

THERAPEUTIC DRUG MONITORING AND ADVERSE DRUG REACTIONS OF LITHIUM IN PATIENTS DIAGNOSED WITH BIPOLAR AFFECTIVE DISORDER AT A TERTIARY CARE CENTER IN EASTERN NEPAL

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ABSTRACT

Lithium is a widely used mood stabilizer in management of bipolar affective disorder but its narrow therapeutic index (0.6–1.2 mmol/L) requires therapeutic drug monitoring to ensure both efficacy and safety. This descriptive cross-sectional study was conducted in the Psychiatry Ward of B.P. Koirala Institute of Health Sciences, Dharan, Nepal, over a period of 9 months (July 2022 to March 2023). Serum lithium concentrations and associated adverse drug reactions following lithium therapy in hospitalized patients with bipolar affective disorder was assessed, while also categorizing serum lithium levels as sub therapeutic, therapeutic, or supra-therapeutic. A total of 46 patients diagnosed with bipolar affective disorder and receiving lithium therapy were enrolled via convenience sampling. The mean age of participants was 29.13±9.25 years, with a male predominance (58.7%). Most patients (63.0%) had serum lithium levels within the therapeutic range (0.6-1.2 mmol/L), while 21.7% were sub-therapeutic (<0.6 mmol/L) and 15.2% were above the therapeutic range (>1.2 mmol/L). The most common adverse drug reaction was hand tremor (33.0%), followed by weight gain (22.7%), difficulty concentrating (16.7%), leukocytosis (7.6%), hypothyroidism (6.1%), nausea (4.5%), polyuria (4.5%) and polydipsia (4.5%). The findings highlights that although most patients achieved therapeutic lithium levels, a significant proportion had levels outside the target range. Routine monitoring of serum lithium levels, along with timely dose adjustments is therefore essential to optimize treatment outcomes and minimize adverse effect.

KEYWORDS

Adverse drug reactions, bipolar disorder, lithium, therapeutic drug monitoring

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INTRODUCTION

Bipolar affective disorder is a severe mental illness characterized by recurrent episodes of mania and depression, affecting millions worldwide.¹ In Nepal, its prevalence is estimated at 0.2% of the general population.² Lithium remains a first-line mood stabilizer for its efficacy in acute management and maintenance therapy.^{3,4}

However, lithium's use is complicated by its narrow therapeutic index (0.6–1.2 mmol/L for maintenance).⁵ Levels below this range may be ineffective, while levels exceeding 1.5 mmol/L can lead to toxicity, manifesting as nausea, tremors, confusion, and even seizures or coma.^{6,7} Individual variations in pharmacokinetics and drug interactions further complicate dosing. Therefore, therapeutic drug monitoring of lithium is indispensable for the safe and effective treatment of bipolar affective disorder.

Data on lithium monitoring and its adverse effect profile in the Nepalese population are scarce. This study aimed to determine serum lithium levels and document associated adverse drug reactions in patients with bipolar affective disorder at a tertiary care center in Eastern Nepal.

MATERIALS AND METHODS

This was a descriptive cross-sectional study conducted in the Psychiatry ward at B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, from July 2022, to March 2023. Ethical clearance was taken from Institutional Review Committee of BPKIHS (Ref: 366/079/080-IRC). After obtaining the necessary permission from the concerned authorities for data collection, a lab reports of patient's blood sample that was collected under fasting conditions (12 hours post-dose) on the 6th day of lithium therapy and analyzed by Beckman Coulter automated analyzer (DxC 700 AU), was reviewed.

Patients' starting lithium dose, serum lithium concentrations and any associated observed adverse drug reaction was recorded in pre-designed proforma which included demographic data, lithium dosing, serum lithium concentrations, any observed ADRs. The recorded data was entered in Microsoft Excel and descriptive analysis was done by using SPSS-20.

RESULTS

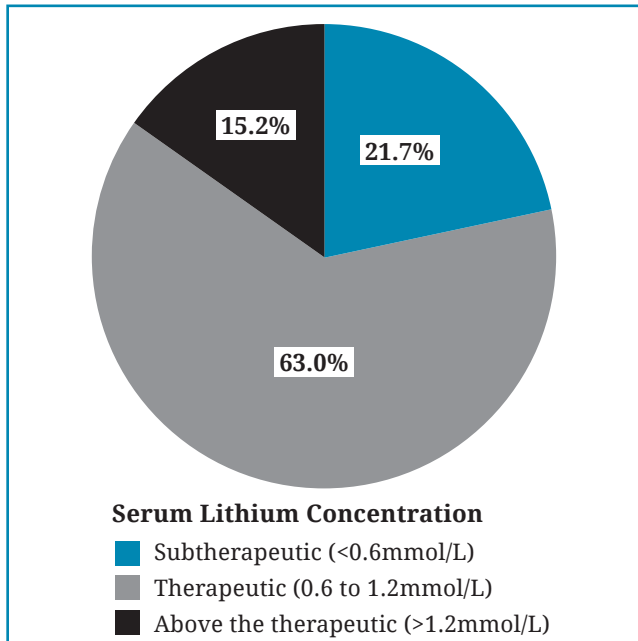
The study included 46 patients as summarized in Table 1. The majority were male (58.7%),

