ISSN 2582 – 6050

Available Online at www.ijpba.info
International Journal of Pharmaceutical & Biological Archives 2020; 11(4):198-203

RESEARCH ARTICLE

Adverse Drug Reactions of Lithium Monotherapy in Bipolar Affective Disorder: An Observational Study in Eastern Nepal

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Received: 25 October 2020; Revised: 30 November 2020; Accepted: 23 December 2020

ABSTRACT

Introduction: Lithium is the most effective long-term therapy for bipolar affective disorder (BPAD). Its therapeutic benefits may be restricted by frequent adverse drug reactions (ADRs) and low therapeutic index. We evaluated the pattern of ADR of lithium monotherapy in patients with BPAD. **Materials and Methods:** An observational study was conducted in 213 patients presenting to psychiatric outpatient department and diagnosed with BPAD and taking lithium monotherapy at least for 3 months. Data collection was done from December 15, 2018, to December 14, 2019. Sociodemographic profile, relevant laboratory investigations, and ADRs were recorded on a self-designed proforma. Descriptive statistics were used to analyze the data. Chi-square test was used to correlate the association between ADR and baseline variables using Statistical Package for the Social Sciences (Version 22.0). $P < 0.05$ was considered statistically significant. **Results:** Out of 213 patients, 110 (51.6%) were male. Mean age was 32.06 ± 1.80 years. Sixty-nine (32.4%) patients were substance user. The prescribed dose of lithium ranged from 300 to1200 mg/day. At least one ADR was observed in 139 (65.3%) patients. Tremor (45%) was the most common ADR followed by nausea (9.5%) and sedation (7.8%). **Discussion:** Daily administration of lithium 1000 mg or more was found to be a significant risk factor for occurrence of the ADRs. Weight gain might result in lithium non-compliance and hence the patients must be counseled regarding this to improve medication adherence. **Conclusion:** The prevalence of ADR was high in the patients taking maintenance dose of lithium. The patients need regular follow-up to detect and manage ADR which help to increase the medication adherence. There is an urgent need of active pharmacovigilance to detect the ADR in the patients with BPAD.

Keywords: Adverse drug reactions, bipolar affective disorder, lithium, prevalence

INTRODUCTION

Bipolar affective disorder (BPAD) is characterized by episodes of depression and elevated mood with intervening periods of euthymic state.[1] It affects 1–4% of the population.[2] It is one of the leading causes of disability globally.[3] Due to its chronic and recurrent course, it poses an important burden for the patient and society.[4] The associated anxiety symptoms and psychosis lead to high risks of potentially severe functional impairment, substance abuse, and high rates of suicide and accidents.[5] Pharmacological treatment is the first-line therapy in BPAD. Atypical antipsychotics, benzodiazepines, and mood stabilizers are the most commonly used drugs in BPAD. Lithium remains the most effective and best studied monotherapy as mood stabilizer for the prevention of relapse in BPAD.[6] It appears to be a safer drug when used judiciously with frequent clinical evaluation of the patient with BPAD.[7] However, clinical use of lithium is frequently associated with many adverse

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effects due to its narrow therapeutic index and its toxic effects on various organs.[8] Slight increase in its plasma concentration leads to toxic effects which might decrease medication adherence and quality of life of the patients. Therefore, its therapeutic efficacy should be balanced against its adverse effects and toxicity to maximize its therapeutic effect.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of the adverse effects of drugs or any other possible drug-related problems.[9] It is one of the key component of drug safety, public health programs, and clinical practice.[10] Continuous monitoring of ADRs is essential. An active pharmacovigilance study is required to detect the frequency and pattern of adverse drug reactions.[11] Pharmacovigilance activities are still in nascent stage in Nepal. Clinical development of most of the drugs happens in the developed countries, mainly in the west. Hence, the efficacy and safety data available may not be applicable to Nepalese patients due to difference in the prescribing practice, pharmaceutical preparation, and genetic variables.[12] Data on ADRs occurring due to lithium monotherapy in BPAD in Nepal are scarce. The objective of this study was to evaluate the pattern of ADR of lithium monotherapy in patients with BPAD.

