Original Research Article

Mood Stabilizers: Use, Drug Interactions, and Lithium Toxicity

.

ABSTRACT

Aims: This study aims to investigate the pharmacological management of Bipolar Affective Disorder (BAD) with a focus on lithium carbonate therapy, addressing the risks of toxicity, the role of polypharmacy, and the importance of patient adherence to treatment. The work also emphasizes the need for proper monitoring and education for patients undergoing lithium therapy in Psychosocial Care Centres (CAPS).

Methodology: A combination of clinical observations and laboratory tests, including the Osmotic Fragility Test, were conducted in CAPS facilities in Palmas (TO) and Mutuípe (BA) to assess the medications commonly used in the treatment of BAD. A review of literature and analysis of medication prescriptions were also incorporated to explore polypharmacy and medication interactions. Serum lithium levels and renal function were monitored to identify potential risks of toxicity.

Results: The study revealed that polypharmacy is prevalent in the treatment of BAD, with patients frequently prescribed lithium alongside other medications such as antipsychotics and antidepressants. Lithium toxicity was identified as a significant concern, with laboratory tests showing evidence of erythrocyte damage. Despite the efficacy of lithium in stabilizing mood and preventing relapses, the narrow therapeutic window necessitates careful monitoring. The study also highlighted the importance of multidisciplinary care and therapeutic workshops in improving patient adherence.

Conclusion: Lithium carbonate remains a cornerstone of BAD treatment, but its use requires vigilant monitoring to prevent toxicity and ensure therapeutic efficacy. Healthcare professionals must educate patients about the risks associated with lithium, emphasize adherence to prescribed regimens, and monitor closely for adverse reactions. Integrated care approaches, including psychotherapeutic interventions and family support, are essential for enhancing patients' quality of life and supporting long-term psychiatric recovery. Further research is needed to optimize lithium therapy protocols and minimize risks associated with polypharmacy.

Keywords:Bipolar affective disorder, lithium carbonate, toxicity.

1. INTRODUCTION

Bipolar Affective Disorder (BAD) is a chronic and recurrent mental health condition that significantly affects an individual's quality of life, leading to functional and cognitive impairments, as well as an increased risk of premature death (GRANDE et al., 2016). It is characterised by the occurrence of manic episodes (bipolar mania), hypomanic episodes, and depressive episodes (bipolar depression) (MCINTYRE; CALABRESE, 2019). According to the latest International Classification of Diseases (ICD-11, 2018), this disorder is defined by mood dysregulation, with the presence of manic episodes (type I) or hypomanic episodes (type II), and major depression in both diagnoses, alongside the possibility of mixed episodes.

Unipolar depression, also referred to as Major Depressive Episode, is the primary cause of morbidity in patients with bipolar disorder and is associated with higher morbidity and mortality rates compared to patients with bipolar mania. Depressed individuals are at a higher risk of suicide, panic attacks, inter-episode symptoms, and psychosis (KAPCZINSKI; QUEVEDO, 2016). This condition is characterised by a depressed mood or loss of interest/pleasure in nearly all activities for at least two weeks, accompanied by four or more additional symptoms, which may include changes in sleep and/or psychomotor speed, feelings of guilt and worthlessness, fatigue, and a reduced ability to think or concentrate (BOSAIPO; BORGES; JURUENA, 2017).

Initially, treatment for Bipolar Affective Disorder (BAD) involves the use of mood stabilisers, anticonvulsants, or atypical antipsychotics, which, when combined with psychosocial interventions such as individual or group psychotherapy and psychoeducation groups, have been shown to significantly benefit patients (ROSA; LEÃO, 2022). To ensure effective treatment adherence, it is crucial that medication is combined with psychosocial interventions. Although pharmacotherapy remains the primary treatment for BAD, it provides only partial symptom relief when used in isolation.

Another critical point is that prolonged management with mood stabilisers can also impair adherence and lead to psychosocial harm, highlighting the importance of combining pharmacological treatment with psychosocial interventions to promote patient autonomy (OLIVEIRA et al., 2019). Lithium is one of the first-line drugs for managing both acute manic and depressive episodes in BAD (BOSAIPO; BORGES; JURUENA, 2017). However, in addition to its effects on the central nervous system, lithium has systemic impacts on multiple organs, including the kidneys, heart, motor plate, and the thyroid and parathyroid glands. It may cause hypothyroidism, hyperthyroidism, goitre, ophthalmopathy through various mechanisms, nephrogenic diabetes insipidus, and other disorders. The adverse effects are typically reversible after discontinuation of the drug.

However, some patients may experience irreversible renal damage due to chronic interstitial nephropathy (LERENA et al., 2022). Symptoms of lithium toxicity include tremor, polyuria, polydipsia, bradycardia-tachycardia syndrome, oedema, ataxia, dermatological conditions (such as acne and psoriasis), increased appetite, dysentery, emesis, and decreased thyroid function (MALHI et al., 2020; PARIZOTTI et al., 2021). Therefore, it is essential to assess adherence to lithium treatment, for which lithium serum levels (lithium monitoring) are measured. Despite this, it is well known that lithium, at high concentrations, can be toxic to the human body due to its narrow therapeutic index, making frequent monitoring of serum levels necessary (WON; KIM, 2017).

