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Challenges of Therapeutic Drug Monitoring and Usage of Lithium in Managing Psychiatric Disorders: A Review

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Abstract: Lithium is referred by all key guidelines as a first-line treatment for bipolar disorder (BD) maintenance therapy. Therapeutic drug monitoring (TDM) is necessary while using lithium as lithium treatment. The concern arose when there is one article discussed about the declining of usage of lithium in certain countries such as US and Canada. However, the prescription rates of lithium in United Kingdom and Scandinavia do not show a downward trend. The aim of this study was to determine the challenges of TDM and usage of lithium in managing psychiatric disorders. A total of 32 articles have mentioned the challenges in TDM and usage of lithium. Descriptive statistics was done to identify the challenges in TDM and usage of lithium in psychiatric disorders. There is a total of 25 and 27 challenges found in TDM and usage of lithium in psychiatric disorders respectively. The most stated challenges in TDM of lithium were drug-drug and drug-disease interactions (16.07%), poor compliance (14.28%) and different therapeutic levels or dose suggested by different authors or guidelines (14.28%). The most stated challenges in usage of lithium in psychiatric disorders were potential toxicity (16.85%), side effects of lithium (16.85%), narrow therapeutic range (15.73%) and needs frequent monitoring (15.73%). However, the usage of lithium in certain countries remains still high may be due to the benefits of lithium to psychiatric patients in reducing risk of manic relapse and depressive relapse. Although there are 52 challenges found in the TDM and usage of lithium, there is no definite article or statement stating that the usage of lithium is declining. Future multi-national study is needed to study the extend challenges in TDM and usage of lithium in developed countries as compared to developing countries.

Keywords: Therapeutic drug monitoring; Challenges; Lithium; Psychiatric Disorders

1. Introduction

For almost 70 years, lithium has been the drug of choice for those with bipolar disorder (BD). All pertinent guidelines advise using it as the primary method of treatment for maintenance therapy[1]. Despite the hazards associated with high blood levels of lithium and the development of several new mood stabilizers, lithium remains a primary medication for treating mood disorders[2]. Therapeutic drug monitoring (TDM) is necessary while using lithium due to its limited therapeutic index and the possibility of non-compliance by mental patients; Lithium treatment needs ongoing monitoring for side effects and careful serum concentration monitoring[3].

On the other hand, The Clinical Biochemistry laboratory information systems at the University Hospitals of North Midlands, Salford Royal Foundation Trust, and Pennine Acute Hospitals were queried for information on serum lithium levels and request intervals from 2012 to 2018. Lithium levels on the majority were outside the recommended UK therapeutic range (0.4–0.99 mmol/L); 19.2% below the range and 6.1% above the range. 4.2% of the requests were found at the extremes (< 0.1 mmol/L or ≥1.4 mmol/L). Most requests were from general practice (56.3%) or mental health units (34.4%), though those in the toxic range (≥1.4 mmol/L) were more likely to be from secondary care (63.9%)[4].

In a prospective, non-randomized, observational study done in India, It was discovered that patients whose symptoms were tracked using therapeutic medication monitoring saw a considerable improvement. Lithium medication is prescribed after consulting with a clinical pharmacologist to ensure the best possible dosage and patient benefit[5].

Generally, improvement in clinical outcomes can be measured by observing the improvement of the signs and symptoms of bipolar disorders. Normally, Lithium takes 1–2 weeks to start working, and a 4- to 6-week treatment term is needed to gauge the drug's full therapeutic response[6]. A study was carried out by Nobuhiro O. and his colleagues to investigate analyzed the impact of the regulatory warnings requiring routine TDM for lithium and assessed the prevalence of TDM for lithium. Although TDM for lithium was strongly advised by the guidelines, the results showed that its prevalence was low[7].

Based on an article published by.Tibrewal, Ng[8], it was stated that the usage of lithium is declining. Furthermore, there is no systematic review carried out on determining the challenges of TDM and usage of lithium in managing psychiatric disorders as well as to prove whether the statement stated is true or not. There is also no research carried out to study

whether the challenges involved in TDM on lithium are affecting the extent of usage of lithium. The aim of the study was to determine the challenges of TDM and usage of lithium in managing psychiatric disorders. More specific objective is to determine whether the challenges of TDM on Lithium is affecting the extend of usage of Lithium.

2. Methodology

2.1 Study Design

This research is a systematic review and a summary of clinical literature that will identify the challenges faced in TDM and usage of lithium in psychiatric disorders. The components being discussed in the clinical literature summary are the title of study, methodology, sample size, main findings and the focus of the study.

2.2 Inclusion Criteria

All relevant publications that has been published in Malaysia and internationally that mentioned "Therapeutic Drug Monitoring" and/or 'Clinical Pharmacokinetics services" and/or "Lithium" and/or "challenges" and/ or "usage" are included in this study.

2.3 Exclusion Criteria

The published articles that are not in English are excluded due to error that might occurred when translating the article. Other than that, abstracts with insufficient information, for example without full articles with details of result and discussion related to TDM or challenges in usage of lithium are excluded out. This is to ensure a complete view of the study is grasped. Non-lithium research article is also excluded to avoid bias and to focus the study solely on the TDM of lithium.

