EFFICACY OF LITHIUM IN SCHIZOPHRENIA

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SUMMARY

60 Schizophrenic patients were given $\text{LiCo}_3$/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 features showed significant reduction in severity with lithium. However, CPZ treatment 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 exemplified 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; Marguiles, 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 Groce 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 Although none were asymptomatic while on lithium, seven worsened when lithium was withdrawn.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...
addiction, illness requiring 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 Impressions 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 Affleck, 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 I). 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<0.01) 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 terminal 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*         | 2.65b          | 2.85*         | 2.75*        | 3.09          | 3.62          |
| C                          | 3.43 | 3.20         | 2.89          | 2.10c          | 1.95*         | 2.60*        | 2.24          |
| 2. Anxiety                 | L    | 3.57         | 3.15          | 2.56c          | 2.39c         | 2.31c        | 2.65b         | 3.20          |
| C                          | 3.20 | 3.29*        | 2.98*         | 2.21b          | 1.82c         | 2.55         | 3.13          |
| 3. Emotional withdrawal    | L    | 4.47         | 3.85b         | 3.14c          | 2.82c         | 2.69c        | 3.00c         | 3.51b         |
| G                          | 4.00 | 3.90*        | 3.19c         | 2.91c          | 2.51c         | 3.10c        | 3.62*         |
| 4. Conceptual disorganization. | L    | 4.37         | 4.22*         | 3.29c          | 3.27c         | 3.14c        | 3.46c         | 3.94          |
| C                          | 4.70 | 3.82c        | 2.81c         | 2.50c          | 1.96c         | 2.74c        | 3.19c         |
| 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          | 0.93b          | 0.73c         | 0.79c        | 0.88c         | 1.32          |
| C                          | 1.37 | 1.36         | 0.99b         | 0.81b          | 0.74a         | 1.22         | 1.62          |
| 7. Manicircisms & Postur-  | L    | 1.60         | 1.59          | 1.47           | 1.40          | 1.41         | 1.64          | 2.10          |
| ing                        | C    | 1.70         | 1.11b         | 0.70b          | 0.66c         | 0.32c        | 0.73b         | 0.83b         |
| 8. Grandiosity             | L    | 1.03         | 1.83          | 0.89           | 1.02          | 0.93         | 1.08          | 1.40          |
| C                          | 2.17 | 1.20*        | 0.70          | 0.38c          | 0.23c         | 0.62b        | 0.80b         |
| 9. Depressive mood         | L    | 0.97         | 0.87          | 1.00           | 0.65b         | 0.46b        | 0.75          | 1.18          |
| G                          | 0.97 | 0.96         | 0.79          | 0.95           | 1.01          | 0.50         | 1.18          |
| 10. Hostility              | L    | 2.47         | 2.63          | 1.84c          | 1.99b         | 1.74b        | 2.28          | 2.73          |
| C                          | 3.47 | 2.23c        | 1.36c         | 1.11c          | 0.83c         | 1.06c        | 2.37*         |
| 11. Suspiciousness         | L    | 3.80         | 3.84b         | 2.67c          | 2.85c         | 2.68c        | 2.80b         | 3.27*         |
| C                          | 4.40 | 3.40c        | 2.50c         | 1.85c          | 1.48c         | 2.63c        | 3.06b         |
| 12. Hallucinatory behav-   | L    | 3.90         | 3.61*         | 2.75c          | 2.41c         | 2.20c        | 2.38c         | 2.79*         |
| iour                       | G    | 4.13         | 2.86c         | 2.09c          | 1.69c         | 1.40c        | 1.82c         | 2.24*         |
| 13. Motor Retardation      | L    | 1.90         | 1.47          | 1.16a          | 1.01a         | 0.91b        | 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                          | 2.67 | 1.79c        | 1.03c         | 0.89c          | 0.61c         | 1.56b        | 1.97          |
| 15. Unusual thought con-   | L    | 4.20         | 4.24          | 3.60b          | 3.70a         | 3.16         | 3.51b         | 3.91          |
| tent                      | C    | 4.53         | 3.06b         | 3.17c          | 2.67c         | 2.31c        | 2.85c         | 3.19b         |
| 16. Blunted affect         | L    | 4.00         | 3.47b         | 2.88c          | 2.69c         | 2.54c        | 2.91c         | 3.47*         |
| C                          | 3.73 | 3.60a        | 2.96c         | 2.75c          | 2.62c         | 2.72c        | 3.03b         |
| 17. Excitement             | L    | 1.27         | 1.41a         | 0.83b          | 1.10          | 0.84a        | 1.31          | 1.55          |
| C                          | 2.27 | 1.19a        | 0.53          | 0.39c          | 0.23c         | 0.86c        | 1.05b         |
| 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         | 1.06c         | 0.66c          | 0.44c         | 1.22c        | 1.37b         |

**Total Scores**

|                  | L    | After I week | After II week | After III week | After IV week | After V week |
|------------------|------|--------------|---------------|----------------|---------------|--------------|
|                  | 47.37| 35.60c       | 34.77c        | 32.78c         | 37.83c        | 44.92        |