Given the risks associated with the primary medication used, it is essential to broaden the understanding of other drugs recommended for the treatment of Bipolar Affective Disorder (BAD), including potential drug interactions. Furthermore, it is crucial to investigate the effects of lithium carbonate on human blood cells in order to assess its safety concerning this tissue, as alterations in blood cells can lead to physiological and biochemical damage. The osmotic fragility test emerges as a viable option, as it is low-cost, easy to perform, and widely accessible, commonly used to assess the resistance or fragility (lysis) of erythrocytes when exposed to variations in sodium chloride osmotic concentrations.Thus, the aim of this study was to investigate the most prescribed medications for bipolar affective disorder at a Psychosocial Care Centre, assess the drug interactions of these medications, and further examine the toxicity of lithium carbonate.

2. MATERIAL AND METHODS

2.1 Medication Survey

Initially, a survey was conducted with the pharmacy team at the Psychosocial Care Centre – Alcohol and Drugs (CAPS-AD) in Palmas, Tocantins, through a guided visit. The medications prescribed for the treatment of Bipolar Affective Disorder (BAD) were identified and selected. Data collection occurred between december 2023 and march 2024, with approval from local supervision. As the data were secondary, the medication list was organized into a table. Subsequently, a documentary and bibliographic comparative study was carried out to compile relevant information, including dosage forms, therapeutic indications, potential drug interactions, and adverse effects of the medications used to treat BAD.

2.2 Medications Provided by the Unified Health System(SUS)

A comprehensive documentary review was conducted using medication data for Bipolar Affective Disorder (BAD) from CAPS-AD, with particular reference to Ordinance No. 3, dated March 9, 2015. This ordinance outlines the medications recommended for the treatment of mental health disorders under the Unified Health System (SUS). The review focused on identifying and categorizing the medications currently in use at CAPS-AD, followed by a detailed comparison with the medications listed in the SUS/Brazil guidelines. The objective was to assess the alignment between the prescribed treatments at CAPS-AD and the national standards set forth by SUS, as well as to evaluate any discrepancies or gaps in the availability of medications for BAD treatment across different regions. This comparison is crucial for understanding the accessibility and adequacy of mental health care under the SUS framework, ensuring that patients with BAD receive optimal and evidence-based treatment.

2.2 Osmotic Fragility Test - Lithium

Following the medication survey at CAPS-AD, lithium carbonate was selected for an ex vivo experimental toxicity study, in which biological material is obtained from a living organism. The osmotic fragility test was used to assess whether this medication affects the integrity of human erythrocyte membranes. This technique is a simple, low-cost method that evaluates variations in red blood cell resistance when exposed to saline solutions with decreasing concentrations (PARDINI, 2015). Male participants were selected for peripheral blood collection, with inclusion criteria requiring abstinence from both licit and illicit drug consumption for 48 hours prior to collection. Participants were recruited voluntarily based on availability. The collection process took place at the Basic and Health Sciences Laboratory (LACIBS) at the Federal University of Tocantins (UFT), which adheres to biosafety guidelines. This laboratory is equipped for blood collection, technique development, and result analysis.

For the erythrocyte osmotic fragility test (FOE), a 5 mL peripheral blood sample was collected by venipuncture from each participant using a Vacutainer® kit with an EDTA-containing tube as an anticoagulant. The collection was performed by a registered nurse and a qualified pharmacist. Aliquots of 50 µL of blood were exposed to increasing concentrations of lithium carbonate (0.03, 0.06, 0.12 mg/mL) diluted in 0.9% NaCl. After 60 minutes of exposure, the blood samples were subjected to NaCl solutions with increasing concentrations: 0.12%, 0.24%, 0.48%, 0.60%, 0.72%, and 0.9%. The samples were homogenized and incubated in a controlled water bath at 37°C for 60 minutes. After incubation, the tubes were centrifuged at 1500 rpm for 10 minutes, and the supernatant was analyzed using a Thermo Scientific® Genesys 10S UV-VIS spectrophotometer at 540 nm.

The data obtained through spectrophotometry were used to construct hemolysis curves for each individual, which formed the basis for the statistical analysis of erythrocyte osmotic fragility and comparisons of variables. Statistical analysis was performed to compare FOE data between groups (SILVA, 2015).The data were first subjected to normality analysis, followed by ANOVA, with Tukey's post-hoc test applied at a 95% significance level using the GraphPad Prism software. All procedures were carried out at the Basic and Health Sciences Laboratory (LACIBS) at the Federal University of Tocantins, Palmas-TO campus. The study was submitted to and approved by the Ethics Committee (No. 066/2013).

3. RESULTS AND DISCUSSION

Bipolar Affective Disorder (BAD) is a complex psychiatric condition with an unknown cause, often characterised by sudden mood swings ranging from depression to manic episodes. It is essential to inform patients that Bipolar Disorder is typically chronic and progressive, with frequent recurrences and, at times, severe episodes (YATHAM et al., 2018). In this context, the family plays a crucial role as a support and safety network. When integrated with community involvement and the healthcare team at the Psychosocial Care Centre (CAPS), a comprehensive support network is formed, including activity workshops, meetings, and integrative practices aimed at reintegrating the individual into society (SANTANA, 2021).

A support network encompasses interpersonal relationships and the strategic recognition and enhancement of bonds, which can be categorised into two systems: the Informal System and the Formal System. The Informal System includes family, friends, neighbours, and civil society institutions (NGOs, religious organisations, associations, and clubs) that provide social support to individuals affected by health conditions. The Formal System comprises public institutions and services offering care, support, and assistance to individuals and society, including health services (Family Health Strategy - FHS, Psychosocial Care Centres - CAPS, outpatient clinics, and hospitals), social assistance services (CRAS, CREAS, shelters, and hostels), child protection councils, courts, schools, INSS, housing departments, among others (FUSTER, 1997; FUSTER, OLAIZOLA, & OCHOA, 2002).

