

Review Article

Long-term lithium therapy and the risk of kidney damage: integrative literature review*Terapia a longo prazo com lítio e o risco de danos renais: revisão integrativa da literatura***Jefferson Pereira Sarmiento¹, José Valdilânio Virgulino Procópio², Rafaela de Oliveira Nóbrega³**

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ABSTRACT: The purpose of this study has been to evaluate the potential adverse effects to the kidneys associated with a long-term-lithium treatment in patients who have bipolar disorders, based on an integrative literature review. The articles were identified in the SciELO, Medline (Pubmed), and “Biblioteca Virtual em Saúde” (BVS) (Virtual Health Library) databases, published from 2010 to 2021. Eighteen articles adhered to the applied inclusion and exclusion criteria. Taking lithium for a prolonged period was verified as it is associated with a reduced glomerular filtration rate; however, other variables must be considered as age and associated comorbidities. But on the other hand, the evolution of terminal stage chronic renal disease has not been associated with it by taking the medication. The investigation from the study has revealed that the drug in therapeutic dosages and with continual laboratory monitoring has not demonstrated toxicity or severe side effects to the kidneys bringing about its discontinuity related to mood flareups.

Keywords: Lithium carbonate; Adverse effects; Kidney.

RESUMO: Este estudo objetivou avaliar os potenciais efeitos adversos nos rins associado ao tratamento de longo prazo com lítio em pacientes com transtorno bipolar, a partir de uma revisão integrativa literatura. Os artigos foram identificados nas bases de dados SciELO, Medline (Pubmed) e Biblioteca Virtual em Saúde (BVS), publicados entre 2010 e 2021. Aplicados os critérios de inclusão e exclusão, identificaram-se 18 artigos para a análise. Verificou-se que o tratamento com lítio durante um período prolongado está associado à redução da taxa de filtração glomerular, porém, outras variáveis devem ser consideradas como idade e comorbidades associadas. Por outro lado, não foi associado evolução da doença renal crônica em estágio terminal por uso do medicamento. A investigação dos estudos revelou que a droga em doses terapêuticas e com monitoramento laboratorial contínuo não demonstrou toxicidade ou efeitos colaterais severos nos rins sendo a sua descontinuação relacionada com exacerbações do humor.

Palavras-chave: Carbonato de lítio; Efeitos adversos; Rim.

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INTRODUCTION

John Cade, in the 1940s, was the pioneer who discovered that lithium salts brought about a constraining effect on the excitability of laboratory animals. He continued his study on human beings and noticed that lithium displayed a positive impact on the treatment of mania, making it the preferred drug for treating all phases of bipolar disorder in several international guidelines^{1,2}. Through randomized studies, he also demonstrated that lithium achieved good results in treating depression, reducing the risks of suicide and short-term mortality³.

The awareness of the proven efficacy of lithium as a mood stabilizer has made it validated; however, it is not absent of adverse events throughout its therapeutic usage; thus, close care and attention must be paid to its handling⁴. It highlights the importance of routinely verifying the plasma dosage as an element of the blood, renal, and thyroid functions. The calcium and sodium dosages before and after the treatment are among the required precautions⁵.

The motive for such measures is subsidized by the narrow range of the therapeutic index, enabling a significant number of medicinal interactions and important clinical manifestations, such as gastrointestinal disorders, tremors, skin diseases, hyperparathyroidism, insipid diabetes, and others. Lithium concentrations range from 0.6 to 1.2 mmol/L as these are considered therapeutic, yet lower targets are suggested from 0.4 to 0.8 mmol/L for the elderly^{6,7}.

Lithium is the lightest alkaline metal in its group, and it displays physical-chemical characteristics such as charge and sizes like sodium. Thus, it is freely filtered by the glomeruli and reabsorbed in the proximal tubules⁸. As the kidneys directly excrete it, long-term therapy from inferred renal insufficiency may occur; however, more recent publications addressed the prevalence of dialytic severe renal damage arising from the therapy of metallic salts^{9,10}.