Table 1: Baseline characteristics of the study population (n=46)

| Variables | Categories | n | % |
|-------------------------------------|------------------|--------------|-------|
| Gender | Male | 27 | 58.7 |
| | Female | 19 | 41.3 |
| Age (years) | 10 – 20 | 5 | 10.9 |
| | 21 – 30 | 27 | 58.7 |
| | 31 – 40 | 9 | 19.6 |
| | 41 – 50 | 2 | 4.3 |
| | > 51 | 3 | 6.5 |
| Residence | Dhanusha | 2 | 4.3 |
| | Siraha | 2 | 4.3 |
| | Udaypur | 2 | 4.3 |
| | Saptari | 5 | 10.9 |
| | Morang | 17 | 36.9 |
| | Sunsari | 11 | 23.9 |
| | Bhojpur | 1 | 2.2 |
| | Dhankuta | 1 | 2.2 |
| | Jhapa | 4 | 8.7 |
| Taplejung | 1 | 2.2 | |
| Marital status | Married | 25 | 54.3 |
| | Unmarried | 20 | 43.5 |
| | Divorced | 1 | 2.2 |
| Educational status | Illiterate | 2 | 4.3 |
| | Primary | 5 | 10.9 |
| | Secondary | 14 | 30.4 |
| | Higher secondary | 16 | 34.7 |
| Occupation | Bachelor & above | 9 | 19.5 |
| | Unemployed | 18 | 39.1 |
| | Housewife | 8 | 17.4 |
| | Farmer | 3 | 6.5 |
| | Business | 12 | 26.08 |
| Religion | Service | 5 | 10.9 |
| | Hindu | 38 | 82.6 |
| | Christian | 8 | 17.4 |
| | Ethnicity | <i>Kirat</i> | 9 |
| <i>Madhesi</i> | | 14 | 30.4 |
| <i>Chettri</i> | | 7 | 15.2 |
| <i>Brahmin</i> | | 9 | 19.6 |
| <i>Dalit</i> | | 4 | 8.7 |
| <i>Janjati</i> | | 3 | 6.5 |
| Duration of illness (BPAD) in years | < 1 | 5 | 10.8 |
| | 2 – 10 | 32 | 69.6 |
| | 11 – 20 | 5 | 10.8 |
| | > 20 | 4 | 8.7 |
| Family History of BPAD | Yes | 18 | 39.1 |
| | No | 28 | 60.8 |

Table 2: Therapeutic drug monitoring parameters (n=46)

| Variables | Mean \pm SD | Median | Range |
|------------------------|---------------------|--------|-------------|
| Starting dose (mg) | 904.35 \pm 64.83 | 900 | 600 – 1050 |
| Serum lithium (mmol/L) | 0.81 \pm 0.30 | 0.72 | 0.33 - 1.76 |
| Adjusted dose (mg) | 780.00 \pm 197.48 | 750 | 600 – 1050 |

