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Revisiting the role of therapeutic drug monitoring in optimizing treatment outcomes in patients of bipolar affective disorders receiving lithium therapy: a prospective observational study

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ABSTRACT

Background: Lithium continues to be considered first-line therapy for treatment of acute mania, acute mixed bipolar disease and long-term prophylaxis of bipolar disorder. Present study was done to study the pattern of drug therapy in bipolar affective disorder patients with special reference to lithium in the routine psychiatric outpatients care setting of a tertiary care teaching hospital as well as to understand the prospect of therapeutic drug monitoring in optimization of lithium therapy based on outcome.

Methods: It was a prospective, non-randomized, observational study of a cohort of subjects who are suffering from bipolar affective disorders and on lithium therapy. Patients were prospectively followed up three monthly for three visits with therapeutic drug monitoring of their plasma lithium level, as and when advised by the treating physician, and pre-formed questionnaires.

Results: Results revealed there was significant improvement in symptoms of patients who were monitored with therapeutic drug monitoring and prescribed lithium therapy in accordance with clinical pharmacological consultation for optimal dosing resulting in optimal benefit to patients.

Conclusions: With regular therapeutic monitoring, optimal target serum lithium levels can be achieved with dosage modifications thereby reducing the risk of toxicity with improved drug compliance. Thus, individualization of dosing and optimization of treatment can be achieved by dependable analytical laboratory services, better psycho-education, family support and overall a disease-based management team approach with the involvement of clinical Pharmacologist to meet the complexities of lithium therapy.

Keywords: Bipolar affective disorder, Lithium, Therapeutic drug monitoring, Therapeutic optimization, Young Mania Rating Scale

INTRODUCTION

Despite the introduction of many other mood stabilizers, lithium continues to be considered first-line therapy for treatment of acute mania, acute mixed bipolar disease and long-term prophylaxis of bipolar disorder. The clinical history of lithium for the treatment of affective disorders

began with the 1949 report by John Cade that he had successfully treated ten manic patients with lithium. Presently almost all major international psychiatric associations' guidelines all over the world recommend lithium as a first-line therapy for bipolar disease, including the American Psychiatric Association, The World Federation of Societies of Biological Psychiatry,

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the Canadian Network for Mood and Anxiety Treatments, the International Society for Bipolar Disorders and Indian Psychiatric Society both in adults as well as children and adolescents. Bipolar disorder is a serious mental disorder characterized by episodes of depression, hypomania/mania and mixed episodes, with interepisodic recovery. The disease usually starts in adolescence or early adulthood and has significant negative impact on the life of the sufferer and their caregivers.

Lithium is widely distributed into most body tissues and fluids. However, it is unevenly distributed among several tissue compartments; for instance, the lithium concentration is higher in saliva and in the thyroid than in serum.⁵ Lithium has a narrow therapeutic index and a number of adverse effects that often result in poor adherence to treatment.⁶ Toxicity occurs at serum concentrations greater than 1.5-2.0 mmol/L and is characterized by coarse tremor, apathy, hyperreflexia, hypertonia, nausea, diarrhea, myoclonus, seizures, acute renal failure, cardiac dysrythmia and coma. Serum concentrations greater than 3.5 mmol/L are potentially lethal and necessitate hemodialysis.⁷

Therapeutic drug monitoring (TDM) is generally defined as the clinical laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures.⁸ Thus it refers to the individualization of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range or window by combining knowledge of pharmacokinetics, and pharmacodynamics, and subsequent assessment of the efficacy and safety of a particular medication in a variety of clinical settings. ⁹ The goal of this process is to individualize therapeutic regimens for optimal patient benefit. Clinical pharmacologists use pharmacokinetic principles to assess interpretations of TDM for calculating the right dose of the drug needed. TDM requires a multidisciplinary approach. Accurate and clinically meaningful drug concentrations are attainable only by complete collaboration by a TDM team, typically comprised of scientists, clinicians, nurses, and along with pharmacists.9

