Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medicine

Effects at the Thyroid Level of the use of Lithium in Bipolar Patients

Daniela Carolina Salcedo Restrepo[1*], Diego Alexander Rios Dussan[2], Ludin Alexandra Rueda Becerra[3], Cindy Goretti Thola Pérez[4], Luis José Payares Celins[5], Ricardo Antonio Rendón Muñoz[6], Claudia Alejandra Benavides López[7], María Alejandra Marzola Villalba[8]

[1]General Physician, Universidad del Sinú, Montería
[2]General Physician, Universidad Militar Nueva Granada, Bogotá
[3]General Physician, Universidad de Santander, Colombia
[4]Physician Epidemiologist, Universidad Autónoma de Bucaramanga, Colombia
[5]General Physician, Universidad de Sucre
[6]General Physician, Uniremington de Medellín
[7]General Physician, Universidad Cooperativa de Colombia
[8]General Physician, Universidad del Sinú, Cartagena

DOI: 10.36347/sjams.2021.v09i12.005 | **Received:** 29.10.2021 | **Accepted:** 03.12.2021 | **Published:** 10.12.2021

***Corresponding author:** Daniela Carolina Salcedo Restrepo

Abstract **Original Research Article**

Background*:** Mood disorders also known as affective disorders include unipolar and bipolar disorders. Manic-depressive disorder, more contemporary identified as bipolar disorder, is a chronic and complex disorder. Mood stabilizers and antipsychotics are the mainstay of acute treatment for bipolar mania and depression. Lithium is the gold standard for treating bipolar disorder**.** ***Methodology: A narrative review was carried out through various databases from January 2009 to November 2021; the search and selection of articles was carried out in journals indexed in English. Keywords were used: Thyroid; lithium; bipolar; Thyroiditis; Goiter; Hypothyroidism. ***Results:*** Lithium is abundantly present at the thyroid level, the uptake of iodine being reduced. Causing as a collateral effect the increase in TSH, increasing uptake. These various alterations caused by lithium can lead to developing goiter and hypothyroidism, being the most frequent. ***Conclusions:*** This review offers an updated approach to the pathophysiological mechanisms caused by lithium as well as the main alterations produced by it.

Keywords: Thyroid; lithium; bipolar; Thyroiditis; Goiter; Hypothyroidism.

Copyright © 2021 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

INTRODUCTION

The "state of mind" is defined as a pervasive and sustained feeling or emotion that dominates a person's behavior and affects the perception of it [1]. Mood disorders also known as affective disorders include unipolar and bipolar disorders [1, 2].

Manic-depressive disorder, more contemporaneously identified as bipolar disorder, is a chronic and complex mood disorder characterized by a combination of manic, hypomanic, and depressive episodes, with subsyndromic symptoms existing between mood episodes [2, 3].

In acute management, the main objectives are to guarantee the safety of patients and those close to them, to achieve clinical and functional stabilization with the fewest possible adverse effects [4, 5].

Mood stabilizers and antipsychotics are the mainstay of acute treatment for bipolar mania and depression [6]. Mood stabilizers are the main pharmacological agents for the treatment of bipolar affective disorder, especially in the maintenance phase of mania [7, 8].

Lithium is the gold standard for treating bipolar disorder, as long-term use has been shown to reduce the risk of suicide. Lithium was the first mood stabilizer and remains the first-line treatment option. The mechanism of action of lithium is unknown [7, 8, 9]. It is rapidly absorbed, has a small volume of distribution, and is excreted unchanged in the urine. Lithium Alters the metabolism of neurotransmitters, specifically catecholamines and serotonin [10, 11].

Lithium can cause several adverse effects, depending on the dose. Among which we find many endocrinological and metabolic alterations, but in order

not to make this work extensive, we want to focus on the thyroid effects caused by lithium, since they are among the most frequent endocrinological alterations. For this reason we want to carry out this work to identify the most recent studies on the effects of lithium at the thyroid level, in order to provide updated and accurate information available to date.

