

## ONCE DAILY LITHIUM IN THE PROPHYLAXIS OF MOOD DISORDERS

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### SUMMARY

*This retrospective chart review attempts to compare the utility, safety and efficacy of once daily (OD) versus divided dose (DD) lithium therapy in the prophylaxis of mood disorders. Sixty-six patients who met DSM-III-R criteria for mood disorders were grouped into those on OD Lithium (n=31) and those on DD lithium (n=35). The groups were matched on sociodemographic and clinical variables. The total daily dose was similar in the two groups, but the OD group tended to have higher serum lithium levels while the DD group tended to have a greater number of affective episodes during the period of follow up. The implications are discussed.*

*Key Words: Mood Disorders; Mania; Depression; Lithium, Prophylaxis for mood disorders*

### INTRODUCTION

There are two schools of thought regarding the use of lithium in the prophylaxis of mood disorders (Schou et al., 1982) i.e. in a single once daily (OD) or in divided doses (DD). After the initial concerns about renal damage in the absence of lithium toxicity (Kassirer, 1983), later reviews (Schou, 1988) and biopsy studies (Hetmar et al., 1991) have shown that lithium does not cause significant effects on glomerular filtration rate or renal morphology. The OD dosage school avers that this dosing improves compliance, and that the side effects related to the peak blood levels of lithium occur during sleep (Lauritsen et al., 1981). The DD schools proposed that a more sustained, uniform level would be less damaging to the kidney.

There have been various attempts to compare OD and DD lithium dosing patterns in mood disorders. Most results have shown that the side effect profile of the OD dosage schedule is comparable to DD dosing, and that the benefits were better with OD therapy in terms of compliance (Plenge & Mellerup, 1986; Muir et al., 1989).

In India, it is our experience that lithium is largely given in divided doses. No studies have examined OD lithium therapy. In this study, we,

therefore, analyzed the benefits and risks of OD as compared with DD Lithium therapy in patients who had been prescribed lithium carbonate for the prophylaxis of mood disorders during the same period. We hypothesized that OD lithium therapy would be comparable in efficacy to DD lithium and would have relatively fewer side effects.

### MATERIAL AND METHODS

Consecutive patients utilizing the inpatient and outpatient facilities of one unit of the Department of Psychiatry at the National Institute of Mental Health and Neurosciences, Bangalore, identified during a one year period, and who met DSM III-R criteria (American Psychiatric Association, 1987) for mood disorder were selected for the study. Only patients who were on lithium for the prophylaxis of mood disorders and who were compliant on medication during the period of follow-up were included in the study.

Sixty-six patients fulfilled the criteria for the study. Out of them, 31 were on OD dosing and 35 on DD dosing schedules. The case charts of these patients were screened systematically and the data were collected using a semistructured proforma. Variables such as

lithium dose, serum lithium levels, use of additional treatment, adverse drug reactions and the occurrence of further episodes were operationalized as reported by Suresh et al (1995). Serum levels of lithium (measured by flame photometry) and side effects recorded by the treating clinician were noted. The data regarding cessation of treatment, change from one dosing pattern to another and occurrence of further episodes were also collected as recorded by the treating clinician during the period of follow up. The data available in the case charts were found sufficiently detailed for the purpose of the study.

Blindness could not be ensured as the raters had to go through the case notes in detail where the dosing pattern is written explicitly. The consequent bias was avoided by operationalizing certain variables and by having the rating done by three of the authors (RM, KPS and KMRP). Various definitions for clinical variables that have been used in Table 1 were according to DSM-III-R (American Psychiatric Association, 1987). Further details can be obtained from Suresh et al (1995).

The sociodemographic and clinical parameters were assessed as independent variables and the treatment, side effects and outcome as dependent variables. Comparisons between the two groups were effected using different statistical methods depending on the variable characteristics. Qualitative data were compared using Yates' continuity-corrected  $X^2$  square test and Fisher's (2-tail) exact probability test. The Mann-Whitney U test was used when the assumptions for parametric tests were not satisfied. The independent sample t test was used to compare means of independent groups. Analysis of Covariance (ANCOVA) was used to covariate out the biasing effect of total dose over serum levels between the two groups; the result was that serum lithium levels were near significantly higher in the OD group as compared with DD group ( $F 1, 47=3.53, p=0.066$ ). The data were analyzed using the Statistical Package for Social

Sciences (SPSS, Ver.4.01).

## RESULTS

The mean age (SD) of the sample was 33.2 (12.6) years in the OD group and 26.1 (9.5) years in the DD group. The comparison showed that the groups did not differ on any of the sociodemographic and clinical variables (Table 1).

**TABLE 1: SOCIODEMOGRAPHIC AND CLINICAL VARIABLES IN OD & DD LITHIUM GROUPS**

	OD(n=31)	DD(n=35)	SIGNIFICANCE
Age (years)			
Mean (SD)	33.23(12.63)	28.09(9.52)	NS*
Sex Male	24(77.4%)	24(68.6%)	NS**
Female	7(22.6%)	11(31.4%)	
Diagnosis			
Unipolar	13	14	NS**
Bipolar	15	18	
Mean previous episode			
Mania	0.86(1.04)	1.38(1.83)	NS*
Depression	0.79 (1.03)	0.34(0.7)	NS*
Total	1.64(1.5)	1.72(2.04)	NS*
Family history positive			
Affective	5(17%)	3(9%)	NS*
Non affective	8(28%)	4(9%)	NS*
Previous good response to lithium	1(3.2%)	2(5.7%)	NS***
Elated grandiose	23	26	NS***
Psychotic	13(41.9%)	15(44.0%)	NS**
Dysphoria	6(19%)	3 (8.6%)	NS***
Thought disorder	5(16%)	4(11%)	NS***

\* Mann-Whitney U test; \*\*Continuity corrected Chi-square test; \*\*\*Fisher's exact Probability (2-tail) test

The proportion of various categories of mood disorders in the two groups was comparable.