2.4 Data Collection

The articles were obtained from the internet, using Google search, ScienceDirect database, GoogleScholar, ClinicalKey and ProQuest database. Articles were sourced by searching using keywords, "Therapeutic Drug Monitoring", "TDM" and "Lithium". After all the relevant articles had been searched, selecting of the appropriate articles was done based on inclusion and exclusion criteria.

2.5 Analysis of Result

Analysis of data by descriptive statistics was done to identify the challenges and extend of usage of lithium in psychiatric disorders. Results were divided into two parts which is the analysis of articles based on the title, objectives, methodology, findings or results and

statistical analysis and another is to determine the challenges of TDM and usage of lithium in psychiatric disorders.

3. Results and Discussions

A total of 32 articles have mentioned the challenges in TDM and usage of lithium (Table 1). The concern arose when there is one article discussed about the declining of usage of lithium in certain countries such as US and Canada. However, the prescription rates in United Kingdom and Scandinavia remain high[8]. Therefore, this study was designed to identify the challenges of Therapeutic Drug Monitoring and Usage of Lithium in Managing Psychiatric Disorders and determine if the challenges affects the extend of usage of Lithium. All the reviewed articles have strictly followed the inclusion and exclusion criteria that stated in methodology.

The most listed challenges in TDM of lithium was drug-drug and drug-disease interaction which stated 9 times in the articles that were being reviewed, followed by poor compliance and require compliance assessment which has been mentioned 8 times. Different therapeutic levels suggested by different authors or guidelines or vary in dose or dosing interval was stated 5 times which become the top third mentioned challenge in TDM of lithium. On the other hand, the most listed challenges in usage of lithium in psychiatric disorders was narrow therapeutic index of lithium which was stated 14 times, followed by frequent monitoring needed and potential toxicity by lithium which stated 14 times each in the total articles reviewed. Since only the challenges in TDM and usage of lithium were determined with their number of articles, there is no statistical analysis was done to determine whether the challenges actually influence the extend of usage of lithium in psychiatric disorder.

The most mentioned challenges category in TDM of lithium is drug-drug and drug-disease interactions. It was stated 9 times, which is 16.07% out of the total challenges in TDM of lithium. This is because drug-drug interaction will either increase or decrease the plasma concentration of lithium and therefore affects the clinical outcomes of the patients. Increasing in plasma concentrations may lead to toxicity where the patients experience more side effects or adverse effects and decreasing in plasma concentrations may lead to therapeutic failure and increase risk of relapse of BD in patients. The most often prescribed medications with lithium interactions are ACE inhibitors, angiotensin II receptor antagonists, diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs). Plasma lithium concentrations will rise in response to ACE inhibitors and angiotensin II receptor antagonists and cause potential toxicity where diuretics will have same effects but acts by increasing sodium reabsorption which decrease the clearance of lithium. NSAIDs will inhibit

cyclo-oxygenase, reduce prostaglandin E2 and reduce vasodilation of afferent arteriole. This decreases the glomerular filtration and therefore reduce lithium secretion.

Besides, the most significant illness state affecting the pharmacokinetics of lithium is renal impairment since lithium is almost entirely removed via the kidney. In proportion to creatinine clearance, the rate of clearance of lithium decreases. Lithium clearance to creatinine clearance is 20% in people, but it rises to roughly 30% during manic episodes. The average half-life of lithium in patients with renal failure extends as a result of the decrease in clearance. Therefore, potential drugs interactions should be avoided and frequent monitoring on patients diseased conditions and renal state is needed to maintain lithium concentration in therapeutic range and avoid toxicity.

Second most mentioned challenge in TDM of lithium is poor compliance, which stated 8 times and 14.28% out of the challenges in TDM of lithium. This is because poor compliance to medication regimen can lead to therapeutic failure. Missing dose or taking medication at wrong interval can cause fluctuation in lithium concentration and may cause the lithium concentration falls outside therapeutic range. Therapeutic failure can also increase the risk of relapse of BD in patients. Third most mentioned challenge in TDM of lithium is different maintenance daily dose or therapeutic suggested in guidelines which also stated 8 times and 14.28% out of the challenges in TDM of lithium. Different suggestions in guidelines may cause confusion in clinicians when applying the guidelines and some clinicians may suggest the maintenance dose based on their experiences. At the same time, different maintenance daily dose may be benefit to patients due to their different disease state and conditions.

Besides than the most stated challenges, variation in blood sample taken time, inter-laboratory assay, pregnancy, inter-individual variations, different months of years and protein binding to drug can also affects the concentration level of lithium. Professionalism variation is also considering a challenge in TDM of lithium as clinicians may interpret the serum concentration level and give recommendation based on own experiences. Lack of pharmacokinetics interpretation and recommendation is another challenge in maintaining the serum concentration of lithium in therapeutic range.