It is crucial to consider the long-term treatment of mania by lithium carbonate to verify the medication's potentiality to cause irreversible damage to the kidneys. For example, the scarcity of studies was stressed on the subject of pharmaceutical companies that did not sponsor randomized controlled studies to confirm the tolerability of treatment as performed on other mood stabilizers was added to that perspective¹⁴. Thus, the purpose of this research work has been to review the available study results in the literature on the potential adverse effects associated with the long-term treatment with lithium and clarify any eventual doubts from professionals about the harm caused by the drug to the kidneys.

METHODOLOGY

The researchers adopted the integrative type of bibliographic review, as this method adheres with research standards on strictness, clarity, and replication as these characteristics are inherent or not to the primary data scientific method. After defining the theme for this research study focused on following up on answering the leading question: what are the adverse renal effects from the long-term lithium medication therapy?

The inclusion criteria were defined as follows: complete articles published from January 01, 2010, to June 30, 2021; available online, in English, Spanish, or Portuguese; carried out on human beings, and addressing the selected subject. The exclusion criteria were editorials, letters to the editor; dissertations; theses; books; reports on experiences, case reports, opinion articles, and duplicates that had previously been included.

It was followed by a selection of universal descriptors to be employed by consulting the "Descritores em Ciências da Saúde" (DeCS) (Health Science Descriptors), through the "Biblioteca Virtual em Saúde" (BVS) (Virtual Health Library) and the *Medical Subject Headings* (MeSH) from the *National Library of Medicine*, being selected by the following English language descriptors (lithium, long-term care, and kidney), Spanish (*litio, cuidados a largo plazo and riñón*), and Portuguese (*lítio, assistência de longa duração and rim*). These jointly resulted in the following search strategy: in English "*((lithium) AND (long-term care)) AND (kidney)*," in Spanish "*((litio) AND (cuidados a largo plazo)) AND (riñón)*" and in Portuguese "*((lítio) AND (assistência de longa duração)) AND (rim)*." The following electronic databases were used as a source for searching electronic data *PubMed Central*® (PMC), *Scientific Electronic Library Online* (SciELO), and "Biblioteca Virtual em Saúde" (BVS) (Virtual Health Library).

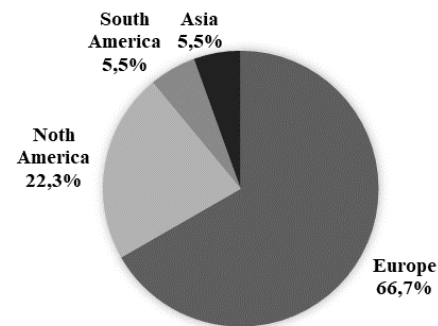
RESULTS

One hundred and eighty-one publications were found after the initial search applying the descriptors in the different languages 181 in PubMed, 16 in SciELO, and 920 in BVS. The second step applied the inclusion and exclusion criterion filters; the quantity was reduced to 19 articles from PubMed, 1 in SciELO, and 58 in BVS. Among these, after previous reading of the titles, abstracts, there were 41 duplicates; 37 articles remained for a complete reading. After rereading each manuscript, 18 articles were identified for this bibliographic review.

Among the 18 articles included in the final sample, twelve (66.7%) were from Europe, four (22.3%) from North America, one (5.5%) from South America, and

one (5.5%) from Asia (Figure 1). The United Kingdom was noteworthy as the most significant number of articles were from that country, supplying a total of four (22.2%), followed by Canada (11.1%), Denmark (11.1%), and the United States (11.1%) with two articles from each one. The most significant number of articles were published in 2014, 5 studies, followed by 2021 with 3 publications, and two articles in both 2016 and 2013, respectively. There was only one article from the other years.

Chart 1 displays the detailed information on the author, publication year, type of study, and purposes of the included studies.



Source: Prepared by the authors.

Figure 1. This graph shows the distribution of articles based on the continents where they were published.

Chart 1. Characteristics of the articles included in the integrative review.

