Lithium – A History

Samantha Tracy

Cummings Graduate Institute for Behavioral Health Studies

DBH 9010: Psychopharmacology

Dr. Janet Cummings

May 14, 2022

Lithium – A History

Lithium is the third element found on the periodic table; the lightest metal. It is also one of the oldest elements, as one of the three created during the Big Bang. The most common use for lithium is in the manufacture of batteries and machinery. But in salt form, lithium is a common and effective medication for bipolar disorder. While efficacy of lithium as a mood stabilizer has never been in question, the cost-benefit ratio due to side effects has. The debate continues in scientific literature.

History

Lithium is a naturally occurring element found all over the globe. Thousands of years ago, mineral baths (i.e., Lithium baths) were recommended by the likes of Galen and Hippocrates for the treatment of manic and depressive states (Bekker & Bykov, 2019). During the seventeenth century, Danish scientists and brothers, Carl and James Lange, “rediscovered” lithium salts as a treatment for manic depression (Malhi & Outhred, 2017). A World War II POW, John Cade, spends his time as a prisoner developing a disease theory of mental illness and the use of lithium salts as a treatment for psychiatric symptoms (2017). None of these great minds understood the mechanism of action of lithium on mood disorders, because that is still an unknown today.

Mechanism of Action

Although lithium is the oldest psychiatric medication, scientists are still not sure of the mechanism of action (Preston, O’Neal, & Talaga, 2021). Researchers believe lithium limits dopamine receptor sensitivity, resulting in reducing manic symptoms. Lithium may also increase serotonin production, resulting in improving depressive symptoms. As stated above, the exact mechanism of action is not known, but scientists believe lithium disrupts phosphoinositol and cyclic AMP second messenger systems (Jope, 1999). In doing so, the creation of protein kinase C (PKC) is disrupted. Excess PKC is theorized to be a cause of manic symptoms.

New research is being conducted to determine the neurorestorative qualities of lithium. Bipolar disorder has been linked to reduced gray matter volume, leading to neurocognitive decline. However, long-term lithium treatment has shown an increase in gray matter volume (Abu-Hijlah, et. Al, 2021). Because of this discovery, lithium is now being researched as a potential treatment for degenerative disorders such as Alzheimer and Parkinson’s. The mechanism for action for this feature of lithium treatment is also unknown. Abu-Hijlah, et. Al. (2021) posit lithium “modulates endoplasmic reticulum stress proteins”. Malhi & Outhred (2017) write that the neuroprotective properties are due to the initiation and maintenances of a “cascade of cellular processes” over time.

Lithium may also affect actual brain structures as seen in MRI studies. Lopez, et. Al (2017) report evidence of altered brain structures in persons diagnosed with bipolar disorder, specifically the amygdala and hippocampus. In reviewing MRIs of patients before and after two years of lithium therapy, show increased volume of the amygdala, hippocampus, and thalamus structures. Lopez, et al, suggest lithium monotherapy may cause regeneration of brain structures.

Benefits of Lithium

Lithium is the gold standard for bipolar disorder treatment. Not only does lithium provide acute treatment of mania symptoms and suicidality, but long-term treatment can also reduce future mood episodes (Malhi, et al, 2020). Lithium is effective in reducing suicide deaths in persons with bipolar disorder. In regards to effectiveness, Bauer, et al (2016) found that lithium treatment resulted in significantly less hospitalizations than second generation antipsychotics, the alternative treatment option.

Lithium is not a patented pharmaceutical, leading to low costs. According to drugs.com, Lithium is, on average, sold at 22 cents per pill. In comparison, the alternative medications for bipolar disorder, the second-generation antipsychotics, are all patented. Even the generic versions, such as aripiprazole, risperidone, and olanzapine have higher costs than lithium per pill.

Side effects of Lithium

Lithium has a very narrow therapeutic window from effectiveness to toxicity. Within that window, the benefits reported above take place. There are side effects within the therapeutic window, often during initiate of medication. Common side effects include gastrointestinal distress, fatigue, weight gain, and polyuria (Preston, O’Neal, & Talaga, 2021). Long term use may result in hypothyroidism, which can be treated with thyroid medication, and renal dysfunction.

Toxicity levels start at 1.5 mEq/l serum levels. Toxicity may result in slurred speech, confusion, seizure, and eventually death. Because of the risk of toxicity, regular blood serum monitoring is necessary. While inconvenient, monitoring provides quantitative measurement of levels to provide the most effective treatment (Malhi, et.al, 2020).

Conclusion

Is lithium a wonder drug? If used correctly and monitored regularly, maybe. No other medication or treatment has been found to reduce suicidality with rates compared to lithium. Safe dosing and monitoring results in limited side effects. Each prescriber and patient need to communicate a cost benefit analysis for their situation.

Throughout history, lithium has proven itself as a gold standard medication for bipolar disorder. Although side effects, specifically those at the toxic level are to be avoided, overall, the use of lithium as an effective mood stabilizer has been proven. Decades of research shows the effectiveness, and continued research will explore the other facets of lithium therapy.

References

Abu-Hijleh, F.A., Prashar, S., Joshi, H., Sharma, R., Frey, B.N., & Misra, R.K. (2021). Novel mechanism of action for the mood stabilizer lithium. *Bipolar Disorders, 23*(1), 76-83. https//doi.org/10.1111/bdi.13019

Bauer, M.S., Miller, C.J., Li, M., Baior, L.A., & Lee, A. (2016). A population-based study of the comparative effectiveness of second-generation antipsychotics vs older antimanic agents in bipolar disorder. *Bipolar Disorders, 18*(6). 481-489. <https://doi.org/10.1111/bdi.12425>

Bekker, R.A., & Bykov, Y.V. (2019). Lithium preparations in psychiatry, addiction medicine, and neurology. (To the 70th anniversary of John Cade’s discovery). Part 1. History. *Acta Biomedica Scientifica, 4*(1). 72-80. <https://doi.org/10.29413/ABS.2019-4.1.11>

Jope, R.S. (1999). A bimodal model of the mechanism of action of lithium. *Molecular Psychiatry, 4*(1), 21-25. <https://doi.org/10.1038/sj.mp.4000444>

Lopez, J.C., Vargas, C., Diaz, Z.A.M., Palacio, J.D., Castrillon, G., Bearden, C., & Vieta, E. (2017). Increased hippocampal, thalamus and amygdala volume in long-term litium- treated bipolar 1 disorder patients compared with unmedicated patients and healthy subjects. *Bipolar Disorders, 19*(1), 41-49. <https://doi.org/10.1111/bdi.12467>

Malhi, G.S., Bell, E., Boyce, P., Hazell, P., Murray, G., Bassett, D., Bryant, R.A., Hopwood, M., Lyndon, B., Mulder, R., Porter, R.J., Singh, A., & Gershon, S. (2020). Make lithium great again! *Bipolar Disorders, 22*(4), 325-327. <https://doi.org/10.1111/bdi.12942>

Malhi, G.S., & Outhred, T. (2017). Lithium Therapy, Bipolar Disorder – and Neurocognition. *Psychiatric Times, 34*(1), 1-5.

Preston, J., O’Neal, J.H., & Talaga, M.C. (2021). *Handbook of clinical psychopharmacology for therapists.* (Ninth edition.) New Harbinger Publications, Inc.