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Original Article

Clinical, Biochemical and Neurological Outcomes in Bipolar Patients with Lithium Intoxication at a Tertiary Care Hospital Sindh

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ABSTRACT

Background: Bipolar disorder (BD) affects a significant portion of the global population, with lithium being a cornerstone in its treatment. However, the therapeutic index of lithium is narrow, and its effectiveness can be overshadowed by the risk of toxicity, especially at higher serum levels. Understanding the impact of varying lithium concentrations on clinical, biochemical, and neurological outcomes is crucial in the management of BD.

Objective: To assess the clinical, biochemical, and neurological changes associated with different levels of lithium toxicity in patients with bipolar disorder and to determine the safe and effective range of lithium serum levels.

Methods: A prospective cross-sectional study was conducted at Jinnah Post Graduate Medical Center, Karachi, involving 100 bipolar disorder patients on lithium therapy, categorized into three groups based on their serum lithium levels: Category I (<1.2 mmol/L), Category II (1.2 – 2.5 mmol/L), and Category III (>2.5 mmol/L). Clinical assessments, laboratory investigations (including renal and thyroid function tests), and neurological evaluations were conducted. Data were analyzed using SPSS version 25, with the t-test and Chi-square test employed for quantitative and qualitative comparisons, respectively.

Results: Patients with serum lithium levels above 2.5 mmol/L (Category III) demonstrated significantly higher rates of clinical toxicity, renal dysfunction, and neurological complications compared to lower lithium level groups. Renal function parameters (serum creatinine and urea) and thyroid function (TSH levels) were notably altered in Category III. The incidence of neuropsychiatric symptoms was also significantly higher in this group, with severe neurotoxic effects observed in 27% of these patients.

Conclusion: The study highlights the critical importance of maintaining serum lithium levels within a therapeutic range to avoid severe adverse effects. Lithium levels above 2.5 mmol/L significantly increase the risk of renal dysfunction, thyroid abnormalities, and neurotoxicity. Regular monitoring and individualized treatment adjustments are essential for optimizing patient safety and treatment efficacy.

Keywords: Bipolar Disorder, Lithium Toxicity, Serum Lithium Levels, Renal Dysfunction, Neurotoxicity, Thyroid Function.

INTRODUCTION

Bipolar disorder, affecting about 2% of the global population, is a highly heritable mental illness characterized by extreme mood swings, ranging from manic highs to depressive lows (1)(2). This condition commonly begins in young adulthood and is a significant cause of disability and premature death. Notably, the incidence of bipolar disorder among Pakistani students is reported to be 14.3%, with the 20–21-year age group being particularly affected (3). Despite advances in neuroscience and the emergence of antipsychotics and targeted antiepileptics, lithium remains a cornerstone in the treatment of bipolar disorder, acclaimed for its exceptional efficacy in all treatment phases and its ability to prevent self-harm in individuals with bipolar disorder or severe depression (4).

Journal of Health and Rehabilitation Research 2791-156X JHRR

Lithium's role in psychiatry is complex due to its chemical interactions with various biological functions, yet its exact mechanism in mood regulation remains unclear. Its actions may involve changes in cell membrane functions, serotonin and norepinephrine activity, and effects on phosphatidylinositol metabolism, with one hypothesis suggesting the inhibition of glycogen synthase kinase 3 (GSK3) enzymes (6). Lithium's side effects are categorized by the affected systems or organs, such as the genitourinary system, digestive tract, brain, thyroid gland, metabolic processes, and heart. Some side effects appear during the initial phase of treatment and may subside with continued use, but others can occur at any time and significantly impact the success of lithium therapy (7). The recommended therapeutic plasma level for bipolar disorder is 0.5-1.2 mmol/L, with regular monitoring advised to maintain levels within this range. However, due to its narrow therapeutic index, toxic effects can occur if levels exceed 1.2 mmol/L, prompting suggestions for lower initial plasma concentrations (8). Toxicity becomes significant at levels above 1.5 mmol/L, with severe symptoms such as convulsions and confusion occurring at levels over 2 mmol/L, potentially leading to coma and death (9).

Lithium toxicity can result from various scenarios, including acute overdosing, fluctuations in therapeutic doses, and chronic toxicity. Chronic intoxication develops over time due to systemic ailments and drug interactions (10). Neurotoxicity is a severe consequence of lithium toxicity, which can be either reversible or irreversible. Reversible neurotoxicity is characterized by the absence of persistent brain damage following an episode of toxicity, while irreversible effects include cerebellar dysfunction, memory loss, parkinsonian disorders, choreoathetosis, brain stem conditions, and peripheral neuropathies, persisting for over two months after cessation of lithium therapy (11). Clinically, lithium neurotoxicity is often associated with chronic cerebellar impairment and demyelination, particularly in the cerebellum, leading to dystaxia and dysarthria (12).