The Psychosocial Care Centres (CAPS), established by Ordinance No. 3088 of 23 December 2011, are strategic components of the Psychosocial Care Network (RAPS). CAPS serves as a space for rehabilitation, open to the community, primarily designed for individuals experiencing mental distress or disorders. Family involvement is integral, and the multidisciplinary team focuses on the user's rehabilitation within their health territory. The Psychosocial Care Centre – Alcohol and Drugs (CAPS-AD), restructured by Ordinance No. 130 of 26 January 2012, provides care for individuals facing intense psychological distress caused by the use of crack, alcohol, and other substances. It also addresses adverse clinical situations that hinder the establishment of social connections and life projects.

3.1 Medication Survey

At the CAPS in Palmas, TO, it was observed that patients with Bipolar Affective Disorder (BAD) often use a combination of multiple medications. The most commonly prescribed drugs include bupropion (150 mg), lithium carbonate (300 mg), clonazepam (2 mg and 0.5 mg), chlorpromazine (25 mg and 100 mg), quetiapine (25 mg and 100 mg), sertraline (50 mg), and sodium valproate (500 mg and 250 mg) (Table 1). These medications are typically used to stabilize mood or manage episodes of bipolar depression, addressing the wide-ranging symptoms associated with the disorder, which may include extreme mood swings, irritability, and feelings of hopelessness.

Despite the frequent use of polypharmacy, it is generally recommended to avoid combining multiple medications whenever possible. The current medical guidelines advocate for the use of a single medication, especially for the treatment of BAD or associated depressive episodes. This approach aims to minimize the risks associated with polypharmacy, such as adverse drug interactions and increased side effects, while also improving treatment adherence. Clinicians are encouraged to carefully assess the individual needs of each patient and consider a more streamlined approach to medication management, with the goal of achieving the best possible outcomes with the least amount of medication necessary.

The treatment of Bipolar Affective Disorder (BAD) is often compromised, primarily due to misdiagnosis, which leads to the inappropriate prescription of medications that do not effectively address the underlying condition. This misstep can worsen the patient's clinical situation or significantly delay the initiation of appropriate and effective treatment (SILVA; DIAS; ROSALINO, 2017). Lithium, a naturally occurring metal, plays a central role in psychiatric treatment and is most commonly available in the form of lithium carbonate. Over the past five decades, lithium carbonate has been the standard pharmacological treatment for BAD, demonstrating significant efficacy in preventing manic and depressive episodes and reducing the likelihood of recurrence (KENDALL et al., 2016; FERENSZTAJN-ROCHOWIAK et al., 2021).

It is estimated that between 70% to 80% of patients diagnosed with BAD are treated with lithium as an adjunct therapy, primarily for suicide prevention and reducing the risk of recurrence (PENHA et al., 2019; PARIZOTTI et al., 2021; LOPES, 2019). However, it is important to note that lithium is not always used as a standalone treatment, which necessitates frequent monitoring of lithium serum levels to ensure its therapeutic efficacy and minimize the risk of toxicity. This monitoring is particularly critical given the narrow therapeutic window of lithium and its potential for side effects if not properly dosed.

Table 1. Medications most frequently used for the treatment of BAD at CAPS-AD in Palmas, TO, including their names, usual dosages, indications, posology, and associated drug interactions.

Medications / dosage	Indications	Posology	Drug interaction
Bupropion/ 150mg	Treatment of Major Depressive Disorder (MDD) and alcohol dependence.	Initial dose for most adults is one 150 mg tablet per day. The physician may increase the dose to 300 mg (two tablets) daily if symptoms do not improve. Do not take more than one tablet at a time. Doses should be spaced at least 8 hours apart. Avoid taking the medication near bedtime as it may cause insomnia.	Herbal medicines or supplements (e.g., vitamins), monoamine oxidase inhibitors (MAOIs), and other medications should be monitored.
Lithium Carbonate 300mg	Manic episodes in bipolar disorders; prevention of recurrent mania; prophylaxis of depressive phases; and treatment of psychomotor hyperactivity.	Variable and typically ranges from 900 mg to 1800 mg per day, divided into two doses. A single daily dose is not recommended during initial treatment or when doses exceed 1800 mg/day. Dosages should be tailored individually and adjusted as needed. Plasma lithium levels (lithiumemia) must be monitored to achieve therapeutic levels, generally between 0.8 and 1.4 mEq/L.	Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and phenylbutazone, as well as diuretics like hydrochlorothiazide and chlorothiazide.
Clonazepam 0.5mgand 2mg	Anxiolytic and anticonvulsant for epilepsy, infantile spasms (West syndrome), anxiety disorders, mood disorders, psychotic syndromes, restless legs syndrome, burning mouth syndrome, vertigo, and balance disorders.	For mood disorders, the dosage ranges from 1.5 mg to 8 mg/day. Recommended dose: 2.0 to 4.0 mg/day.	Central nervous system depressants, alcohol, antidepressants, sleep medications, certain analgesics, antipsychotics, anxiolytics, anticonvulsants, gastrointestinal drugs, and grapefruit juice, as they may enhance medication effects.
Chlorpromazine 25mg and 100mg	Treatment of acute psychiatric conditions and control of chronic psychoses.	Ranges from 25 mg to 1600 mg/day, depending on clinical needs. Initial treatment should start with low doses (25 to 100 mg), repeated 3–4 times daily, as needed, to achieve symptom control (maximum dose: 2 g/day).	Levodopa, lithium, and sultopride are contraindicated or not recommended due to interactions.
Quetiapine 25mg and 100mg	Schizophrenia; monotherapy or adjunctive therapy for manic episodes in bipolar disorder; depressive episodes in bipolar disorder; and maintenance treatment of bipolar I disorder.	Dose titration is as follows: Day 1: 50 mg; Day 2: 100 mg; Day 3: 200 mg; Day 4: 300 mg. Doses may increase to 400 mg by Day 5 and up to 600 mg by Day 8. Antidepressant efficacy has been demonstrated at doses of 300–600 mg, with no additional benefit observed above 600 mg during short-term treatment.	Alcohol, medications affecting brain function or behavior, drugs causing electrolyte imbalance or QT prolongation, anticholinergic agents, and certain antifungals, antibiotics, and antivirals.
Sertraline 50mg	Depression (including depression with anxiety), panic disorder, post-	Oral administration, once daily, preferably at the same time each day, with or without food. Maximum	Monoamine oxidase inhibitors (MAOIs), pimozide.