In psychiatric pharmacotherapy, there are different central nervous systems drugs, which are potentially toxic if not used in judicious ways. Among these, depression, anxiety and bipolar disorders are quite common in clinical practice in our country and primary care often fails to address the appropriate treatment because of lack of proper monitoring. The benefits of using TDM for tricyclic antidepressants, antipsychotic drugs and moodstabilizing drugs have been reported in different studies. 10-12 Amongst the mood-stabilizing drugs like lithium, TDM implementation while in therapy is strongly recommended. 13 It is recommended that whenever lithium is to be started, it needs to be started in low doses, preferably in divided doses and the dose needs to be titrated upwards with monitoring of serum lithium levels. As steady state levels of lithium are achieved after about 5 days of starting lithium or dose increment, the levels are be done after 5 days of start of treatment or change in the dose; and the levels may be checked earlier if patient manifests any feature of toxicity.³ The serum levels of lithium, for management of acute episode of bipolar disorders, are in the range of 0.6 to 1.0 meq/litre and for prophylaxis range from 0.6 to 0.8 meq/litre; while some suggest that serum levels as low as 0.4 to 0.8 meq/litre may be sufficient for prophylaxis, albeit are associated with higher risk of relapse.³

Present study was done to study the pattern of drug therapy in bipolar affective disorder patients with special reference to lithium in the routine psychiatric out patients care setting of a tertiary care teaching hospital as well as to understand the prospect of therapeutic drug monitoring in optimization of lithium therapy based on outcome.

METHODS

The study was conducted in a tertiary care hospital of Kolkata, West Bengal, India. All stable, ambulant bipolar affective disorders patients on lithium therapy attending the Psychiatry OPD, and willing to participate in this study were enrolled. The participants have undertaken therapeutic drug monitoring as and when advised by their treating physician.

It was a prospective, non-randomized, observational study of a cohort of subjects who are suffering from bipolar affective disorders and on lithium therapy attending the Psychiatry OPD. Inclusion criteria was subjects who are suffering from bipolar disorders and on lithium therapy attending the psychiatry OPD and willing to participate, patients from all age groups and both the sexes were included. Those who understood the purpose of the study and are ready to provide information regarding their health status and those who signed an informed consent document were chosen. Exclusion criteria was subjects not willing to participate, any condition resulting in severe learning and/or intellectual disability and those unable to comprehend for any other reasons were excluded from the study. The study was commenced after obtaining approval from institutional ethics committee and continued for a span of 9 months. Data was analyzed at the end of study. The treatment outcome of such patients on lithium therapy optimized with regular therapeutic drug monitoring over a period of time based on study tools was compared with the baseline for statistical significance.

Authors have prospectively observed a cohort comprising of bipolar affective disorder patients and followed the treating psychiatrist's advice of lithium monitoring and complied with dosage modifications thereafter, if any. Patients were prospectively followed up three monthly for three visits with therapeutic drug monitoring of their plasma lithium level, as and when advised by the treating physician. Therapeutic drug monitoring of lithium when advised and referred to our department by the treating

physician was done at each visit for 3 consecutive visits and its indications noted. There is a lack of a proper population pharmacokinetic based recommendation for the acceptable optimal concentration of lithium level for long term maintenance treatment of Indian bipolar patients. Although the accepted target concentration for acute bipolar mania as documented and practiced is 0.8 to 1.1 meq/L; but for the purpose of this study which included all types bipolar patients, the widely accepted APA guideline suggested optimal target serum concentration of lithium for long term maintenance was taken as 0.5 to 1.2 meg/L. All decisions relating to management of the patient including drugs dosage modification and advice for any investigations were given by the treating physician only. Investigators did not interfere in the management of patient and only observed the proceedings.

At the baseline visit 1, the demographic characteristics, laboratory investigations along with co-morbidity and concomitant medications prescribed were noted. Subjects and their accompanying family members were interviewed by pre-structured questionnaire, investigation reports, past prescriptions and case notes, where available and were reviewed at every visit for 3 visits.

