ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY
APJMT 14;3 http://apjmt.mums.ac.ir September 2025

ORIGINAL ARTICLE

Clinicoepidemiological Pattern of Lithium Poisoning: Comparison of Two Decades in Tehran, Iran

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Abstract

Background: Lithium has been identified as a substance of significant toxicological concern, with the potential to inflict permanent damage to the central nervous system (CNS). This study examined cases of lithium poisoning over a period of ten years and compared them with cases from the previous decade.
Methods: This cross-sectional and retrospective study was conducted on patients with lithium poisoning. The study population comprised 491 patients. Information regarding the patients was retrieved from the hospital archives using a checklist. Subsequent to discharge, patients were monitored for post-operative outcomes. Subsequent to the completion of the study, a comparison was made between the results obtained and those from the previous decade.
Results: Among the 491 patients (mean age 33.6±15.1 years, 65% female) included in the study, 75.6% exhibited reduced systolic blood pressure. Lithium levels exhibited a substantial decrease following dialysis (p=0.016). The mortality rate was documented to be 1.6%. During subsequent follow-up, 0.4% of the subjects resumed lithium treatment, 1.8% attempted suicide, and 15.2% consulted a psychiatrist. It is noteworthy that cases of poisoning have increased fourfold over the past decade (P<0.001). Patients who consumed more than 40 grams of the drug demonstrated a substantial decrease in the primary outcome (P=0.021). The proportion of hospitalizations lasting over two days decreased from 50% to 20.4% (P<0.0001).
Conclusion: The identification of lithium toxicity cases is facilitated by epidemiological data, thereby enabling a targeted management approach. A multifaceted approach is imperative to minimize toxicity risks. This approach should include the implementation of restricted re-prescription for suicidal use, stringent pharmacy controls, comprehensive family education on interactions, and regular renal monitoring.

Keywords: Toxicity, Lithium, Epidemiological Study, Poisoning, Decade

How to cite this article: Zarei S, Ramezani M, Akbarzadeh Kolahi S, Shadnia SH, Mostafazadeh B, Erfan Talab Evini P, Rahimi M. Clinicoepidemiological Pattern of Lithium Poisoning: Comparison of Two Decades in Tehran. Asia Pac J Med Toxicol 2025; 14(3): 79-85.

INTRODUCTION

Lithium intoxication is a condition that remains underdefined and often underestimated. Lithium, a monovalent cation with a molecular weight of 7 Dalton, has been utilized as a therapeutic agent for the treatment of mania and bipolar disorder since the 1950s. However, improper use can result in a broad range of complications, including cardiovascular, central nervous system, and kidney disorders, in scenarios of acute, acute-on-chronic, or chronic intoxication [1]. Lithium is not subject to metabolic processes or protein binding, and its bioavailability approaches 100% under typical conditions. Additionally, lithium is rapidly absorbed by the body. However, it should be noted that serum lithium levels exclusively reflect the concentration present within the extracellular space. However, the effects of lithium manifest subsequent to its transfer into the intracellular compartment. This

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phenomenon underscores the possibility that patients with markedly elevated serum levels may remain asymptomatic. It has been observed that lithium accumulates in the liver, bone, muscle, and thyroid. However, the highest concentrations of lithium are found in the brain and kidneys [2].

Acute lithium poisoning is characterized by the ingestion of substantial quantities of lithium, either intentionally in suicide attempts or accidentally (as in the case of children). The symptoms of acute poisoning tend to be mild because the elimination half-life of lithium is relatively short in individuals not receiving lithium therapy [3,4]. Acute toxicity resulting from chronic use occurs when a patient on long-term lithium treatment suddenly consumes a large quantity of lithium. The symptoms of toxicity manifest with greater severity in comparison to the acute type, as the elimination half-life of lithium is prolonged in such individuals [5]. The phenomenon of chronic toxicity manifests in individuals undergoing lithium therapy, characterized by an escalating daily dosage and a concomitant reduction in glomerular filtration rate (GFR), despite the presence of various risk factors. A paucity of research has been conducted on the epidemiological traits of individuals experiencing lithium toxicity. The influence of factors such as gender, age, race, and socioeconomic status on its occurrence remains uncertain [6,7].

While the mortality rate associated with lithium intoxication is generally low, management of these cases often necessitates intensive care over an extended period, with treatment decisions that are frequently multifaceted and complex. Concerns have been raised regarding the potential risk of permanent neurological damage. It is suggested that timely interventions, such as fluid resuscitation and enhanced elimination methods, including extracorporeal treatments (ECTRs) for selected patients, could help reduce the brain's exposure duration to toxic lithium levels [8].

