Evaluation of lithium therapy in chronic and periodic alcoholism

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Abstract: The use of lithium as a therapeutic agent in the treatment of chronic alcoholic patients with depression has been investigated in a double blind study with active medication and placebo. Lithium appears to modify the patients' drinking habits significantly ($p < 0.01$) when the readmission rate of the groups are compared. Of those patients who had to be readmitted for their drinking, the lithium group had fewer episodes as compared to the control group. Although both groups were less depressed at the end of one year, as compared to their depression ratings at the beginning of the project, there was not a significant difference between groups (analysis of covariance), *ie,* there was a placebo response which may have disguised a real difference. Other parameters studied included serum magnesium levels and thyroid function which showed that the clearance of iodine from the plasma by the thyroid gland was significantly increased ($p < 0.005$).

KEY INDEXING TERMS

Chronic alcoholism *Lithium therapy* *Lithium thyroid*

The vast number of persistently proposed treatments for alcoholism (from psychoanalysis to lysergic acid diethylamide [LSD]) indicates the extreme difficulty in determining the effectiveness of therapy. Many authors have stated that it is reasonable to assume that most alcoholics are suffering from depression, which raises the question as to whether or not control of the affective disturbance in these patients would influence their addiction. A search of the literature indicated that lithium had not been systematically investigated as a possible therapeutic tool in the treatment of chronic alcoholism. The only study was that of Fries[1] carried out on 17 patients in a clinic; the author himself stated the data were inconclusive because many patients failed to take the medication.

Varied therapeutic responses have been reported[2,3] in the use of antidepressive medications, especially the tricyclic group. It has been questioned whether tricyclics remain effective when administered in chronic fashion for many years, and the time course of alcoholism would seem to indicate that some form of continuous therapy is required. Lithium, on the other hand, has been administered for periods up to 15 years without any reported untoward effects.[4] Therefore, in this respect lithium would seem to fit the requirements of a medication for treating chronic alcoholism. In the study to be described, either lithium or placebo was administered in a double blind fashion to patients with chronic alcoholism associated with depression. Patients with manic depressive

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(bipolar) or recurrent endogenous (unipolar) depressions were not included. All patients had required hospitalization for their excessive drinking.

Methods

The design was double blind with patients randomly assigned to either lithium or placebo and maintained on this schedule for 48 weeks. At the end of this period the placebo group was crossed over to active medication whereas the active medication group remained on lithium; that is, at the end of 96 weeks those patients originally assigned to the lithium group had had 96 weeks of continuous lithium therapy whereas the placebo group had had 48 weeks of placebo followed by 48 weeks of lithium. The patients were selected from the Alcoholic Treatment Program of a Veterans Administration Hospital. All 73 patients were on inpatient status at the time of their selection. Almost all had been suffering from acute effects of alcohol intoxification when admitted to the hospital. They had completed a routine detoxification program and were usually on one of the tranquilizing medications at the time of their selection. On the average, subjects had been hospitalized not less than one month when selected.

The initial selections were a function of the psychiatric and medical services. As stated, the principal criteria for selection were (1) chronic alcoholism, and (2) nonpsychotic depression. Chronic alcoholism is defined for purposes of this study by code No. 303 proposed by the American Psychiatric Association and outlined in the *Diagnostic and Statistical Manual of Mental Disorders.*[5] Several subcategories are defined; for the present study, patients were in the category 303.1 (habitual excessive drinking) and 303.2 (psychologically and physically addicted to alcohol).

TABLE I

AGE DISTRIBUTION

ALL PATIENTS COMPLETING FIRST YEAR-PROTOCOL

Group I (Placebo) N = 14			Group II (Lithium) N = 16		
Years	No.	%	Years	No.	%
25-34	0	0	25-34	1	6
35-44	5	36	35-44	4	25
45-54	7	50	45-54	6	38
55-64	2	14	55-64	5	31

Seventeen patients were habitual excessive drinkers and 56 were alcohol addicts. Duration of the disease in all patients was five years or more. Table I shows the age distribution of those patients who completed 48 weeks.

