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EFFICACY OF LITHIUM IN SCHIZOPHRENIA

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SUMMARY

60 Schizophrenic patients were given $LiCo_3$/Chlorpromazine for 4 weeks, in a double blind cross over study with two placebo crossovers of 1 week before and two weeks after active treatment. Several core schizophrenic featrues showed significant reduction in severity with lithium. However, CPZ tretament was superior in terms of improvement, as compared to the other group on MBPRS and CGIS. Target symptoms may be one situation, where lithium could be tried and these results are discussed.

Several anecdotal studies have examplified the successful use of Lithium in Schizophrenia and have hence triggered of a running debate regarding its use in these disorders (Cade, 1949 ; Carrere and Pochard, 1954 ; Glesinger, 1954 ; Margulies, 1955 ; Rice, 1956 ; Annel, 1969 ; Sikes and Sikes, 1970). Others have opined, that although lithium does not control the underlying schizophrenic process, it does help overactivity which is often an associated feature of this illness (Gershon and Yuwiler, 1960 and Gershon, 1968). Other successful uses have been demonstrated in infantile psychoses (Gram and Rafaelsen, 1972) and aggressive behaviour (Dostal and Zvotsky, 1970 ; Sheard, 1971 and Tupin *et al.*, 1973). Lithium has been used successfully as an adjunct to the treatment of chronic schizophrenia in open and double blind studies (Meiers, 1970 ; Teber, 1970 ; Small *et al.*, 1975 ; Vanputten and Sanders, 1975 ; and Growe *et al.*. 1979). Alexander *et al.* (1979) in a six week study between lithium and two placebo crossovers demonstrated a reduction in psychosis in nine patients. Although none were asymptomatic while on lithium, seven worsened when lithium was withdrawn. Improvement in core schizophrenic symptoms, i.e. disordered thought and speech were demonstrated in an extension of the above study (Van Kammen and Defraites 1979). Lithium was also found beneficial in periodic catatonia (Gjessing, 1967) ; Takahashi and Gjessing, 1972 ; Petursson, 1976 and Wald and Lerner, 1976). On the other hand lithium has been contraindicated in schizophrenia by several workers (Hekimian *et al.* 1969 ; Johnson, 1970 ; Hollister, 1972). Shopsin *et al.*, (1971) and Shopsin, (1973) go on to say that not only does lithium worsen schizophrenic symptomatology but also precipitates neurotoxicity. A perusal of literature thus reveals conflicting results as regards the position of lithium in schizophrenia and the ambiguities surrounding this issue contribute to the difficulty in delineating lithium's therapeutic usefulness.

AIM

To evaluate the efficacy of lithium carbonate as an anti-psychotic agent in schizophrenia.

SAMPLE AND METHODOLOGY

60 male schizophrenics (Hebephrenic, Catatonic, Paranoid, Residual) diagnosed according to I.C.D.-IX (1977) were taken up for the study after a written informed consent. The exclusion criteria were : age ($<$20 yrs. or $>$50 yrs., physical illness contraindicating lithium, OBS, drug/alcohol

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addiction, illness reuqiring ECT or other forms of treatment and remission in placebo period.

After a detailed psychiatric history, clinical examination, and biochemical screening (pre-lithium) weekly ratings were done on MBPRS and Clinical Global Impressin Scale. Drugs were randomly administered i.e. Li/CPZ, in two treatment groups in a controlled double blind manner with two placebo crossovers of 1 wk before and 2 weeks after the period of active medication which lasted for 4 weeks. Identical capsules were used to dispense placebo and drugs. Ser. Li. was maintained within the therapeutic range and the rater was blind to these values. The Mean Ser. Li. level was 0.65 ± 0.2 mEq/l. The most frequent doses of Li and CPZ were 991.7 mg/day and 826.7 mg/day respectively.