MATERIALS AND METHODS

An observational study was conducted at the outpatient Department of Psychiatry, B.P. Koirala Institute of Health Sciences (BPKIHS) from December 15, 2018, to December 14, 2019. The patients aged 18 years and above and diagnosed with BPAD and taking lithium as monotherapy for at least 3 months were enrolled in the study. Pregnant patients, those taking other psychotropic drugs such as benzodiazepines, antipsychotics, antidepressants, and antianxiety drugs, and patients not giving consent and patients <18 years of age were excluded from the study.

A self-designed pro forma was used to collect sociodemographic profile (name, age, sex, marital status, socioeconomic status, educational status, and occupation), comorbid conditions, laboratory investigations (urine RE/ME, urea/creatinine, thyroid function test, and ECG), and ADRs. The objective of the study was explained to the patients at the time of consultation in psychiatry outpatient department and written consent was taken. The relevant data were collected directly in the pro forma by reviewing the health card of the patients and by face-to-face interview at the interval of 3 months for 1 year.

The data were entered into MS Excel 2007. Descriptive statistics such as mean, frequency, percentage, and standard deviation were calculated. Chi-square test used for analyzing categorical data. $P < 0.05$ was considered as statistically significant. All statistical calculations were performed using Statistical Package for the Social Sciences Version 22.0 (Chicago, USA).

RESULTS

Out of 213, 110 (51.6%) patients were male, 170 (80.3%) literate, and 108 (50.7%) were aged more than 40 years. Sixty-nine (32.4%) patients were substance user. Eight patients (3.8%) had comorbidities. Three (1.4%) patients were taking other drugs [Table 1]. Mean age (± Standard deviation) was 32.06 ± 1.80 years. The age of the patients ranged from 18 years to 72 years.

Table 1: Sociodemographic characteristics of the patients (*n*=213)

Variables	Category	Frequency (%)
Gender	Male	110 (51.6)
	Female	103 (48.4)
Age in years	18–40	108 (50.7)
	More than 40	105 (49.3)
Educational level	Illiterate	42 (19.7)
	Literate	171 (80.3)
Substance user	Yes	69 (32.4)
	No	144 (67.4)
Comorbidity	Yes	8 (3.8)
	No	208 (96.2)
Taking others drugs	Yes	3 (1.4)
	No	210 (98.6)
Duration of lithium treatment in year	Up to 3	166 (77.9)
	More than 3	47 (22.1)
Dose of lithium in mg	300–1000	165 (77.5)
	More than 1000	48 (22.5)

A total of 231 ADRs were observed in 139 patients giving rise to the prevalence of 65.3%. Urine RE/ME, renal function test (serum urea and creatinine), and ECG were within normal limits in all patients. Tremor (45%) was the most common ADR followed by nausea (9.5%), sedation (7.8%), leukocytosis (7.4%), and hypothyroidism (5.6%) [Figure 1].

Most of the patients (48.2%) had two ADR followed by single ADR (41%) [Figure 2].

ADR was significantly more common in patients taking more than 1000 mg lithium/day ($P < 0.05$) [Table 2].

DISCUSSION

The present study has reported the pattern of ADRs in patients with BPAD who were being treated with lithium monotherapy in outpatient setting. About two-third of the patients (65.3%)