MATERIALS AND METHODS

A narrative review was carried out, in which the PubMed, Scielo and ScienceDirect databases, among others, were searched. The collection and selection of articles was carried out in journals indexed in English from 2009 to 2021. As keywords, the following terms were used in the databases according to the DeCS and MeSH methodology: Thyroid; lithium; bipolar; Thyroiditis; Goiter; Hypothyroidism In this review, 52 original and review publications related to the subject studied were identified, of which 20 articles met the specified inclusion requirements, such as articles that were in a range not less than 2009, which were articles of full text and to report on the effects at the thyroid level of the use of lithium in bipolar patients. As exclusion criteria, it was taken into account that the articles did not have sufficient information and that they did not present the full text at the time of their review.

RESULTS

PHYSIOPATHOLOGICAL MECHANISMS OF LITHIUM AT THE THYROID LEVEL

In order to understand the thyroid effects, which occur in bipolar patients, it is convenient to study and understand the pathophysiological mechanisms of lithium at the thyroid level [8].

Lithium has been shown to be abundant in the thyroid. The uptake of diaactive iodine is reduced at the thyroid level and in the salivary glands due to the effects caused by lithium, as shown in in vivo and in vitro studies in rats [9, 12].

This leads us to suppose that thyroid radioactive iodine uptake could be reduced or increased after the administration of lithium in humans. Lithium could induce a low uptake of iodine at the thyroid level due to an excessive retention of iodide. This hypothyroidism that occurs could be regulated by increased secretion of thyroid stimulating hormone (TSH) and increased uptake [11, 12].

Another effect that we find at the thyroid level is the role of the synthesis and release of hormones, as it is inhibited by the levels of lithium in the blood. This inhibitory effect is due to the alteration of tubulin polymerization and the inhibition of the action of TSH on cyclic adenosine monophosphate (c-AMP) [10, 11].

Iodotyrosine coupling defects are caused by the alteration of the thyroglobulin structure, causing an impairment in the conformation and function of proteins [5, 11].

Lithium administration is associated with a reduction in liver deiodination and free thyroxine clearance (T 4). The latter induces a decrease in the activity of the enzyme 5 'deiodinase type I [8, 12].

Initial inhibition of thyroid hormone synthesis and release by lithium results in increased TSH concentrations leading to thyroid enlargement [12].

MAIN ALTERATIONS AT THE THYROID LEVEL DUE TO THE USE OF LITHIUM

The main thyroid alterations that we can find in patients receiving lithium for the treatment of bipolar disorder are:

1. Goiter
2. Hypothyroidism
3. Hyperthyroidism
4. Autoimmune thyroiditis

Goiter

Goiter is the most common clinical finding observed among patients receiving lithium therapy (Image 1). It occurs as a diffuse and non-sensitive neck swelling [13].

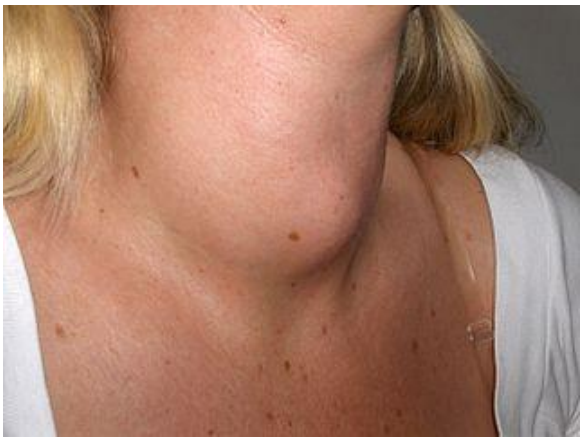

Image 1: Thyroid enlargement by the use of lithium

Excessive stimulation of the thyroid gland by TSH increases thyroid hormone production. The entire gland may be enlarged, but sometimes there may only be lumps known as thyroid nodules [17].

Thyroid ultrasound has been shown to be a simple, inexpensive, and sensitive method for the detection of goiter and thyroid abnormalities in patients receiving lithium therapy. The approach to the management of lithium-induced goiter is comparable to that of the healthy population. However, levothyroxine replacement therapy is more preferred among patients with significant thyroid enlargement and accompanying compressive symptoms [14].