The mean daily (SD) lithium dose was 1003.3 (85.3) mg (range 600 - 1500 mg) in the OD group and 1028.6 (221.7) mg (range 600 - 1800mg) in the DD group. The mean serum level was slightly higher in the OD group ( $0.72 \pm 0.12$  mEq/L) as compared with that in the DD group ( $0.65 \pm 0.19$  mEq/L). The duration of follow up was  $10.6 \pm 6.5$  months in the OD group and  $11.2 \pm 5$  months in the DD group. The differences in the above parameters were not significant (Table 2).

**TABLE 2:**  
**LITHIUM TREATMENT PARAMETERS IN OD & DD LITHIUM GROUPS**

VARIABLE	OD(n=31)	DD(n=35)	SIGNIFICANCE
Mean (SD) daily dose (mg/day)	1003.30(85.3)	1028.60(221.7)	NS*
Range (mg/day)	600 - 1500	600 - 1800	
Mean (SD) serum lithium level (mEq/L)	10.6(6.5)	11.2(8.5)	NS**
Mean duration of treatment (in months)	10.6(6.5)	11.2(8.5)	NS*

\*Mann - Whitney U test

\*\* t test with modified d f to correct for heterogeneous variances

An ANCOVA was performed to ascertain whether after covarying out the effect of the dose, the serum levels differed between the two groups. The frequency of side effects, change in dose or therapy due to side effects and need for extra treatment (e.g. addition of carbamazepine) did not differ significantly between the two groups (Table 3). However, 3.2% of OD lithium patients had further episodes during the course of follow up, while 20% in the DD group had relapses. This finding just misses statistical significance.

**TABLE 3:**  
**SIDE EFFECTS AND OUTCOME**

VARIABLE	OD(n=31)	DD(n=35)	SIGNIFICANCE*
Side effects seen	2(6.5%)	4(11.4%)	NS
Need to stop lithium	0(0%)	2(5.7%)	NS
Need for dose reduction	0(0%)	0(0%)	NS
Need to change schedule	0(0%)	0(0%)	NS
Need for extra prophylaxis	3(9.7%)	6(17%)	NS
Further affective episodes	1(3.2%)	7(20%)	p=0.058

\*Fisher's exact probability (2-tail) test

Values reported are number and percentage of patients

## DISCUSSION

This is the first study in India attempting a comparative evaluation of single daily dose lithium therapy versus a divided dose regimen in the prophylaxis of mood disorders. Earlier, Suresh et al (1995) reported the use of OD lithium in acute mania. Lithium being a drug which has to be taken for a prolonged period, it is also important to explore the utility of a simpler dosage schedule in the long term management of mood disorders. This study aimed to explore such a possibility.

There are two interesting positive findings in this study. First, after correcting for dosage influences, the OD lithium schedule was found to produce higher 12- hour serum lithium levels than the DD lithium schedule. This is believed to correlate with the therapeutic efficacy of lithium. Second, the frequency of relapse was higher in the DD than in the OD lithium group. This may be because of better compliance to OD lithium but also raises a theoretical possibility of a therapeutic advantage with such a regimen. Also, the OD lithium group had higher serum lithium levels; although the mean level did not differ significantly from that of DD group, it must be kept in mind that the difference may be yet have been clinically significant.

The two groups did not differ on other outcome measures of efficacy and adverse effects. The net conclusion is that OD lithium

may carry a slight advantage over DD lithium in the prophylaxis of mood disorders.

In several studies, the OD dosing pattern has been found to favorably compare with the DD pattern (Plenge & Mellerup, 1986; Muir et al., 1989). It has been shown that a once-daily dose can ensure an adequate 12 hour serum level to provide prophylaxis. Of note, the area under the curve for serum lithium, plotted against time has also been found to be equal in the two groups (Plenge & Mellerup, 1986).

Could dose peaking with OD lithium predispose to renal adverse effects? In the absence of toxicity, renal damage with lithium is unlikely (Hetmar et al., 1991). The renal pathology usually manifests in the early stages as abnormalities in renal concentrating mechanisms. The studies measuring 24 hour urine output in patients on lithium have also proved that OD dosing is more favorable in reducing polyuria (O'Donovan, 1993). In fact, it is recommended that shifting over to OD regimen can be therapeutic in lithium-induced polyuria (Martin, 1993).

In conclusion, OD and DD lithium regimen groups were comparable in sociodemographic and clinical variables. The side effects and the dosages of lithium did not differ significantly in the two groups but showed a trend towards higher serum levels on smaller total daily doses, with lower incidence of further episodes in the OD lithium group. Due importance needs to be given to schedule of lithium administration as this can have important practical and therapeutic implications in the prophylaxis of mood disorders.

This preliminary study suggests the need for future research with larger samples, prospective design, random allocation to treatment groups, structured assessments of efficacy and adverse effects and formal evaluation of renal function. It is hoped that the findings of the present study encourage research on OD lithium therapy.

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