	traumatic stress disorder (PTSD), social anxiety disorder, and premenstrual dysphoric disorder. Indicated for adults and children aged 6 years and older in cases of obsessive-compulsive disorder (OCD).	recommended dose: 200 mg/day.	
Sodium Valproate 500mg and 250mg	Monotherapy or adjunctive therapy for partial complex seizures, whether isolated or associated with other types of seizures.	Initiate with 10–15 mg/kg/day, increasing by 5–10 mg/kg/week until the optimal clinical response is achieved. Optimal response is generally observed at doses below 60 mg/kg/day.	Liver disease or significant hepatic dysfunction, mitochondrial disorders caused by POLG gene mutation (e.g., Alpers-Huttenlocher syndrome), children under 2 years with suspected POLG-related disorders, urea cycle disorders, porphyria.

At a CAPS facility in Mutuípe, BA, other medications such as carbamazepine (200 mg), risperidone (3 mg), haloperidol (5 mg and 2 mg/mL), clonazepam (2.5 mg/mL), valproic acid (50 mg/mL), and long-acting haloperidol decanoate (50 mg/mL, intramuscular) are frequently dispensed as part of the therapeutic regimen (SANTANA, 2021). While these drugs can contribute to managing the condition, the complexity of polypharmacy increases the potential for harmful interactions, particularly between antipsychotics and antidepressants. Such interactions can result in adverse reactions like agitation and motor disturbances, which not only jeopardize patient safety but may also lead to non-adherence to the treatment plan or early withdrawal from care. These challenges underscore the importance of careful medication management and monitoring in treating BAD.

At the CAPS 'Esperança' in Recife, PE, therapeutic workshops combined with pharmacological treatment were reported as effective and well-received by patients, offering valuable guidance. However, it was observed that most patients remained on polypharmacy regimens, which introduces a host of potential risks (BARROS; DUARTE, 2020). The reliance on multiple medications increases the risk of adverse drug interactions, complicating the overall treatment process. In a study by Balen et al. (2017), it was found that 7.4% of severe potential drug interactions involved the combination of chlorpromazine and haloperidol, highlighting the significant health risks of such combinations, including reduced efficacy, excessive potentiation of therapeutic effects, and increased treatment costs (FRIEDRICH; BLATTES, 2022).

Further complicating the issue, Liu et al. (2017) noted that for each additional capsule taken by a patient, the risk of non-adherence to treatment increases by 12%. This statistic emphasizes the challenge of ensuring patient compliance in polypharmacy regimens, where the burden of managing multiple medications can overwhelm patients and lead to treatment abandonment or inconsistent adherence.

Given the potential risks associated with polypharmacy in the management of BAD, it is crucial to consider treatment regimens that minimize the number of medications, reduce the risk of harmful interactions, and optimize therapeutic outcomes. The integration of non-pharmacological interventions, such as therapeutic workshops, alongside pharmacological treatment, can play an essential role in improving patient adherence and overall care satisfaction.

3.2Medications Provided by the Unified Health System (SUS)

The treatment of bipolar depression should ideally involve monotherapy, taking into account the patient's prior response history, medication tolerability, and potential contraindications. Monotherapy is preferred as it provides more effective symptom control with lower risks of drug interactions and side effects. However, when monotherapy is insufficient or when there are contraindications or intolerance to lithium, combination therapies may be adopted. Some of the most common combinations include fluoxetine with olanzapine, lithium carbonate, or valproic acid. Lamotrigine and quetiapine are considered first-line monotherapies, with quetiapine being the second most evidence-based medication for the treatment of bipolar depression (BRASIL, 2016).

Lithium carbonate remains a Level 1 recommendation for all phases of Bipolar Affective Disorder (BAD) treatment, including bipolar depressive episodes. Its effectiveness in preventing both manic and depressive episodes is well-established, making it one of the key medications for mood stabilization and relapse prevention (BRASIL, 2016). Lithium use is particularly critical in cases with a high risk of suicide or recurrent depressive episodes. In addition, the Ministry of Health in Brazil has approved a range of medications for the direct treatment of BAD within the Brazilian Unified Health System (SUS), including clozapine, lamotrigine, olanzapine, quetiapine, and risperidone. These medications, initially indicated for other health conditions, were incorporated into the treatment of BAD as per the official announcement on March 10, 2015 (BRASIL, 2015).