Author	Year	Type of study	Objectives
Aiff et al. ¹¹	2019	Longitudinal	Investigate the impact of the comorbidities in the severe renal lesion during the lithium treatment.
Aprahamian et al. ¹²	2014	Randomized double-blind	Evaluate the long-term effect of the low-dosage lithium treatment on renal function in elderly patients with slight cognitive impairment.
Bocchetta et al. ¹³	2013	Cohort	Examine renal function in patients treated by lithium in a controlled group of patients who other mood stabilizers have treated.
Chaturaka et al. ¹⁴	2014	Transversal	Compare the renal function values in patients who have taken lithium for a long term submitted to matched controls.
Close et al. ¹⁵	2014	Cohort	Estimate the related risk of renal insufficiency and renal insufficiency in bipolar disorder patients based on the usage adjusted to age and other known variables for renal disease.
Hayes et al. ¹⁶	2016	Cohort	Compare the negative result rates among patients who have been prescribed lithium and/or other mood stabilizer drugs.
Hayes et al. ¹⁷	2021	Cohort	Develop a model for classifying individuals who face a high-or low risk for decreased renal function after starting the lithium treatment.
Janowsky et al. ¹⁸	2011	Transversal	Review the medical reports on patients who suffer from mental deficiency treated by lithium, which develops renal insufficiency.
Jonczyk-Potoczna et al. ¹⁹	2016	Transversal	Evaluate the abnormalities from renal ultrasonographic scanning in patients who have been long-term treated with lithium and correlate the exam finding on renal function.
Kessing et al. ²⁰	2015	Cohort	Compare the chronic renal disease rates in the irreversible final stage among individuals who had been exposed to lithium and other drugs to non-exposed individuals.
Kessing et al. ²¹	2017	Cohort	Compare the chronic renal disease rates and progression to the final stage in a patient cohort diagnosed with chronic renal disease and continue taking lithium compared to those who did not. There was also a controlled patient cohort who were taking other psychotropic drugs.
Pahwa et al. ²²	2021	Cohort	Investigate the prevalence of chronic renal disease in patients who have been long-term treated with lithium; compare with characteristics of patients who develop chronic renal disease; identify the risk factors and observe if the continuation of lithium after diagnosing chronic renal disease is associated with the disease.
Rej et al. ²³	2013	Longitudinal	Verify if elevated lithium levels correlated with other variables are associated with decreased renal function in the geriatric population.
Rej et al. ²⁴	2014	Cohort	Analyze if geriatric psychiatric patients display an increased risk of renal dysfunction compared with an elderly control group and if the exposure to lithium and other factors are essential risk predictors.
Tredget et al. ²⁵	2010	Case-control	Evaluate the effects of chronic lithium treatment on renal function in patients who suffer from mood disorders treated at an affective disorder clinic.
Van Alphen et al. ²⁶	2021	Cohort	Establish the incidence of chronic renal disease and the course of renal function in patients treated with lithium salts.
Werneke et al. ²⁷	2012	Systematic literature review	Establish a decision-making model where lithium is or another anticonvulsive drug is taken for the maintenance treatment for bipolar affective disorder and to verify if the suicidal risks and relapse were compared to the risk of developing terminal stage renal disease.
Zaidan et al. ²⁸	2014	Cohort	Determine if patients treated with lithium face an increased risk of renal tumors.

Source: Prepared by the authors.

In the study performed by Aiff et al.¹¹, there were 1,741 individuals, who displayed a relationship to the slow progression of renal insufficiency, as there was an increased rate of patients diagnosed with other comorbidities, mainly cardiovascular as hypertension, angina, arrhythmias, cardiac insufficiency, and peripheral vascular disease.

Chaturaka et al.¹⁴ describe that taking long-term-lithium therapy is related to lower glomerular filtration levels compared to matched controlled groups based on age and gender. In this study, the average glomerular filtration rate value (eGFR) was 79.71 ml/min/1.73m² in treated patients. However, the controlled matched groups based on age and gender displayed an average value of 89.31 ml/min/1.73m². In counterpart, Clos et al.²⁹ noticed that the average annual decrease in eGFR was 1.3 mL/min/1.33m² in the group treated with lithium. Yet, there was no significant statistical difference in the results found in the control group.

