HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 1 (2023)

The Various Methods to Prevent Lithium Toxicity in Treatment for Patients with Bipolar Disorder

Diksha Sriram[1] and Clara Liao[2#]

[1]Polygence
[2]Yale University
[#]Advisor

ABSTRACT

Bipolar disorder (BD) is a serious mental illness that leads to considerable shifts in mood, energy, and physical activity levels, impairing a person's ability to complete day-to-day tasks. About 4.4% of adults in the US report having experienced an episode of BD at least once in their life, and approximately 82.9% of people with BD are left severely impaired. To combat this, doctors prescribe lithium, which is an effective mood stabilizer that can regulate the extreme highs and lows of BD. However, lithium is a toxic substance when it exceeds the therapeutic range, requiring frequent trips to the hospital to evaluate blood lithium levels Such monitoring may not always be effectively feasible, especially for patients experiencing a mental health crisis or patients in rural areas without local medical facilities. Research studies have been conducted to provide patients with alternative methods to avoid lithium toxicity including ways to check the lithium levels on their own. Additionally, studies investigate the ideal dosing regimen to prevent toxic side effects, while others aim to prevent toxicity before it happens.

Introduction

Mental health research is often gravely overlooked in the field of neuroscience (Boston & Ma 02115 +1495-1000, 2016). Specifically, bipolar disorder (BD), is a mental illness that affects many individuals yet has minimal published research studies. BD, also known as manic-depressive disorder, leads to considerable shifts in mood, energy, and physical activity levels that impair a person's ability to complete day-to-day tasks. A survey conducted by the National Comorbidity Survey Replication (NCS-R) details that about 4.4% of adults in the U. S. from 2001-2003 experienced BD at some time in their lives. While this number is a seemingly small percentage, this percentage makes up a substantial part of the U. S. population. Furthermore, approximately 82.9% of people with BD are severely impaired in terms of their ability to complete everyday tasks, such as simply getting out of bed (NIMH » bipolar disorder, n. d.). Patients are typically quickly villainized due to their inability to control mood swings, leaving them untreated and isolated. Patients that can seek help are typically prescribed lithium (Lithibod or Eskalith in pill form once or multiple times a day) to manage their illness as it is an effective mood stabilizer. Lithium can regulate the extreme mood swings characteristic of BD by regulating cell signaling pathways. Due to the slim therapeutic range of 0.6-1.0 mEq/L of lithium in the blood as well as the erratic fluctuation of lithium levels, patients on lithium treatment must make frequent trips to the hospital for blood tests in order to prevent lithium toxicity (bipolar disorder | NAMI: National Alliance on Mental Illness, n. d.). Realistically, these hospital visits are not feasible for all patients, especially those experiencing an imminent mental health crisis or individuals with less socioeconomic stability and medical resources.

Studies have been performed to resolve the frequency of lithium toxicity in treatment for BD patients. This review outlines the details of lithium toxicity as well as the strengths and weaknesses of various models that have been created to combat it. The first section explains the behaviors and effects typical of BD, as well as the current status of lithium treatment for patients. The second section discusses lithium toxicity in detail, including how the drug can

affect a patient physically and mentally. A key issue is the importance of how long patients need to achieve a therapeutic dose, often requiring frequent visits to the hospital. The final section discusses various methods that have attempted to reduce or eliminate lithium toxicity in patients. These approaches are a vital baseline toward progress for patients who struggle with lithium toxicity.

