

## ADVERSE SIDE EFFECTS OF LITHIUM AND FASTING (RAMADAN)

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### ABSTRACT

**Objectives:** To find out adverse side effects of lithium in bipolar affective disorder patients in the month of Ramadan.

**Material and Methods:** This descriptive study was carried out at the Department of Psychiatry, Postgraduate Medical Institute, Lady Reading Hospital Peshawar from September to November 2006. Sixty two subjects were included in the study by non probability convenient sampling. The patients suffering from Bipolar Affective Disorder using Lithium were assessed on a check list of dose related side effects and toxicity signs resulting from Lithium.

**Results:** Sixty two patients completed the pre Ramadan assessment while fifty seven and fifty six attended the mid-Ramadan and post-Ramadan assessment respectively. Majority of the patients were male ( $n=53$ ), married ( $n=44$ ) and on average had lower educational status (mean years of education =  $8.02 \pm 4.5$ ). Except weight gain ( $p$ -value = 0.006), there was no statistically significant difference in the adverse side effects of Lithium in pre-Ramadan ( $n=15$ , 24.2%) as compared to mid-Ramadan ( $n=4$ , 6.5%) period. The toxicity associated with Lithium did not differ significantly between the pre-Ramadan and post-Ramadan period.

**Conclusion:** Following the routine protocol of the use of lithium, it can be safely prescribed without the undue fear of adverse side effects during Ramadan.

**Key Words:** Adverse side effects, Toxicity, Lithium, Fasting (Ramadan).

### INTRODUCTION

The efficacy of lithium in bipolar disorder is recognized by the most recent evidence-based clinical guidelines for bipolar disorder, which recommend it as a first-line treatment<sup>1,2</sup>. Furthermore in a meta analysis of 14 randomized controlled trials, Smith *et al* provided strong evidence for the prophylactic efficacy of lithium, which prevented relapse to any mood episode with a hazard ratio of 0.68 (95% CI 0.53–0.86)<sup>3</sup>.

However Lithium remains a difficult drug to manage in routine clinical practice. In a country like Pakistan where summer may last for upto 6 months Lithium therapy can cause more problems. This may be even more difficult as majority of our

patients may be working in open field. Lithium competes with sodium for excretion and due to dehydration lithium can accumulate in body. The narrow therapeutic Index associated with Lithium may result in toxic effects developing very quickly. During fasting in month of Ramadan these problems may further exacerbate. Fasting may cause dehydration and decrease glomerular filtration, which may increase serum levels of renally dependent psychotropics such as lithium<sup>4</sup>. Of particular concern is lithium's potential for nephrotoxicity. Lithium can affect either tubular or glomerular kidney function<sup>5</sup>. In tubular dysfunction, which is more common, the kidney's ability to concentrate urine is reduced<sup>5</sup>. Diabetes insipidus, the most common renal complication of lithium

**EDUCATION STATUS**

Education status	Number of Pt (n=62)	Percentage
Illiterate	5	8.06%
Primary	8	12.90%
Middle	9	14.51%
Matriculation	27	43.54%
Intermediate	5	8.06%
Graduate	4	6.45%
Master	3	4.83%

Table 1

therapy, is marked by polyuria and polydipsia, and can progress to severe dehydration. Furthermore, the intraluminal lithium concentration can increase to toxic levels.

Clinical concerns that may arise during Ramadan include inability to take medications during the day, dehydration and other physical changes which may change drug metabolism and psychiatric symptom exacerbation. In patients with bipolar disorder, one study described a high rate (45%) of breakthrough manic or depressive episodes during Ramadan, despite stable lithium levels<sup>6</sup>. Fasting-related changes in circadian rhythms and insomnia are thought to contribute to psychiatric symptom exacerbation.

This study was planned to investigate effects of use of prophylactic lithium treatment in the month of Ramadan. Specifically we aimed to examine the safety and side effects profile of Lithium in patients using Lithium.

**MATERIAL AND METHODS**

The patients were recruited from out patient clinics of Postgraduate Medical Institute, Lady Reading Hospital Peshawar, a tertiary care teaching facility serving the NWFP population. Majority population in North West Frontier Province religiously follows to the Islamic values and during Ramadan and fasting is strictly observed. Although, Islamic Jurisprudence allows a number of exemptions, including for those who are ill, these are rarely followed and anyone who can fast, try to observe Ramadan fasting.

