commonly observed side effects include fine tremors, muscular weakness, polyuria, polydipsia and constipation. All the side effects were easily managed and none had a fatal sides-effect. A reappraisal in the light of existing literature of lithium prophylaxis on manic depressive psychosis is done.

Ever since Cade (1949) observed the antimanic effect of lithium and Schou et al. (1954) conducted extensive clinical studies to elucidate its application in the treatment of Affective Disorders, reports continue to appear in the world literature which affirm the element's, unique position in the pharmacotherapeutic armamentarium of psychiatrists.

Hartigan (1963) for the first time reported on the prophylactic effects of lithium on manic as well as depressive episodes. This property, of lithium was later on confirmed by studies comparing frequency and intensity of episodes of mania and depression 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 through controlled trials involving placebo and imipramine (Fieve et al., 1968; Fieve and Mendelewicz, 1972; Prien et al., 1973b and Stallone et al., 1973). As a result of the modifying influences introduced by the therapeutic activity of lithium it has now become essential to view the patient and his illness for a much longer period.

However, in India, very few studies have highlighted the role of lithium as an antimanic-depressive drug (Prakash and Sethi, 1978; Venkoba Rao and Hariharsubramaniam, 1978; Narayanan et al., 1979; Tandon et al., 1981 and Venkoba Rao et al., 1982). The most obvious reason for such scanty information is the existence of very few lithium clinics primarily because of inadequate facilities to monitor lithium therapy in a majority of centres across the country. The present communication is based on data collected at our clinic which has been in existence for more than 7 years.

MATERIAL AND METHODS

The Lithium Clinic was established in the Department of Psychiatry, King George's Medical College, Lucknow in 1977. Since then the clinic has been

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providing specialized services to the vast population of the state of Uttar Pradesh and surrounding regions of North India. The clinic functions on all weekdays and caters to the patients of our hospital, private clinics, and referrals from other psychiatric hospitals. Besides the present study, antipsychotic effects of lithium in schizophrenia, effect of lithium on memory and renal functions, chronic myeloid leukemia during lithium therapy (case report) and megaloblastic anaemia secondary to lithium (case report) have also been studied in the clinic. Lithium and its role in controlling aggression being studied presently.

This present report is an open 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 the pre and post lithium characteristics of recurrences. Other open and single blind studies have been reported (Schou, 1959; Wharton and Fieve, 1966; Blinder, 1968; Vander Velde, 1970 and Venkoba Rao et al., 1982) and found to be quite valid on reappraisal following the controlled studies referred to earlier.

Over a period of 7 years 692 patients from our and other psychiatric hospitals and private clinics were registered in the lithium clinic and were available for evaluation on one or more occasions. Comprehensive information however (especially follow-up evaluations), was available for our hospital patients only, since patients from other sources were being followed up at their respective clinics/hospitals Although patients belonging to our hospital numbered 285, the present report refers to 122 subjects since they fulfilled the minimum criteria of 1) receiving lithium for at least 6 months continuously 2) having had at least 5 serum lithium estimations done and 3) having been evaluated at least once in 6 months while on follow-up.

Before a patient was started on lithium therapy, he/she was assessed for suitability; the process involving critical evaluation of clinical data including diagnosis (according to International Classification of Diseases-Ninth Revision, W. H. O., 1977) and biochemical measures including a complete haemogram and urinalysis, blood urea, blood sugar, serum creatinine, serum chloesteral, serum electrolytes (Na^+,K^+), liver function tests, ECG and weight charting. Other specialized investigations were done as and when required. In patients taken up for lithium therapy, lithium carbonate was administered 300-1650 mg/day in two or three divided doses. After 48 to 72 hours of commencement of lithium blood samples were drawn twelve hours after the last oral dose of lithium. The serum lithium was estimated by flame photometry, using Amdisen's method (Amdisen, 1967). Two or three estimations were done at weekly intervals and the dose was adjusted according to the clinical condition and also to keep the serum levels within the therapeutic range. There after, for the first three months, the patients were reviewed once in 2-3 weeks and later at longer intervals. During each review serum lithium was estimated, besides recording clinical assessment, side-effects, weight charting and use of other concomitant medication. Every patient was informed about possible side-effects and an instruction sheet for the same provided. The follow-up record was maintained on a lithogram.

The criteria for relapses were the persistence of disturbed mood and biological symptoms like insomnia, anorexia and alteration of psychomotor activity for more than 72 hours (Venkoba Rao et al., 1982).