**L= Lithium, C= Chlorpromazine. a=p<0.05, b=p<0.01 c=p<0.001**
**Table II—Significant differences between lithium and chlorpromazine of MBPRS**

| Items                      | After 1 wk. | After 2 wk. | After 3 wk. | After 4 wk. | After 5 wk. | After 6 wk. |
|----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 1. Somatic concern         |             | L+++        | C+          | C+          |             |             |
| 2. Anxiety                 |             |             |             |             | C+          |             |
| 4. Conceptual disorganization |             |             |             |             |             |             |
| 5. Guilt Feelings          | L+++        |             |             |             |             |             |
| 7. Mannerisms & Posturing  |             |             |             |             |             |             |
| 8. Grandiosity             |             |             |             |             |             |             |
| 9. Depressive mood         |             |             |             |             | L+          |             |
| 10. Hostility              |             |             |             |             |             |             |
| 11. Suspiciousness         |             |             |             |             |             |             |
| 12. Hallucinatory behaviour|             |             |             |             |             |             |
| 13. Motor Retardation      |             |             |             |             |             |             |
| 14. Uncooperativeness      |             |             |             |             |             |             |
| 15. Unusual thought content|             |             |             |             |             |             |
| 16. Excitement             |             |             |             |             |             |             |
| 19. Pressure of speech     |             |             |             |             |             |             |

**Total scores**

|             | C           |             |             |             |             |             |

- G+ = Chlorpromazine significantly better than lithium (p<0.05)
- C+++ = Chlorpromazine significantly better than lithium (p<0.01)
- L+++ = Lithium significantly better than chlorpromazine (p<0.001)
- L+ = Lithium significantly better than chlorpromazine (p<0.05)
- L++ = Lithium significantly better than chlorpromazine (p<0.01)
- 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 1 wk. | After 2 wk. | After 3 wk. | After 4 wk. | After 5 wk. | After 6 wk. |
|----------------|----------|-------------|-------------|-------------|-------------|-------------|-------------|
| Severity of illness | L 5.33  | 5.14        | 4.6c        | 4.41c       | 3.94c       | 4.41c       | 4.53b       |
|                 | C 5.43   | 4.67c       | 4.14c       | 3.49e       | 3.26c       | 4.20c       | 4.37b       |
| Global improvement | L 3.73  | 3.73        | 3.58c       | 3.21c       | 2.68c       | 3.16b       | 3.51        |
|                 | C 3.43   | 3.43        | 2.86c       | 2.62c       | 2.29c       | 2.90b       | 3.29b       |

L = Lithium; G = Chlorpromazine; a = p<0.05; b = p<0.01; c = p<0.001
TABLE IV—Significant differences between lithium and chlorpromazine of CGIS

| After   | After   | After   | After   | After   | After   |
|---------|---------|---------|---------|---------|---------|
| I wk.   | II wk.  | III wk. | IV wk.  | V wk.   | 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. Alexender et al. (1979) have also reported that lithium responders show signs of improvement during the 1st 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 anti-psychotic properties and is not a specific anti-manic agent. Target symptoms 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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REFERENCES

Alexander, P. E., Van Kamm, D. P. and Bunney, W. E. Jr. (1979a). Antipsychotic Effects of Lithium in Schizophrenia. Amer. J. Psychiat. 136 : 3, 283.

Ansell, A. L. (1969). Lithium in the treatment of children and adolescents. Acta Psychiat. Scand., 207 : 19.

Blinder, M. (1968). Some observations on the use of lithium carbonate. Int. J. Neuropsychiat. 4, 26.

Cade, J. F. J. (1949). Lithium salts in treatment of psychotic excitement. Med. J. Aust., 2, 36, 319.

Carrere, M. and Pochard, A. (1954). Lithium carbonate in the treatment of psychomotor excitation syndromes. Ann. Med. Psychol. 112, 506.

Davis, K. L., Hollister, L. E. and Fritz, W. C. (1978). Neuroleptic induced mesolimbic dopaminergic receptor hyperactivity. Presented at 33rd Annual Meeting, Society for Biological Psychiatry, Atlanta, Georgia.

Dostal, F. L. and Zvolotky, P. (1970). Antiaggressive effect of lithium salts in severe mentally retarded adolescents. Int. Pharmacopsychiat. 5, 203, 207.

Gershon, S. (1968). Use of Lithium Salts in Psychiatric Disorders. Dis. Nerv. Syst., 31.

Gershon, S. and Yuwiler, A. (1960). Lithium ion: A specific psychopharmacological approach to the treatment of mania. Int. J. Neuropsychiat. 1, 229.

Gersing, G. R. (1967). Lithium citrate loading of a patient with periodic catatonia. Acta Psychiat. Scand. 43, 372.

Gersing, B. (1954). Evaluation of Lithium in treatment of psychotic excitement. Med. J. Aust., 41, 277.
Gamm, L. F. and Rafaelsen, O. J. (1972). Lithium treatment of psychotic children and adolescents: A controlled clinical trial. Acta Psychiatr. Scand., 48, 253.