Section I: Bipolar disorder and the status of lithium treatment for patients

1.1: Basic behaviors and effects of bipolar disorder

Bipolar disorder is a mental health condition that causes extreme mood swings and includes emotional highs (mania) and lows (depression). Mania and hypomania entail feeling euphoric, full of energy, or unusually irritable. Conversely, states of depression leave patients feeling sad and hopeless, causing them to lose interest in most activities. The combination of these symptoms negatively affect sleep, energy, activity, judgment, behavior, and the ability to think clearly (Bipolar Disorder - Symptoms and Causes, n. d.). BD is diagnosed when a patient has experienced manic or hypomanic episodes that can be brought on by genetics, stress, or neurobiology. While both manic and hypomanic episodes are a subcategory of mania, manic episodes are severe occurrences that last for a week or more, while hypomanic episodes only last for a few days. Manic periods are characterized by impulsive behavior, reckless decisions, and unusual risks. These risks include the imminent danger of suicide because patients experiencing a manic episode are unaware of the negative consequences of their actions. Conversely, a depressive episode can often be detrimental to where a patient cannot get out of bed. Some patients experiencing a depressive episode may struggle to fall asleep and stay asleep while others sleep much more than average. For an individual in a depressive episode, minor decisions can become extremely overwhelming, and feelings of loss, personal failure, guilt, or hopelessness can also lead to thoughts of suicide (Bipolar Disorder | NAMI: National Alliance on Mental Illness, n. d.). According to the DSM 5, bipolar disorder is categorized into four types: Bipolar I disorder, Bipolar II disorder, Cyclothymic disorder, and "other" or "unspecified" bipolar disorder. A bipolar I disorder diagnosis is assigned to patients that have had at least one manic episode surrounded by a major depressive or hypomanic episode. Bipolar II disorder is assigned to patients who have had one major depressive episode and at least one hypomanic episode, but not a manic episode. Cyclothymic disorder means that a patient has had many periods of hypomania symptoms and periods of depressive (less severe than major depression) symptoms for at least two years for adults, and one year for teenagers and children (Bipolar Disorder - Symptoms and Causes, n. d.).

1.2: Overview of lithium treatment

Lithium, the mainstay treatment for BD, is the lightest of all alkali metals, having a density that is only half that of water. Lithium's mechanism of action lies within its ability to induce various biochemical and molecular effects on neurotransmitter/receptor-mediated signaling, gene expression, signal transduction cascades[1], hormonal, and circadian regulation (Machado-Vieira et al., 2009). In other words, mechanisms involved in lithium treatment replicate functions that are biologically disrupted due to BD (Won & Kim, 2017). Historically, lithium has been known to be effective at treating acute mania and depressive episodes (Carter et al., 2013). Lithium effectively reduces the frequency of severe mood episodes and suicidal behaviors. To further demonstrate these ramifications, a research group studied euthymic[2] BD patients treated with lithium were compared to healthy and untreated controls for the ability to assess safe and advantageous decision-making (Adida et al., 2015). Participants were asked to make a series of 100

[1] Molecular circuits that detect, amplify, and integrate external signals in order to generate beneficial responses that mediate the sensing and processing of stimuli (Berg et al., 2002)

[2] Patients in a tranquil mental state (Adida et al., 2015)

choices from four different decks of cards with no prior information on them aside from the knowledge that some are parlous compared to others. The goal of the experiment was to determine if patients would choose the superior deck through their preceding experience and memory. Control participants and BD patients on lithium treatment were found to select significantly more cards from the safe decks than patients who were not on lithium treatment, as shown in Figure 1 (Adida et al., 2015). The patients' behavior in picking more cards from the safe decks show that since the controls and patients on lithium treatment had no statistically significant difference between them, they show comparable decision-making behaviors.

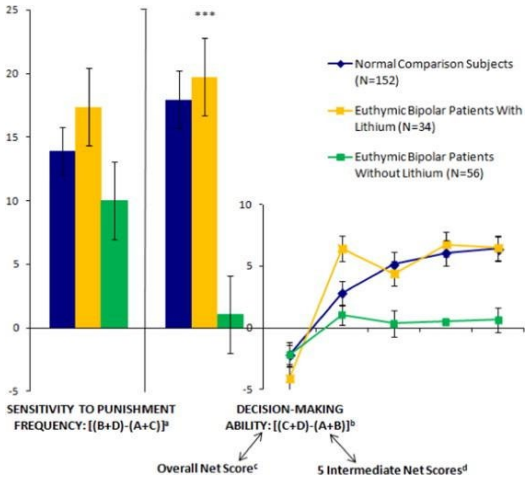

Figure 1. The bar graph displays the results of a decision-making task – BD patients treated with lithium compared to untreated control patients (Adida et al., 2015)

It is vital to note that euthymic BD patients on lithium treatment also had lower suicide attempts, fewer feeding and eating disorders, and less obsessive-compulsive related disorders (Adida et al., 2015). Lithium continues to demonstrate its ability to reverse pathophysiological[3] changes such as increased oxidative stress, endoplasmic reticulum dysfunction, and environmental stress (Machado-Vieira et al., 2009). The key to keeping a patient in a euthymic state is regular monitoring of lithium levels in the blood to ensure they remain within the recommended therapeutic range.

