Available online on 15.09.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

Therapeutic Drug Monitoring and Safety Considerations of Lithium Therapy in Mood Disorder

Anne George [1], Alana Ansari [1], Alfa Mohammed [1], Aparna Sajeevan [1], Meera Ramanath [2], T Tamilselvan [3]*

[1] Pharm.D Interns, Nehru College of Pharmacy, Thrissur, Kerala, India

[2] Assistant Professor, Department of Psychiatry, P K DAS Institute of Medical Sciences, Palakkad, Kerala, India

[3] Professor and Head, Department of Pharmacy Practice, Nehru College of Pharmacy, Thrissur, Kerala, India

Article Info:

Article History:

Received 17 June 2026
Reviewed 04 Aug 2026
Accepted 27 Aug 2026
Published 15 Sep 2026

Cite this article as:

George A, Ansari A, Mohammed A, Sajeevan A, Ramanath M, Tamilselvan T, Therapeutic Drug Monitoring and Safety Considerations of Lithium Therapy in Mood Disorder, Journal of Drug Delivery and Therapeutics. 2026; 16(9):60-64 *DOI:* https://doi.org/10.22270/jddt.v16i9.7978

For Correspondence:

T Tamilselvan, Professor and Head, Department of Pharmacy Practice, Nehru College of Pharmacy, Thrissur, Kerala, India

Abstract

Background: To study the Therapeutic Drug Monitoring and safety considerations of lithium in mood disorders. **Methodology:** The study was carried out for a period of six months, a total of 35 participants were screened from both in-patients and out-patients who visited the Department of Psychiatry, diagnosed with Mood Disorders and on lithium therapy. From that, 30 patients were enrolled into the study based on the inclusion and exclusion criteria. All categorical variables would be described as frequency and percentage. All continuous variables would be described as mean. **Result:** A total of 30 Bipolar Affective Disorder (BAPD) patients, in which 19 females and 11 males were enrolled in the study. The mean age of respondents was 45±15.59 (18-72 years). In post follow up, there was a significant increase in therapeutic level and reduction of sub-therapeutic and supra-therapeutic levels. Pearson Correlation between average serum lithium concentration and average total daily dose was found to be 0.9994 which means there is an extremely high positive linear correlation between variables. A consistent and strong relationship (0.9706) among patient weight and serum lithium levels. A strong positive correlation (0.996) among patient age and serum lithium levels. **Conclusion:** This study underscores that personalized lithium monitoring improves treatment outcomes and safety, with weight-based dosing offers potential benefit and large study needed for confirming long-term effects.

Keywords: TDM, Lithium, Drug Safety, ADR, BPAD

INTRODUCTION

Mood Disorders or affective disorders are extraordinarily complex disorders with significant association with many neurological disorders[1]. These are common psychiatric disorders leading to increase morbidity and mortality. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V), it is categorized as bipolar disorder (BD) and depressive disorders[2]. BD is a chronic, recurring condition that leads to functional impairment that increases lifetime suicidal risk. According to WHO, BD comes under 10 disabling disorder in both developed and developing countries[3]. Classified as Bipolar I Disorder and Bipolar II Disorder[4].

Lithium is a mood stabilizing agent, used to treat manic and depressive episodes as well as maintenance therapy and adjunctive agent in Major Depressive Disorder in combination with antidepressants, and in management of schizoaffective disorders. Lithium is considered as gold standard treatment in treating BPAD[5]. It is having narrow therapeutic index and number of adverse events that results in poor adherence. Toxicity occurs when serum concentration is greater than 1.5 – 2 mmol/L and is characterized by tremor, apathy, hyperreflexia, seizures, ARF, cardiac dysrhythmia and coma[6]. Meta analysis confirmed the efficacy of Lithium particularly in prevention of manic relapse and less in case of depressive relapse. Up to 80% of patients show positive response to Lithium[7].

Therapeutic Drug Monitoring (TDM) refers to quantification of drug concentration in serum or plasma. It is used to Optimize doses in individual patients[5]. It is a clinical laboratory measurement of chemical parameters which influences drug prescribing procedures. And thus optimizes the dosage regimen by combining pharmacokinetic and pharmacodynamics knowledge and assess the efficacy and safety of a particular medication. TDM principles are used to choose right doses of drug needed[4]. TDM requires multidisciplinary approach. The indications of TDM includes efficacy, compliance, drug-drug interactions,

toxicity avoidance and therapy cessation monitoring.

Measuring low plasma concentrations helps to check poor compliance. It is important for drugs with narrow therapeutic ranges[8]. In TDM using appropriate bio markers plasma concentration of drug can be checked[7]. This study was aimed to study the TDM and safety considerations of Lithium in mood disorder patients.