Other drugs, such as carbamazepine, haloperidol, and fluoxetine, are also used in the treatment of BAD. Carbamazepine, for instance, is particularly useful when lithium is not well-tolerated or when there are comorbid conditions that require additional treatment (BRASIL, 2016). The primary goal of pharmacological therapy remains symptom remission, followed by maintenance therapy to prevent recurrences and worsening of depressive or manic episodes.

However, it is crucial to note that the inappropriate or unnecessary use of combination therapies can significantly increase treatment costs and delay patient recovery. This typically happens when there is no clear definition of the patient's therapeutic needs or when healthcare professionals do not strictly follow treatment guidelines. Many CAPS (Psychosocial Care Centers) fail to fully adhere to SUS protocols, which undermines treatment efficacy. Inconsistent access to recommended medications can lead to ineffective treatments, prolonged recovery periods, and an increased risk of relapses and more severe episodes (BRASIL, 2015). Therefore, strict adherence to treatment protocols and continuous

monitoring of patients are essential to ensure therapeutic effectiveness and improve the quality of life for individuals with BAD.

3.3 Osmotic Fragility Test - Lithium

Lithium carbonate is the most commonly used medication for Bipolar Affective Disorder (BAD) and remains the most effective treatment for mood stabilization, as demonstrated by studies and observations at the Alcohol and Drug Psychosocial Care Centre in Palmas-TO. It plays a crucial role in preventing both manic and depressive episodes and reducing the risk of recurrence in BAD patients (PEREIRA et al., 2019; LOPES, 2019). Despite its effectiveness, lithium does not always achieve the desired mood stabilization, and its narrow therapeutic range presents a significant challenge, especially given the potential for toxicity. Importantly, lithium remains the only medication that has been shown to directly prevent suicide in patients with BAD (SARAI et al., 2018).

One method used to assess lithium's potential toxicity is the Osmotic Fragility Test, a widely used laboratory screening tool to evaluate erythrocyte membrane fragility when exposed to varying osmotic concentrations of sodium chloride. In a recent study, this test was employed to examine the effects of lithium carbonate on human erythrocytes. The results are presented in Figure 1, which illustrates the observed haemolysis following lithium administration. Absorbance data from the test revealed that increased light absorption—indicative of higher haemoglobin levels—was noted across all medication concentrations compared to the control group. Haemolysis was observed in the majority of the tested concentrations, except at NaCl concentrations of 0.48% and 0.72% in the 0.06 mg/mL group, where no significant differences were detected compared to the control group (QUADROS; BRITO JUNIOR, 2022). These findings suggest that lithium can induce erythrocyte damage, underscoring the importance of monitoring its use.

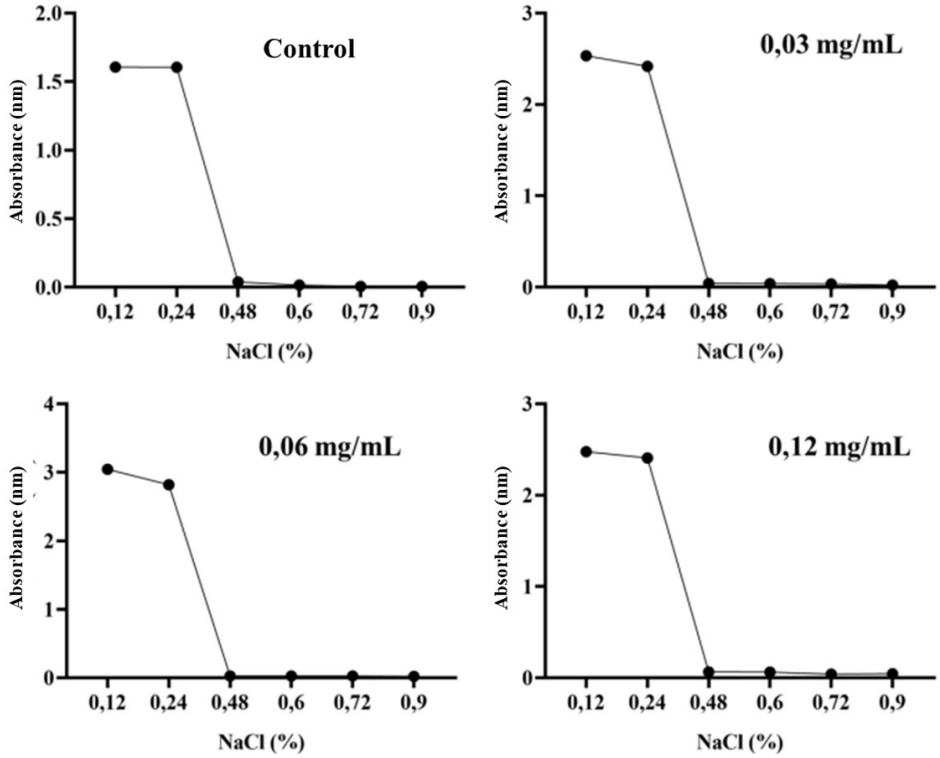

Fig.1. Absorbance results from the Osmotic Fragility Test on human erythrocytes (n=3) in the control group and drug-treated groups (0.03, 0.06, and 0.12 mg/mL).