The top 4 mentioned challenges in usage of lithium are potential toxicity (16.85%), side effects of lithium (16.85%), narrow therapeutic range (14.28%) and needs frequent monitoring (14.28%). All these challenges are related to each other as this is due to the special pharmacokinetics of lithium where lithium has a narrow therapeutic index which means small differences in dose or blood concentration may lead to serious therapeutic failures or adverse drug reactions. A reduce in dose or concentration will increase risk of relapse and increase in

dose will then lead to potential toxicity in patients and cause serious adverse effects. Even with proper therapeutic monitoring to maintain the lithium plasma level in therapeutic range, some patients will still experiences side effects of lithium in both short term and long term use. Short term side effects include muscle weakness, lethargy, polydipsia, polyuria, nocturia, headache, impairment of memory or concentration, confusion, impaired fine motor performance, and hand tremors. Long term side effects include affecting thyroid functions, potential lithium-induced nephrotoxicity and lithium induced nephrogenic diabetes insipidus (NDI). Some patients also experience changes in physical parameters such as weight, blood pressure, glucose levels and BMI during lithium use. This is why frequent monitoring is needed to minimize the side effects and adverse effects in patients. Monitoring not only covers the serum plasma concentration of lithium but also the renal functions and conditions of patients who are on lithium treatment. Slow decline in renal function ('creeping creatinine') is not easily detected. Special precautions has to be given to pregnant women and patients with renal failure as these conditions will affects the pharmacokinetics of lithium and different approach for lithium serum levels may be required. Maternal toxicity at the time of delivery, lithium has been associated with neonatal complications including cyanosis, hypotonicity, hypothyroidism, neuromuscular abnormalities, and nephrogenic diabetes insipidus. Other challenges in usage of lithium are slow onset of action, administration is complex and there are several contraindications to lithium include substance abuse, medical comorbidities.

Other than that, collaboration between psychiatrist, nephrologist and patients themselves is needed to ensure effective and optimal BD treatment. Other challenges in usage of lithium are some current guidelines lack advice on managing side effects of lithium, non-pharmacist managed TDM of lithium and there are some reasons lead to not monitoring patients during treatment such as inadequate funding and uncooperative patients. Additionally, some clinicians request each monitoring parameter independently, which can add to the workload and make healthcare personnel more aware of their surroundings. Psycho-education and family support are also an important aspect in supporting and motivating patients to continue the treatment. There is still debate on the efficacy and effectiveness of lithium in uni-polar MDD and under-prescription of lithium can be attributed to bias against lithium commercially.

Due to quite a number of challenges were identify, they may be the reasons causing the declining of lithium usage but the exact influence was unsure since there is no statistical analysis was done. In response to the article.Tibrewal, Ng[8] which mentioned the usage of lithium is declining, this study has shown that this statement is true to certain extend as the

usage of lithium is declining in certain countries such as US, Canada, Switzerland, Germany, Austria and Denmark. The usage of lithium in United Kingdom and Scandinavia still high as lithium is still the first line treatment in BD and brings benefits to psychiatric patients by reducing risk of manic relapse and depressive relapse when compared to other drug such as valproate. Lithium is only mood-stabilizing agent that not only has efficacy in BD but has also been shown to reduce the rate of hospitalization in uni-polar depression. This may be the reason where the use of lithium still remains high in certain countries or settings.

4. Limitation of Study

The limitation is that for some articles, only the abstracts were available and full article could not be sourced.

5. Future Study

Multi-national study is needed to study the extend challenges in TDM and usage of lithium in developed countries as compared to developing countries. Although PRISMA. Guidelines was not followed in this systematic review, but the components in PRISMA were included under methodology. PRISMA guidelines should be strictly followed for future systematic reviews study[9].

6. Conclusion

Based on the articles has been reviewed, there are total 25 challenges found in TDM of lithium and total of 27 challenges found in usage of lithium in psychiatric disorders. The most stated challenges in TDM of lithium were drug-drug and drug--disease interactions, poor compliance and different therapeutic levels or dose suggested by different authors or guidelines. The most stated challenges in usage of lithium are potential toxicity, side effects of lithium, narrow therapeutic range and needs frequent monitoring. Other factors that leading to declining of lithium usage in managing psychiatric disorders may be due to other treatment option such as second generation mood stabilizing anticonvulsants carbamazepine and valproate or introduction of newer drugs such as lumateperone which use as alternatives to lithium managing psychiatric disorders. However, the usage of lithium in certain countries remains still high may be due to the benefits of lithium to psychiatric patients in reducing risk of manic relapse and depressive relapse. This is because lithium is still the first line treatment in BD and brings benefits to psychiatric patients by reducing risk of manic relapse and depressive relapse. Multi-national study is needed to study the extend challenges in TDM and usage of lithium in developed countries as compared to developing countries.

Supplementary Materials: Table 1: Challenges in TDM and usage of lithium in psychiatric disorders and the statistical analysis used

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Supplementary File

Table 1. Challenges in TDM and usage of lithium in psychiatric disorders and the statistical analysis used