The objective of this study was to analyze the epidemiological features of lithium poisoning cases and assess their clinical outcomes. A critical component of this epidemiological study entailed a meticulous examination of patients and subsequent follow-up contact to ascertain the persistence of clinical symptoms, the extent of severity, and the presence of any indications of improvement.

METHODS

This cross-sectional and retrospective study targeted patients with lithium poisoning who were referred to Loghman Hakim Hospital in Tehran. The study reviewed patient information from 2011 to 2020. A total of 501 patient files were examined, with 10 excluded due to incomplete information, resulting in a final review of 491 patients.

Following the acquisition of the requisite permits and ethical approval from the university, data concerning patients diagnosed with lithium poisoning were extracted from the hospital archives using a checklist.

The collected information included demographic details (age and gender), cause of poisoning, time interval before the visit, lithium dose consumed, neurological symptoms of poisoning, patients' vital signs upon admission (heart rate, respiratory rate, blood pressure, and GCS), treatments administered, procedure outcomes, and discharge status.

The extracted data was subsequently categorized based on reference values, with some quantitative data converted into qualitative data. Subsequently, the patients were contacted, and the residual complications, their severity, and the reintroduction of lithium were evaluated. Subsequent to this, a comparison was made between the results obtained and those reported in the study by Mostafazadeh and colleagues [9] at the aforementioned center.

The analysis was conducted using SPSS version 26 software, employing the Chi-square test and Paired t-test. A P-value of less than 0.05 was considered to be indicative of a significant difference.

RESULTS

Table 1 presents the patient's demographic details and medical background. The mean age of the sample was 33.6 years, with a standard deviation of 15.1 years.

Of the patients included in the study, 172 (35%) were male, and 319 (65%) were female. The patients demonstrated an average utilization of 23.00 ± 19.84 lithium tablets, accompanied by an average lithium dosage of 5.96 ± 6.9 g. The time interval between consumption and hospital admission was found to be 70.67 ± 18.42 minutes. Intentional lithium use was identified as the primary cause in 357 cases (72.7%) of patients. Of the cases, 180 (36.7%) had a documented history of suicide, while 398 (81.1%) had a medical history marked by psychiatric illnesses. In the majority of cases, the specific type of psychiatric illness was not identified; however, depression was the most frequently observed psychiatric condition among the evaluated patients, affecting 103 cases (21%) of them. The duration of hospitalization was 2.72 ±5.20 days. The majority of patients (88.4%) presented with a GCS score of 15.

The mean values of patients' vital signs and blood tests are shown in Table 2. Of the patients, 5.3% (26 individuals) exhibited bradypnea, while 12.6% (62 individuals) demonstrated tachypnea. Thirty-two patients (6.5%) demonstrated bradycardia, while 106 patients (21.6%) exhibited tachycardia. A decrease in systolic blood pressure was observed in 371 patients (75.6%). Conversely, an elevated diastolic blood pressure was documented in 76 patients (15.5%), while a reduced diastolic blood pressure was observed in 107 patients (21.8%). A decrease in blood oxygen saturation below 90% was observed in 16 patients (3.3%). Intubation was performed in 33 (6.7%) patients.

Table 1. The patient's demographic details and medical background

Variables		Number (%) or Mean±SD	Confidence intervals 95%
Gender	Male	172 (35%)	30.08%-39.2%
	Female	319 (65%)	60.8%-69.2%
Age (year)		33.6±15.1	32.27-34.93
Lithium level (mEq/L)		1.28±1.07	1.19- 1.37
Lithium dose (gr)		5.96 ±6.9	5.35- 6.57
Interval from intake to hospital admission (minutes)		18.41±70.6	12.18- 24.64
Number of tablets taken		19.84±23.0	17.8- 21.88
Intentional consumption		357 (72.7%)	68.8%- 76.6%
History of suicide attempt	Yes	180 (36.7%)	32.4%- 40.8%
	No	291 (59.3%)	54.9%- 63.7%
	Unknown	20 (4%)	2.3%- 5.9%
Psychiatric illnesses			
Depression		103 (21%)	17.4%- 24.6%
Bipolar		83 (16.9%)	13.6%- 20.7%
Schizophrenia		6 (2.1%)	0.25%- 2.00%
Adjustment Disorder		14 (2.8%)	1.4%- 4.2%
Unspecified		193 (39.3%)	35.00%-43.6%
The duration of hospitalization (day)		2.72 ±5.20	2.27- 3.17
Mortality rate		8 (1.6%)	0.5%- 2.7%