Hypothyroidism / Subclinical Hypothyroidism

It is a very prevalent condition among patients on lithium treatment. The etiology of lithium-associated hypothyroidism and subclinical hypothyroidism is mainly related to inhibition of thyroid hormone synthesis and release [15].

Women over 50 years of age, the presence of a family history of thyroid disease and thyroid autoantibodies, the risk of developing lithium-induced hypothyroidism has been shown to be significantly high. Therefore, all patients who present these risk factors, and receive lithium therapy, should undergo thyroid function tests, as well as all patients who require lithium therapy [16].

Hyperthyroidism / Autoimmune thyroiditis

This condition can occur in patients taking lithium, but it is much less common than goiter and hypothyroidism [16].

Lithium-induced hyperthyroidism is characterized primarily by transient, painless thyroiditis. Some published reports have also shown that lithium is associated with granulomatous thyroiditis, lymphocytic thyroiditis, or nonspecific thyroiditis [17].

Although it is not entirely clear, this transient and painless thyroiditis is believed to be due to a possible direct toxic effect of lithium on the thyroid gland. Another proposed mechanism in the pathogenesis of lithium-induced hyperthyroidism / thyrotoxicosis is related to autoimmunity and autoantibody production [17].

Lithium treatment increases B cell activity and reduces suppressor ratios to cytotoxic T cells. Inducing thyroid autoimmunity among susceptible individuals [18].

Patients with lithium-induced hyperthyroidism are best treated with antithyroid drugs such as carbimazole with or without steroids [17]. Radioactive iodine or thyroidectomy should be reserved for patients with lithium-induced Graves disease, especially in cases of poor adherence to antithyroid drugs [17, 18].

If patients have lithium-induced thyroiditis, ablative radioactive iodine is not indicated due to poor uptake. In such cases, conservative treatment with regular monitoring is recommended [19].

In this work, an exhaustive search was carried out for the most frequent conditions caused by lithium in bipolar patients, of which the most frequent was goiter, as we can see in Table 1 in their order of frequency [18, 20].

Table 1: Most frequent conditions in bipolar patients treated with lithium

Thyroid conditions	Frequency
Goiter	82%
Hypothyroidism	16%
Hyperthyroidism / Autoimmune thyroiditis	2

DISCUSSION AND CONCLUTION

Lithium is abundantly present at the thyroid level, reducing iodine uptake. Causing as a collateral effect the increase in TSH, increasing uptake. These various thyroid alterations caused by lithium can lead us to develop goiter and hypothyroidism, being the most frequent.

In their retrospective cross-sectional study, Kwan et al identified that women and using lithium too frequently, causing high or toxic levels of lithium in the blood, are risk factors for developing the various thyroid alterations, already exposed. In his study, he identified that the risk is much higher in patients who ingest other types of related drugs, such as sodium valproate [16]. A strength of the current study is the methodology implemented, with respect to the literature search, and steps in the selection of relevant articles, quality assessment and data extraction. However, this study has several limitations, which should be taken into account before reaching a conclusion, among these are the little evidence from analysis of clinical trials, in vitro and in vivo, to accurately determine the pathophysiological mechanisms and thyroid effects caused by lithium.

REFERENCES

1. Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2016). Bipolar disorder. *The Lancet*, *387*(10027), 1561-1572.
2. Whiteford, H. A., Ferrari, A. J., Degenhardt, L., Feigin, V., & Vos, T. (2015). The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. *PloS one*, *10*(2), e0116820.
3. Blanco, C., Compton, W. M., Saha, T. D., Goldstein, B. I., Ruan, W. J., Huang, B., & Grant, B. F. (2017). Epidemiology of DSM-5 bipolar I disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions–III. *Journal of psychiatric research*, *84*, 310-317.
4. Solé, B., Bonnin, C. M., Mayoral, M., Amann, B. L., Torres, I., González-Pinto, A., ... & Torrent, C. (2015). Functional remediation for patients with