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
Non-compliance by psychiatric patients. In order to effectively assess the need for dosage alteration, it is important to adhere to standard blood draw times. Failure to do so may result in less useful information about lithium levels. The therapeutic range of lithium doses can vary widely, typically ranging from 300-3000mg per day, with the average dose falling between 900-1800mg/day. However, it's important to balance therapeutic serum levels with clinical observation of patient response, as well as potential side effects or toxicity. It's also worth noting that significant drug interactions can occur between lithium and certain anti-inflammatory agents (such as indomethacin, phenylbutazone, and ibuprofen). These interactions may lead to decreased lithium clearance and an increase in serum levels..	Narrow therapeutic index (0.6 to 1.0 mmol). Needs constant monitoring. Patients need to be given careful instructions regarding changes in their diet and exercise patterns when taking lithium. Failure to do so can lead to potential health risks. One such risk is increased retention of lithium, which can occur in states of sodium depletion. This can raise the potential for toxicity and lead to serious neurological, endocrinological, cardiac, and renal toxicities. To avoid these dangers, it is important to monitor lithium levels closely and take necessary precautions to prevent toxic buildup. Patients should also be advised to stay well hydrated and maintain a healthy balance of sodium in their diets.	No statistical analysis done.	Aishah and Foo[10]
Drug-drug interaction.	Lithium has a narrow therapeutic index of 0.6 to 1.0 mmol, which requires constant monitoring to ensure safe and effective treatment.	No statistical analysis done.	Alldredge, Corelli[6]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	Patients need to be given careful instructions regarding changes in their diet and exercise patterns when taking lithium. Failure to do so can lead to potential health risks, such as increased retention of lithium, which can occur in states of sodium depletion. This can raise the potential for toxicity and lead to serious neurological, endocrinological, cardiac, and renal toxicities. Short-term side effects are commonly observed when starting lithium or after a dosage increase, including muscle weakness, lethargy, polydipsia, polyuria, nocturia, headache, impairment of memory or concentration, confusion, impaired fine motor performance, and hand tremors. Long-term adverse effects include drug-induced diabetes insipidus, renal toxicity, hypothyroidism with or without goiter formation, electrocardiographic abnormalities, leukocytosis, weight gain, and dermatologic changes. Before initiating lithium therapy, patients should undergo a complete physical examination, and a general serum chemistry panel, complete blood cell count with differential, thyroid function tests, urinalysis, and urine toxicology screen for		

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	substances of abuse should be obtained. Additional testing is recommended for patients with renal dysfunction or baseline cardiac disease (such as an electrocardiogram). Follow-up testing in the following areas should be conducted every 6-12 months to monitor for potential adverse effects: serum lithium concentration, renal function, thyroid function, electrolyte levels, and weight. Close monitoring and careful attention to potential side effects can help ensure safe and effective lithium therapy.		
Slight variability of lithium levels in different months of the year.	No challenges in usage of lithium of lithium found.	No statistical analysis done.	Medhi, Prakash[11]
No challenges in TDM of lithium found.	Patients on long-term therapy are at greater risk of lithium toxicity. Lithium toxicity can cause electroencephalogram (EEG) abnormalities which can be correlated with the degree of neurotoxicity. Therapeutic range of lithium is very narrow, which requires regular monitoring to prevent toxicity.	No statistical analysis done.	Madhusudhan[12]
No challenges in TDM of lithium found.	Debate on the efficacy and effectiveness of lithium in unipolar MDD.	The data were analyzed using multivariate statistical methods to assess	Baethge, Gruschka[13]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
		relationships between variables. Descriptive statistical methods were used to calculate average values and rates. To identify predictors of interest, a multiple linear regression analysis was conducted, with the MI as the dependent variable. This approach allowed for the exploration of potential associations between the MI and other independent variables. In addition, survival analyses were performed to examine the time to first recurrence. Cox regression was used with the same independent variables used in the regression analysis, allowing for a more in-depth	

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
		exploration of potential risk factors for recurrence. Overall, these statistical approaches enabled the examination of complex relationships between variables and provided valuable insights into the factors influencing MI and recurrence. A level of significance of 5% was established, with a 2-tailed test for all analyses.	
Compliance needs to be evaluated to avoid increasing rates of relapse.	Li+ has a narrow therapeutic index, plasma levels must be closely monitored to verify maintenance pharmacotherapy to prevent side effects.	No statistical analysis done.	Camus, Henneré[14]
Drug-drug interactions. In the initial treatment of acute mania, many clinicians recommend a serum concentration of lithium between 0.8-1.2 mEq/L. This range is believed to be effective in managing acute manic symptoms.	Lithium possesses a narrow therapeutic index. Toxic effects of lithium become more likely as serum concentrations rise, and most patients will experience some toxic effects with concentrations above 1.5 mEq/L.	No statistical analysis done.	Cates and Sims[15]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
However, during long-term maintenance treatment, lower serum concentrations of 0.6-1.0 mEq/L are generally recommended to prevent the recurrence of manic episodes. This narrower range is believed to be sufficient to maintain symptom control while minimizing the risk of lithium toxicity. It is important to note that the optimal serum concentration of lithium can vary depending on individual patient factors, such as age, renal function, and the presence of comorbidities. Close monitoring of serum lithium levels and clinical response is essential to ensure that treatment is safe and effective over the long term. Suspected non-compliance. Steady-state serum concentrations of lithium can be influenced by a range of factors, including changes in medication, diet, and medical conditions. For example, the development of a medical condition such as diarrhea can impact lithium absorption and alter serum concentrations. Similarly, significant increases in sweating can result in the loss of electrolytes, including sodium, which can affect lithium clearance and serum levels.			

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
The initiation, alteration, or discontinuation of medications that interact with lithium can also impact serum concentrations, and careful monitoring is required to ensure that lithium levels remain within the therapeutic range. Finally, changes in salt intake or diet can influence lithium levels, with low-salt diets potentially leading to increased lithium retention and higher serum levels. Overall, it is important to be aware of these factors and to monitor serum lithium levels closely to ensure that treatment remains safe and effective over the long term. Samples obtained prior or after that time-frame. The dosing interval can also affect the interpretation of lithium concentrations. The accuracy and reliability of the laboratory can certainly impact the interpretability of serum lithium concentration determinations. There are a variety of dosing strategies for lithium treatment that aim to reduce the need for frequent serum concentration determinations and minimize the time required to reach a therapeutic dose.			