Statistical Analysis : was carried out on weekly total scores and individual items of the scales, using the Student's 't' test, Chi Square test and comparative efficacy of the two drugs by analysis of covariance, using the initial ratings as covariates for each successive ratings.

OBSERVATIONS

60 male schizophrenic patients comprised the total sample (30 in each group, i.e. Li and CPZ). The treatment groups were analysed for comparability of age weight, and Vaillant's prognostic indicators using the Students 't' test. None of the variables showed significant differences between the two treatment groups. The type of onset (Criteria of Forrest and Mileck, 1975) was analysed using the Chi-Square test, and no significant difference was found between the two groups.

MBPRS : Baseline mean scores and adjusted mean scores (after analysis of covariance) in each week of treatment for all items of MBPRS were analysed (Table 1). In terms of total scores, Li produced a significant improvement ($p<0.01$) after 1 week, which increased to highly significant levels ($p<0.001$) from week II to week V. CPZ showed highly significant improvement ($p<0.001$) from Wk I till end of Wk VI. The items found to be highly significant ($p<0.001$) in terms of improvement at any time during Li treatment were : anxiety, emotional withdrawal, conceptual disorganization, tension, hostility, suspiciousness, hallucinatory behaviour, and blunted affect. Somatic concern, depressive mood, motor retardation, unusual thought content and excitement were influenced at lower levels of significance ($p<0.01$ and $p<0.05$). Guilt feelings, mannerisms and posturing, grandiosity, uncooperativeness and pressure of speech were not significantly influenced at any time by lithium during the trial.

Significant differences in terms of improvement between the two treatment groups are shown in Table II.

Lithium was significantly better than CPZ on the item of guilt feelings ($p<0.001$) and pressure of speech ($p<0.10$) after week I. After week II, results favoured Li on somatic concern ($p<0.01$) while CPZ was superior on the parameters of : mannerisms and posturing and pressure of speech ($p<0.01$) ; grandiosity and uncooperativeness ($p<0.05$) and trends towards improvement for hostility and suspiciousness ($p<0.10$). For wks III and IV, CPZ showed a superior response than Li for almost all the items at various levels of significance, but for depressive mood ($p<0.05$) and motor retardation ($p<0.10$) which were favoured by lithium treatment at the end of wk. IV. During the treminal two placebo weeks, there were trends favouring lithium on conceptual disorganization, guilt feelings and depressive mood while CPZ continued to show significant improvement on mannerisms and posturing, pressure of speech, anxiety and trends for unusual thought content and conceptual disorganization. Overall, CPZ