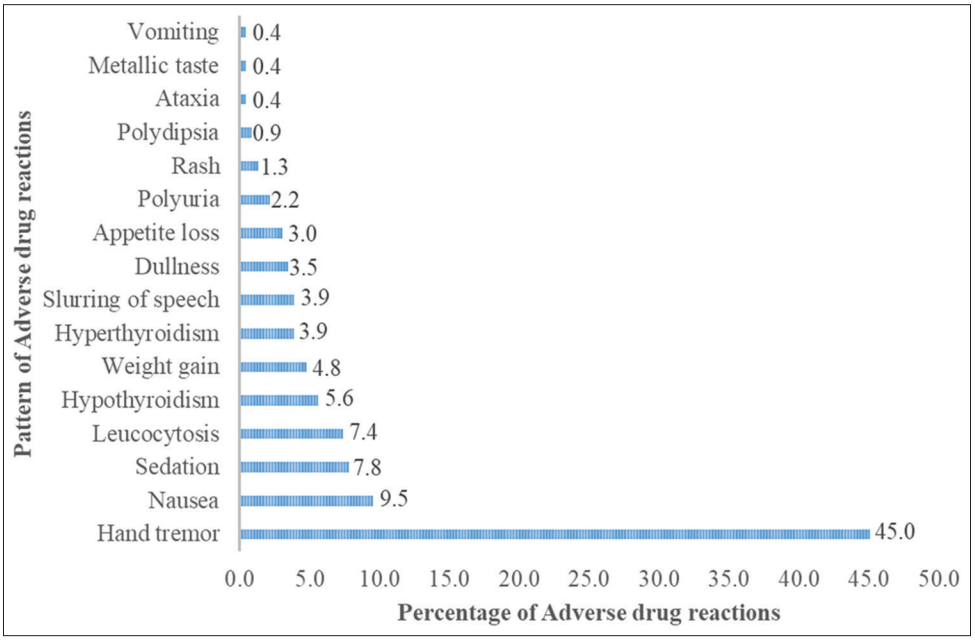

Figure 1: Pattern of adverse drug reactions due to lithium therapy (*n*=231)

Table 2: Association of occurrence of adverse drug reactions with baseline variables (*n*=213)

Variables	Category	ADR		*P*-value
		Yes (%)	No (%)	
Gender	Male	66 (60.0)	44 (40.0)	0.096
	Female	73 (70.9)	30 (29.1)	
Age in years	18–40	71 (65.3)	37 (34.3)	0.881
	>40	68 (64.8)	37 (35.2)	
Educational level	Illiterate	28 (66.7)	14 (33.3)	0.831
	Literate	111 (64.9)	60 (35.1)	
Substance use	Yes	43 (62.3)	26 (37.7)	0.533
	No	96 (66.7)	48 (33.3)	
Comorbidity	Yes	6 (75.0)	2 (25.0)	0.555
	No	133 (64.9)	72 (35.1)	
Taking others drugs	Yes	2 (66.7)	1 (33.3)	0.959
	No	137 (65.2)	73 (34.8)	
Duration of lithium treatment	Up to 3	105 (63.3)	61 (36.7)	0.248
	>3	34 (72.3)	13 (27.7)	
Dose of lithium	Up to 1000 mg	95 (57.6)	70 (42.4)	0.000*
	>1000 mg	44 (91.7)	4 (8.3)	

*Statistically significant at $P < 0.05$ (Chi-square test)

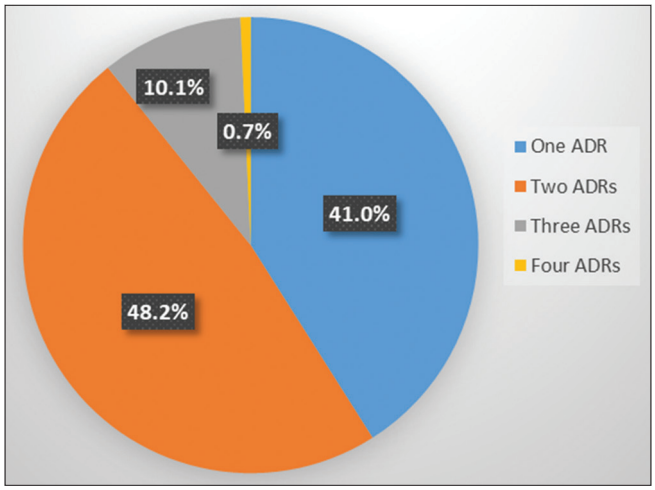

Figure 2: Numbers of adverse drug reactions in patients taking lithium (*n*=139)

had at least one ADR in the study indicating high prevalence of ADR. Venkoba *et al*. had reported a high prevalence (81%) of ADR.[13] A lower prevalence of ADR (16%) had been reported by Panchal *et al*.[14] About 60% of the patients had more than 1 ADR in the present study. In contrast to this finding, only 14% of patients had more than 1 side effect in a study by Venkoba *et al*.[13] None of the patients had abnormal laboratory findings related to renal and cardiac function in the patients. Daily administration of lithium 1000 mg or more was found to be a significant risk factor for occurrence of the ADRs and similar finding was also reported in another study.[15] Any patients taking lithium more than 1000 mg/day must be counseled well regarding the possible ADRs of the drug to improve the patient compliance. Such patients must be also followed up more frequently for early detection and management of ADRs.