According to Janowsky et al.¹⁸, who longitudinally followed up patients using lithium through serum creatinine, the decreased eGFR is similar to the gradual intermittent increase the serum creatinine concentrations until the lithium is suspended in patients who have suffered some renal alteration due to the monitoring of the same obtained from the related frequency in patients who were treated with lithium and who reached a concentration of 1.3 – 1.4 mg/100 mL, watchfulness must be even more ostensive. Despite also reporting a decrease in renal function in some patients taking lithium, Tondo et al.³⁰ describe that it was not found as a significant frequency of renal disease in the terminal stage.

The evidence shows the progressive nature of CRD, as it is not possible to revert previously caused damages. There are reports of a more significant number of suicides and mood crises in patients who have stopped taking the drug³¹.

There is a cohort study including 6,671 eligible people. Among the 2,148 taking lithium, they displayed an increase in adverse renal and endocrine events; however, there was decreased weight gain compared with other alternative mood stabilizers used in clinical practice. In conclusion, the authors stated that despite the implications from side effects of long-term handling of patients, the benefits outweigh the risks faced, as there is no doubt regarding the efficacy of lithium carbonate for bipolar disorder and the prevention of suicide^{12,16}.

In the study conducted by Bocchetta et al.¹³ including a sample of 209 patients, 139 of them had taken lithium for over 12 months and displayed a 27.3% decrease of eGFR in the treated group, while the portion of individuals who had not taken the medication decreased their rate by 5.7%. The hypothesis considered the longer the treatment was performed, the more serious the risk of a negative result²⁶. However, some studies point out some

variables can have interfered in that result, among them, age, as in that elderly age bracket, the most significant decline in renal function occurs^{15,17,24}.

A retrospective study was performed by Ott et al.³² consistent with that suspicion whereas an age over 65 was an independent risk factor for renal intoxication from taking lithium. Besides age, hypertension, diabetes mellitus, nephrotoxic medicines (thiazide diuretics, non-steroid anti-inflammatories) and cumulative lithium dosage during prolonged treatment are considered strong predictors of renal lesion^{22,33}. Castro et al.³⁴ followed up 1,445 patients compared with the control group of 4,306 observed a significantly reduced risk compared to those who took a daily dosage of lithium, different from the results found in individuals taking prolonged-release preparations.

Kessing et al.²⁰ showed the increased risk of chronic renal disease from taking any medication class through a 2-cohort populational study where patients have bipolar disorders. Besides that, the outcome in renal disease in the terminal stage has not been directly associated with taking lithium, especially when its use is well-monitored^{21,25}. These findings corroborate with the results of Rej et al.²³, where, according to them, increased concentrations of lithium in the bloodstream do not necessarily correlate with severe effects in renal function after 2 to 4 years of follow-up, as long as the patients are well-monitored with periodic exams every 3 to 6 months.

The association between prolonged lithium treatment and increased renal tumors proposed by Jonczyk-Potoczna et al.¹⁹ through a sample of 120 patients, as 30 were defined as the control group, as that promoted concern in the medical community considering the reported presence of renal macrocysts in 22% of the individuals treated with lithium compared to the 16% in the control group. The increased percentage of cysts larger than 3 centimeters also negatively impacted renal function. It is important to emphasize that these changes are not common, and the average treatment time was over 20 years. Compared to the finding by Zaidan et al.²⁸, who reported a significant increase in the frequency of renal cancer and oncocytoma in patients treated with lithium compatible with gender, age, and renal function. Whether renal tumors are malign or benign, the diagnoses of renal tumors were 8.2% greater in patients treated with lithium than in the general population.

On the other hand, some studies do not report any association between the use of long-term lithium and the increased risk of cancer in the upper urinary tract. Besides that, a series of anticarcinogenic effects was described when lithium was prescribed in therapeutic dosages^{35,36}. Currently, there is also a growing trend in the amount of evidence indicating the use of short-term lithium usage displaying potential renoprotective effects and favorable reparative activity in organs due to the GSK3 protein blockage³⁷.

DISCUSSION

Using integrative review was displayed as an essential tool in analyzing ample systematic subsidies in the literature, seeking answers to a leading question, contributing to the praxis being guided by the science as it indeed reveals.