Adverse event history, medication history, medication compliance, treatment outcome based on TDM follow-up advises and other relevant details including ancillary laboratory investigations were captured. They were followed up for 9 months study period and on each and every such occasion the drug adherence and treatment outcome analyzed based on study questionnaires. The patients were given the results of the serum lithium estimation test within 7 days of collection of blood sample. If the serum lithium levels were found to be above target therapeutic level the patients or their family members along with their treating physician were informed over telephone and patients were requested to urgently call their physician and also attend the OPD for dosage modification. The compliance and treatment outcome were scored using validated questionnaires and compared with the baseline data and were also analysed statistically. The adverse events during this study period were also captured on standard PvPI format for further analysis.

The parameters which were closely studied were clinical presentation, toxic symptoms, disease progression, comorbidities, lithium dosage, co-medications, drug adherence, reason for lithium monitoring and serum lithium levels and its follow-up advices, if any. The visit 2 and 3 to our department usually occurred after 1-3 months intervals or earlier if the physician suspected any toxicity or made lithium dosage modifications.

Quantitative measurement of serum lithium was done by flame photometer. The following study tool was also applied and used to assess the outcome of the BPAD on every visit to our department for lithium TDM like Young Mania Rating Scale (YMRS). The YMRS is a rating scale used to evaluate manic symptoms at baseline and over time in individuals with mania. The scale is generally done by a clinician or other trained rater with expertise with manic patients and takes 15-30 minutes to complete. It is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Additional information is based upon clinical observations made during the course of the clinical interview. The items are selected based upon published descriptions of the core symptoms of mania. There are four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behaviour), while the remaining seven items are graded on a 0 to 4 scale. These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients. There are well described anchor points for each grade of severity. Typical YMRS baseline scores can vary a lot. They depend on the patients' clinical features such as mania (YMRS = 12), depression (YMRS = 3), or euthymia (YMRS = 2). Sometimes a clinical study entry requirement of YMRS >20 generates a mean YMRS baseline of about 30. Strengths of the YMRS include its brevity, widely accepted use, and ease of administration. The usefulness of the scale is limited in populations with diagnoses other than mania.14

RESULTS

Overall 30 cases of stable BPAD patients on lithium were enrolled from the OPD, 15 were males and 15 females, aged from 16 years to 56 years. The average age of the participants was 35.73 yrs and the average height was 159 cms and with mean BMI kg m⁻² (SD) 26.74 (+4.4). Within them all 33% of the patients were vegetarians and 66% non-vegetarians. While 10% of the patients consumed tobacco in various forms and 10% were alcoholic.

The demographic profiles along with baseline clinical findings are depicted in Table 1. The patients were also receiving different other medications. The percentages of patients on different classes of medications are depicted in Table 2.

In the Young's Mania Rating Scale the baseline mean score was at 23.06 although the patients mostly stabilised with more than 2 weeks of lithium therapy. Thus the Visit 1 YMRS scores were 23.06 (SD =8.34) which during the visit 2 and visit 3 were further reduced to 19.1 (SD =6.60) and 18.43 (SD =6.35) which were significant reduced (P value equals 0.0456, at 95% CI between 0.08 to 7.85) and (P value equals 0.0186, at 95% CI between 0.80 to 8.4) when compared with the visit 1 score as depicted in the Table 3 and Figure 1 and individual patient's scoring at 3 visits are depicted in the Figure 2.

Table 1: Demographic profiles.

Number of participant (n)	Total = 30	
Gender, n (%)	Male, 15 (50.0%)	Female, 15 (50.0%)
Average age (years) (SD)	34.6 (11.39)	
Average body wt. (Kg) (SD)	46.81(6.83)	
Height (cm) (SD)	159.8 (3.44)	
Blood pressure mmHg (SD)	Systolic 124 (10)	Diastolic 80 (8.1)
Mean BMI kg m ⁻² (SD)	28.72 (3.1)	
Dietary habits n (%)	Veg -10 (33%)	Non-Veg - 20 (67%)
Addiction, n (%)	Smoking, 03 (10%)	Alcohol and others 3 (10%)

Table 2: Percentages of patients on different classes of medications.