1.3: The use of flame photometry in hospitals

Flame photometry is an inorganic chemical analysis primarily used to determine the concentration of metal ions, specifically lithium, in a solution. This is done by dissociating the alkali metals and alkaline earth metals using a thermal energy flame (*Flame Photometry (Theory): Inorganic Chemistry Virtual Lab: Chemical Sciences: Amrita Vishwa Vidyapeetham Virtual Lab*, n. d.). For BD patients, this method is used by medical labs to monitor lithium levels in the blood to prevent lithium toxicity. A flame photometer is made up of a flame source, nebulizer, mixer chamber, optical system/filter, and photo detector. First, a flame photometer evaporates the solvent, leaving solid particles behind. These solid particles are heated in the flame to produce gaseous atoms and ions, absorbing energy from the flame to excite electrons to higher energy levels. Upon returning to the ground state, the electrons within the atoms emit electromagnetic radiation specific to wavelengths of their element. The intensity of emitted light at specific wavelengths is used to measure the concentration of that element (*Flame Photometry (Theory): Inorganic Chemistry Virtual Lab: Chemical Sciences: Amrita Vishwa Vidyapeetham Virtual Lab*, n. d.). Flame photometry is used for

[3] Disordered psychological processes associated with disease or injury (Machado-Vieira et al., 2009)

multiple metal ions in a hospital setting, suggesting that measurements could be inaccurate and/or imprecise due to the detection of multiple ion concentrations being measured at once (Qassem et al., 2019). Precision is crucial for BD patients because the therapeutic, non-toxic range of lithium is narrow, between 0.6-1.0 mEq/L. With such an urgency in reporting test results, patients may not be able to wait for the long turnaround time of flame photometry results, which could take a full day (Qassem et al., 2019). Furthermore, flame photometry is not always even available at every hospital due to its high cost. However, patients must monitor their lithium levels at the hospital as frequently as every 3-4 months in addition to renal and thyroid function tests that must be conducted every 2-3 months (Shah et al., 2017). This places a high barrier to safe usage and can result in a higher rate of toxicity or medical nonadherence.

Section II: Lithium toxicity and subsequent damaging effects

2.1: Physical side effects of treatment for patients

Therapeutic concentrations of lithium in the blood must remain between 0.6-1.0 milliequivalents per liter (mEq/L). Concentrations above that range may result in lithium toxicity. Lithium toxicity can lead to weight gain and cognitive impairment as well as damaging effects on the kidneys, renal system, thyroid gland, and parathyroid glands (Gitlin et al., 2016). In severe cases, concentrations in blood at or above 2.0 mEq/L could result in death. Maintaining a therapeutic range can be impacted by salt intake, caffeine, and drug usage (Novell et al., 2014). The toxicity of lithium includes symptoms that are commonly thirst, excessive urination, nausea, diarrhea, and tremor. Nausea, found in 10-20% of patients on treatment, is more prevalent early on and a tolerance can be developed overtime. Diarrhea normally develops after six months of treatment. Tremors are the most common side effect. BD patients have symmetric hand tremors, making it difficult to distinguish between essential (caused by a nervous system disorder) and physiological (present in all people under certain conditions) tremors (Gitlin, 2016).

All potential side effects can lead to medical nonadherence. Multiple factors could influence the severity of side effects. These factors include misidentifying the patients' symptoms as due to a different disease, drug interactions that impact the effectiveness of lithium, or taking another prescribed drug that can induce synergistic or antagonistic effects. Most research on negative drug interactions focuses on the depression aspect of BD (Gitlin, 2016).