Table 2. The patients' vital signs and blood tests

Variables	Mean	Standard deviation	Confidence intervals 95%
Systolic blood pressure (mmHg)	116.34	15.87	114.94- 117.74
Diastolic blood pressure (mmHg)	72.22	12.50	71.11- 73.33
Respiratory rate (breaths/min)	17.06	5.82	16.55- 17.57
Heart rate (beats per minute)	87.12	21.26	86.10- 88.14
Body temperature (°C)	37.07	3.28	36.81- 37.33
Oxygen saturation (percent)	96.35	2.78	96.07- 96.63
RBC (10^6/µL)	4.8	3.4	4.6- 5.00
WBC (10^6/µL)	11.4	29.3	10.13- 12.67
Hb (gr/dL)	15.3	13.3	14.15- 16.45
PLT (10^3/µL)	262.3	180.4	254.21- 270.39
Na (mEq/L)	138.5	15.2	137.44- 139.56
K (mmol/L)	4.1	0.7	4.05- 4.15
Bun (mg/dl)	27.6	13.7	26.61- 28.59
CPK (U/L)	118.3	137.7	109.22- 127.38
PCO2 (mmHg)	40.9	7.9	40.20- 41.60
PH	7.34	0.4	7.30- 7.37
HCO3 (mEq/L)	24.3	5.3	23.83- 24.771

The majority of patients (94.3%) did not manifest neurological symptoms. The most frequently reported symptom was sleeplessness, noted in 24 cases, followed by agitation in 3 cases and tremor in 1 case. Of the total cases, 153 individuals (31.2%) exhibited acidosis, while 31 individuals (6.3%) demonstrated alkalosis. Hyponatremia was identified in 67 patients (13.6%), whereas hypernatremia was noted in 39 patients (7.9%).

Hypokalemia was observed in 48 patients (9.8%), while hyperkalemia was identified in 9 patients (1.8%). A reduction in creatine phosphokinase (CPK) levels was observed in 24 patients (4.9%), while an increase in CPK levels occurred in 22 patients (4.5%).

Two patients underwent dialysis: one patient received the treatment once, while the other patient received the treatment three times. The mean lithium level prior to dialysis was 1.96 ± 1.05 mEq/L, and following dialysis, it decreased to 1.18 ± 0.46 mEq/L (p = 0.016). This decline was deemed to be statistically significant (Figure 1). The mortality rate was 1.6% (8 cases). The most prevalent complications were renal complications and depression, which were observed in 5 (1.0%) and 9 patients (1.8%), respectively. Of the patients who were evaluated after discharge, 21 cases had suffered from lithium complications (Figure 2).

The most prevalent complications were renal complications and palpitations, which were observed in 9 (1.8%) and 8 (1.6%) patients, respectively. A total of two patients (0.4%) resumed lithium treatment. A total of nine cases (1.8%) exhibited repeated suicide attempts, and 76 patients (15.2%) were referred to a psychiatrist. A comparison with the previous decade revealed a significant increase in poisoning cases over the recent decade, approximately fourfold (P<0.001) (Table 3).

The age and gender distribution of poisoning remained unchanged. The number of poisoned patients who consumed more than 40 grams of the drug has decreased significantly over the past decade compared to the decade before (0.2% vs. 4.6%, P = 0.021). The proportion of patients who were hospitalized for more than two days has significantly declined from 50% in the previous decade to 20.4% in the recent decade (p < 0.0001). The recovery rate exhibited no alteration. The present study did not analyze ICU admissions directly. However, given that all intubated cases are admitted to the ICU, a substantial reduction was noted compared to the previous decade (6.7% vs. 87%, P<0.0001).