Main Classes of Drug	No. of patients receiving (%)
Mood stabilizers (other than lithium)	13 (43.33)
Anti-cholinergic	6 (20)
Anti-psychotics	27 (90)
Anti-convulsant	9 (30)
Anti-depressant	6 (20)
Sedatives	9 (30)
Levo-thyroxine	6 (20)
Betablockers	5 (16.67)
Calcium channel blockers	3 (10)
Others	6 (20)

Table 3: Mean manic symptom score by YMRS (Young's Mania Rating Scale).

	Visit 1	Visit 2	Visit 3
Mean YMRS score	23.06	19.1	18.43
SD	8.34	6.60	6.35
SEM	1.52	1.20	1.16
P value		equals 0.0456*	equals 0.0186*
CI (95% confidence interval between)		0.08 to 7.85*	0.80 to 8.4*
N	30	30	30
* versus Visit 1, p-value less than 0.05 is considered as significant			

Daily dosage of lithium prescribed and as recorded at the 3 visits of the study period is shown in Table 4. The Therapeutic drug monitoring (TDM) of serum lithium

levels of the 30 patients of BPAD were carried out in the morning 10-12 hrs after previous dose of lithium tablets taken on the night before. The TDM was done on 3 occasions on referral from the clinicians and results are shown in the table and individual patient's levels are depicted in the Figure 3. Serum concentration of lithium (mean) at different study visits are expressed in Table 5. Target lithium serum concentration achievement after 3 visits are given in Table 6.

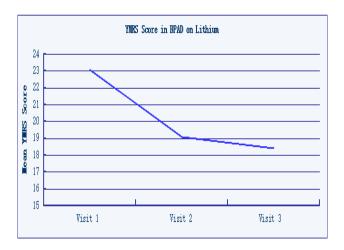


Figure 1: YMRS scores in bipolar affective disorders on lithium.

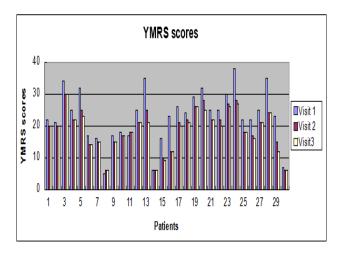


Figure 2: Manic symptom score of individual bipolar patients during lithium therapy.

Table 4: Daily dosage of lithium prescribed in different visits.

Daily dose of	Visit 1	Visit 2	Visit 3
lithium	(n)	(n)	(n)
900 mg	14	3	3
600 mg	14	25	25
300 mg	2	2	2
N	30	30	30

During Visit 1, three patients complained of the following adverse drug reactions - pedal oedema (n=1)

and hand tremor (n=2). In both the cases of hand tremor, TDM revealed excessive high levels of lithium and subsequently the dose of lithium was reduced by the physician. On the subsequent visit, the patients reported improvement soon after dosage reduction of lithium. In the pedal oedema case, stoppage of resperidone and quetiapine had lead to its improvement. All other patients have well-tolerated the lithium tablets in the dosage prescribed.

Table 5: Mean serum lithium levels in bipolar patients in different visits.

Mean serum lithium levels in bipolar patients	Visit 1	Visit 2	Visit 3
Mean serum lithium (mEq/L)	1.059	0.891	0.875
SD	0.5753	0.2338	0.2209
SEM	0.1050	0.0427	0.0403
p value		equals 0.1438*	equals 0.1117*
N	30	30	30
* versus Visit 1, non-significant			

Table 6: Target lithium serum concentration achievement after different visits.

Serum lithium	Visit 1 (n)	Visit 2 (n)	Visit 3 (n)
>1.2 meq/L	9	2	1
0.5 - 1.2 meq/L	19	28	29
<0.5 meq/L	2	0	0
N	30	30	30

DISCUSSION

Bipolar disorder (BD) is a major medical, social and economic burden worldwide, characterized by recurrent changes in mood. Bipolar I consists of cycles of mania and depression, Bipolar II of cycles of hypomania and depression. Its management is a critical but unfulfilled challenge for psychiatry. Lithium is extremely helpful for most patients. It can help control symptoms of mania and prevent recurrent manic episodes. It can also help treat bipolar depression and reduce suicide risk. When administered to healthy volunteers, lithium caused lethargy, dysphoria, a loss of interest in interacting with others, mental confusion, slowed performance on cognitive and motor tests, altered circadian rhythm. Besides, lithium increased auditory and visual evoked responses in healthy volunteers. 16,17