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
Despite their potential benefits, there is limited empirical evidence to support the effectiveness of these methods in achieving a more rapid clinical response. As such, clinicians must carefully weigh the benefits and risks of these dosing strategies, and closely monitor patients to ensure that they receive safe and effective treatment. This may involve adjusting dosages or serum concentration monitoring schedules based on individual patient response and any changes in their medical status or medication regimen.			
No challenges in TDM of lithium found.	Requiring closer monitoring. Tests were requested outside expected testing frequencies.	No statistical analysis done.	Parfitt, Duff[4]
Therapeutic range results does not correlate to expected clinical outcomes.	Suspected toxicity or toxicity in sub-therapeutic range patients. Patient compliance assessment after regimen changes Therapeutic failure	No statistical analysis done.	Ratanajamit, Soorapan[16]
The physiological changes that occur during pregnancy can significantly impact the plasma concentrations of many	Narrow therapeutic window	No statistical analysis done.	Volkmann, Bschor[1]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
mood stabilizing medications, making it challenging to maintain therapeutic drug levels. These changes include increased plasma volume, cardiac output, and hepatic blood flow, as well as decreased plasma albumin concentration and delayed gastric emptying, which can all contribute to lower drug concentrations in the bloodstream. In addition, changes in renal glomerular filtration rate and prolonged gastrointestinal transit times can further complicate efforts to maintain therapeutic drug levels during pregnancy. As a result, clinicians must carefully monitor drug concentrations and adjust dosages as needed to ensure that pregnant patients receive safe and effective treatment. Close collaboration between obstetricians and psychiatrists is also essential to ensure the best possible outcomes for both the mother and the developing fetus..	Discontinuing treatment for BD during this time increases the risk of symptom worsening and compromise of functional capacity. In rare cases, lithium toxicity in the mother at the time of delivery can lead to complications in the newborn, such as respiratory distress, cyanosis (bluish discoloration of the skin due to lack of oxygen), hypotonicity (low muscle tone), hypothyroidism (low thyroid hormone levels), neuromuscular abnormalities, and nephrogenic diabetes insipidus (inability to concentrate urine). Therefore, it is important to monitor maternal lithium levels closely during pregnancy and adjust the dosage as necessary to prevent toxicity. Concentration monitoring should begin by 10 weeks gestation or at the first prenatal evaluation of the patient. As preeclampsia worsens prior to delivery, GFR decreases and women can become oligouric, increases lithium level and lead to toxicity.		
No information found.	Lithium treatment can cause cardiac adverse effects and proarrhythmic electrocardiographic changes, which may include QT-prolongation, T-wave	Time-varying Cox regression was used to associate the differences in mood	Christensen, Mohr[17]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	changes, sinus bradycardia, and ventricular tachyarrhythmia. These effects can be particularly concerning in patients with underlying cardiac conditions or in those taking medications that can also affect cardiac function. Therefore, regular monitoring of cardiac function and electrolyte levels is important during lithium treatment. This classification is based on expert consensus and low-level evidence. The study suggests that lithium is not associated with increased rate of out-of-hospital cardiac arrest. Although lithium was not associated with cardiac arrest, it cannot derive from the present study that lithium does not cause arrhythmia.	stabilizer exposure with the hazard rate of cardiac arrest. The Cox regression models were fitted using a nested-case control design with up to five controls matched on sex, year of first bipolar disorder diagnosis, and birth year. Co-medication and comorbidities were adjusted up to the start of the exposure window. Reported were hazard ratios for the varying exposure references.	
Drug-drug interactions with lithium can affect pertinent lab values.	Pharmacokinetic and toxic properties of lithium leading to potential toxicity in some patients. Lithium can cause renal (kidney) toxicity, including impaired kidney function, chronic kidney disease, and in rare cases, irreversible kidney damage. Lithium can also affect thyroid function,	No statistical analysis done.	Hefazi and Lee[18]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	causing hypothyroidism (underactive thyroid) or hyperthyroidism (overactive thyroid). Additionally, lithium can cause electrolyte imbalances, such as low sodium levels (hyponatremia) or high calcium levels (hypercalcemia). These adverse effects highlight the importance of careful monitoring of lithium levels and regular assessment of kidney and thyroid function in patients taking lithium.		