2. 2: Mental side effects of treatment for patients

The main side effects of lithium treatment are physiological, but sometimes it may accompany psychological detriments as well. Lithium is highlighted as an important treatment because of its ability prevent suicidal thoughts that may be otherwise fatal for an untreated BD patient. However, some patients avoid getting treatment altogether to avoid the frustration of frequent mandatory visits for testing at medical facilities (Qassem et al., 2019). Continual hospital visits can also make a patient feel discouraged because it might appear that they do not have control over their treatment. An instance of discouragement can also cause a patient to take even more lithium in a bid to feel in control of their illness. Exceeding therapeutic concentration can lead to severe side effects and even the aforementioned potentially terminal effects (Qassem et al., 2019).

2. 3: Detrimental effects on the renal system

Lithium can cause damage to the renal system. Specifically, it harms the tubular function of the kidneys, which returns nutrients, fluids, and other substances that have been filtered from the blood that the body needs back to it. Harm to the kidneys often leads to polyuria, which is the production of abnormally diluted urine (Carter et al., 2013). Polyuria is caused by the reduction of aquaporins (channels that transfer water) in the cellular membrane of collecting duct cells (cells in the kidney that influence the body's electrolyte and fluid balance). Due to the reduction in aquaporin

channels, patients receiving lithium have shown a 15% reduction in maximum urinary output when compared with control patients (BD patients who were not taking lithium) (Carter et al., 2013). Lithium toxicity on the renal system are dependent on the dose and duration of treatment. Exposure to increased lithium levels in the blood increases the chances for a patient to develop End-Stage Renal Disease (ESRD)[4] from 6 to 8-fold. Recent studies have reported increasing instances of solid renal tumors in persistent lithium users as compared to the general healthy population (Alsady et al., 2016). Therefore, lithium's harmful effects on the renal system are among the most prominent repercussions of treatment.

Nationwide, prescriptions for lithium treatment continually decrease due to the high risk of toxicity and difficulty in obtaining precise medical laboratory tests (Machado-Vieira et al., 2009). However, available evidence concerning lithium treatment suggests that many patients should primarily be treated with lithium due to its anti-suicidal properties. In fact, current research shows that lithium may be the only treatment that reverses suicidal thoughts and tendencies (Sani et al., 2017). Thus, it is critical to find a method of monitoring and measuring lithium concentration in the blood.

Section III: Attempts to resolve the prevalence of lithium toxicity

3.1: Improvement and updates to the dosing regime

The optimal dosing regimen for lithium treatment is still uncertain, due to dosing instructions being contradictory between prescribers. To address this, Carter et al. (2013) performed a meta-analysis of 20 published trials that contained search terms like, "lithium," "drug administration schedule," "dose-response relationship," "once-daily," "twice daily," and "sustained release." These trials investigated the various options for dosing: immediate and single release products, schedules for single daily dosing (SDD), multiple daily doses 2-4 times a day (MDD), and alternate daily doses. Results showed that a SDD improved compliance to lithium treatment and patients' tolerability profile. If lithium is taken once before bed, it could allow for side effects to occur during the sleep cycle and minimize the effect of drowsiness and nausea. In the first set of trials that were analyzed, lower urine volumes were found in the SDD group (2380 mL in 24 hours) compared to the 2830 mL in 24 hours for MDD patients (P=0. 05). Less frequent lithium administration was also associated with lower urine volume. However, the groups in this trial were not well matched with each other for a fair trial, since the urine collection method differed between groups, and the therapeutic history of individuals in the SDD group differed, making the data less reliable. Trial sets 2 and 3 observed lower negative side effects such as thirst and diarrhea with SDD. A major concern with these studies is that the patients were already stabilized on lithium at the time of experimentation, making it possible that irreversible renal damage may have already occurred, causing a false reduction in urinary output. Trial set 4 looked into alternate daily doses and concluded that it is not effective for severe cases of BD. Results did not indicate the impact on less severe cases of BD.

In summary, there were no trials where SDD was found to worsen symptoms, and SDD regimens were typically well tolerated. Therefore, it was recommended that patients take their single daily dose prior to sleeping. Unfortunately, the studies used were dated and contained multiple limitations. The conclusions reached by Carter et al. (2013) are considered unreliable and did not address the problem of preventing lithium toxicity, just managing it once it had occurred.