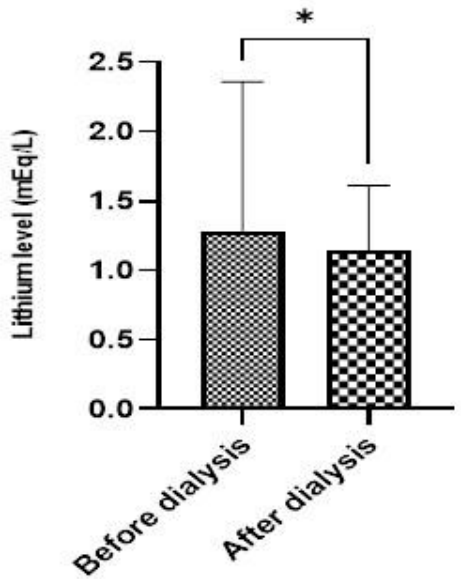

Figure 1. Lithium levels at the beginning and after dialysis
*** P≤0.05**

Table 3. Comparison between the previous and recent decades

		Previous decade	Recent decade	P-value
Total patients		108	491	<0.001
Gender	Male Female	43 (39.8%) 65 (60.2%)	172 (35%) 319 (65%)	0.348
Age	<20 years 20-40 years >40 years	36 (33.3%) 51 (47.2%) 21 (19.4%)	107 (21.8%) 250 (50.9%) 124 (25.3%)	0.204
Admission to hospital (after intoxication)	< 6 hrs 6-12 hrs >12 hrs	64 (59.3%) 5 (13.9%) 20 (18.5%)	284 (57.8%) 52 (10.6%) 49 (10%)	0.403
Lithium amount taken	<20 gr 20-40 gr >40 gr	72 (66.7%) 11 (10.2%) 5 (4.6%)	324 (66%) 16 (3.3%) 1 (0.2%)	0.021
Previous history of seizures		5.6%	0.2%	0.059
Psychiatric disorder		60.2%	81.1%	0.077
History of previous suicide attempt		36.1%	36.7%	0.907
Addiction		4.6%	2.9%	0.480
GCS	<15 15	5 (5.6%) 102 (94.4%)	53 (10.8%) 434 (88.4%)	0.051
Hospitalization period	<2 days >2 days	50% 50%	78.4% 20.4%	<0.0001
Fate patients	Recovered Not recovered	102 (94.4%) 5 (5.6%)	457 (93.1%) 34 (6.9%)	0.774

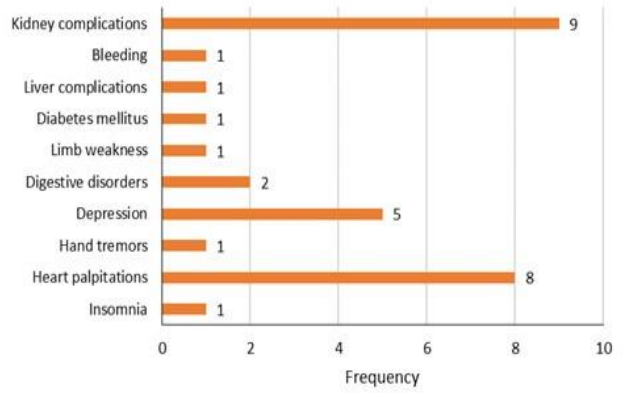

Figure 2. Frequency distribution of various complications after discharge in patients

DISCUSSION

The clinical manifestations of lithium intoxication exhibit a broad spectrum, ranging from asymptomatic cases to severe toxic effects. Any patient receiving lithium treatment who exhibits altered consciousness, vomiting, pronounced tremors, or cerebellar symptoms should be presumed to have lithium intoxication and treated accordingly until further clarification is obtained. The clinical presentation of lithium toxicity can vary depending on the pattern of toxicity [10]. The objective of this study was to ascertain the epidemiological characteristics of lithium poisoning cases and to assess their clinical outcomes. The poisoning pattern was then subjected to further analysis in comparison with a study from the prior decade.

A comparison over two decades revealed a significant increase in poisoning cases, potentially attributed to various factors. Pharmacokinetic interactions involving lithium are associated with the influence of other substances on renal lithium clearance, which can either elevate or diminish serum lithium concentrations. It is imperative to prioritize the examination of interactions that have the potential to elevate lithium levels, as these may culminate in lithium toxicity, which can result in the manifestation of neurotoxic symptoms and organ damage [11]. It is imperative to note that abruptly discontinuing the consumption of coffee or tea may result in a significant reduction in lithium clearance, which could potentially lead to lithium intoxication [12]. In elderly patients with renal impairment, lithium toxicity may paradoxically occur even within the therapeutic range, potentially causing misdiagnosis and delayed treatment, which can result in permanent neurological damage [13].

The mean age of the subjects was found to be 33.6 years, with a standard deviation of ±15.1 years. Of the patients included in the study, 172 (35%) were male and 319 (65%) were female. A comparison between the two decades revealed no variation in the age or gender distribution patterns of poisoning. Heald et al. observed in 2022 that 22 patients, with a mean age of 65 years (ranging from 36 to 89), were studied for lithium toxicity [14]. Chan et al. also reported that 156 (64%) of the subjects were female, which, in concordance with the recent assessment, indicates a higher prevalence of poisoning in females [15]. Rahmani and colleagues also evaluated the data of 21 cases of lithium-poisoned patients and observed that out of 21 patients, 10 (47.6%) were male and 11 (52.4%) were female. Moreover, the majority of lithium-poisoned patients (47.6%) were between the ages of 20 and 29, aligning with the recent epidemiological evaluation [16].