Lithium carbonate has a high bioavailability of 80–100% and is primarily excreted through the kidneys. Due to its structural similarity to sodium, lithium is often reabsorbed in place of sodium, particularly when sodium levels are low, resulting in an accumulation of lithium in the bloodstream. This reabsorption process increases the risk of nephrotoxicity, particularly in individuals with impaired renal function (ALVES, 2021; MCKNIGHT et al., 2019). Reduced glomerular filtration rates can further impair lithium excretion, leading to elevated serum levels and an increased risk of toxicity. Lithium's therapeutic index is narrow, and therapeutic doses generally range from 300 mg/day to a maximum of 1800 mg/day. Adjustments are required for older adults, who are at greater risk of renal impairment and increased adverse effects.

Despite being effective at therapeutic doses, lithium is associated with a range of adverse effects, such as nephrotoxicity, oedema, polyuria, tremors, nausea, vomiting, and cognitive disturbances. These side effects often contribute to non-adherence to treatment (ÖHLUND et al., 2018; MELEIRO, 2018; ALASTANOS; POTTER; CROUSE, 2019). Co-administration of lithium with antipsychotics, non-steroidal anti-inflammatory drugs (NSAIDs), or certain antidepressants can exacerbate the risk of neurotoxicity and nephrotoxicity (ALMEIDA, 2020; CÂMARA et al., 2019; ALVES, 2021). Lithium intoxication can occur as a result of chronic kidney dysfunction or accidental overdoses, even when serum levels remain within the therapeutic range (EL BALKHI et al., 2017; BAIRD-GUNNING et al., 2016; PERRONE, 2020).

Symptoms of lithium toxicity generally develop gradually and progressively, and there is no specific detoxification treatment. Symptomatic management is used, with common symptoms including tremors, polyuria, polydipsia (potentially indicative of diabetes insipidus or nephrotoxicity), bradycardia-tachycardia syndrome, oedema, ataxia, acne, and psoriasis. Lithium toxicity can also cause ECG abnormalities, elevated cardiac markers, and cardiac injury (MALHI et al., 2020; PARIZOTTI et al., 2021). Following bariatric surgery, altered pharmacokinetics can further increase the risk of lithium toxicity, resulting in neurological complications (HAMID et al., 2020; FIGUEIREDO; LEMOS, 2020).

One major factor contributing to lithium toxicity is drug interactions. Studies indicate that a significant portion of lithium prescriptions involves interactions with other drugs, which can increase the risk of toxicity. For instance, Pasqualoto et al. (2018) found that 75% of lithium prescriptions involved drug interactions, with 44.4% classified as high risk, 23.9% as moderate risk, and 6.5% as low risk. The co-administration of lithium with selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram, and sertraline, or with antipsychotics like chlorpromazine and haloperidol, can lead to additional side effects, including rigidity, stupor, dyskinesia, oliguria, and an increased risk of cardiotoxicity (BALEN et al., 2017; PEREIRA et al., 2019). Additionally, antidepressants can trigger rebound effects, including manic episodes, which may result in treatment discontinuation (ELISABETSKY et al., 2021; TUNC; TUNC, 2022).

To mitigate the risks associated with lithium therapy, healthcare professionals must closely monitor patients for signs of toxicity. Nurses play a pivotal role in educating patients and families about proper medication administration, hydration, and ongoing safety measures. By ensuring that lithium is administered at appropriate intervals, fostering adherence to treatment protocols, and maintaining a strong collaborative relationship with the multidisciplinary care team, healthcare providers can optimize lithium therapy while minimizing potential harm (JANSEN et al., 2022). In summary, the key to successful lithium therapy lies in vigilant monitoring, early detection of toxicity, and patient-centered care.

4. FINAL CONSIDERATIONS

Based on the tests and studies conducted in this work, it is clear that lithium toxicity is a recognized concern, with potential to cause significant health impairments. Regular monitoring, including serum lithium levels and renal function assessments, is crucial for managing patients on lithium carbonate therapy. Healthcare professionals must remain vigilant for symptoms indicative of toxicity, allowing for prompt dosage adjustments and appropriate symptomatic treatment.

An essential aspect of patient care is educating individuals about the adverse reactions associated with lithium, recognizing signs of toxicity, and understanding the need for potential dose adjustments. Empowering patients with this knowledge enhances treatment adherence and encourages active participation in their care. Although concerns about side effects can contribute to treatment discontinuation, providing clear guidance and ongoing support can help mitigate these challenges and foster patient commitment to psychiatric care.

Given the complexities surrounding lithium therapy, ongoing research and testing are necessary to refine current approaches and improve patient outcomes. More studies will help establish enhanced protocols and monitoring strategies to minimize risks and optimize the benefits of lithium in treating bipolar affective disorder (bad).

Finally, it is crucial to integrate comprehensive treatment protocols for bad, including a combination of psychotherapeutic interventions, medication, and family support, to truly enhance the patient's quality of life. Nurses play a key role in ensuring seamless integration of these services and in continuously monitoring for signs of toxicity risk. The use of an individualized care plan, developed through the nursing care systematisation (ncs), is instrumental in safeguarding patient well-being, promoting adherence to treatment, and supporting long-term psychiatric recovery.

CONSENT AND ETHICAL APPROVAL

Ethical approval for this study was granted by the Research Ethics Committee for Human Subjects at the Federal University of Tocantins (approval number: 066/2013).