Lithium is excreted by the kidneys, with its half-life varying based on kidney function and water intake, being approximately eighteen hours in young individuals and thirty-six hours in older adults (13). Preventing lithium poisoning involves careful prescription, patient education, and consistent clinical and biochemical monitoring. Mild effects are managed with oral fluids and electrolytes, while more severe cases may require intravenous saline, cathartics, charcoal cleansing, and even hemodialysis to prevent neurotoxicity (14)(15)(16).

The purpose of this study is to evaluate the clinical, biochemical, and neurological changes associated with lithium toxicity in bipolar disorder patients, employing periodic monitoring of lithium levels.

MATERIAL AND METHODS

This prospective cross-sectional study was conducted at Jinnah Post Graduate Medical Center, Karachi, from June to November 2023. It involved 100 bipolar disorder patients undergoing lithium treatment. The study began with the collection of medical histories and physical assessments of participants, focusing on renal, digestive, respiratory, cardiac, and neurological health, including signs of toxicity. Meticulous records of each patient's age, gender, patient code, admission status (in-patient or outpatient), and type of healthcare facility were maintained. Concurrently, electrolyte, renal, and hepatic function tests were performed alongside lithium level estimations. Key laboratory assessments included blood urea nitrogen, serum creatinine, TSH levels, serum electrolytes, and complete blood count.

Participants were included if they were over 18 years old and prescribed lithium. Exclusion criteria encompassed individuals below 18 years or those with liver dysfunction, seizures, neuroleptic conditions, metabolic derangements, or organic neurological disorders confirmed by CT or MRI scans. The study stratified participants into three categories based on serum lithium levels: Category I with levels below 1.2 mmol/L, Category II with levels between 1.2 and 2.5 mmol/L, and Category III with levels above 2.5 mmol/L. Lithium concentrations and blood biochemical characteristics were analyzed using standard procedures, with serum lithium measured at its lowest during steady state, five days post medication commencement. Patient demographics, clinical features (including renal, digestive, respiratory, and cardiac conditions, neuropsychiatric symptoms), and concurrent medications (such as antipsychotics, antidepressants, and lamotrigine) were evaluated.

The diagnosis of bipolar disorder was established through a clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) (27), the Structured Clinical Interview for Diagnosis (SCID) scale (26), and a requirement for participants to have a Young Mania Rating Scale (YMRS) score of less than 15 at the start of the study and every three months thereafter (28). Participants were followed from the date of enrollment to the date their outcome data were collected.

Data were analyzed using SPSS version 25. Quantitative data were examined using the t-test, while qualitative data comparisons across the three categories were conducted using the Chi-square test. A p-value of less than 0.05 was considered statistically significant.

Journal of Health and Rehabilitation Research 2791-156X JHRR

RESULTS

In this comprehensive study, we examined a cohort of 100 patients with bipolar disorder undergoing lithium treatment, categorized into three groups based on their serum lithium levels: Category I with levels below 1.2 mmol/L (n=35), Category II with levels between 1.2 and 2.5 mmol/L (n=35), and Category III with levels above 2.5 mmol/L (n=30). The demographic analysis revealed a mean age of 44.16 ± 12.80 years across the groups, with no significant age difference noted (p = 0.534). Gender distribution showed a higher percentage of males (58%) than females (42%), with a significant difference in gender across categories (p = 0.005) (Table 1).

In terms of diagnosed conditions, ADHD was observed in 100% of Category I patients, decreasing in prevalence in the higher lithium level categories, resulting in an overall prevalence of 75%. Oppositional Defiant Disorder (ODD) was consistently high in Categories I and II (86%) but less prevalent in Category III (47%). The frequency of other conditions, such as Conduct Disorder, Social Avoidance, Obsessive-Compulsive Disorder (OCD), and Psychosis, varied across categories but did not show a clear trend correlating with lithium levels. Notably, more than two comorbid anxiety disorders were found in 40% of Category I patients, decreasing in the higher categories (Table 1).