TABLE I—*Adjusted means and significant changes from baseline on MBPRS*

Item		BL	After I week	After II week	After III week	After IV week	After V week	After VI week
1. Somatic concern	L	3.50	3.10[a]	2.85[b]	2.85[a]	2.75[a]	3.09	3.62
	C	3.43	3.20	2.89	2.19[c]	1.95[c]	2.60[a]	3.24
2. Anxiety	L	3.57	3.15	2.56[c]	2.39[c]	2.31[c]	2.65[b]	3.20
	C	3.20	3.29[a]	2.98[c]	2.21[b]	1.82[c]	2.55	3.13
3. Emotional withdrawal	L	4.47	3.83[b]	3.14[c]	2.82[c]	2.69[c]	3.00[c]	3.51[b]
	C	4.00	3.90[a]	3.19[c]	2.91[c]	2.51[c]	3.10[c]	3.62[a]
4. Conceptual disorganization.	L	4.37	4.22[a]	3.29[c]	3.27[c]	3.14[c]	3.46[c]	3.94
	C	4.70	3.82[c]	2.81[c]	2.50[c]	1.96[c]	2.74[c]	3.19[c]
5. Guilt feelings ..	L	0.10	0.14	0.46	0.03	0.02	0.02	0.03
	C	0.27	0.23	0.12	0.07	0.05	0.05	0.07
6. Tension ..	L	1.93	1.44	0.93[b]	0.73[c]	0.79[c]	0.88[c]	1.32
	C	1.37	1.36	0.99[b]	0.81[b]	0.74[a]	1.22	1.62
7. Mannerisms & Posturing.	L	1.80	1.59	1.47	1.40	1.41	1.64	2.10
	C	1.70	1.11[b]	0.70[b]	0.66[c]	0.32[c]	0.73[b]	0.83[b]
8. Grandiosity	L	1.03	1.83	0.89	1.02	0.93	1.08	1.40
	C	2.17	1.20[a]	0.70[c]	0.38[c]	0.23[c]	0.62[b]	0.80[b]
9. Depressive mood ..	L	1.20	0.87	1.00	0.65[a]	0.46[b]	0.75	1.18
	C	0.97	0.96	0.79	0.95	1.01	0.98	1.18
10. Hostility ..	L	2.47	2.63	1.94[c]	1.99[b]	1.74[b]	2.28	2.73
	C	3.47	2.23[c]	1.36[c]	1.11[c]	0.83[c]	1.86[c]	2.37[a]
11. Suspiciousness ..	L	3.80	3.84[b]	2.67[c]	2.85[c]	2.68[c]	2.80[b]	3.27[a]
	C	4.40	3.40[c]	2.50[c]	1.85[c]	1.48[c]	2.63[c]	3.06[b]
12. Hallucinatory Behaviour.	L	3.90	3.61[a]	2.75[c]	2.41[c]	2.20[c]	2.38[c]	2.79[c]
	C	4.13	2.86[c]	2.09[c]	1.69[c]	1.40[c]	1.82[c]	2.24[c]
13. Motor Retardation	L	1.90	1.47	1.16[a]	1.01[a]	0.91[b]	1.16	1.33
	C	0.97	1.53	1.47	1.32	1.39	1.27	1.34
14. Uncooperativeness	L	2.13	2.25	1.90	1.81	1.89	2.07	2.63
	C	2.87	1.79[c]	1.03[c]	0.89[c]	0.61[c]	1.56[b]	1.97
15. Unusual thought content.	L	4.20	4.24	3.60[b]	3.70[a]	3.16	3.51[b]	3.91
	C	4.53	3.86[b]	3.17[c]	2.67[c]	2.31[c]	2.89[c]	3.19[b]
16. Blunted affect ..	L	4.00	3.47[b]	2.88[c]	2.69[c]	2.54[c]	2.91[c]	3.40[a]
	C	3.73	3.60[a]	2.96[c]	2.75[c]	2.62[c]	2.72[c]	3.03[b]
17. Excitement ..	L	1.27	1.41[a]	0.83[b]	1.10	0.84[a]	1.31	1.55
	C	2.27	1.19[a]	0.53[c]	0.30[c]	0.23[c]	0.86[c]	1.05[b]
18. Disorientation ..	L	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	C	0.00	0.00	0.00	0.00	0.00	0.00	0.00
19. Pressure of Speech ..	L	1.73	1.81	1.44	1.67	1.59	2.11	2.49
	C	3.13	2.03	1.06[c]	0.66[c]	0.44[c]	1.22[c]	1.37[b]
Total Scores ..	L	47.37	45.21[a]	35.60[c]	34.77[c]	32.78[c]	37.85[c]	44.92
	C	51.33	40.69[c]	30.67[c]	25.33[c]	21.60[c]	30.59[c]	36.78[c]