**INCLUSION CRITERIA**

The patients meeting the ICD 10 criteria for Bipolar Affective Disorder and stable on Lithium prophylaxis were eligible for the study.

We therefore included all the patients who informed us that they planned to observe Ramadan fasting. Six months before the Ramadan 2006 (1427 Hijri), 72 patients meeting the inclusion and

**AGE DISTRIBUTION**

Age (Year)	Number of Pt (n=62)	Percentage
<20	6	9.67%
21-30	30	48.38%
31-40	12	19.35%
40-50	8	12.92%
51-60	6	9.67%

Table 2

exclusion criteria who were on Lithium maintenance therapy, were screened. Sixty two (62) patients meeting the inclusion criteria and planning to fast agreed to participate in this study.

**EXCLUSION CRITERIA**

Subjects having associated diseases like diabetes, hypertension and renal disorders taking respective medications were excluded. Pregnant females were also excluded from the study. Similarly patient suffering from schizoaffective illness treatment resistant depression on lithium treatment were excluded.

The patients were assessed on the following points:

- Pre Ramadan (1 week before Ramadan, 13th to 21st September 2006/19th to 27th Sha'aban 1427).
- Mid Ramadan (2nd week of Ramadan, 5th to 7th October 2006/11th to 13th Ramadan 1427)
- After Ramadan (two weeks after Ramadan, 2nd to 4th November 2006/9th to 11th Shawwal 1427).

The following biochemical parameters and mental state scales were used for the assessment:

- Serum Lithium
- Serum Electrolytes

**OCCUPATIONAL STATUS OF THE SAMPLE**

Occupation	Number of Pt (n=62)	Percentage
Farmer	11	17.74%
Unemployed	10	16.12%
Business	9	14.51%
Laborer	9	14.51%
House Wife	8	12.90%
Student	6	9.67%
Government servant	5	8.06%
Teacher	3	4.83%
Driver	1	1.61%

Table 3

## COMPARISON OF LITHIUM ADVERSE EFFECTS IN PRE RAMADAN & MID RAMADAN

Side effects	Pre Ramadan	Mid Ramadan	P- Value
	N (n %)	N (n %)	
Polyuria/Polydipsia	34 (54.8%)	35 (61.4%)	0.857
Weight Gain	15 (24.2%)	4 (7%)	0.006*
Tremor	27 (43.5%)	16 (28.1%)	0.038*
Sedation/lethargy	16 (25.8%)	23 (40.4%)	0.176
Impaired Coordination	0	0	--
G.I Distress	17 (27.4%)	14 (24.6%)	0.534
Hair Loss	12 (19.4%)	7 (12.3%)	0.213
Leukocytosis	0	0	--
Acne	11 (17.7%)	9 (15.8%)	0.625
Edema	4 (6.5%)	0	0.042*
Cardiac Conduction Problems	0	0	--
Cognitive problem	2 (3.2%)	0	0.154
Total	62	57	

Table 4

- Serum Creatinine
- Hamilton Depression Rating Scale HDRS,
- Young Mania Rating Scale YMRS,

Thorough physical examination was carried on all patients to detect the side effects and toxicity of the Lithium. A check list of following side effects and toxicity resulting from Lithium was used.

- Dose related side effects:
  - 1 Polyuria /polydipsia
  - 2 Weight gain
  - 3 cognitive problems
  - 4 Tremors
  - 5 Sedation
  - 6 Impaired coordination
  - 7 G.I distress
  - 8 Hair loss
  - 9 Leukocytosis
  - 10 Acne
  - 11 Edema
  - 12 Cardiac conduction problems.
- Toxicity signs:
  - 1 Anorexia
  - 2 Nausea/ vomiting
  - 3 Diarrhea

- 4 Restlessness
- 5 Muscle fasciculation
- 6 Choreoathetoid movements
- 7 Hypertonicity
- 8 Ataxia
- 9 Dysarthria
- 10 Confusion

The assessment of lithium was carried out by Atomic Absorption Spectroscopy (AA).