Table 1 Demographic Elements

Demographic Elements	Category I (<1.2mmol/L) n=35	Category II (1.2 – 2.5mmol/L) n=35	Category III (>2.5 mmol/L) n=30	Total N=100	p Value
Age in Years (Mean ± SD)	42.25 ± 12.60	45.41 ± 12.76	43.96 ± 13.54	44.16 ± 12.80	0.534
Gender					0.005
Male	22 (63%)	26 (74%)	10 (33%)	58 (58%)	
Female	13 (37%)	9 (26%)	20 (67%)	42 (42%)	
Diagnosed Conditions					0.199
ADHD	35 (100%)	30 (86%)	10 (33%)	75 (75%)	
ODD	30 (86%)	30 (86%)	14 (47%)	74 (74%)	
Conduct Disorder	13 (37%)	8 (23%)	5 (17%)	26 (26%)	
Social Avoidance	10 (29%)	6 (17%)	2 (7%)	18 (18%)	
OCD	8 (23%)	8 (23%)	7 (23%)	23 (23%)	
Psychosis	20 (57%)	17 (49%)	4 (13%)	41 (41%)	
>2 Comorbid Anxiety Disorders	14 (40%)	8 (23%)	6 (20%)	28 (28%)	
Encopresis	0 (0%)	4 (11%)	5 (17%)	9 (9%)	
Bulimia	1 (3%)	0 (0%)	4 (13%)	5 (5%)	
Enuresis	4 (11%)	4 (11%)	3 (10%)	11 (11%)	
Manic Episode Features					0.09
Interval of Hypomania or Mania	11.41 ± 1.57	12.52 ± 2.58	14.34 ± 1.09	13.77 ± 1.4	0.06
Average Length of Sickness (Years)	5.22 ± 1.09	5.62 ± 1.64	5.24 ± 2.43	5.56 ± 2.6	0.234
Manic Episode Starting Age	18.41 ± 8.24	28.28 ± 16.42	33.52 ± 9.54	28.12 ± 14.5	0.03
Age of Depression Onset	28.55 ± 12.65	21.28 ± 7.09	26.22 ± 12.64	27.08 ± 9.2	0.05
Depression before the Start of Mania	13 (37%)	15 (43%)	12 (40%)	40 (40%)	0.023
Bipolar Disorder	35 (100%)	35 (100%)	30 (100%)	100 (100%)	1
Index Presentation of BD	13 (37%)	6 (17%)	11 (37%)	30 (30%)	0.80
Psychotic	27 (77%)	18 (51%)	9 (30%)	54 (54%)	0.71
Neuroleptics	25 (71%)	15 (43%)	10 (33%)	50 (50%)	0.056
Mixed Presentations	30 (86%)	25 (71%)	20 (67%)	75 (75%)	0.216
Drug Intake					0.005

Journal of Health and Rehabilitation Research 2791-156X JHRR

Anti-depressants	30 (86%)	5 (14%)	15 (50%)	50 (50%)	
Anti-psychotics	22 (63%)	14 (40%)	9 (30%)	45 (45%)	

The evaluation of manic episode features indicated that the interval of hypomania or mania, the average length of illness, the age of onset for manic episodes, and the age of depression onset differed among the groups. The interval of hypomania or mania was longest in Category III (14.34 ± 1.09 years), with a significant difference in starting age for manic episodes among the groups (p = 0.03) (Table 1).

Table 2 Frequency of Mild Adverse Effects Across Different Levels of Lithium Intoxication

Adverse Effects	Category I (<1.2mmol/L) n=35	Category II (1.2 – 2.5mmol/L) n=35	Category III (>2.5 mmol/L) n=30	Total N=100
Tremors	02 (6%)	0 (0%)	01 (3%)	03
Tiredness	01 (3%)	02 (6%)	01 (3%)	04
Nausea	0 (0%)	0 (0%)	0 (0%)	00
Vomiting	02 (6%)	05 (14%)	01 (3%)	08

Table 3 Frequency of Moderate Adverse Effects Across Different Levels of Lithium Intoxication

Adverse Effects	Category I (<1.2mmol/L) n=35	Category II (1.2 – 2.5mmol/L) n=35	Category III (>2.5 mmol/L) n=30	Total N=100
Confusion	04 (11%)	01 (3%)	01 (3%)	06
Anger	01 (3%)	01 (3%)	0 (0%)	02
Palpitations	01 (3%)	01 (3%)	03 (10%)	05
Increased Muscle Tone	03 (9%)	03 (9%)	03 (10%)	09

Regarding medication intake, a significant difference was observed in the use of antidepressants and antipsychotics across the categories (p = 0.005). A higher percentage of Category I patients were on antidepressants (86%) compared to Categories II and III. Similarly, the use of antipsychotics was most common in Category I (63%) and least common in Category III (30%) (Table 1).