Tremor was the most common ADR in the present study and this finding was consistent with the findings reported by Gelenberg *et al*.[16] In contrast to this, increase in urination was the most common ADR in an Indian study.[17] Tremor of hands is indistinguishable from essential or physiologic tremor and may improve spontaneously after years of treatment. Higher lithium levels correlate with greater risk of tremor.[18] Nausea was also observed in significant number of patients in our study and it is one of the least distressing of ADR of lithium. Tolerance to nausea commonly occurs overtime. Administration of lithium after meals, using a multiple daily dose regimen, or using sustained-release formulations can reduce nausea; however, multiple dosing can be hindrance for patient compliance. Extended-release formulations as well as limiting nicotine and caffeine can reduce neurological side effect like tremors.[19]

Hypothyroidism (5.6%) was more common that hyperthyroidism (3.9%) in the present study. A high prevalence of hypothyroidism (8.5%) and lower prevalence of hyperthyroidism (0.74) was reported by Hayes *et al*.[20] The prevalence of thyroid dysfunction in lithium-treated patients varies substantially across studies.[21] Lithium treatment increases the risk of clinical hypothyroidism up to 5-fold, through complex mechanisms that are unrelated to dose.[22] Lithium reduces thyroxine secretion leading to an increase in TSH and the associated clinical picture of hypothyroidism resulting in lethargy, depression, weight gain, and dry skin. Antithyroid effect of lithium is due to inhibition of thyroid hormone release from the thyroid gland. Lithium also decreases iodine trapping with the gland and inhibits synthesis of thyroid hormones and leads to hypothyroidism.[23] Therefore, monitoring thyroid function in the patients taking lithium as prophylaxis in BPAD is vital.

Weight gain was also observed in 4.8% of patients in the present study; however, the magnitude of the weight gain was not assessed in the study. Mechanisms of lithium-associated weight gain are still unclear. Increased thirst leading to the ingestion of high-calorie drinks might play a significant role in these patients.[24] Lithium may alter other core mechanisms that cause weight gain.[25] Weight gain is among the prevalent and distressing of lithium-associated side effects. It might result in lithium non-compliance and hence the patients must be counseled regarding this to improve medication adherence. Skin rash was observed only in 1.3% of the patients in the present study. In contrast to this finding, skin reactions were observed in 19.3% of the patients in an Indian study.[26] The difference might be due to long-term follow-up in the Indian study. The prevalence of lithium-induced skin reactions ranges between 3% and 34%.[27] The clinician should be aware about skin reaction

secondary to lithium therapy and educate the patients about such skin reactions before starting the treatment to improve the patient compliance.

The present study offers a representative profile of the ADRs which can be expected in the psychiatry outpatients department in patients taking lithium and due care must be taken to avoid these ADRs and to maximize the patient compliance. It is beneficial to use the lowest possible dose of lithium to prevent immediate and long-term ADR in a patient who is on long-term maintenance therapy. Potential organ toxicity due to chronic lithium therapy requires more vigilance. The present study might have missed certain ADRs during the study period since some of them may have been transient or not severe enough to significantly trouble the patient to remember it and report. The study was done in the outpatient department only and thus the ADRs in hospitalized patients with BPAD might have been missed. Assessment of causality, severity, and preventability of ADR could not be conducted.

CONCLUSION

The study has highlighted the pattern of lithium-induced ADRs in patients of BPAD. The prevalence of ADR was high in the patients taking lithium in our context and hand tremor was the most common ADR. The dose of lithium more than 1000 mg/day was identified as possible risk factor for high occurrence of ADRs. Medication adherence and quality of life of patients taking lithium in BPAD can be improved by early detection and management of ADR. The patients need regular follow-up to detect and manage the ADR. A pharmacovigilance program would be highly useful in these patients to monitor and manage ADR. A prospective observational study conducted across multiple hospitals in patients with BPAD and taking lithium could be conducted to generalize the study findings.

CONFLICTS OF INTEREST

The author declares that they have no conflicts of interest.

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