OBSERVATIONS

Characteristics of the Sample:

TABLE I—*Characteristics of the sample*

		N	%
Sex	Male	108	88.5
	Female	14	11.5
Diagnosis	M. D. P. Unipolar-mania (296.0)	16	13.1
	M. D. P.-Unipolar-Depressed (296.1)	18	14.8
	M. D. P.-Bipolar-Mania (296.2)	56	45.9
	M. D. P.-Bipolar-Depressed(296.3)	32	26.2
Duration of lithium treatment	6 Months to 1 year	36	29.5
	1 To 3 Years	52	42.6
	3 To 5 Years	22	18.0
	5 To 7 Years	12	9.9

As shown in table-I the majority of patients were males (88.5%), having M. D. P. bipolar-mania as the most frequent diagnosis (45.9%) followed by M. D. P. bipolar-depressed (14.8%) and M. D. P. unipolar-mania (13.1%). The patients on lithium therapy for 1-3 years (42.6%) constituted the largest group followed by those on therapy from 6 months to 1 year (29.5%), 3 to 5 years (18.0%) and 5-7 years (9.9%).

Frequency of relapses:

In regard to the frequency of manic depressive relapses in the different lithium intake groups, about one third of the sample (40 out of 122) had no relapse. Majority of the relapsed patients had one or two manic and/or depressive relapses. The response was even better when categories of bipolar affective disorder and unipolar mania only are considered (38 out of 104 had no relapse) indicating lithium to be less effective in the prophylaxis of unipolar depression (Table II).

Relapses at follow-up:

Table-III shows the number of patients relapsing at different years of follow-up in patients taking lithium for

TABLE II—*Frequency of relapses in lithium intake groups*

Period of lithium intake	No. of patients	Number of relapses: Mania 1	2	3	4	Depression 1	2	3	4	No relapses
6 *Months to* 1 *year*										
—Unipolar	12	2	2	—	—	4	2	—	—	2
—Bipolar	24	16	1	—	1	13	4	—	1	6
1 *To* 3 *years*										
—Unipolar	20	3	2	—	—	4	3	2	—	6
—Bipolar	32	10	6	4	—	5	9	6	—	12
3 *To* 5 *years*										
—Unipolar	2	—	—	—	—	—	1	1	—	—
—Bipolar	20	4	4	2	1	1	5	1	1	8
5 *To* 7 *years*										
—Unipolar	—	—	—	—	—	—	—	—	—	—
—Bipolar	12	2	2	1	1	3	2	1	—	6

TABLE III—*Relapses at Follow-up*

Period of lithium intake	No. of patients	No. of patients relapsing at year of follow-up												
		Mania							Depression					
		1	2	3	4	5	6	7	1	2	3	4	5	6	7
3 *To* 5 *years*															
—Unipolar	2	—	—	—	—	—	—	—	2	4	—	—	—	—	—
—Bipolar	20	11	7	3	1	—	—	—	12	7	2	1	—	—	—
5 *To* 7 *years*															
—unipolar	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—Bipolar	12	6	4	2	1	—	—	—	6	2	—	—	—	1	1

3-5 years and 5-7 years. While the number of bipolar patients having manic relapses during 1st year in the 3-5 years lithium intake group were 11, they were decreased to 7,3 and 1 during 2nd, 3rd and 4th year respectively and none in the 5th year. A similar pattern was seen in relation to depressive relapses in the same group and to manic relapses in the 5-7 years lithium intake group. The number of patients having depressive relapses during the 1st year in the later group were 6 and were decreased to 2 in the 2nd year, none during 3rd to 5th year ard only one patient had mild episodes of short duration during 6th and 7th year. Thus, one is able to observe a reduction in the frequency of relapses as the duration of maintenance treatment with lithium increases and lithium to be equally effective in manic as well as depressive relapses in bipolar illness.