[4] A medical condition where a person's kidneys cease functioning on a permanent basis (Alsady et al., 2016)

3.2: Potential methods to create personalized testing devices

While research on lithium treatment is sparse, studies have been conducted that aim to develop methods for patients to measure lithium concentrations in the blood without traveling to the hospital. These methods involve colorimetry, optical spectroscopy, and electrical impedance. By finding such a method, it is possible to create a personalized sensor. A personalized sensor for patients would result in the option for less frequent hospital trips and the ability to get quicker medical attention by detecting a toxic concentration early on.

Colorimetry is a method used to determine the concentration of colored compounds within a solution. A study by Qassem et al. (2016) presented results when using a colorimetric based method and testing human plasma that had been spiked with lithium. The goal of the study was to develop a personal lithium blood level analyzer. It was hypothesized that colorimetric determinations of lithium concentration in drops of human plasma may produce accurate concentration predictions. 60 mEq/L (milliequivalents per liter) lithium carbonate solutions in saline were prepared and diluted. Frozen mixed pool blood plasma from healthy individuals was used for testing. A total of 8 samples with lithium concentrations ranging from 0. 6-2. 0 mEq/L were tested using a spectrophotometer. After using the optical spectrophotometer, the spiked samples containing the highest amount of lithium had more intense absorptions of light. The resulting spectra of the procedure showed variations related to lithium (Qassem et al., 2016).
Figure 2 displays the accuracy of the wavelengths and measurements taken by the spectrophotometer. Partial Least-Squares calibration showed a high correlation coefficient and a low root mean error, providing the data with reliability. This indicates the possibility of reducing the required wavelengths to measure lithium levels into a small, personalized sensor. Future work for this study included improving the predictability of calibration by testing it on unknown samples and building miniaturized systems that would still provide accurate readings of lithium (Qassem et al., 2016).

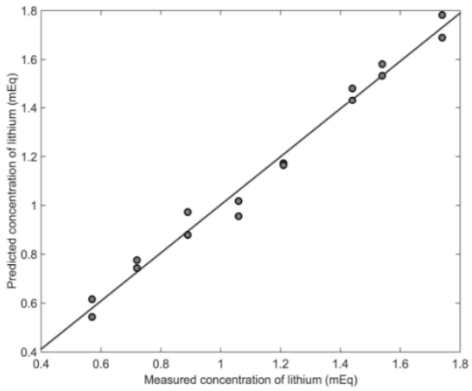

Figure 2. This graph shows the comparison between actual measurements of lithium in the sample as compared to the measurement read using the specific wavelengths found using the Partial-Least Squares Regression method (Qassem et al., 2016)

Another study conducted by Qassem et al. (2019) aimed to use a combination of optical methods and electrical impedance to create a method for patients with BD to check the lithium levels in their blood from home. It was hypothesized that the combination of optical and electrical impedance spectroscopy would provide both the sensitivity and specificity required to track lithium concentration in the blood. Optical spectroscopy is how matter interacts with electromagnetic radiation, while electrical impedance measures the resistance of a current, providing-high sensitivity to changes. A flame photometer was used to verify the lithium concentration in the samples used. Results deeming the measurements from the experiment as similar to those from the flame photometer. The experiment concluded that optical and electrical impedance analysis can work together to provide specificity and accuracy in lithium blood content when compared to medical laboratory protocols. The researchers also mentioned creating a small, personal device

using this method, which would allow patients to monitor their own blood lithium level, providing a measure of control over their disease (Qassem et al., 2019). As opposed to the team's 2016 study, the method of spectroscopy and electrical impedance provided more precise measurements of lithium concentrations, which is crucial because the therapeutic range is narrow. One drawback to this method is the use of blood samples to measure lithium levels, an invasive procedure that may not be feasible for unstable patients or their caregivers.

3.3: Alternatives to lithium treatment

A straightforward solution to prevent lithium toxicity would be to implement a different treatment altogether. Antidepressants in combination with antimanic or antipsychotic medications are viewed as potential alternatives for long-term treatment of BD, though the efficacy may be compromised (Sani et al., 2017). Many limitations arise with the use of other treatments.