Fifty per cent of the patients were separated or divorced. Formal education of the group averaged between 11 and 12 years.

Table II shows the procedures carried out during the first 48 weeks of the project. The selection period varied but never exceeded one month duration. The control period and initial medication period were of one month duration.

During the control period all medication was discontinued to eliminate, as far as possible, other drug influences upon the study and in particular the study of thyroid function. Laboratory indices (Table II) included a complete blood count, urinalysis, and determinations of blood urea nitrogen, blood sugar, cholesterol, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase, sodium, potassium, chloride, bilirubin, and magnesium. The asterisk in the table represents the frequency with which all of these tests were done; for example, the MSER[6] (a computerized mental status evaluation report) and the ZUNG self-rating scale[7] (a questionnaire completed by the patient which enables quantitation of the degree of improvement or regression compared to a baseline reading for that patient) were carried out twice during the control period, once during the initial medication period and bimonthly thereafter.

Table III compares the previous history of the placebo group *vs* the previous history of the active medication group. Again, one-year periods were compared; this indicated that members of the group were similar at the time of their assignments to either lithium or placebo.

TABLE II

PROCEDURES DURING FIRST 48 WEEKS OF PROJECT

Data Collection	Selection Period	Control Period	Initial Medication Period	Months of Medication 2	3	4	5	6	7	8	9	10	11	12
Psychiatric evaluation	*													
Medical evaluation	*	*	****	*	*	*	*	*	*	*	*	*	*	*
E.K.G.; chest roentgenogram	*													
Random drawing		*			*						*			
Laboratory work-up		*						*	*			*		
Li. Mg.		*	****	*	*	*	*	*	*	*	*	*	*	*
Thyroid isotope		*												*
F.T4 T4		*	*	*	*	*	*	*	*	*	*	*	*	*
MSER and ZUNG SDS†		**	*	*		*		*		*	*	*		*
Psychiatric follow-up			*	*		*		*		*				

†*MESR: computerized mental status evaluation report; ZUNG: self-rating questionnaire.*

TABLE III

DISABLING DRINKING EPISODES
COMPARISON PLACEBO GROUP PREVIOUS HISTORY I'S LITHIUM GROUP PREVIOUS HISTORY*

No. of Episodes	Placebo	Lithium
0 - 1	5	5
2 - 3	5	8
> 3	4	3

**Chi square difference not significant.*

Our interest in the effects of lithium on thyroid studies during this period included determination of the thyroid and urinary clearance of iodide, absolute iodine uptake and plasma levels of free iodide, serum thyroxine, and free thyroxine levels by radioisotope techniques. During the initial medication period, serum lithium levels were determined weekly, and the medication adjusted to achieve a range of 0.6 to 1.2 mEq/liter. The patients on placebo were given a similar number of tablets.

To maintain the double blind conditions in this study, bloods were collected on patients whether they were receiving placebo or active medication and placebo medication was also adjusted occasionally to help maintain the blind status. One investigator (JCW), not involved in psychiatric or psychological evaluation of the patients, and one laboratory technician were the only people who knew who was receiving lithium and who was not. This investigator (JCW) adjusted the medication to achieve satisfactory blood levels of lithium in those patients using the active medication. The results were recorded in a separate book for the laboratory; this book was then given to JCW and only returned to the laboratory when the next group of samples were to be analyzed. During the crossover period at the end of the first 12 months the placebo patients were crossed to lithium and therefore required more frequent blood analysis to adjust their intake to a suitable level. To maintain the blind status in this situation a similar number of blood samples were collected on all patients whether they

were previously on active medication or placebo. The difficulties in maintaining a blind situation when patients are receiving a drug which has side effects such as one finds occasionally with lithium–*eg,* tremor, polyuria, gastrointestinal disturbance, at the beginning of treatment–may make it important that as far as possible the investigators have little input to the data to be analyzed. However, the physical manifestations of chronic alcoholism encompass many of the side effects observed with lithium and thus make detection by professional staff more difficult. In addition, the medical care was the responsibility of JCW and the psychiatric care that of OC. The psychiatrist (OC) did not elicit medical information from the patients.