Basic Data :

Table IV and V reveal the basic data in regard to frequency of serum lithium estimations, mean serum lithium

TABLE IV—*Frequency of estimation and mean serum lithium levels*

Duration of lithium therapy	Frequency of serum lithium estimation	No. of patients	Mean serum lithium levels (mEq/L)	Range
6 Months to 1 Year	5—9	26	0.61±0.23	0.10—1.12
	10—14	10	0.54±0.22	0.06— .81
1 To 3 Years	5—9	26	0.66±0.23	0.13—1.36
	10—14	12	0.63±0.19	0.19—1.20
	15—19	8	0.62±0.21	0.30—1.25
	20 & above	6	0.72±0.24	0.40—1.35
3 To 5 Years	5—9	6	0.60±0.23	0.12—1.20
	10—14	4	0.59±0.15	0.25—0.92
	15—19	6	0.65±0.18	0.22—1.06
	20 & above	6	0.56±0.31	0.08—1.17
5 To 7 Years	5—9	—	—	—
	10—14	2	0.56±0.13	0.38—0.78
	15—19	4	0.71±0.19	0.18—1.18
	20 & above	6	0.76±0.21	0.10—1.25

TABLE V—*Mean serum lithium level according to dose*

Dose of lithium mg/Day	No of eastimation				Mean serum lithium mEq/L				Range			
	6 Mths To 1 Yr.	1 To 3 Yrs.	3 To 5 Yrs.	5 To 7 Yrs.	6 Mths To 1 Yr.	1 To 3 Yrs.	3 To 5 Yrs.	5 To 7 Yrs.	6 Mths. Yo 1 Yr.	1 To 3 Yrs.	3 To 5 Yrs.	5 To 7 Yrs.
300	1	—	18	—	0.34	—	0.19	—	0.34	—	0.08—0.30	—
450	54	72	56	1	0.52	0.49	0.52	0.48	0.20—0.75	0.23—0.80	0.24—0.83	0.78
500	—	28	16	7	—	0.59	0.44	0.51	—	0.32—0.81	0.32—0.73	0.25—0.58
600	86	170	150	21	0.53	0.62	0.57	0.76	0.10—1.00	0.17—1.20	0.27—0.85	0.63—0.94
625	1	16	—	—	0.64	0.60	—	—	0.64	0.42—1.00	—	—
750	60	172	124	100	0.60	0.70	0.62	0.68	0.06—1.00	0.13—1.00	0.32—1.20	0.10—1.25
900	55	74	44	92	0.62	0.73	0.59	0.70	0.23—1.10	0.32—1.25	0.16—1.08	0.30—1.18
1000	19	52	30	28	0.68	0.78	0.64	0.86	0.40—1.00	0.13—1.35	0.40—0.95	0.48—1.20
1050	9	12	8	13	0.75	0.64	0.71	0.87	0.34—0.94	0.55—0.74	0.31—1.00	0.62—1.05
1200	1	16	18	1	0.12	0.69	0.73	0.92	1.12	0.32—0.98	0.48—1.10	0.92
1250	—	7	6	—	—	0.70	0.73	—	—	0.83—1.36	0.54—0.90	—
1350	1	1	—	1	1.10	0.90	—	0.92	1.10	0.90	—	0.92
1500	7	—	6	5	0.95	—	1.055	0.80	0.64—1.11	—	1.05—1.06	0.72—0.87
1650	—	—	—	1	—	—	—	0.80	—	—	—	0.80

levels and relationship between the dose and serum levels in the four lithium intake groups. The frequency of serum lithium estimation was 5-14 times in 6 months to 1 year group and 5-20 times and above in the other three groups. Majority of patients have mean serum lithium levels between 0.5 to 0.8 mEq/L and with the increase in the dosage of lithium these levels increased correspondingly.

Side effects

Table VI shows the nature and frequency of side-effects as seen in the clinic sample. Fine tremors were most frequent (30.9%) followed by muscular weakness (26.1%), polydipsia (21.2%), constipation (19.6%), polyuria, drowsiness, oedema and anorexia (16.3% each). One patient each had azoospermia, megaloblastic anaemia and chronic myeloid leukemia. The side-effects were easily managed and none had a fatal side-effect.

TABLE VI—*Side effects*

	Side Effects	N	%	
1.	Fine tremors	38	(30.9)	
2.	Muscular weakness	32	(26.1)	
3.	Polydipsia	26	(21.2)	
4.	Constipation	24	(19.6)	
5.	Polyuria, drowsiness, oedema, anorexia	20	(16.3)	Each
6.	Dryness of mouth	12	(9.8)	
7.	Weight gain, bodyache, headache, distaste of mouth	10	(8.2)	Each
8.	Diarrhoea	8	(6.5)	
9.	Nausea, dizziness, forgetfulness, muscular cramps and fasciculations	6	(4.9)	Each
10.	Vomitting	5	(4.1)	
11.	Stomatitis, slurred speech, palpitation	4	(3.3)	Each
12.	Blinking of eyes, Breathlessness, heaviness of abdomen, blurring of vision, skin erruptions, facial grimacing	2	(1.6)	Each
13.	Azzospermia, megaloblastic anaemia, chronic myeloid leukemia	1	(0.8)	Each