Grobe, G. A., Crayton, J. W., Klass, D. B. et al., (1979). Lithium in chronic schizophrenia. Amer. J. Psychiat., 136 : 4a, 454.

Heikman, L., Gershon, S., Hardesty, A. S., et al. (1969). Drug efficacy and diagnostic specificity in manic depressive illness and schizophrenia. Dis. Nerv. Syst. 30 : 747.

Hollister, L. E. (1972). Mental Disorders—Antipsychotic and Antimanic drugs. New Eng. J. Med. 286, 18 : 984.

Johnson, G. (1970). Differential response to lithium carbonate in manic depressive and schizoaffective disorders. Dis. Nerv. Syst. 31 : 613.

Klawans, H. L., Weiner, W. J., Naeslund, P. A. (1977). The effect of lithium on an animal model of tardive dyskinesia. Prog. Neuropsychopharmacol., 1 : 53.

Liebowitz, J. H., Rydu, V., Gershon, E. S. et al. (1976). A psychopharmacogenetic case report: Lithium responsive post psychotic antisocial behaviour. Compr. Psychiat. 17(5) : 635.

Marcouiller, M. (1935). Suggestions for the treatment of schizophrenic and manic depressive patients. Med. J. Aust., 42, 137.

Martorano, J. (1972). Target symptoms in lithium carbonate therapy. Compr. Psychiat. 13 : 533.

Meiers, R. (1970). Lithium carbonate as adjunct in the treatment of schizophrenia. Schizophrenia : 2 : 87.

Peterson, H. (1976). Lithium treatment of a patient with periodic catatonia. Acta Psychiatr. Scand., 54, 248.

Priem, R. F., Caffey, Jr. E. M. and Klett, C. J. (1972). A comparison of lithium carbonate and Chlorpromazine in Treatment of Exited Schizoaffectives. Arch. Gen. Psychiat., 27, 182.

Rice, D. (1956). Use of lithium salts in the treatment of manic states. J. Ment. Sci. 102, 604.

Sibert, M. (1959). Lithium excretion test: Clinical application and interpretation. Aust. J. Psychiat., 3, 390.

Sheard, M. H. (1971). Effect of lithium on human aggression. Nature. 230 : 113.

Shapin, B. (1973). The use of lithium in schizophrenia. Psychopharmacol. Bull., 9 : 50.

Shapsin, B., Kim, S. S. and Gershon, S. (1971). A controlled study of Lithium vs. Chlorpromazine in acute schizophrenics. Brit. J. Psychiat., 119, 437.

Siikes, J. G. and Siikes, S. C. (1970). Lithium carbonate treatment in Psychiatry. Dis. Nerv. Syst. 31, 52.

Simpson, G. M., Branchey, M. H., Lee, J. H., et al. (1976). Lithium in Tardive Dyskinesia. Pharmacopsychiatry, 9, 76.

Small, J. G., Kullans, J. J. and Milstein, V. et al. (1973). A placebo controlled study of lithium combined with Neuroleptics in chronic schizophrenic patients. Amer. J. Psychiat. 132, 12 : 1315.

Takahashi, S. and Gershon, L. R. (1972). Studies of periodic catatonia-IV. Longitudinal study of catecholamine metabolism, with and without drugs. J. Psychiatr. Res. 9 : 293.

Tebbe, S. (1970). The effect of lithium salts on some psychiatric syndromes. Paper presented at 7th Congress of Internationale Neuropsychopharmacologic Prague, August, 1970.

Tuypin, J. P. (1969). Lithium salts : valuable clinical drug and research tool, in mental health programme reports, Vol. 3, Public Health Service Publication No. 876. Deptt. of Health. Ed. and Welfare.

Tuypin, J., Smith, D. B., Clandon, T. I. et al. (1973). The long term use of lithium in Aggressive Prisoners. Compr. Psychiat. 14, 4 : 311.

Van Putten, T. and Sanders, D. G. (1975). Lithium in treatment failures. J. Nerv. Ment. Dis., 161, 4 : 255.

Van Kammen, D. P. and DeFrates, E. G. (1979). Lithium treatment in schizophrenia: A review of treatment and prophylaxis in schizophrenia, schizoaffective disorders, and periodic catatonia. In Lithium : Controversies and Unresolved Issues (eds. ; T. B. Cooper, S. Gershon, NS, Kline and M. Schou. Amsterdam, Excerpta Medica).

Wald, D. and Lerner, J. (1976) : Lithium in the treatment of periodic catatonia : A case report. Amer. J. Psychiat. 135 : 6, 751.

White, R. B., Schlagenhauf, G. and Tupin J. P. (1966). Treatment of manic depressive states with lithium carbonate. Corr. Psychiat. Ther ; 6, 239.

World Health Organization (1977). Manual of the International Statistical Classification of Diseases, Injuries and causes of Death. Vol. 1. Based on the recommendations of the Ninth Revision Conference, 1975 and adopted by the Twenty Ni.th World Health Assembly. Geneva, W.H.O.

Zall, H., Therian, P. G. and Myers, J. M. (1968). Lithium Carbonate : A Clinical study. Amer. J. Psychiat. 125, 4, 549.