A word as to why this collaborative study with the Veterans Administration Hospital in Maine was done. The unreliability of chronic alcoholics is well documented. To carry out the study as described with alcoholics from a catchment area in or within close proximity to a large city is virtually impossible. However, Togus is the only psychiatric center available to the V.A. patient in the whole of Maine. In addition, patients were selected whose residences were within a maximum area approximately 150 miles from the hospital. Previous experience demonstrated that we could maintain good contact and follow-up with these patients. If patients did suffer from major drinking which required detoxification, the only hospital in the area to which they could come was the hospital in which the study was being carried out. Therefore, we had much greater control of the patient population than we possibly could have at many other more research-oriented hospitals.

The patients were given medication (lithium or placebo) for a five-week period and blood levels as stated were monitored at monthly intervals. Thus, if a patient inadvertently missed a recall, contact was made immediately and a fresh appointment made for that patient within a week so that he was not without medication. If the patient missed a recall, did not respond to the social worker contact, and was then not seen at the subsequent monthly recall (by which time he had been without medication for a three-week period), he was regarded as a treatment failure and dropped from the project. The patients on active medication could also have serum levels checked to determine whether they were taking medication as prescribed whereas obviously the placebo group could not. However, we did not experience any great difficulty in maintaining acceptable serum lithium levels in medicated patients; rather, if a patient was not taking the medication as prescribed he failed to appear for his monthly recall.

Results

A high attrition rate is expected in any outpatient study (our own experience in many such studies is about 50 per cent) and is often higher when alcoholic patients are involved. The patient population selected for this study was as unreliable as expected; the tendency to drop out and disappear was high. Of the 73 patients selected, 43 (59 per cent) failed to take medication as prescribed during the first follow-up period of 48 weeks. Of the remaining 30, 14 were from the placebo group and 16 were from the lithium group. There were no dropouts due to drug intolerance. The present report is mainly concerned with the 30 patients who completed 48 weeks of continuous treatment and the 21 patients who completed 96 weeks of continuous treatment.

We chose the objective criterion of changes in the number of disabling alcoholic episodes to evaluate the effects, if any, of lithium treatment. For the purpose of this study, disabling drinking was defined as drinking to the point of interference with normal daily life, necessitating admission to hospital for detoxification. The quantitative determination was the number of such episodes. Table IV is an analysis of the episodes of disabling drinking for the 30 patients maintained on medication for the full 48 weeks (placebo or lithium). Sixty-four per cent of the placebo group as compared with 25 per cent of the lithium group were involved in such drinking episodes. The significance of this difference was at the $p < 0.05$ level (chi-square).

TABLE IV

ANALYSIS OF EPISODES OF DISABLING DRINKING*
(48 Weeks)
(N=30)

Group 1 (Placebo) (N=14)				Group 2 (Lithium) (N=16)			
Episodes				Episodes			
One or More		None Known		One or More		None Known	
No. Pts.	%	No. Pts.	%	No. Pts.	%	No. Pts.	%
9	64	5	36	4	25	12	75

**Chi square difference significant at $p < .05$.*

TABLE V

COMPARISON OF FIRST YEAR LITHIUM AND PLACEBO
VS PREVIOUS YEAR HISTORY OF DRINKING EPISODES

Placebo Group* (N=14)			Lithium Group† (N=16)		
Number of Patients	Previous Year	Placebo Year	Number of Patients	Previous Year	Lithium Year
2	6	6	3	0	0
4	3	1	9	2	0
5	4	5	14	5	2
7	4	0	15	4	0
10	3	5	20	2	0
13	0	0	21	3	5
28	1	0	22	3	0
36	2	2	24	2	0
48	3	10	25	1	0
58	5	4	40	2	0
65	2	1	41	2	1
66	1	0	43	1	0
72	1	1	55	1	0
73	1	0	57	1	0
			59	5	1
			68	2	0
Total	36	35	Total	36	9

**Chi square difference not significant.*
†Chi square difference significant at $p < 0.01$.

When the nine patients on placebo and the four patients on lithium who did relapse were analyzed for the number of disabling drinking episodes by the Mann-Whitney U-Test, a significant difference at the 0.025 level was found, indicating that, in addition to the difference in number of patients who had disabling episodes, among those patients who did have episodes the rate was less in the lithium-treated group than in the placebo group.