The statistical analysis was performed using SPSS 13. The chi square test was used for comparing the categorical variables while analysis of variance (ANOVA) was used for continuous data.

## RESULTS

The average length of fasting day during the Ramadan was 11 hour 40 minutes. The Ramadan in 2006 was between 25th September to 24th October. The average temperature during the fasting day was 83 F/28 C.

Sixty two patients completed the pre Ramadan assessment while 57 and 56 attended the mid Ramadan and post Ramadan assessment respectively. The mean age of the sample was 31.45 + 10.84. Majority of the patients were male (n=53), married (n=44, 71 %) and on average had lower educational status (mean years of education = 8.02 + 4.5). The mean duration of illness for the sample was 8.06 + 7.47 years. The details of the

### COMPARISON OF ADVERSE EFFECTS IN MID RAMADAN AND POST RAMADAN

Side effects	Mid Ramadan	Post Ramadan	P- Value
	N (n %)	N (n %)	
Polyuria/Polydipsia	35 (61.4%)	30 (53.6%)	0.369
Weight Gain	4 (7%)	4 (7.1%)	0.999
Tremor	16 (28.1%)	15 (26.8%)	0.836
Sedation/lethargy	23 (40.4%)	24 (42.9%)	0.853
Impaired Coordination	0	0	....
G.I Distress	14 (24.6%)	9 (16.1%)	0.248
Hair Loss	7 (12.3%)	6 (10.7%)	0.769
Leukocytosis	0	0	...
Acne	9 (15.8%)	7 (12.5%)	0.592
Edema	0	1 (1.8%)	0.315
Cardiac Conduction Problems	0	0	...
Cognitive problem	0	0	...
Total	57	56	

Table 5

sociodemographic features are given below as table 1, 2 and 3.

The adverse effects and toxicity of Lithium reported by the patients and detected on clinical examination during follow up visits are compared (Table 4 and 5). It is obvious that except weight gain there was no statistically significant difference in the side effects and toxicity of the Lithium in Pre Ramadan and Post

Ramadan period. Less number of patients gained weight during Lithium treatment. The toxicity associated with Lithium did not differ significantly between the Pre Ramadan and Post Ramadan period (Table 6 and 7).

### DISCUSSION

Use of lithium for the treatment of bipolar disorder may be declining<sup>7</sup>. This may be despite the fact that the knowledge about the efficacy and

### TOXICITY SIGNS ASSOCIATED WITH LITHIUM IN PRE RAMADAN AND MID RAMADAN

Toxicity Signs	Pre Ramadan	Mid Ramadan	P- Value
	N (n %)	N (n %)	
Anorexia	12 (19.4%)	12(21.1%)	0.999
Nausea / Vomiting	8 (12.9%)	9 (15.8%)	0.108
Diarrhoea	4 (12.9%)	5 (8.8%)	0.729
Restlessness	11 (17.7%)	19 (33.3%)	0.093
Muscle Fasciculation	3 (4.8%)	1 (1.8%)	0.3.9
Choreoathetoid Movements	0	1 (1.8%)	0.315
Hypertonicity	0	0	----
Ataxia	0	0	----
Dysarthria	0	1 (1.8%)	0.315
Drowsiness	0	0	----
Confusion / Delirium	0	1 (1.8%)	0.315
Total	62	57	

Table 6

## TOXICITY SIGNS ASSOCIATED WITH LITHIUM IN MID RAMADAN AND POST RAMADAN

Toxicity Signs	Mid Ramadan	Post Ramadan	P- Value
	N (n %)	N (n %)	
Anorexia	12(21.1%)	8 (14.3%)	0.329
Nausea / Vomiting	9 (15.8%)	7 (12.5%)	0.592
Diarrhoea	5 (8.8%)	3 (5.4%)	0.465
Restlessness	19 (33.3%)	7 (12.5%)	0.008*
Muscle Fasciculation	1 (1.8%)	0	0.315
Choreoathetoid Movements	1 (1.8%)	0	0.315
Hypertonicity	0	0	----
Ataxia	0	0	----
Dysarthria	1 (1.8%)	0	0.315
Drowsiness	0	0	----
Confusion / Delirium	1 (1.8%)	0	0.315
Total	57	56	

**Statistics:** Chi Square test was used to analyze the significance between Pre & Mid Ramadan and Mid & Post Ramadan. P-value <0.05 considered as statistically significant.