DISCUSSION

Our data offer strong support for the lithium proplylaxis in bipolar affective disorder. Out of 122 patients receiving lithium for a period between 6-months to 7 years, 40 patients had no relapse. Eighty two patients experienced recurrences while on continuous lithium treatment but they were marked by lessened frequency, number, intensity and duration. These relapses of mania or depression required lesser concomitant phenothiazines or antidepressants along with lithium and only few of them required hospitalization or treatment with electroconvulsive therapy. Thus, there was a substantial reduction in cost involved in the management of the patient. Such observations have been referred to by Fieve (1976) and Venkoba Rao *et al.* (1982). There have been numerous favourable reports on lithium prophylaxis in bipolar illness (Hartigan, 1963 ; Baastrup and Schou, 1967 ; Prien 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 followup 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. Although in our series the number of unipolar depressives was too small to help draw any firm conclusion, it was observed that as compared to bipolar illness or to unipolar mania, lithium was found to be less effective in the prophylaxis of unipolar depression. However, in the manic and depressive relapses of bipolar illness lithium was found to be equally effective.

The retention of insight in a majority of patients enabled them to sense that the recurrence was around the corner and to report at the clinic earlier thereby facilitating early treatment and a quicker control of symptoms. In years to come there is a likelihood of change in the symptomatology of the manic depressive episodes when it is claimed that lithium specifically alters the core symptom viz. the affective and ideational features of the illness (Goodwin and Zis, 1979). One should therefore be prepared to recognize the truncated or metamorphased episodes of affective illness in patients already on lithium. This situation is analogous to the treated long term illness like tuberculosis (Venkoba Rao *et al.*, 1982).

The majority of our patients had mean serum lithium levels ranging from 0.5 to 0.8 mEq/L thereby indicating that in our setting patients of affective disorder are well maintained at the lower side of the usually recommended maintainence level i.e. 0.6—1.2 mEq/L. In all the four groups of lithium intake, a dose range of 300 mg. to 1500 mg was suffcient to bring about the desired clinical response and an increase in the dosage of lithium is accompanied by a corresponding increase in the values of level which always remained within the recommended therapeutic range, though mostly on the lower side. Hullin (1979) suggested that the levels from 0.4 to 0.8 mEq/L would suffice for prophylaxis, though recognizing the need for higher levels of 0.6—1.2 mEq/L for controlling acute manic episodes.

The side-effects encountered during the course of lithium therapy in our clinic population were in one-third of the sample, a frequency which was lower than the reports of Hewick *et al.* (1977) who reported minor side-effects in over 40% of patients stabilized on long-term lithium therapy and of Johnston *et al.* (1979) who observed side effects in about two-third of the patients. One of the reasons for this discrepancy may be due to the maintainence of our patients on the lower side of the therapeutic range the other reason can be due to cross cultural variation. The frequency of fine tremors (30.97%), muscular weakness (26.1%), polydipsia (21.2%), constipation (19.6%) and polyuria (16.3%) as seen in our sample more or less correspond to the reports in the literature.

An attempt was made to correlate the side-effects with serum lithium levels and it was observed that below 0.3 mEq/L diarrhoea was the most prominant side effect which decreased on increasing the dose of lithium carbonate. Bone *et al.* (1980) reported the most frequent cause of drop-out had been severe diarrhoea on very low dosage. Above the serum level of 1.0 mEq/L along with usual side effects we observed muscular cramps, fasciculations, slurred speech, blinking of eyes, facial grimacing and forgetfulness which were not noticed on lower levels. All the side effects were easily managed and no fatal side effect occurred in our sample although megaloblastic anaemia and chronic myeloid leukemia were detected in one patient each.

CONCLUSION

Experiences with lithium at this centre provided further proof of its

therapeutic and prophylactic efficacy in bipolar and unipolar patients, though more in bipolars. The longer the duration of treatment lesser were the frequency, number, intensity and duration of manic depressive relapse. Majority of patients were maintained on the lower side (0.5—0.8 mEq/L) of the usually recommended therapeutic range (0.6—1.2 mEq/L) for lithium prophylaxis. Commonly observed side effects include fine tremors, muscular weakness, polyuria, polydipsia and constipation. All the side-effects were easily managed and none had a fatal side-effect though megaloblastic anaemia, chronic myeloid leukemia and azoospermia were observed in one patient each.

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