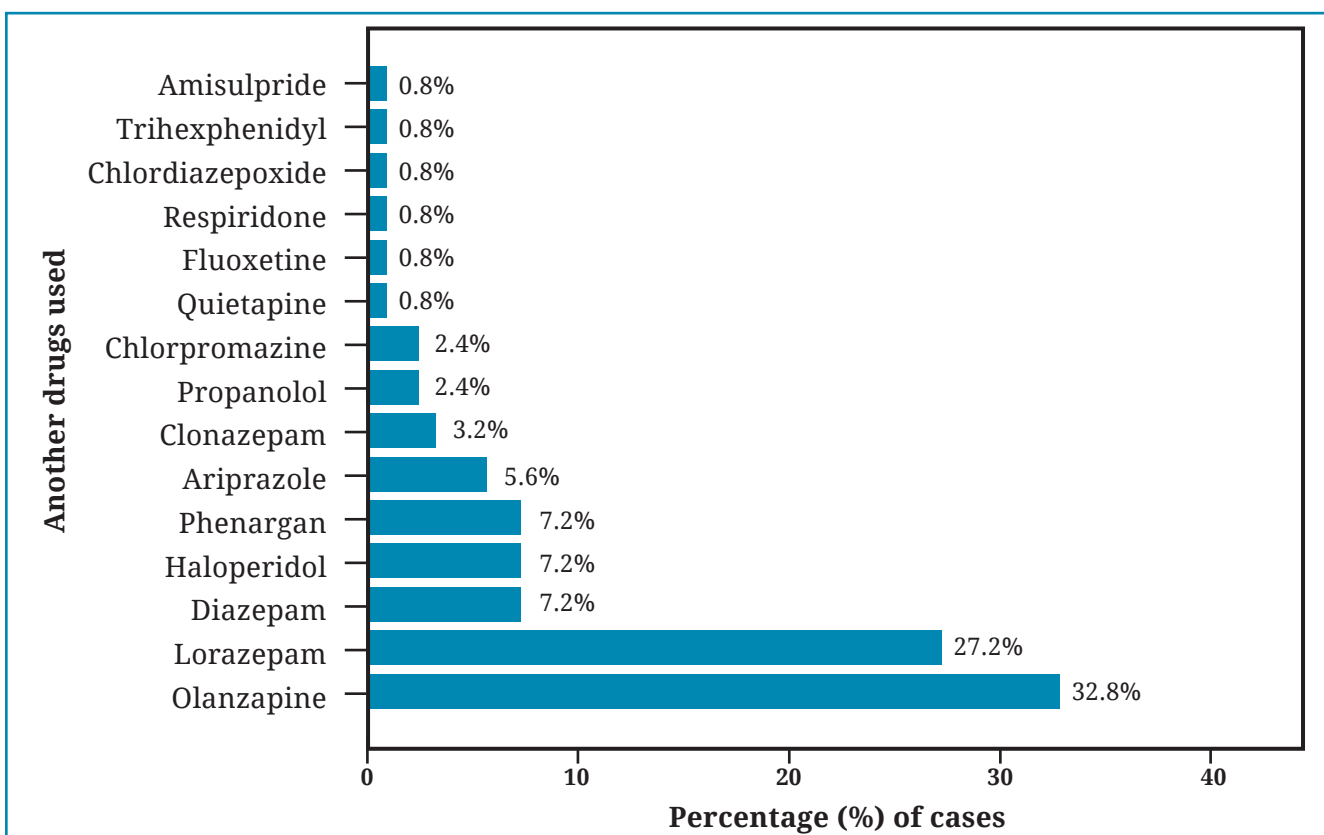
**Fig. 1:** Distribution of serum lithium levels among patients (n=46)

aged 21-30 years (58.7%), and unemployed (39.1%). Most patients (69.6%) had an illness duration of 2-10 years, and 39.1% reported a family history of bipolar disorder.

The mean starting dose of lithium was 904.35 \pm 64.83 mg, with 900 mg being the most common dose (87%). The mean serum lithium concentration was 0.81 \pm 0.30 mmol/L. After monitoring, the dose was adjusted to a mean of 780 \pm 197.48 mg (Table 2).

Therapeutic drug monitoring revealed that 29 patients (63%) had levels within the therapeutic range, 10 (21.7%) were sub-therapeutic, and 7 (15.2%) were above the therapeutic range (Fig. 1).

A total of fifteen different drugs were co-administered to all the patients. On average, a minimum of three drugs were prescribed to the majority of patients. The most frequently co-administered drug was Olanzapine (32.8%), followed by Lorazepam (27.2%) (Fig. 2).

**Fig. 2:** List of co-administered drugs to the patients (n=46)

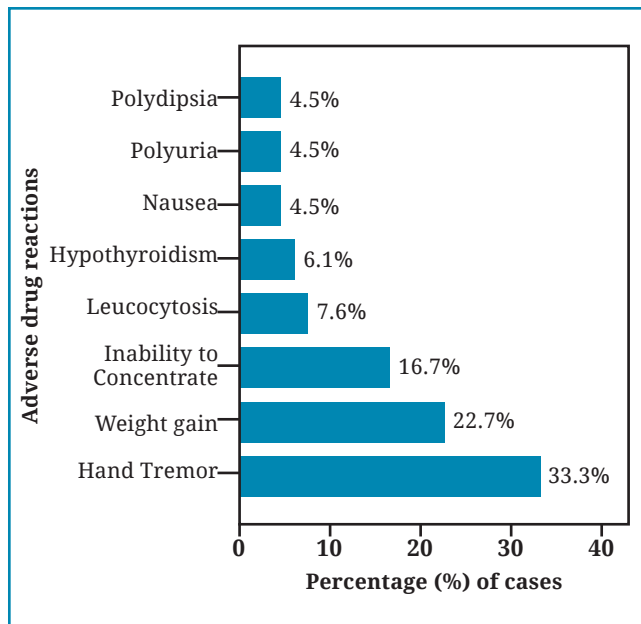


Fig. 3: List of adverse drug reactions observed in the patients (n=29)

A total of eight types of adverse drug reactions (ADRs) were observed in 29 out of 46 patients. The most common ADR was hand tremor, reported in 22 patients (33.3%), followed by weight gain in 15 patients (22.7%) and difficulty in concentration in 11 patients (16.7%) (Fig. 3).