The analysis of adverse effects showed that mild effects like tremors and tiredness were more common in Category I, with vomiting being more frequent in Category II. However, there were no reports of nausea across any groups (Table 2). Moderate adverse effects like confusion, anger, palpitations, and increased muscle tone were relatively evenly distributed across the categories, with no specific trend (Table 3). In contrast, severe adverse effects such as elevated body temperature, low blood pressure, unconsciousness, and fits were notably more frequent in Category III, highlighting the increased risk of severe outcomes with higher lithium levels (Table 4).

The overall analysis of adverse events revealed a higher total frequency in Category III (83%), with severe effects being most prevalent in this group (50%). This finding underscores the heightened risk of severe adverse effects at higher lithium concentrations (Table 5).

Systemic clinical signs varied significantly across the categories, particularly in the renal and cardiovascular systems, where a higher prevalence was noted in Category III (renal system: 14%, cardiovascular system: 7%). However, central nervous system (CNS) signs were more evenly distributed, without a significant difference across categories (Table 6).

Table 4 Frequency of Severe Adverse Effects Across Different Levels of Lithium Intoxication

Adverse Effects	Category I (<1.2mmol/L) n=35	Category II (1.2 – 2.5mmol/L) n=35	Category III (>2.5 mmol/L) n=30	Total N=100
Elevated Body Temp.	01 (3%)	01 (3%)	02 (7%)	04 (4%)
Low Blood Pressure	02 (6%)	0 (0%)	04 (14%)	06 (6%)
Unconsciousness	0 (0%)	03 (9%)	04 (14%)	07 (7%)
Fits	0 (0%)	03 (9%)	05 (17%)	08 (8%)

Table 5 Relation of Adverse Events Across Various Lithium Levels Categories

Journal of Health and Rehabilitation Research JHRR

Adverse Effects	Category I (<1.2mmol/L) n=35	Category II (1.2 – 2.5mmol/L) n=35	Category III (>2.5 mmol/L) n=30	Total N=100
Mild	05 (14%)	07 (20%)	03 (10%)	15 (15%)
Moderate	09 (26%)	06 (17%)	07 (24%)	22 (22%)
Severe	03 (9%)	07 (20%)	15 (50%)	25 (25%)
Total	17 (49%)	20 (57%)	25 (83%)	62 (62%)

Table 6 Systemic Clinical Signs Among Different Categories of Patients with Lithium Intoxication

Signs	Category I (<1.2mmol/L) n=35	Category II (1.2 – 2.5mmol/L) n=35	Category III (>2.5 mmol/L) n=30	p-value
Renal System	01 (3%)	04 (12%)	04 (14%)	0.041
Digestive System	01 (3%)	08 (23%)	02 (7%)	0.082
Respiratory System	02 (6%)	04 (12%)	02 (7%)	0.304
Cardiovascular System	01 (3%)	02 (6%)	02 (7%)	0.036
CNS	08 (23%)	14 (40%)	10 (34%)	0.612

Table 7 Severity of Neuropsychiatric Clinical Features Across Different Categories of Toxic Lithium Levels

Severity	Category I (<1.2mmol/L) n=35	Category II (1.2 – 2.5mmol/L) n=35	Category III (>2.5 mmol/L) n=30	p-value
Mild	08 (23%)	04 (12%)	0 (0%)	0.032
Moderate	01 (3%)	06 (17%)	02 (7%)	
Severe	02 (6%)	04 (12%)	08 (27%)	

Table 8 Biochemistry of Patients with Toxic Levels of Lithium

Lab Parameter	Category I (<1.2mmol/L) n=35	Category II (1.2 – 2.5mmol/L) n=35	Category III (>2.5 mmol/L) n=30	p-value
Sodium (mEq/dl)	139 ± 4.39	140 ± 3.44	142 ± 3.55	0.652
Potassium (mEq/dl)	4.0 ± 0.78	3.98 ± 0.62	4.5 ± 0.36	0.449
Chloride (mEq/dl)	106 ± 4.02	108 ± 3.71	109 ± 2.89	0.784
S. Creatinine (mg/dl)	1.0 ± 0.49	1.25 ± 0.51	1.73 ± 1.34	0.001
Urea (mg/dl)	14 ± 5.55	16 ± 6.28	29 ± 15.45	0.001
TSH-conc (mU/l)	1.66 ± 0.039	5.34 ± 0.299	6.9 ± 0.777	0.002
Haemoglobin (g/dl)	12.2 ± 0.57	11.8 ± 0.99	11.5 ± 1.77	0.067
TLC per ml	10700 ± 2549	11349 ± 3239	7950 ± 4008	0.933
Platelets (x 103/ml)	274 ± 52.7	274 ± 57.11	266 ± 98.69	0.186

Neuropsychiatric clinical features showed a notable trend, with mild symptoms being most prevalent in Category I and severe symptoms increasing in frequency in Category III (27%). This trend was statistically significant for mild symptoms (p = 0.032) (Table 7).