ACKNOWLEDGEMENTS

This work was supported by the national council for Scientific And Technological Development (CNPQ) – Brazil, and by PROPESQ / Federal University Of Tocantins (UFT).

REFERENCES

Alastanos, J. N., Potter, T. G., & Crouse, E. L. (2019). Lithium-related medication problems in nonpsychiatric inpatient medical units. American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists, 76(Supplement_4), S96–S101. https://doi.org/10.1093/ajhp/zxz212.

Almeida, A. A. (2020) Lithium in biochemistry and therapeutics, Rev. Elem. Science, 8(03), 036. doi.org/10.24927/rce2020.036.

Alves, F. B. (2021). Lithium in the treatment of Bipolar Disorder: do the benefits outweigh the risks? Open Repository. https://repositorio-aberto.up.pt/bitstream/10216/134306/2/478761.pdf.

Baird-Gunning, J., Lea-Henry, T., Hoegberg, L. C., et. al. (2017). Lithium poisoning. Journal of critical care medicine, 32(4), 249-263. https://doi.org/10.1177/08850666166515.

Balen, E., Giordani, F., Fernandes, M. F. C., et al. (2017). Potential drug-drug interactions between psychotropic medications. Brazilian Journal of Psychiatry, 66(3), 172-177. https://doi.org/10.1590/0047-2085000000167.

Barros, M. G. de, & Duarte, F. S. (2020). Potential adverse reactions related to antipsychotics or antidepressants and associated drugs in patients at the “Esperança” Psychosocial Care Center (CAPS) in Recife. VITTALLE - Journal of Health Sciences, 32(1), 56–69. https://doi.org/10.14295/vittalle.v32i1.8793.

Bosaipo, N. B., Borges, V. F., & Juruena, M. F. (2017). Bipolar disorder: a review of conceptual and clinical aspects. Medicine (Ribeirão Preto), 50(1), 72-84. http://dx.doi.org/10.11606/issn.2176-7262.v50isupl1.p72-84

Brazil. Ministry of Health. ORDINANCE No. 3, OF MARCH 9, 2015. https://bvsms.saude.gov.br/bvs/saudelegis/sctie/2015/prt0003_09_03_2015.html.

Brazil. Ministry of Health. Recommendation Report. https://www.gov.br/saude/pt-br/assuntos/protocolos-clinicos-e-diretrizes-terapeuticaspcdt/arquivos/2016/pcdt_transtornoafetivobipolar_tipoi.pdf.

da Câmara, M. M. G. C., Araújo, C. S., Bianchi, M. W., et. al. (2020). Systematic literature review: Lithium in chronic renal failure associated with diabetes insipidus. Brazilian Journal of Health, 3(1), 758-764. https://doi.org/10.34119/bjhrv3n1-059.

El Balkhi, S., & Mégarbane, B. (2016). Lithium toxicity: Clinical presentations and management. In The Science and Practice of Lithium Therapy (1st ed.). Switzerland: Springer International Publishing.

Elisabetsky, E., Herrmann, A. P., Piato, A., et.al. (2021). Simplifying psychopharmacology: Psychotropic drugs for clinical and recreational use (1st ed.). Brazil: Blucher.

EUROFARMA. Products. 2023. https://eurofarma.com.br/produtos/buscar.

Ferensztajn-Rochowiak, E., Chłopocka-Woźniak, M., & Rybakowski, J. K. (2020). Ultra-long-term lithium therapy: all-important matters and a case of successful 50-year lithium treatment. Brazilian Journal of Psychiatry, 43(4), 407- 413. https://doi.org/10.1590/1516-4446-2020-1111.

Figueiredo, C., & Lemos, J. (2020). Lithium, an old friend and a forgotten enemy. Journal of the Brazilian Medical Association, 66(12), 1625-1627. https://doi.org/10.1590/1806-9282.66.12.1625

Friedrich, M. L., & Blattes, M. W. (2021). Psychotropic drugs in mental health: potential drug interactions in childhood and adolescence. Disciplinarum Scientia Health, 22(3), 35-47. doi.org/10.37777/dscs.v22n3-004

Fuster, E. G. (1997). Social support in community intervention. Buenos Aires: Paidos.

Fuster, E. G., Olaizola, J. H., Ochoa, G. M. (2002). Assessment of resources and psychosocial stressors in the community. Madrid: Synthesis.

Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2016). Bipolar disorder. The Lancet, 387(10027), 1561-1572. doi.org/10.1016/S0140-6736(15)00241-X.

. Hamid, O. I. A., Ibrahim, E. M., Hussien, M. H., et. al. (2020). The molecular mechanisms of lithium-induced cardiotoxicity in male rats and its amelioration by N-acetyl cysteine. Human and Experimental Toxicology, 39(5), 696-711. doi.org/10.1177/0960327119897759.

Kapczinski, F., Quevedo, J. (2016). Bipolar disorder: theory and clinical practice (2nd ed.). Porto Alegre: Artmed.

. Morriss, R. K., Mayo-Wilson, E., Meyer, T. D., et. al. (2016). NICE guidance on psychological treatments for bipolar disorder. The Lancet Psychiatry, 3(4), 317-320. doi.org/10.1016/S2215-0366(16)00082-1.