Traditional antidepressants on their own come with their own risks and side effects. Some antidepressants may increase the risk of switching between mania and depression, creating a rapid cycle acceleration (Ott, 2018). Antidepressants may also lead to the onset of mixed depressive states that are more severe and suicidal than non-mixed depressive states. Furthermore, these mixed depressive states are less likely to respond to any drug treatment altogether.

Some studies have shown that antipsychotics such as quetiapine may be a viable alternative treatment as they are effective in treating acute bipolar depression (Sani et al., 2017). Valproate, an anticonvulsant, is an FDA-approved drug for the treatment of acute mania. Multiple studies have indicated that it has preventive effects against recurrences of acute mania and depression (Post et al., 1998). However, in a 1995 study, only 50% of BD patients showed a greater response rate than they did to lithium, suggesting that lithium may still be a more effective treatment despite its limited therapeutic dosage range. It seems that antipsychotic drugs are still most effective in treating BD when used in combination with lithium treatment, which once again highlights the necessity for ensuring safe usage of lithium treatment (Sani et al., 2017).

Conclusion

There are currently no available methods for patients to check lithium levels on their own, especially those with lithium levels outside of the therapeutic range. Qassem et al. (2019) investigated methods using optical spectroscopy and electrical impedance, which proved to be accurate and precise, although invasive. These methods stemmed from an earlier experiment using colorimetric methods and spectrophotometry, which introduced the possibility of a personal device for patients to use and the prevention of frequent hospital visits (Qassem et al., 2016). Other researchers focused on minimizing the damage to the renal system once lithium toxicity occurred, which was done by identifying the optimal dosing regimen for patients (Carter et al., 2013). Once the optimal dosing regimen was identified, side effects like nausea, diarrhea, and hand tremors could be minimized (Gitlin, 2016). While lithium remains highly toxic, it is the best therapeutic agent for patients struggling with BD for its multitude of benefits on decision-making, reduction in suicidal thoughts, and prevention of risky behaviors caused by BD (Adida et al., 2015). It is important to note, however, that lithium toxicity may still develop, even within the therapeutic range in the blood (Sani et al., 2017).

Future steps in researching lithium treatment also include determining a way to predict the efficacy of lithium treatment for different subtypes of BD (Won & Kim, 2017). It is also important to be able to determine the difference between non-responsiveness and medical nonadherence to medication. Identifying these biomarkers allows for the creation of customized individual treatments for subtypes. (Scott et al., 2018). In doing so, lithium treatment will only be used when necessary and effective, thereby reducing cases of lithium toxicity.

BD is a serious mental illness for which treatment is a major challenge. Identifying a method for patients to track their lithium levels is a step closer to providing autonomy, a sense of control over their disease, and recognizing the importance of mental health treatment advances in the scientific community.

References

Adida, M., Jollant, F., Clark, L., Guillaume, S. , Goodwin, G. M., Azorin, J. -M., & Courtet, P. (2015). Lithium might be associated with better decision-making performance in euthymic bipolar patients. *European Neuropsychopharmacology*, *25*(6), 788–797. https://doi. org/10. 1016/j. euroneuro. 2015. 03. 003

Alsady, M. , Baumgarten, R. , Deen, P. M. T. , & de Groot, T. (2016). Lithium in the Kidney: Friend and Foe? *Journal of the American Society of Nephrology : JASN*, *27*(6), 1587–1595. https://doi. org/10. 1681/ASN. 2015080907

Berg, J. M. , Tymoczko, J. L. , & Stryer, L. (2002). Signal-Transduction Pathways: An Introduction to Information Metabolism. *Biochemistry. 5th Edition*. https://www. ncbi. nlm. nih. gov/books/NBK21205/

Bipolar disorder | NAMI: National Alliance on Mental Illness. (n. d.). Retrieved November 7, 2021, from https://www. nami. org/About-Mental-Illness/Mental-Health-Conditions/Bipolar-Disorder/Treatment

Bipolar disorder—Symptoms and causes. (n. d.). Mayo Clinic. Retrieved October 20, 2021, from https://www. mayoclinic. org/diseases-conditions/bipolar-disorder/symptoms-causes/syc-20355955