bipolar II disorder: improvement of functioning and subsyndromal symptoms. *European Neuropsychopharmacology*, *25*(2), 257-264.
5. Malhi, G. S., Tanious, M., & Berk, M. (2012). Mania: diagnosis and treatment recommendations. *Current psychiatry reports*, *14*(6), 676-686.
6. Grande, I., Hidalgo-Mazzei, D., Nieto, E., Mur, M., Saez, C., Forcada, I., & Vieta, E. (2015). Asenapine prescribing patterns in the treatment of manic in-and outpatients: Results from the MANACOR study. *European Psychiatry*, *30*(4), 528-534.
7. Hayes, J. F., Pitman, A., Marston, L., Walters, K., Geddes, J. R., King, M., & Osborn, D. P. (2016). Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: a UK population-based electronic health records study. *JAMA psychiatry*, *73*(6), 630-637.
8. Perveen, T., Haider, S., Mumtaz, W., Razi, F., Tabassum, S., & Haleem, D. J. (2013). Attenuation of stress-induced behavioral deficits by lithium administration via serotonin metabolism. *Pharmacological Reports*, *65*(2), 336-342.
9. K Rybakowski, J. (2016). Effect of lithium on neurocognitive functioning. *Current Alzheimer Research*, *13*(8), 887-893.
10. Kibirige, D., Luzinda, K., & Ssekitoleko, R. (2013). Spectrum of lithium induced thyroid abnormalities: a current perspective. *Thyroid research*, *6*(1), 1-5.
11. Bocchetta, A., & Loviselli, A. (2006). Lithium treatment and thyroid abnormalities. *Clinical Practice and Epidemiology in Mental Health*, *2*(1), 1-5.
12. Lazarus, J. H. (2009). Lithium and thyroid. *Best practice & research Clinical endocrinology & metabolism*, *23*(6), 723-733.
13. Kraszewska, A., Abramowicz, M., Chłopocka-Woźniak, M., Sowiński, J., & Rybakowski, J. (2014). The effect of lithium on thyroid function in patients with bipolar disorder. *Psychiatr Pol*, *48*(3), 417-428.
14. Czarnywojtek, A., Zgorzalewicz-Stachowiak, M., Czarnocka, B., Sawicka-Gutaj, N., Gut, P., Krela-Kazmierczak, I., & Ruchala, M. (2020). Effect of lithium carbonate on the function of the thyroid gland: mechanism of action and clinical implications. *Journal of Physiology and Pharmacology*, *71*(2), 191-199.
15. Lieber, I., Ott, M., Öhlund, L., Lundqvist, R., Eliasson, M., Sandlund, M., & Werneke, U. (2020). Lithium-associated hypothyroidism and potential for reversibility after lithium discontinuation: Findings from the LiSIE retrospective cohort study. *Journal of Psychopharmacology*, *34*(3), 293-303.
16. Tsui, K. Y. Q. (2015). The impact of Lithium on thyroid function in Chinese psychiatric population. *Thyroid research*, *8*(1), 1-8.
17. Dr. Chris. Thyroid Enlargement (Goiter) from Lithium Use. HealthHype.com. https://www.healthhype.com/thyroid-enlargement-goiter-from-lithium-use.html
18. Pomarol-Clotet, E., Alonso-Lana, S., Moro, N., Sarro, S., Bonnin, M. C., Goikolea, J. M., ... & Salvador, R. (2015). Brain functional changes across the different phases of bipolar disorder. *The British Journal of Psychiatry*, *206*(2), 136-144.
19. Ng, F., Mammen, O. K., Wilting, I., Sachs, G. S., Ferrier, I. N., Cassidy, F., ... & Berk, M. (2009). The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. *Bipolar disorders*, *11*(6), 559-595.
20. Vieta, E., Langosch, J. M., Figueira, M. L., Souery, D., Blasco-Colmenares, E., Medina, E., ... & Bellivier, F. (2013). Clinical management and burden of bipolar disorder: results from a multinational longitudinal study (WAVE-bd). *International Journal of Neuropsychopharmacology*, *16*(8), 1719-1732.