Despite major advances in the pharmacological management of psychiatric illnesses over recent decades, high rates of poor compliance and considerable genetic variability in the metabolism of psychotropic agents like lithium have conferred application of such treatments quite difficult. One means of minimizing such problems

has been the use of therapeutic drug monitoring (TDM). At present, TDM of serum concentrations is the only available means of estimating brain levels, but despite the obvious limitations, has proven to be of considerable value. Studies revealed that rates of noncompliance with lithium are high, with the range being 18-53%.

Lithium concentrations can be measured by either flame photometry atomic absorption emission or spectrophotometry. The need to monitor lithium levels was first proposed by Talbott by demonstrating that lithium-related deaths in cardiac patients were due to extremely high serum levels. 19 Substantial variations in lithium levels over a 24 h period was then observed by Amdisen.²⁰ Because of the relatively long half-life of lithium, steady state levels do not occur for 5-7 days. As the standardized concentration was determined for divided dosages, a 10% to 26% increase in levels can be expected if there is a change to once daily (usually night time) dosing.7 The salt common used for medicinal purpose is lithium carbonate or lithium citrate as a capsule, extended release tablet or a liquid solution. Dosing may be 2-3 or 3-4 times per day, depending on need and the extended release version. Usually each tablet, capsule or teaspoon of liquid contain 300 milligrams and 400 milligram in sustain release variety are also available. Formulations containing 150, 250, 450 milligrams are also available in India. Exact doses and dosing schedules are based on blood test results, body mass, diet, symptoms, and individual response. The goal of therapy is to minimize the dose in order to minimize side effects while also ensuring to maintain a high enough and constant enough level of lithium in blood to prevent mood swings. There are numerous variables that can influence the interpretation of drug concentration data like route and dose of drug given, co-medications, time of blood sampling, handling and storage conditions, precision and accuracy of the analytical method, validity of pharmacokinetic models and assumptions, and, clinical status of the patient (i.e. disease, renal/hepatic status, biologic tolerance to drug therapy, etc.).²¹

The study was a prospective, observational study of a cohort of 30 subjects who were suffering from bipolar affective disorders and on lithium therapy attending the Psychiatry OPD in a tertiary care medical college hospital. The treatment outcome of such patients on lithium therapy optimized with regular therapeutic drug monitoring over a period of time based on study tools was compared with the baseline for statistical significance.

A cohort of thirty ambulant stable bipolar affective disorder patients on lithium therapy was enrolled. At Visit 0, the baseline demographic characteristics, laboratory investigations along with co-morbidity and concomitant medications prescribed were noted. Subjects and their accompanying family members were interviewed by pre-structured questionnaire, investigation reports, past prescriptions and case notes, and reviewed at

every visit for 3 visits. On the advice and referral of the psychiatrist, serum lithium estimation was carried out at our department's laboratory. Therapeutic drug monitoring of lithium when advised and referred to our department by the treating physician was done at each visit for 3 consecutive visits and its indications noted. Optimal target level serum concentration of lithium for long term maintenance in Bipolar affective disorder for this study was taken to be as 0.5 to 1.2 meq/L. In patient whose serum lithium level were observed to be outside the target concentration were referred back to the OPD for dosage modification, if any. The decisions regarding therapeutic management of the patient including drugs and investigations were taken by the treating physician only. Investigators did not interfere in the management of patient and only observed the proceedings. If any dosage modification were made as a follow up of lithium TDM, the patients were again advised by the psychiatrist for repeat estimation of serum lithium after 1 week. All patient were observed for up to 3 lithium estimations, relevant data captured and studied. Also the adverse event history, medication history, medication compliance, treatment outcome based on TDM follow-up advises and other relevant details including ancillary laboratory investigations were captured. They were followed up for 9 month study period and on each and every such occasion the drug adherence and treatment outcome scores based on study tools were compared with that of the baseline visit 1 for analysis.