Different therapeutic levels suggested by different authors Different maintenance daily dose according age range No strong evidence in favour of three-times-daily schedule for lithium administration (classic 2-3 times, some recommended one single evening dose for sustained release).	Lithium has been reported to have adverse effects on cognitive function, particularly with long-term use. Some studies have reported negative effects on vigilance, attention, memory, and learning. However, other studies have suggested that these effects may be dose-dependent and reversible upon discontinuation of the drug. The exact mechanisms behind lithium's cognitive effects are not fully understood, but may involve changes in neurotransmitter function or alterations in brain structure and function. Patients taking lithium should be closely monitored for any cognitive changes, particularly those on long-term therapy.	No statistical analysis was done.	Grandjean and Aubry[19]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
No challenges in TDM of lithium found.	Its administration is complex and often requires sophisticated management and assiduous monitoring. Recommendations addressing the practical use of lithium lack consistency.	No statistical analysis done.	Malhi, Gessler[20]
Lack of pharmacokinetics interpretation and recomendation.	No challenges in usage of lithium found.	-No statistical analysis done.	Guo, Guo[21]
Types of assays used in determination of lithium concentration, different resut leading to different interpretations. Drug-drug interaction.	Adverse effects. Narrow therapeutic range. Combined use of lithium with other medications may moreover result in substantial increase in lithium levels and thereby precipitating intoxication.	No statistical analysis done.	Delattre, Van de Walle[3]
No challenges in TDM of lithium found.	Narrow therapeutic index. Non-pharmacist managed TDM of lithium.	These findings suggest that pharmacist management of patients receiving lithium therapy can improve monitoring and education, leading to better patient outcomes. Pharmacist involvement can help identify potential drug interactions and provide	Johnson, Smith[22]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
		education regarding the importance of regular lithium level monitoring, pregnancy testing, and dietary considerations to prevent toxicity. This highlights the importance of interdisciplinary collaboration in the management of patients on complex medication regimens.	
No challenges in TDM of lithium found.	Due to its narrow therapeutic range, lithium levels need to be carefully monitored to avoid toxicity. Lithium is primarily excreted by the kidneys, and any decline in kidney function can increase the risk of toxicity. Therefore, it is important to monitor renal function regularly when using lithium. Although the long-term effects of lithium on renal function are not well established, some studies suggest that chronic use of lithium may lead to a decline in glomerular filtration rate (GFR). As a result, renal function should be monitored every 6 months in patients taking lithium. Additionally,	STATA SE V.12.1 was used for the analysis (StataCorp, 2011, Stata Statistical Software: Release 12 . College Station, Texas, USA: StataCorp LP). Lithium patients from the database were classified according to exposure group, and their gender and age at the time of the exposure	Kirkham, Skinner[23]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	lithium levels should be monitored at least every 3 months to ensure that the concentration remains within the therapeutic range (usually 0.6–1.0 mmol/L), as levels above 0.8 mmol/L have been associated with higher risks of toxicity and side effects.	event was recorded and used to calculate eGFR. A random effects repeated measures mixed model with an interaction with time was run to establish if there was a relationship between follow-up eGFR and the lithium level exposure group, adjusting for baseline eGFR.	
In addition to the factors mentioned, other external factors that can affect lithium serum levels include changes in diet, changes in physical activity levels, and changes in renal function. These factors can make it challenging to maintain stable lithium serum levels and may require frequent monitoring and adjustment of the lithium dose.	Narrow therapeutic index. Careful therapeutic drug monitoring is needed. The recommended therapeutic range for lithium serum levels for maintenance treatment is typically between 0.6 and 1.0 mmol/L, rather than 0.6 and 0.8 mmol/L. However, the optimal range may vary based on individual patient factors and should be determined in consultation with a healthcare provider. The illness stage may further require a different approach for lithium serum levels.	Responses were analyzed using the Statistical Package for Social Sciences Version 24.0 for Windows (SPSS 24.0; SPSS Inc, Chicago, IL). Data were analyzed using descriptive statistics. Target lithium serum levels were presented with the use of boxplot statistics using Tukey's Hinges.	Nederlof, Heerdink[24]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	Long-term use of lithium can lead to chronic kidney disease and irreversible renal damage. The risk of kidney damage increases with the duration of lithium use and with higher serum lithium concentrations. Therefore, regular monitoring of renal function and lithium serum levels is recommended for patients on long-term lithium therapy. If kidney damage is detected, the dose of lithium may need to be reduced or the medication may need to be discontinued.		
	Just a quick clarification, while lithium can affect thyroid function, it is actually more commonly associated with hypothyroidism rather than goiter. Goiter is the enlargement of the thyroid gland, which can occur due to various reasons including iodine deficiency or autoimmune thyroid disease.		
	Physical parameters such as weight and blood pressure may undergo changes during lithium treatment. Local monitoring systems may vary, and healthcare professionals may be influenced by different factors, such as institutional or laboratory protocols, scientific literature, and personal experience.		