L=Lithium, C=Chlorpromazine. a=$p < 0.05$, b=$p < 0.01$ c=$p < 0.001$

TABLE II—*Significant differences betewen lithium and chlorpromazine of MBPRS*

Items	After I wk.	After II wk.	After III wk.	After IV wk.	After V wk.	After VI wk.
1. Somatic concern ..	..	L++	C+	C+	..	..
2. Anxiety	..	..	..	..	C+	..
4. Conceptual disorganization	..	..	C	C++	L	C
5. Guilt Feelings ..	L+++	..	..	..	..	L
7. Mannerisoms & Posturing	C+	C++	C+	C+++	C++	C+++
8. Grandiosity ..	C+	C+	C++	C+	..	..
9. Depressive mood ..	..	..	..	L+	..	L
10. Hostility	..	C	C+	C+	..	..
11. Suspiciousness ..	..	C	C++	C++	..	..
12. Hallucinatory behaviour	C+	..	C	C+	..	..
13. Motor Retardation ..	..	..	..	L	..	..
14. Uncooperativeness ..	..	C+	C++	C+++	..	..
15. Unusual thought content	..	..	C++	C	C	C
17. Excitement ..	..	..	C++	C+	..	..
19. Pressure of speech ..	L	C++	C+	C++	C++	C+
Total scores ..	C	..	C++	C++	C++	C

C+=Chlorpromazine significantly better than lithium ($p<0.05$)
C++=Chlorpromazine significantly better than lihtium ($p<0.01$)
C+++=Chlorpromazine siguificantly bettre than lithium ($p<0.001$)
L+=Lithium significantly better than chlorpromazine ($p<0.05$)
L++=Lithium significantly better than chlorpromazine ($d<0.01$)
L+++=Lithium significantly better than chlorpromazine ($p<0.001$)
C=Trends favouring C. P. Z. ($p<0.10$) ; L=Trends favouring Li. ($p<0.10$).

showed a tendency for better improvement on majority of the items during the period of the study as compared to lithium.

CGIS (SEVERITY OF ILLNESS AND GLOBAL IMPROVEMENT)

The baseline mean scores and adjusted means (after analysis of covariance) in each week of treatment showed highly significant improvement in severity of illness with lithium ($p<0.001$) after the II wk to end of wk V, and significant improvement ($p<0.01$) after wk VI. Lithium induced global improvement was significant at $p<0.001$ after wk II up to wk IV and at $p<0.01$ after wk V. With CPZ improve-

TABLE III—*Adjusted means and significant changes from baseline of CGIS*

		BL	After I wk.	After II wk.	After III wk.	After IV wk.	After V wk.	After VI wk.
Severity of illness ..	L	5.33	5.14	4.6[c]	4.41[c]	3.94[c]	4.41[c]	4.53[b]
	C	5.43	4.67[c]	4.14[c]	3.43[c]	3.26[c]	4.20[c]	4.57[b]
Global improvement ..	L	..	3.73	3.58[c]	3.21[c]	2.68[c]	3.16[b]	3.61
	C	..	3.43	2.86[c]	2.62[c]	2.29[c]	2.90[b]	3.29[b]

L=Lithium ; C=Chlorpromazine ; a=$p<0.05$; b=$p<0.01$; c=$p<0.001$

TABLE IV—*Significant differences between lithium and chlorpromazine of CGIS*

	After I wk.	After II wk.	After III wk.	After IV wk.	After V wk.	After VI wk.
Severity of illness ..	C+	C	C++	C+++	..	..
Global improvement ..	C+	..	C+	..	..	..

C+ = Chlorpromazine significantly better than Lithium ($p<0.05$)
C++ = Chlorpromazine significantly better than Lithium ($p<0.01$)
C+++ = Chlorpromazine significantly better than Lithium ($p<0.001$)

ment in severity of illness was similar to Li except for persistent effect after Wk VI (Table III).

From wk I till Wk IV, CPZ was significantly superior to lithium treatment in terms of severity of illness and the global improvement with CPZ was better after Wk I and III of treatment (Table IV).