The biochemistry parameters indicated a significant difference in serum creatinine, urea, and thyroid-stimulating hormone (TSH) concentrations across the categories, with the highest values observed in Category III. This suggests a correlation between higher lithium levels and altered renal and thyroid function. However, no significant differences were found in sodium, potassium, chloride, hemoglobin, total leukocyte count (TLC), and platelet levels (Table 8).

The study highlights the varying impacts of different levels of lithium intoxication on demographic characteristics, diagnosed conditions, manic episode features, drug intake, adverse effects, systemic clinical signs, neuropsychiatric features, and biochemistry parameters in patients with bipolar disorder.

DISCUSSION

In this study, we rigorously investigated the impact of varying serum lithium concentrations on patients with bipolar disorder (BD) undergoing maintenance therapy. It was observed that individuals with serum lithium levels exceeding 2.5 mmol/L exhibited a

significantly higher incidence of toxicity symptoms and notable alterations in clinical, neurological, and biochemical outcomes, compared to those with levels below 1.2 mmol/L and between 1.2-2.5 mmol/L. These findings align with prior research underscoring the correlation between elevated lithium levels and increased adverse outcomes (17). The results underscore the importance of diligent monitoring and management of lithium therapy, as endorsed by the Royal College of Psychiatrists and the NICE guidelines. These guidelines advocate for biannual monitoring in low-risk individuals and more frequent checks every three months for high-risk patients, including the elderly, those on lithium-interacting medications, patients with poor compliance, and individuals with recent plasma lithium levels above 0.8 mmol/L (18).

Renal function, a crucial aspect of overall health, was notably impacted by toxic lithium levels. Participants exposed to lithium levels greater than 2.5 mmol/L displayed decreased renal activity, echoing findings from Kessing et al.'s study, which linked lithium use with an increased risk of chronic kidney disease (19). Additionally, Shine et al. reported that patients monitored for lithium had a higher likelihood of a reduced glomerular filtration rate compared to general healthcare users (20).

Neurotoxicity is a well-known consequence of acute lithium poisoning. Our study found that severe lithium toxicity (>2.5 mmol/L) was associated with heightened neurological issues, compared to milder toxicity states (1.2 and 1.2-2.5 mmol/L). The relationship between lithium levels in the blood and neurotoxicity is not always consistent, and neurotoxicity can occur even at therapeutic doses. Notably, the combined use of lithium and neuroleptics or antidepressants, such as fluoxetine, has been linked to reversible lithium neurotoxicity, suggesting an interaction between dopamine-producing and acetylcholine neurotransmitters in the brain (24)(25).

The study also shed light on lithium's impact on metabolic and endocrine functions, particularly the thyroid gland. Lithium accumulates in the thyroid at concentrations several times higher than in plasma, potentially inhibiting thyroid hormone production and impacting thyroid iodine absorption. This can result in altered thyroid morphology and impaired hepatic deiodination, potentially accelerating thyroid autoimmunity (26)(27).

The research has several strengths, including its comprehensive approach to examining the wide range of clinical, biochemical, and neuropsychiatric outcomes associated with different lithium levels. However, it also has limitations, such as the potential for variability in individual responses to lithium and the influence of concurrent medications, which could affect the generalizability of the findings. Future studies should consider these factors and explore personalized treatment strategies for bipolar patients on lithium therapy, taking into account the complex interplay between clinical symptoms, investigation value deviations, and neurological outcomes.

Our study highlights the critical need for meticulous monitoring of lithium levels to prevent severe adverse effects, especially in high-risk populations. It provides valuable insights into the management of bipolar disorder with lithium therapy, emphasizing the delicate balance between therapeutic efficacy and the risk of toxicity.

CONCLUSION

The findings of this study carry significant implications for the clinical management of bipolar disorder, particularly emphasizing the critical need for vigilant monitoring of serum lithium levels. The study conclusively demonstrates that lithium levels exceeding 2.5 mmol/L are associated with heightened risks of renal dysfunction, neurotoxicity, and disturbances in metabolic and endocrine functions, especially impacting thyroid health. These insights underscore the importance of individualized treatment strategies and frequent monitoring, especially in high-risk groups, to maintain lithium within therapeutic limits and mitigate adverse effects. The research thus reinforces the delicate balance required in lithium therapy for bipolar disorder, highlighting the need for a nuanced approach that integrates clinical, biochemical, and neuropsychiatric considerations to optimize patient outcomes and safety.

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