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	Some healthcare professionals may choose not to monitor patients during lithium treatment for reasons such as a lack of resources (4%), non-cooperative patients (4%), absence of monitoring requirements in guidelines (3%), personal opinion that monitoring is unnecessary (3%), institutional protocols not mandating monitoring (2%), or unawareness of the need for monitoring (2%). Another reason healthcare professionals may not follow guidelines for lithium treatment is the difficulty of applying them in daily clinical practice (4%), which may be due to a lack of resources (2%), difficulty in applying guidelines to their specific patient population (3%), or unawareness of the existence of such guidelines (2%). Some healthcare professionals choose to perform monitoring based on individual patient characteristics (2%), while others may have difficulty choosing between different guidelines (1%). In some cases, healthcare professionals find guidelines to be excessive (1%) or rely on their own interpretation of the scientific literature (1%).		

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	Several respondents reported not following guidelines because they believed the guidelines were not applicable to their patient population. Additionally, most healthcare professionals must request each monitoring parameter separately, which can increase their workload and require them to be mindful of their monitoring responsibilities.		
Therapeutic drug monitoring (TDM) of lithium should be conducted by measuring trough concentrations just before the next scheduled dose. However, some participants may not always arrive on time for their appointments, which may cause deviations from this protocol.	Lithium has a narrow therapeutic index (0.6–1.0 mmol/L). Drug adherence.	The mean and standard deviation of plasma lithium concentrations were estimated from available data in the treatment arm. To generate sham values, a Gaussian distribution was used based on these estimates.	Lesosky, Joska[25]
Interlaboratory variation and inaccuracy of lithium monitoring When measuring control materials, instruments that use reflectance spectrophotometry (RSM) showed an average positive bias of 21%.	Narrow therapeutic window.	No statistical analysis done.	Mose, Damkier[26]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
Annual prevalence of TDM for lithium was low (approximately 15%). Although regulatory warnings were issued, the impact on increasing the prevalence of therapeutic drug monitoring (TDM) for lithium was minimal..	Narrow therapeutic range. Serious lithium poisoning. During the initial and dose-increase phases of lithium administration, serum lithium levels should be measured approximately once a week until the maintenance dose is established. However, adverse drug reactions are still common among patients receiving lithium treatment, and only a relatively small proportion of patients remain free of such reactions.	To assess the impact of the regulatory warning issued in both April and September 2012, a segmented regression analysis was conducted. The segmented regression analysis revealed that the estimated mean prevalence level experienced a sudden increase of 6.9% (P = 0.001) following the regulatory warning issued in April 2012. However, there was no significant change in the prevalence level after the warning in September 2012 (P = 0.47). Furthermore, the trend (slope) of the prevalence during the period from April 2010 to March 2012, prior to the first warning in April 2012, did not significantly change	Ooba, Tsutsumi[7]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
		during the post-warning period from April 2012 to August 2012. Likewise, there was no significant change in the trend observed during the two periods before (April 2012 to August 2012) and after (September 2012 to March 2014) the second warning issued in September 2012.	
Insufficient water and salt intake, as well as the concurrent use of other drugs that reduce the excretion of lithium, can result in elevated lithium plasma levels.	Risk of lithium intoxication. Long-term use of lithium is associated with an increased risk of chronic kidney dysfunction (CKD). This risk becomes greater after using lithium for more than 10 years. Atypical antipsychotics, which are a common alternative to lithium, are associated with metabolic syndrome and an increased risk of mortality due to cardiovascular problems, particularly with long-term use.	No statistical analysis done.	Nolen[27]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
Lack of information for appropriateness of collecting time. Protein binding is a significant factor that contributes to the variation in serum concentration. Drug-drug and drug-disease interactions.	Time intervals after a drug were taken, drug-drug, drug-disease, and drug-nutrient interactions also should be evaluated for accurate TDM interpretation.	All data were expressed as mean ± standard error of the means (SEM) Descriptive statistics were used to evaluate the data, and categorical data were assessed using a Pearson's chi-squared test. Statistical analysis and graphing were conducted using GraphPad Prism V.8.01 (San Diego, CA) and IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp., Armonk, NY).	Ozunal and Belkiz[28]
Methods to predict the dosage of lithium have limitations and should be used with caution. One reason for failure in dosage predictions could be variations in GFR due to changes in mental and physical activity. Some methods are designed specifically for slow-release or rapid-release preparations. There is wide variation in renal clearance of lithium and response to treatment between individuals. Some methods require a higher number of test doses or blood samples, which may not be acceptable for clinicians	Lithium has a narrow therapeutic index. Regular monitoring of blood levels has to be ensured. Potential renal impairment and dangerous toxicity. The specific pharmacokinetic and pharmacodynamic properties of lithium make its therapeutic use complicated. As lithium is primarily excreted through the kidneys, the absence	No statistical analysis done.	Sienaert, Geeraerts[29]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
or patients. Although some methods have potential, the lack of sufficient data on their performance means they cannot be recommended in clinical practice. Clinicians may adapt the titration method based on their own experience and clinical judgment.	of a measure of renal function appears to be a significant limitation.		
No challenges in TDM of lithium found.	Lithium treatment requires frequent monitoring of plasma levels, renal and thyroid functions, which is not required for other mood stabilizers such as anticonvulsants and second-generation antipsychotics. There are also several contraindications for lithium use, such as substance abuse, medical comorbidities, and drug interactions. In addition to the risk of toxicity, lithium can cause side effects such as weight gain, tremors, polydipsia, polyuria, dry mouth, hair thinning, and sexual dysfunction. These side effects can often be managed by adjusting the dosage or adding other medications, but they can also be a significant burden for patients. Lithium has slow onset of action. There is evidence to suggest that bias against lithium commercially may contribute to its under-prescription in the treatment of bipolar disorder.	No statistical analysis done.	Tibrewal, Ng[8]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	Despite its superior efficacy compared to other alternative agents, such as anticonvulsant mood stabilizers and second-generation antipsychotics, some healthcare providers may be more inclined to prescribe these alternative agents due to their perceived lower risk of adverse effects and easier tolerability. This bias may be reinforced by the marketing efforts of pharmaceutical companies promoting alternative agents over lithium. However, the clinical efficacy of lithium in the treatment of bipolar disorder is well-established and should not be overlooked.		