Table 7

side-effects of lithium has increased. Recent meta-analyses confirm the benefits of maintenance lithium treatment and show that it reduces suicide and suicidality. It has been pointed out that the decrease in use of lithium may possibly be due to insufficient training of psychiatrists in the use of lithium therapy and the aggressive marketing of alternative medications that are patentable and therefore more profitable<sup>8,9</sup>. A decline in lithium use has been demonstrated by empirical studies in the USA<sup>10,11</sup>, Canada<sup>12</sup>, and Germany, Switzerland and Austria<sup>13</sup>. In developing countries including Pakistan Lithium still remains popular drug not only due to the efficacy but also due to the effectively low price compared to other mood stabilizers.

In addition to aggressive marketing by the p-pharmaceutical companies for alternatives the major reason for the decline in lithium use might be that it has a reputation among psychiatrists as a toxic drug that is difficult to use. The practical problems associated with monitoring serum lithium levels can pose formidable hurdle in developing country setting. Patients prescribed lithium for the first time should have serum lithium levels measured once a week until levels has stabilized between 0.6 and 0.8 mmol/l. For patients who still have sub-threshold symptoms with functional impairment after 6 months with these lithium levels, and for those who have previously relapsed while on lithium treatment, a 6-month trial of higher doses resulting in stable serum lithium levels of 0.8 to 1.0 mmol/l should be considered<sup>2</sup>.

Maintaining these standards may be difficult in remote areas with little laboratory facilities.

However, these problems should not be the reason to neglect lithium which as pointed out earlier has a demonstrated effect on reducing suicide, suicidality and cardiovascular mortality that may be superior to other antimanic and antidepressant drugs<sup>14,15</sup>. The side-effects of lithium have been studied extensively. There are comprehensive guidelines for the prevention, monitoring and treatment of adverse effects<sup>1,2</sup>. We were able to monitor the side effects and toxicity of Lithium with a simple checklist in this study. Used in routine clinical practice it should be possible to monitor the patients on Lithium during high risk periods such as summer and Ramadan.

To our knowledge present study has the largest sample size in studies which attempted to systematically assess the effects of Lithium in fasting during Ramadan. We have demonstrated that when used carefully the use of Lithium during Ramadan did not result in more adverse or toxic effects. The only side effect which differed in Pre Ramadan and Mid Ramadan was the weight loss in the latter observation period. This probably reflected the weight loss associated with fasting rather than the effect of Lithium. Moreover the only toxicity sign was the increased restlessness in mid Ramadan which can also be confounded with deranged metabolic state such as hypoglycemia in prolonged fasting state.

These findings are in contrast to the

general perception of Lithium being too toxic drug to be used in fasting. Daisley et al described fatal lithium toxicity during fasting in a case report<sup>16</sup>. However in this study we did not find any evidence of toxicity. The literature is generally lacking on the subject. On thorough literature search we did not find a study which has attempted to systematically study the side effects and toxicity of Lithium in systematic way. It is possible that isolated case reports like the one described by Daisley et al are occasional manifestation of Lithium toxicity arise as result of extreme dehydration associated with fasting<sup>16</sup>. One plausible explanation for our findings could be that our patients had relatively low serum Lithium. However, this must be pointed out that this level is within prophylactic range of Lithium use.

Although we did not find evidence of excessive adverse effects during Lithium use in Ramadan, it is advisable to conduct a baseline assessment of renal function before start of fasting in Ramadan for all patients who plan to fast during this month. There should also be measurement of serum electrolytes and creatinine, reanalysis and blood urea nitrogen. Chronic renal failure which may be asymptomatic in the early stages could be precipitated by the dehydration associated with fasting, so it is also vital to monitor serum creatinine more closely. In addition, patients should be advised to report to their physician if they develop diarrhea or feel excessively thirsty.

## CONCLUSIONS

We conclude from the results of this study that by following standard guidelines of use of lithium carbonate, it can be safely prescribed without unnecessary concerns of adverse side effect of it during Ramadan.

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