Bipolar disorder is episodic, and the lifetime risk of recurrence is approximately 90% in individuals who have had a single manic episode; therefore, long-term treatment is necessary for the vast majority of patients. However, medication cannot be effective if patients do not take it. Treatment non-adherence is common in this population and is associated with an increased risk of relapse. A Study found that, among patients hospitalized for acute manic episodes, 64% had been non-adherent with medication in the prior month. Different factors in treatment like adverse effects, and clinicians' treatment considerations, polypharmacy may contribute to decreased adherence to medication. A poor therapeutic alliance between the clinician and the patient can adversely affect adherence as well. 22

In all thirty cases of stable BPAD patients on lithium who were enrolled from the OPD, 15 were males and 15 females, aged from 16 years to 56 years. The average age of the participants was 35.73 yrs and the average height was 159 cms and with Mean BMI kg m⁻² of 26.74. The cohort appears to be a true representation of the local disease population. It was observed, post-lithium estimation in 11 patients the daily dose was reduced from 900mg to 600mg after visit 1. No further changes in lithium dosage were required in visit 2 and 3. Of the 30 patients on lithium, 9 were new cases, receiving lithium treatment less than 4 weeks; additional 8 were on lithium for upto a year and remaining 13 were on long term

lithium therapy, many of who had intermittently discontinued and then restarted therapy.

Apart from lithium, other mood stabilizers (13 patients, 43%) and anti-psychotics (27 patients, 90%) were frequently co-prescribed. On an average it was calculated other than lithium, 3.3 different medications were used per bipolar patient. Thyroid hormones, anti-hypertensive like beta-blockers and calcium channel blockers were also used to treat the patients' co-morbidities.

The routine haematological and biochemical investigation of this study group at baseline and at Visit 2 and 3 were found to be within the normal range including the renal and thyroid profiles in most of the patients, as and when they were advised. In some old cases, the reports of routine investigations were not found and advices for the same were also found missing in their prescriptions.

It was observed that in all, 14 patients were advised a daily dosage of 900 mg of lithium carbonate tablets at Visit 1, while 14 received 600 mg and 2 patients 300 mg, all of which were supplied from the hospital pharmacy. Only one brand of lithium carbonate 300mg tablets (LITHOKAN) was used by all patients, which was supplied from the hospital pharmacy. All patients were taking lithium at least one dose at bedtime. After the serum estimation of lithium at visit 1 and its follow up dosage modification by the physician, only 3 patients still continued with 900 mg, while 25 received 600 mg and 2 patients 300 mg of lithium at visits 2 and 3. Therefore, post-lithium estimation in 11 patients the daily dose was reduced from 900 mg to 600 mg after visit 1. No further changes in lithium dosage were made thereafter.

The mean of visit 1 serum lithium level is 1.059 meq/L, which reduced to 0.891 and 0.875 meq/L during the visit 2 and visit 3 respectively mainly due to dosage adjustment. This raised initial mean serum lithium level also indicates inappropriate dosage of lithium prescribed. The starting dose could have been lower and then slowly titrated upwards depending on the therapeutic response and serum lithium estimation. Thus, before TDM based dose optimization at visit 1, only 19 out of 30 patients (63.3%) could achieve the target range of lithium concentration. While at visit 3, 29 out of 30 patients (96.6%) achieved the optimal target lithium concentration of 0.5 to 1.2 meq/L.

Therapeutic serum concentrations range from 0.5 to 1.2 meq/L as lower serum concentrations are desired for bipolar treatment augmentation and long term maintenance, while 0.8-1.1 meq/L are recommended in the treatment of bipolar affective disorder or mania. Legal 1.25 It has also been seen that the dosage and therapeutic concentration of lithium required for treatment and prophylaxis of mania have been consistently lower for Asian patients than for their Caucasian counterparts. Japanese patients required low therapeutic blood levels of

0.4-0.8 meq/l in contrast to Caucasians who require 0.7-1.3 meq/l. But there was no pharmacokinetic between these two races, and the drug is metabolised in same manner and speed. The difference in response may be because of differences in receptors' sensitivity. 27,28

The measurement of Young's Mania Rating Scale for manic symptoms control, the baseline visit 1 YMRS scores at 23.06 (SD=8.34) significant reduced at the visit 2 and visit 3 to 19.1 and 18.43. These scores are justified in the light of the improvement of the total number of patients achieving the optimal lithium therapeutic concentration due to follow up dose modification, improved treatment adherence and compliance due to reduction of adverse drug effects.