No challenges in TDM of lithium found.	Unsuspected poor compliance. Lithium has several adverse effects. Relapse and irregular treatment.	No statistical analysis done.	Sharma, Joshi[2]
There are numerous variables that can influence the interpretation of drug concentration data, including the route and dose of the 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 (e.g., disease, renal/hepatic status, biologic tolerance to drug therapy, etc.). Therefore, it is important to	Narrow therapeutic index. ithium treatment is associated with a number of adverse effects that can lead to poor adherence. Toxicity can occur at serum concentrations higher than 1.5-2.0 mmol/L, which can cause a range of symptoms such as coarse tremor, apathy, hyperreflexia, hypertonia, nausea, diarrhea,	The baseline mean score in the Young Mania Rating Scale was 23.06, but most patients stabilized with more than 2 weeks of lithium therapy.	Munshi and Pal[5]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
take these factors into consideration when interpreting drug concentration data in clinical practice. Inappropriate dosage of lithium prescribed. The difference in response may be because of differences in receptors' sensitivity. The metabolism of psychotropic agents such as lithium can vary significantly among individuals due to genetic factors, which can make it challenging to apply such treatments effectively." Non-dependable analytical laboratory services.	myoclonus, seizures, acute renal failure, cardiac dysrhythmia, and coma. Poor compliance is associated with an increased risk of relapse. Lack of psycho-education and family support.	During Visit 1, the patients had a mean YMRS score of 23.06 (SD=8.34), which decreased significantly to 19.1 (SD=6.60) during Visit 2 and 18.43 (SD=6.35) during Visit 3 (*P*=0.0456, 95% CI: 0.08 to 7.85 and *P*=0.0186, 95% CI: 0.80 to 8.4, respectively) compared to the Visit 1 score. The individual patient's scoring at the three visits also showed a significant reduction in YMRS scores.	
No challenges in TDM of lithium found.	There has been speculation and research investigating whether or not long-term lithium use can cause a specific type of kidney damage known as lithium nephropathy or lithium-induced glomerular disease. Studies have shown that chronic lithium use can lead to a reduction in kidney function and an increased risk of chronic kidney disease, but it is not yet clear if this is due to a specific type of kidney damage or if it is	No statistical analysis done.	Clos, Rauchhaus[30]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	simply a result of the drug's effects on the kidneys over time. More research is needed to fully understand the relationship between long-term lithium use and kidney damage. Decline in eGFR attributable to lithium exposure.		
No challenges in TDM found.	Collaboration between psychiatrists, nephrologists, and patients is crucial for the proper management of lithium-induced nephrogenic diabetes insipidus (Li-NDI) and lithium nephropathy (Li-NP) as they are prevalent side effects of lithium therapy with significant morbidity. Monitoring of renal function and serum lithium levels is essential in patients receiving lithium therapy to detect any early signs of kidney damage or electrolyte imbalances. Early detection and management of these conditions can prevent further progression to end-stage renal disease. Patients should be educated on the importance of proper hydration and monitoring their fluid intake while on lithium therapy. Additionally, switching to alternative mood stabilizers should be considered in patients with significant kidney dysfunction or those at high risk for developing renal complications.	No statistical analysis done.	Schoot, Molmans[31]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	Current guidelines do not provide specific advice for the personalized prevention and treatment of Li-NDI and Li-NP. It is important to carefully consider the decision to discontinue lithium therapy, taking into account the risk of psychiatric relapse (such as depression, mania, and suicide) and the potential benefits of cessation, along with the potential risks associated with discontinuing lithium therapy. Collaboration between psychiatrists, nephrologists, and patients is necessary to effectively manage and monitor potential side effects of lithium therapy. Renal dysfunction is often irreversible and even progressive despite lithium withdrawal. Slow decline in renal function (‘creeping creatinine’) is not easily detected.		
No challenges in TDM found.	Declining eGFR with age and exposure to lithium. Monitoring serum concentrations of lithium levels relatively frequently, especially in elderly patients. . Small increases in glucose levels and BMI were found.	No statistical analysis done.	Tondo, Abramowicz[32]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
During pregnancy, there are various physiological changes that can affect drug disposition and lead to alterations in serum drug levels. For instance, lithium clearance in the third trimester was observed to be nearly twice the average clearance in non-pregnant individuals, which resulted in a 50% decrease in lithium serum levels. Non-adherence.	Careful monitoring of serum lithium levels is necessary during pregnancy to ensure therapeutic efficacy and avoid toxicity. Women with bipolar disorder who are planning pregnancy or become pregnant should discuss the risks and benefits of lithium therapy with their healthcare provider, and a personalized treatment plan should be developed based on the individual's clinical history and lithium clearance. It may also be necessary to adjust the dosage of lithium during pregnancy to maintain therapeutic levels. Additionally, prenatal screening for potential teratogenic effects should be considered, and the patient should be informed of the risks associated with lithium use during pregnancy. During pregnancy and postpartum, the pharmacokinetics of lithium can be altered due to changes in renal function, volume of distribution, and hormonal influences. Therefore, serum lithium levels should be monitored more frequently in pregnant and postpartum women to ensure therapeutic levels are maintained while avoiding toxicity. Close collaboration between the psychiatrist, obstetrician, and primary care provider	Dose-adjusted serum concentrations in the third trimester were significantly lower than baseline (−34%; CI −44% to −23%, $p<0.001$).	Westin, Brekke[33]

Challenges in TDM of Lithium	Challenges in Usage of Lithium	Statistical analysis	Reference
	is essential for optimal management of bipolar disorder in pregnant and postpartum women.		