. Liu, X., Hatton, R. C., Zhu, Y., et. al. (2017). Consistency of psychotropic drug–drug interactions listed in drug monographs. Journal of the American Pharmacists Association, 57(6), 698-703. https://doi.org/10.1016/j.japh.2017.07.008

Lopes, M. M. (2019). Lithium - characteristics, occurrences, production and use. Federal Center for Technological Education of Minas Gerais. https://www.engminas.araxa.cefetmg.br/wpcontent/uplo.

Lerena, V. S., Leon, N. S., Sosa, S., et. al. (2022). Lithium and endocrine dysfunction. MEDICINE (Buenos Aires), 82(1), 130-137. https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1365137.

Malhi, G. S., Bell, E., Outhred, T., & Berk, M. (2020). Lithium therapy and its interactions. Australian Prescriber, 43(3), 91. doi.org/10.18773/austprescr.2020.024

McIntyre, R. S., & Calabrese, J. R. (2019). Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. Current Medical Research and Opinion, 35(11), 1993-2005. doi.org/10.1080/03007995.2019.1636017

Meleiro, A. M. A. S. Safe management of lithium. [s.l: s.n.]. https://siicsalud.com/pdf/ac_mc24_50818.pdf.pdf.

Mongui, J. E. (2019). Literature review on the toxic effects of pharmacological treatment with lithium carbonate in patients with bipolar disorder. Bogota: Technological Corporation of Bogota.

Mota, A. L., Neto, A. R., de Figueiredo, B. Q., et. al. (2021). Adverse reactions resulting from lithium carbonate treatment: a systematic literature review. Research, Society and Development, 10(11), e342101119853-e342101119853. doi.org/10.33448/rsd-v10i11.19853.

Öhlund, L., Ott, M., Oja, S., et. al. (2018). Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. BMC Psychiatry, 18, 1-10. doi.org/10.1186/s12888-018-1622-1.

Parizotti, S. M. D., Alves Filho, J. R., & de Peder, L. D. (2021). The use of lithium carbonate in bipolar affective disorder-an updated review. RECIMA21-Multidisciplinary Scientific Journal-ISSN 2675-6218, 2(9), e29774-e29774. https://doi.org/10.47820/recima21.v2i9.774

Pardini, H. (2015-2016). Examination manual (1st ed.). Brazil: Hermes Pardini.

Penha, S. R. L. N., Bezerra, G. C. I., Pereira, G. G., et. al. (2019). Adverse effects caused by the use of lithium carbonate in patients with bipolar affective disorder: a review of the literature: a review of the literature. Tocantins Journal of Pathology, 6(2), 65-69. doi.org/10.20873/uft.2446-6492.2019v6n2p65.

Perrone, J., Chatterjee, P. (2015). Lithium poisoning. Wolters Kluwer Health, p. 1–13. http://www.uptodate.com.

Pasqualotto, A., Bitencourt, P. E. R., Nietiedt, N. A., et. al. (2018). Interactions between drugs subject to special control dispensed at the Farmácia Distrital Centro de Porto Alegre, RS, Brazil. Infarma, 30(3), p. 146-151. doi.org/10.14450/2318-9312.v30.e3.a2018.pp146-151.

Quadros, A. D. O., & Brito Junior, L. C. D. (2022). Technical note no. 05/2022/UFPA/PPGAC. Advantages of the osmotic fragility test with samples analyzed after incubation for 24h at 37º C in a water bath. Federal University of Pará. http://repositorio.ufpa.br:8080/jspui/handle/2011/14491

Rosa, A. C. F., & Leão, E. R. (2021). Pain in bipolar disorder: prevalence, characteristics and relationship with suicide risk. Latin American Journal of Nursing, 29, e3463. doi.org/10.1590/1518-8345.4737.3463

Sadock, B. J.; SADACK, V. A.; Sussman, N. (2018). Kaplan & Sadock's Handbook of Psychiatric Pharmacology-6. Brazil: Artmed.

Sarai, S. K., Mekala, H. M., & Lippmann, S. (2018). Lithium suicide prevention: a brief review and reminder. Innovations in clinical neuroscience, 15(11-12), 30. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6380616/

Seeman, M. V.; Gonzalez-Rodríguez, A. (2018). Use of psychotropic medication in women with psychotic disorders at menopause and beyond. Current Opinion in Psychiatry, 31(3), p. 183-192. doi.org/10.1097/YCO.0000000000000410.

Silva, M. de F. da. (2015) Review of the Fragility Curve Technique. https://www.ciencianews.com.br/arquivos/ACET/IMAGENS/bibliotecadigital/hematology/ 43. standardizationshemato/18.pdf.

Silva, L. O. L., Dias, C. A., & Rosalino, F. U. (2017). Therapeutic procedures in bipolar affective disorder: an integrative review. Psychology and Health Journal, 9(3), 63-76. https://doi.org/10.20435/pssa.v9i3.386.

Tunc, E. B., & Tunc, S. (2022). Vortioxetine induced hypomania: a case presentation and review of the literature. Clinical Psychopharmacology and Neuroscience, 20(2), 394. doi.org/10.9758/cpn.2022.20.2.394.

Won, E., & Kim, Y. K. (2017). An oldie but goodie: lithium in the treatment of bipolar disorder through neuroprotective and neurotrophic mechanisms. International Journal of Molecular Sciences, 18(12), 2679. doi.org/10.3390/ijms18122679.

World Health Organization. ICD-11 Implementation or Transition Guide. Geneva, 2019. https://icd.who.int/browse/2024-01/mms/en#1563440232.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., et al. (2018) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disorder. 2018;20(2):97-170. doi:10.1111/bdi.12609.