Boston, 677 Huntington Avenue, & Ma 02115 +1495-1000. (2016, February 11). *Global burden of mental illness underestimated*. News. https://www.hsph.harvard.edu/news/hsph-in-the-news/global-burden-of-mental-illness-underestimated/

Carter, L. , Zolezzi, M. , & Lewczyk, A. (2013). An Updated Review of the Optimal Lithium Dosage Regimen for Renal Protection. *The Canadian Journal of Psychiatry*, *58*(10), 595–600. https://doi. org/10. 1177/070674371305801009

Flame Photometry (Theory): Inorganic Chemistry Virtual Lab: Chemical Sciences: Amrita Vishwa Vidyapeetham Virtual Lab. (n. d.). Retrieved October 24, 2021, from https://vlab. amrita. edu/?sub=2&brch=193&sim=1351&cnt=1

Gitlin, M. (2016). Lithium side effects and toxicity: Prevalence and management strategies. *International Journal of Bipolar Disorders*, *4*(1), 27. https://doi. org/10. 1186/s40345-016-0068-y

Machado-Vieira, R. , Manji, H. K. , & Zarate, C. A. (2009). The role of lithium in the treatment of bipolar disorder: Convergent evidence for neurotrophic effects as a unifying hypothesis. *Bipolar Disorders*, *11*(Suppl 2), 92–109. https://doi. org/10. 1111/j. 1399-5618. 2009. 00714. x

McKnight, R. F. , Adida, M. , Budge, K. , Stockton, S. , Goodwin, G. M. , & Geddes, J. R. (2012). Lithium toxicity profile: A systematic review and meta-analysis. *The Lancet*, *379*(9817), 721–728. https://doi. org/10. 1016/S0140-6736(11)61516-X

NIMH » Bipolar Disorder. (n. d.). Retrieved November 7, 2021, from https://www. nimh. nih. gov/health/statistics/bipolar-disorder

Novell, M. , Guinovart, T. , Blondeau, P. , Xavier Rius, F. , & J. Andrade, F. (2014). A paper-based potentiometric cell for decentralized monitoring of Li levels in whole blood. *Lab on a Chip*, *14*(7), 1308–1314. https://doi. org/10. 1039/C3LC51098K

Ott, C. A. (2018). Treatment of anxiety disorders in patients with comorbid bipolar disorder. *The Mental Health Clinician*, *8*(6), 256–263. https://doi.org/10.9740/mhc.2018.11.256

Post, R. M., Frye, M. A., Denicoff, K. D., Leverich, G. S., Kimbrell, T. A., & Dunn, R. T. (1998). Beyond Lithium in the Treatment of Bipolar Illness. *Neuropsychopharmacology*, *19*(3), Article 3. https://doi.org/10.1016/S0893-133X(98)00020-7

Qassem, M. , Constantinou, L. , Triantis, IasonasI. F. , Hickey, M. , Palazidou, E. , & Kyriacou, P. A. (2019). A Method for Rapid, Reliable, and Low-Volume Measurement of Lithium in Blood for Use in Bipolar Disorder Treatment Management. *IEEE Transactions on Biomedical Engineering*, *66*(1), 130–137. https://doi. org/10. 1109/TBME. 2018. 2836148

Qassem, M. , Hickey, M. , & Kyriacou, P. A. (2016). Colorimetric determinations of lithium levels in drop-volumes of human plasma for monitoring patients with bipolar mood disorder. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*, *2016*, 5160–5163. https://doi. org/10. 1109/EMBC. 2016. 7591889

Sani, G., Perugi, G., & Tondo, L. (2017). Treatment of Bipolar Disorder in a Lifetime Perspective: Is Lithium Still the Best Choice? *Clinical Drug Investigation*, *37*(8), 713–727. https://doi.org/10.1007/s40261-017-0531-2

Shah, N. , Grover, S. , & Rao, G. P. (2017). Clinical Practice Guidelines for Management of Bipolar Disorder. *Indian Journal of Psychiatry*, *59*(Suppl 1), S51–S66. https://doi. org/10. 4103/0019-5545. 196974

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. https://doi.org/10.3390/ijms18122679