These data were analyzed for the degree of depression at the beginning of the study and

after 48 weeks of treatment. Depression scores before treatment and after 48 weeks of treatment were analyzed using a paired *t* test. There was no significant difference between the groups before treatment. After 48 weeks of treatment, there was significant improvement in the depression ratings for both groups. There was, however, no significant difference between the two groups by analysis of covariance.

Table V shows the comparison of a year of placebo medication to the previous year for the same patients, and the comparison of a year of lithium treatment to the previous year for those patients. Placebo had no significant effect upon the drinking habits of the patient whereas lithium clearly did ($p < 0.01$).

Table VI, in which the *N=18,* compares the number of disabling drinking episodes in patients who completed two full years of lithium treatment. These data are compared to their histories in the two years preceding the start of this project. It may be seen that there were 59 disabling drinking episodes during the preceding two years and that every one of the patients had at least one episode. During the first year of lithium treatment three of these patients had disabling drinking episodes. Over the two-year period six patients had disabling drinking episodes throughout the entire treatment period.

TABLE VI

TOTAL NUMBER OF DISABLING DRINKING EPISODES IN PATIENTS COMPLETING TWO-YEAR TREATMENT COMPARED TO PREVIOUS TWO-YEAR PERIOD (N=18)

Patient Number	Previous Two Years	Lithium 1 Year	Lithium 2 Years
2	12	0	1
3	2	0	0
9	2	0	0
13	0	0	0
15	6	0	2
20	3	0	2
22	3	0	0
24	2	0	0
25	1	0	0
28	1	0	0
36	4	1	2
40	2	0	0
43	1	0	0
48	13	4	0
55	1	0	0
57	3	0	0
66	1	1	1
68	2	0	0
Total	59	6	8

The serum lithium levels monitored every four weeks had a mean value of 0.79 mEq/liter with a range of 0.6-1.2 mEq/liter. Dosage range was 600 mg to 1500 mg daily; the average dose was 1200 mg daily. The serum magnesium, cholesterol, blood urea nitrogen, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, lactic dehydrogenase and electrolyte values did not show significant changes when compared to baseline.

The electrocardiogram showed marked lowering of the T waves in five of the patients who were receiving lithium. Two of these tracings were abnormal. There were no significant T wave changes in any of the placebo patients. Findings of electrocardiographic T wave changes attributed to lithium have been reported.[8]

The results of the laboratory indices of thyroid function are shown in Table VII. Palpation for thyroid enlargement showed no abnormality throughout the project. The only variables which showed significant differences were the thyroid clearance of plasma ^{131}I in the lithium group which was at the $p < 0.005$ level and the level of serum-free ^{131}I expressed as % dose/liter at two hours post injection which was significant at the $p < 0.05$ level. The monthly indices of thyroid function remained within normal range except in two patients. One patient was given radiopaque dye for diagnostic purposes; the second patient had a consistently low hormone level but with an increased diffusible fraction resulting in a normal free thyroxin level. Neither of these patients showed effects which could be related to medication.

No major lithium toxicity was observed in this study. Mild gastrointestinal disturbances which may or may not be due to lithium were seen in approximately 5 per cent. Mild hand tremor occurred in about 15 per cent, but this