In the final decade of research, a significant decrease has been observed in the number of patients consuming more than 40 grams of lithium. This finding provides further evidence in support of the hypothesis that toxicity is likely associated with drug interactions during use or alterations in dietary habits [11-13].

In the present study, the mean number of lithium tablets consumed by the patients was 23.00 ± 19.84, with an average lithium dose of 5.96 ± 6.9 g. The mean time interval from consumption to hospital admission was 70.67 ± 18.42 minutes. In addition, Heald et al. observed in 2022 that the median lithium concentration at presentation was 2.2 mmol/L, and it took an average of three days to return to the therapeutic range (14). A study was conducted in 2017 to evaluate the impact of lithium therapy, particularly lithium toxicity, on the development of endocrine and renal disorders in a group of patients at a tertiary referral center in Ireland. The findings of the study demonstrated that the mean and standard deviation of lithium levels were 18.34 ± 21.5 [17].

In the present study, complications were observed in two cases. The most prevalent complications were renal complications and depression. The prevalence of functional disorders was observed in 17 cases, with the most common manifestation being limb numbness. The mortality rate was 1.6%. The mean duration of hospitalization was 2.72 days. A comparison of the two decades indicated a substantial decline in the number of individuals hospitalized for more than two days and requiring intubation in the last decade. This decline may be attributable to a decrease in the dosage of medications administered to patients.

In contrast to the findings of the present study, Heald et al. also observed a mean length of hospital stay of 13 days, with a range of 3 to 95 days, primarily attributable to delayed neurological recovery. The most prevalent symptom was confusion, which was observed in 21 patients (95%), followed by tremor in 18 (82%) and ataxia in 16 (73%) [14]. Patrick et al. also observed that the length of hospital stay was significantly longer for cases with severe neurotoxicity compared with those without severe neurotoxicity [18]. Rahmani et al. also evaluated the data of 21 cases of lithium poisoning patients and observed that among all patients under 50 years of age, the cause of poisoning was suicide.

The most prevalent symptom of poisoning was a decreased level of consciousness (47.6%), and 16 individuals (762) were admitted to the intensive care unit. The present study documented one fatality [16]. However, the recent evaluation revealed eight deaths (1.6%), a figure attributable to the augmented sample size employed in the present study.

The present study, which was conducted on a cohort of patients who were subsequently followed up, revealed that 76 cases (15.2%) exhibited psychiatric visits, one case of lithium re-administration, and seven cases of repeated suicide attempts. Heald et al. also reported that lithium re-administration was observed in two cases [14], which is consistent with the present study, indicating a low prevalence of re-administration. Patrick et al. stated that no relapse was observed in any of the patients [18], which was different from the present study, because in our study, seven cases relapsed. A subsequent study conducted in Ireland also demonstrated that the majority of patients exhibited survival outcomes; however, complications were observed in a subset of patients, with the most prevalent complications being renal impairment and depression [17]. These findings were consistent with our own assessment. A systematic review study also indicated that the manifestations exhibited variability among patients; however, neurotoxicity was the most common, followed by renal and cardiovascular toxicity [15].

LIMITATION

A salient limitation of this study is the incomplete nature of the patient information available in the archives and files. This is a common shortcoming in retrospective studies. It is recommended that subsequent studies examine the factors that contribute to lithium toxicity. Furthermore, multicenter studies will provide additional information.

CONCLUSION

When these cases are considered in conjunction with the epidemiological distribution, it becomes possible to identify patients experiencing lithium toxicity and to provide more targeted management. Fortunately, the re-prescription and use of lithium for suicidal purposes have been subject to significant restrictions, thereby minimizing the risk of re-intoxication. Strict pharmacy controls to prevent over-the-counter access to lithium, in conjunction with educational initiatives aimed at reducing the incidence of drug interactions among families, are imperative measures. Furthermore, it is imperative to engage in regular monitoring of renal function to mitigate the risk of toxicity.

Conflict of interest: The authors declared no conflict of interest.

Funding and Support: The authors declared that this study received no financial support.

Ethics approval: This study was conducted by the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.IAU.PS.REC.1403.355).

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