DISCUSSION

Lithium response in psychiatric disorders has been largely responsible for highlighting the enigmas in psychiatric diagnosis. These problems, nevertheless, are critical in the interpretation of reports relating to therapeutic trials. The differential diagnosis between pure affective disorders and schizophrenia are largely contributing to the contradictory reports relating to lithium response in schizophrenia. Most of the earlier studies using subjective criteria for diagnosis of schizophrenia have confounded the issue of therapeutic response. In this study, the selection criteria used were stringent, are internationally acceptable and only "pure" schizophrenics have been studied. Since the variables of age, weight, Vaillant's prognostic indicators and type of onset were not statistically different between the two groups, the results are more strongly attributable to more specific drug response. Observations have revealed that lithium influenced not only the non-specific but also the core schizophrenic symptoms with a characteristic latency of action of lithium as compared to CPZ, i.e. from II wk onwards. Similar results have also been observed by Prien *et al.* (1972). However, some improvement was also witnessed during the first week e.g. emotional withdrawal, suspiciousness, blunting of affect, somatic concern, conceptual disorganization, hallucinatory behaviour and excitement. Alaxender *et al.* (1979) have also reported that lithium responders show signs of improvement during the Ist wk. and this response may predict the later outcome on lithium. That some parameters remain significantly influenced even during terminal 2 wks of placebo treatment (wks V and VI), is perhaps a reflection of cumulative lithium effect and its gradual excretion. A remarkably significant feature evident from the results was the ineffectiveness of lithium on so-called "manic symptoms" such as grandiosity, pressure of speech and elation. Contrarywise, a number of workers found improvement in affective symptomatology with lithium (Rice, 1956; White *et al.*, 1966; Blinder, 1968; Zall *et al.*, 1968; Serry 1969; Tupin *et al.*, 1969 and Sikes and Sikes, 1970). These studies however, are contaminated with populations of schizo-affective patients and not schizophrenics with affective features. Further, these samples were small and the studies were open and uncontrolled being subject to the error of a personal bias. In keeping with the other studies, we found that Li effectively controlled hyperactivity, excitement and hostility (Gram and Rafaelsen, 1972; Martorano, 1972; Tupin *et. al.*, 1973;

Small *et al.*, 1975 ; Liebowitz *et al.*, 1976 and Growe *et al.*, 1979). Li also successfully improved withdrawal (motor retardation) in this study. Growe *et al.* (1979) have reported trends towards less seclusiveness and reduced retardation with Li treatment. Indirect evidence towards the same is available from studies citing its successful use in periodic catatonia. This entity however, is subject to a nosological confusion and has been cited as a variant of affective disorder. An important factor contributing to the worsening of Shopsin's sample (Shopsin *et al.*, 1971) could be attributed to development of an organic picture which was perhaps a result of high Li dose (Max. Li dose=2.0 G, Ser. Li. levels between 0.65-1.28 m Eq/l.). Since most of their patients were acutely excited schizophrenics, some of them perhaps suffered from transient organic psychoses. Simpson *et al.* (1976) who also found poor results had included chronic, poor prognosis schizophrenics with tardive dyskinesia who might not have responded to any neuroleptic medication available in our armamentarium at present.

Lithium therefore, possesses antipsychotic properties and is not a specific anti-manic agent. Target sumptoms are being increasingly used in therapy with developments in neuropsychopharmacology and affective rage and hyperactivity appear to be related to lithium's therapeutic efficacy (Martorano, 1972 ; Growe *et al.*, 1979). Animal studies have suggested that a combination of Li and neuroleptics may offset some of the chronic changes associated with neuroleptic induced increased dopaminergic receptor activity (Klawans *et al.*, 1977). Similar to the hypothesis of increased nor-adrenergic activity during mania, one can hypothesize that schizophrenic relapse may be associated with increased dopaminergic activity (Davis *et al.*, 1978). Following this reasoning lithium could have prophylactic effects upon psychotic relapse in schizophrenia. We do not claim lithium treatment as the drug of choice for schizophrenia, nor its superiority over CPZ, but it may be that in the coming years we are able to clearly delineate the characteristic clinical picture of schizophrenics responding to lithium. Lithium combined with neuroleptics in chronic neuroleptic resistant schizophrenics forms an area of promising research.

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