TABLE VII

THYROID DATA ON PATIENTS COMPLETING 1 YEAR

Parameter	Lithium (N=15) Pre.	Post.	p	Placebo (N=13) Pre.	Post.	p
Thyroid clearance ^{131}I (ml/min)	5.8	7.8	<.005	5.4	5.2	N.S.
Urinary clearance ^{131}I (ml/min)	32.5	28.8	N.S.	33.2	35.0	N.S.
Plasma inorganic iodide (μg/100 ml)	1.29	0.90	N.S.	1.27	1.02	N.S.
2 hr-serum free iodide ^{131}I (%/dose/liter)	4.1	4.5	<.05	4.2	4.5	N.S.
Absolute iodine uptake (μg/hr)	4.1	3.9	N.S.	3.6	2.9	N.S.
Protein bound iodine (μg/100 ml)	5.2	4.9	N.S.	5.2	5.3	N.S.
Free thyroxine (mMx10^{-11}/liter)	3.2	2.8	N.S.	3.1	2.9	N.S.

was not a problem in maintaining the blind aspects of the study because many of the placebo group also had tremors. It was not necessary to stop medication in any patient because of side effects.

Discussion

Lithium appears to have a marked and statistically significant beneficial effect on chronic alcoholics. We, frankly, did not expect to find such a dramatic improvement following lithium treatment. However, the original hypothesis that chronic alcoholics might be helped by alleviation of depression was not confirmed by this experiment if the measures of depression are adequate. Whether the improved behavior of our patients was or was not related to depression is secondary. Primary is the fact that lithium may be a powerful ally in prevention of periodic or chronic drinking problems.

Alternative hypotheses are (1) lithium brought about a reduction in compulsive behavior (*ie*, drinking); (2) lithium has a direct effect upon the neurotoxicity associated with alcoholism; or (3) there were factors as yet undetected.

Clearly more studies are needed to determine the reason that only some of these patients responded and, if possible, to identify these patients by chemical, psychological, or social measures. Then methods to convert nonresponders to responders could be investigated.

Lithium is one of the medications which can be safely administered for long periods of time. The literature contains descriptions of studies in humans which have been ongoing for 15 years.[4] One of us (NSK) has personally treated more than 600 patients with this medication and experienced little difficulty in controlling dosage level. We emphasize that in alcoholics—and indeed in most patients—continuing medication when in remission is difficult to control and monitor. The WHO estimates that approximately 80 per cent of patients on outpatient status do not take medication as prescribed or do not take medication at all. The fact that lithium can be determined in serum rapidly, easily, and cheaply is particularly useful in monitoring not only for toxicity but to determine if the patient is taking his medication as prescribed.

The thyroid data are consistent with the current view of the effect of lithium on thyroid function in man,[9] *ie*, that lithium does cause an initial decrease in circulating thyroid hormone but that compensatory homeostatic mechanisms return the patient to a euthyroid state although with changed iodine kinetics.

It is our view that treatment of alcoholics with a psychoactive medication will have to be a long-term process since the very nature of the disease seems to indicate this. It is exciting, therefore, that lithium, which can be given for many years and which can be monitored so easily, seems to have some effect upon manifestations of chronic alcoholism.

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References

1. Fries H: Experience with lithium carbonate treatment at a psychiatric department in the period 1964-1967. Munksgaard, Copenhagen, Acta Psychiatrica Scandinavica, Supp 207, 1969.
2. Detre TP: Modern Psychiatric Treatment. Philadelphia, JB Lippincott, 1971, p 307.
3. Hoff EK: Pharmacological methodological adjuncts. *In* Alcoholism. Springfield, Illinois, Charles C Thomas, 1968, pp 175-189.
4. Schou M: Lithium in psychiatric therapy and prophylaxis. J Psychiat Res 6:67-95, 1968.
5. American Psychiatric Association: Diagnosis and Statistical Manual of Mental Disorders (DMS III). Washington, 1968.
6. Laska E, Simpson GM, Bank R: A computerized mental status. Comprehensive Psychiatry 10:2, 1969.
7. Zung WWK: A self-rating depression scale. Arch Gen Psychiat 12:63, 1965.
8. Demers RC, Heninger GR: Electrocardiographic T-wave changes during lithium carbonate treatment. JAMA 218:3,381-386, 1971.
9. Cooper TB, Simpson GM: Lithium and the thyroid, current findings in man. *In* Prange AJ Jr (ed): The Thyroid Axis, Drugs and Behavior. Raven Press, New York.