METHODOLOGY

This study was a prospective observational study was conducted at PK DAS Institute of Medical Sciences in the Department of Psychiatry. The study was approved by the Institutional Ethics Committee.

The study was carried out for a period of six months, a total of 35 participants were screened from both in-patients and out-patients who visited the Department of Psychiatry, diagnosed with Mood Disorders and on lithium therapy. From that, 30 patients were enrolled into the study based on the inclusion and exclusion criteria. Both male and female patients who were on lithium therapy, age greater than 18 years who were willing to give informed consent was included in the study. Pregnant and lactating women and patient who had renal and hepatic failure were excluded from the study.

Sources of data were case sheets of patients and patient laboratory report. Parameters for evaluation were patient demographics, past medical and medication history to know the risk factors, serum lithium concentration to study TDM of lithium and adverse drug reactions to understand safety profile of lithium. A designed data collection from was made to collect patient demographics, such as age, sex, weight, date of admission, reasons for admission, date of discharge, medical history, medication history, occupation status, economic status smoking, alcohol, allergies, family history, sleep, appetite, vital signs, hematology report, renal function report, serum lithium concentration report as per need of the study. Each of the patient 30 patients were followed for 10 days initially and again upto 20 days for follow-up, during which serum lithium concentrations was collected. All the necessary data were collected, recorded and analysed.

The statistical analysis was performed by Statistical Package for Social Sciences software 26.0 version. All categorical variables would be described as frequency and percentage. All continuous variables would be described as mean ± SD. Student t-test was used to compare mean scores between various categorical variables. Paired t-test was used to find the significant difference between follow-ups. Pearson Correlation coefficient would be used to identify correlations between quantitative variables. A p value < 0.05 was considered to be statistically significant.

RESULTS

The present study was undertaken to evaluate the clinical characteristics of patients receiving lithium therapy, patterns of concomitant medication use, serum lithium concentrations at baseline and follow-up, adverse drug reactions, and the relationship between lithium dosage and serum lithium concentration**.** The study also aimed to assess changes in serum lithium concentrations during follow-up and determine the importance of therapeutic drug monitoring in promoting the safe and effective use of lithium in patients with mood disorders.

Demographics and Concomitant Medications of the Subjects

A total of 30 patients receiving lithium therapy for mood disorders were included, with a mean age of 45.15 ± 15.59 years. Females predominated (63%), while males accounted for 37%. A family history of BPAD was reported in 27% of patients, whereas 46% had no relevant family history. Psychiatric illness was the most common comorbidity (26%), followed by BPAD (19%), thyroid dysfunction (11%), and dyslipidemia (10%). Among 59 concomitant medications, antipsychotics were the most frequently prescribed (41%), followed by anticonvulsants (15%) and antidepressants (14%).

Table 1: Demographics and Concomitant Medications of the Subjects

S.No	Parameter	Category	Frequency	Percentage
1.	Gender (N=30)	Female	19	63 %
		Male	11	37 %
2.	Concomitant Medications (N=59)	Antipsychotics	24	41 %
		Anticonvulsants	09	15 %
		Depressants	08	14 %
		Antidepressants	05	08 %
		Antihypertensives	04	07 %
		Antidiabetics	04	07 %
		Thyroid agents	02	03 %
		Anti-hyperlipidemics	01	1.6 %
		Cognitive Enhancers	01	1.6%
		Anticholinergics	01	1.6%
		Total	59	100%

Analysis of Serum Lithium Concentration

At baseline, 33.3% of patients had sub-therapeutic, 63.3% had therapeutic, and 3.3% had supra-therapeutic serum lithium concentrations. During follow-up, among 19 patients, the proportion with therapeutic concentrations increased to 89.5%, while sub-therapeutic levels decreased to 5.3%. The mean lithium concentration changed from 0.49 ± 0.09 to 0.50 ± 0.01 mmol/L in the sub-therapeutic group and from 0.74 ± 0.15 to 0.72 ± 0.14 mmol/L in the therapeutic group. In the supra-therapeutic group, it decreased from 3.57 ± 0.03 to 2.89 ± 0.01 mmol/L. Overall, follow-up demonstrated improved serum lithium control.

Table 2: Serum Lithium Concentration Level

Sl. No.	Serum Lithium Concentration Level	Baseline n (%)	End of Study (EOS) n (%)	Average Lithium Concentration at Baseline (mmol/L)	Average Lithium Concentration at EOS (mmol/L)	Average Total Daily Dose (mg)
1	Sub-therapeutic	10 (33.3%)	01 (5.3%)	0.49 ± 0.09	0.51 ± 0.02	365.03 ± 55.01
2	Therapeutic	19 (63.3%)	017(89.5%)	0.74 ± 0.15	0.72 ± 0.14	355.31 ± 60.02
3	Supra-therapeutic	01 (3.3%)	01(5.3%)	3.57 ± 0.01	2.89 ± 0.03	400.03 ± 0.02

Analysis of Adverse Drug Reactions

Two ADRs (6.6 %) were reported among 30 patients. One patient developed lithium toxicity with ataxia at a serum lithium level of 3.57 mmol/L, which improved following dose adjustment. Another patient developed hyponatremia, managed by withholding lithium and subsequent dose reduction.