DISCUSSION

This descriptive cross-sectional study offers an important snapshot of the clinical use of lithium in patients with bipolar affective disorder (BPAD) at a tertiary care center in Eastern Nepal. The findings emphasize two central aspects of lithium management: the essential role of therapeutic drug monitoring (TDM) in light of substantial inter-individual variability in achieving target serum levels, and the high frequency of adverse drug reactions (ADRs), underscoring the need for rigorous clinical oversight.

A key observation was the distribution of serum lithium concentrations. Notably, 63.0% of patients achieved serum levels within the therapeutic window (0.6–1.2 mmol/L), similar to findings of the results of Munshi and Pal⁸ and Sharma *et al.*,⁹ who reported almost identical proportions of 63.3% and 63.6%, respectively. This consistency across time and settings suggests that when standard dosing is guided by TDM, it can successfully stabilize the majority of patients. The mean serum concentration of 0.81 ± 0.30 mmol/L further indicates dosing practices were generally aligned with the lower-to-mid therapeutic range, adequate for

maintenance therapy and potentially reducing toxicity risk.

However, the fact that 36.8% of total patients had serum concentrations outside the therapeutic range remains a critical challenge. Sub-therapeutic levels (<0.6 mmol/L; 21.7% of patients) risk inadequate symptom control, relapse of BPAD, while supra-therapeutic levels (>1.2 mmol/L; 15.2% of patients) pose an immediate risk of toxicity, particularly when levels exceed 1.5 mmol/L. Since lithium levels were assessed under supervised inpatient conditions, these variations are unlikely to be due to non-adherence. Rather, they reflect marked inter-individual pharmacokinetic differences influenced by renal function, hydration, sodium balance, age, body composition, and genetic factors. These findings reinforce that fixed-dose regimens without TDM are unsafe, as they risk leaving a considerable proportion of patients either underexposed or overdosed.

The prevalence of ADR observed was also high with 29 out of 46 patients reporting ADR that too aligns with the known profile of lithium. Hand tremors (33.0%) and weight gain (22.7%) were the most common, similar to findings reported in other studies.^{10,11} Additional ADRs findings included difficulty concentrating (16.7%), nausea (4.5%), polyuria and polydipsia (each 4.5%), alongside clinically important though fewer common findings of hypothyroidism (6.1%) and leukocytosis (7.6%). These results also suggest the need for routine monitoring of thyroid function and awareness of lithium's hematological effects.

Polypharmacy was also observed among all patients with total of 15 drugs used with minimum of three drugs used in majority of patients, with olanzapine (32.8%) and lorazepam (27.2%) most frequently co-administered. This practice aligns with evidence-based management of acute mania but complicates attribution of ADRs, as effects such as weight gain, sedation, and tremor may be due to multiple drug use. While this represents a limitation, it also reflects real-world practice where lithium is infrequently prescribed as single drug for BPAD management.

Sociodemographic patterns in our study also provides further insights into BPAD management in this setting. A predominance of young males, aged 21–30 (58.7%) and high unemployment (39.1%) suggest possible socioeconomic and cultural influences on illness expression and care-seeking. The presence of family history in nearly 40.0% of patients reaffirms the heritable nature of BPAD. These contextual factors are not merely descriptive but have implications

for treatment adherence, nutrition, hydration, and follow-up, all of which influence lithium pharmacokinetics and tolerability.

LIMITATIONS: This study has limitations. The small sample size and single-center design limit the generalizability of the findings. The concurrent use of other psychotropic medications made it challenging to attribute adverse reactions solely to lithium. A study on lithium monotherapy would provide a clearer picture of its adverse effect profile. Furthermore, pharmacokinetic interactions with co-administered drugs were not investigated.

In conclusion, this study demonstrates that lithium remains an effective cornerstone of BPAD treatment, but its safe use requires individualized dosing guided by TDM. Although the majority of patients can be maintained within therapeutic limits, a substantial proportion are vulnerable to under- or

overdosing without close monitoring. The high incidence of ADRs, particularly neurological and metabolic effects, highlights the need for proactive management strategies and patient education. Future research with larger cohorts, longitudinal follow-up, and integration of renal, thyroid, and pharmacogenetic factors will be critical to optimizing lithium therapy in the Nepalese context. Overall, these findings underscore that TDM is not an optional adjunct but a fundamental requirement for safe and effective lithium pharmacotherapy

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