In this study, all the 30 cases of stable bipolar affective disorder patients on lithium therapy attending the psychiatric outpatients department of a tertiary care teaching hospital were followed up for up to 3 visits for a period of 9 months during which therapeutic drug monitoring of serum lithium was carried out as per the advice of the treating physician. The mean serum lithium levels was estimated at 1.059 meq/L at Visit 1, but subsequently reduced to 0.891 and 0.875 meq/L during the Visit 2 and Visit 3 respectively, mainly due to followup lithium dosage adjustment. It was seen that the serum lithium level in 9 patients was above the therapeutic range of 1.2 meg/L at Visit 1. This was corroborated from the prescription records that during Visit 1, that while 14 patients were receiving daily dosage of 900 mg of lithium carbonate tablets, 14 received 600 mg and 2 patients 300 mg only 3 patients continued with 900 mg dosage at Visit 2. Therefore the lithium dose was reduced from 900 mg to 600 mg daily in 11 patients due to the high lithium test results. Also, no further dosage modifications were made after Visit 2 as the lithium TDM levels were recorded in therapeutic range in all except in 2 patients whose levels were maintained above 1.2 meg/L, as probably they were suffering from acute manic symptoms. Also the lithium TDM levels were detected in the sub- therapeutic range in two patients at Visit 1as these patients non-compliant but later at Visit 2 and 3 the serum levels were recorded within the optimal therapeutic range. This was only possible due to its detection by the serum lithium estimation, adherence testing and follow up counselling. It is observed after repeated TDM almost all the patients achieved the optimal serum levels within the target therapeutic range. Thus the improved outcome in the disease symptoms control could be attributed to the lithium monitoring and its follow up dose modifications along with better drug compliance. Besides, with supervision and monitoring adverse effects of lithium were also vey less and did not compel prescriber or patients to discontinue abruptly.

In this study we observed that sometimes the reason for the request of TDM of lithium requested was not mentioned in the OPD prescriptions. This information may highlights the urgency of communicating back the TDM reports like when requested for acute toxicity or non-compliance. The use of properly designed TDM request form, as provided in the review of literature section is suggested to overcome these issues.

Regarding the limitations of the study, more number of patients could have been recruited to generate better evidence and also population pharmacokinetics of the local population for Serum lithium using flame photometry is very limited and if available could have been compared with. Although sustained released preparations are nowadays preferred for lithium, in this study only one formulation was studied which was provided free of cost from the hospital pharmacy. Also seasonal variability of lithium levels, especially important due to the climate of this part of the country which can cause excessive sweating and sodium loss, could not be studied due to time limitations. Further, the lithium dose prediction with the help of mathematical pharmacokinetic software could have been incorporated for better dose finding after serum lithium estimation.

CONCLUSION

Up to date accurate and complete lithium patient education is proven to significantly enhance outcomes. Medication compliance, symptom level, weight gain and quality of life are all on-going challenges for people taking lithium. Patient education has been demonstrated by research to improve all of these problems. With the results obtained in this study, it can be concluded that with regular therapeutic monitoring, optimal target serum lithium levels can be achieved with dosage modifications, thereby reducing the risk of toxicity and thus improving drug compliance. It significantly improves therapeutic period. success during the study Further, individualization of dosing and optimization of treatment can be achieved by dependable analytical laboratory services, better psycho-education, family support and overall a disease-based management team approach with the involvement of a Clinical Pharmacologist, Psychiatric nurse and Pharmacist to meet the complexities of lithium therapy. Therefore, clinical pharmacological consultation in accordance with psychiatric management may prove to be more fruitful in improving patient care and treatment outcome.

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Institutional Ethics Committee

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