Table 3: Types of Adverse Drug Reaction

S. No	Types of ADR	Frequency (%)
1.	Lithium toxicity (ataxia)	01 (3.3 %)
2.	Hyponatremia	01 (3.3 %)
3.	Total ADR Reported	02 (6.6 %)

DISCUSION

BD is a chronic recurring psychiatric illness that can have a significant impact on patient's mental health. Pharmacist can play an essential role in TDM of lithium in mood disorders. They can assess the compliance, efficacy and safety of lithium therapy thereby providing education and counselling on medication adherence and monitor of potential medication- related side effects. This prospective observational study aimed to study the TDM of lithium and to understand the safety profile of lithium in patients with mood disorders. Here ia a total of 30 patients, 19 were females and 11 males were included in the study according to the inclusion and exclusion criteria. Out of these patients, some of them were identified with comorbidities such as BPAD (19%), psychiatric illness (26%), thyroid dysfunction (11%), DLP (10%).

In this study we analyzed the therapeutic effectiveness of lithium by TDM in mood disorders, its safety profile and monitored ADR. It has been observed in this study that the overall mean ± SD age of all patients was 45±15.59 (18-72) years.

The results of this study show the safety profile of lithium in 30 patients using serum lithium concentration improved notably during follow-up, with more patients achieving therapeutic levels and fewer remaining in the sub-therapeutic range. One patient had previously experienced lithium toxicity with dangerously high serum levels (initially 3.57mmol/L), which improved after withdrawing lithium. Another patient developed hyponatremia while on a standard 400mg twice daily dosage[9]. This were similar to the result of the study conducted by Giltin M. (2016). This suggests improved clinical monitoring and patient adherence.

To understand the relationship between serum lithium concentration and dosage, we have done statistical analysis and it showed a Pearson Correlation coefficient of 0.9994., indicating an extremely strong positive linear relationship between serum lithium concentration and total daily dose. However, the p-value of 0.401 revealed that this relationship was not statistically significant, meaning that the observed association cannot be generalized to the wider popoulation[10]. This result is similar to the study conducted by Malhi et.al. (2017).

Also, a two- sample t-test assuming unequal variances comparing serum lithium across 2 patient groups yielded a p-value of 0.688. this result confirms that there is no statistically significant difference between the mean serum lithium concentrations of the two groups, despite minor numerical differences (0.76 vs 0.82mmol/L).

This study revealed positive correlation between patient body weight and serum lithium concentrations. The correlation between weight and initial serum lithium level was extremely high (r= 0.9994), and remained strong at follow-up (r=0.9455) and also correlation between initial and follow-up lithium levels was also strong (r=0.942), indicating temporary stability in serum concentrations.

These findings imply that heavier individuals may tend

to have higher serum lithium concentrations, possibly due to variations in volume of distribution or renal handling of lithium[11,12,13]. These were similar to 3 different studies conducted by Shoaf, et. al, (1995), Bauer, et. al,(2014) and Lepkifker, et al. (1997). Although lithium dosing is not typically weight-based, these results suggest that weight could be a useful clinical parameter to consider during dose titration and therapeutic drug monitoring.

This study revealed positive correlation between patient age and serum lithium concentrations, particularly in supra-therapeutic group, where older patients exhibited significantly elevated lithium levels[14]. This observation similar with previous study of Rej et.al. (2014). Our finding that initial lithium levels can predict future concentrations align with the pharmacokinetic principle that steady state levels are affected by both dose and renal function. These results suggest the importance of individualized lithium dosing in older adults and need for cautions dose titration and monitoring.

CONCLUSION

This research highlights the importance of personalized lithium monitoring, particularly in groups with intricate comorbidities and multiple medications. Enhanced therapeutic levels observed at follow-up indicate successful clinical management; however, the risk of toxicity, through infrequent, persists and necessitates strict compliance with TDM protocols. the relationship between weight, dosage and serum lithium levels also indicates the possible advantages of weight-adjusted dosing approaches. future research involving larger sample sizes may yield more substantial statistical validation and investigate long-term outcomes.

Acknowledgments: We thank the management, doctors, and nursing staff of the Department of Neurology and Department of Psychology, PK Das Institute of Medical Sciences. Kerala.

Disclosure of conflict of interest: The authors have no conflict of interest regarding this investigation.

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