Adherence to those defined standards is necessary so that the integrative review abides by the following steps: identification of the theme and definition of the leading research question; define the eligibility and exclusion criteria of the bibliographic sources used; research and identify the selected research databases; critical analysis of the selected studies based on predefined criteria; categorization of the research studies; evaluation, interpretation, and presentation of the results in adherence with the integrative review framework³⁸.

When we consider pharmacotherapy that needs to be taken long-range, it is always valid to investigate its safety in clinical practice after commercialization. A discussion has been inserted about the occurrence of renal damage in patients taking lithium in the field of mental health for long periods.

The pertinent literature proved the existence of a possible renal lesion. It often occurs relatively slow; however, the progression is much faster in patients who suffer from comorbidities, including cardiovascular, previous renal disease, and metabolic diabetes mellitus. That can be explained since the kidneys and the cardiovascular system operate jointly to maintain corporal homeostasis. Thus, when there is any alteration, in the beginning, there are compensatory repercussions in the other as then throughout the years, those same mechanisms could cause the lesion.

Other factors must be considered, for example, the dosage used, time of usage, concomitance with other nephrotoxic drugs, and the user's age, as these are independent factors for exacerbating renal damage. The studies have pointed out that lithium in supratherapeutic dosages is associated with an increased risk of the worsening glomerular filtration and the capacity for

concentrating urine in the kidneys^{39,40,41}.

Regarding dosages, it has been verified as time goes on that there has been a change concerning the same. There has been increased clinical control by prescribing smaller dosages of lithium and enhancing monitoring and laboratory control to treat patients with bipolar disorders to decrease medication intolerance. Due to this, improved results in long-term therapy have been achieved, including lower rates of a renal lesion in the final stages^{10,42,43}. There is even laboratory follow-up by Kirkham et al.⁴⁴ performing the recommended retrospective analysis every three months, as the concentrations of lithium carbonate are above 1 mmol/L associated with decreased renal function.

The study evaluation reported increased renal tumors; we have insufficient evidence on the cause; therefore, Licht et al.⁴⁵, in a critical evaluation letter to the editor, described that there were inconsistencies in the guided methodological design of the study; thus, their results do not extend to the general population.

It is also important to emphasize that the risk/benefit evaluation must consider the consequences of discontinuation of usage, as proper control of the bipolar disorder cases is associated with high rates of suicide and increased social interaction difficulties. Thus, even though renal complications are possible, they must be considered individually²⁷.

CONCLUSION

After finishing this review, it was concluded that the occurrence of decreased renal function associated with long-term lithium therapy is present. However, that constataction cannot be the reason for not taking the medication for psychiatric disorders as its efficacy is undeniable, and the benefits greatly outweigh the risks. Besides that, when the therapy is well-monitored, the incidence of chronic renal disease with the necessity for substitute renal therapy is uncommon. Thus, the continued use of lithium is safe from the renal point-of-view in the long-term treatment of mood disorders if the serum concentration is adequately monitored.

Authors participation: *Sarmiento JP*; *Procópio JVV*: developed the body of the article, synthesis of the main findings and preparation of tables and figures. *Nóbrega RO*: structuring the main article proposal, evaluating the articles included, writing guidance and critically reviewing the final proposal.

REFERENCES

1. Albert U, De Cori D, Blengino G, Bogetto F, Maina G. Trattamento con litio e potenziali effetti collaterali a lungo termine: una revisione sistematica della letteratura. *Riv Psichiatri*. 2014; 49(1):12-21. doi: 10.1708/1407.15620.
2. Müller-Oerlinghausen B, Bauer M, Grof P. Commentary on a recent review of lithium toxicity: what are its implications for clinical practice? *BMC Med*. 2012;10:132. doi: 10.1186/1741-7015-10-132.
3. Nikolova VL, Pattanasari K, Hidalgo-Mazzei D, Taylor D, Young AH. Is lithium monitoring NICE? Lithium monitoring in a UK secondary care setting. *J Psychopharmacol*. 2018;32(4):408-415. doi: 10.1177/0269881118760663.
4. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet*. 2012;379(9817):721-728. doi: 10.1016/s0140- 6736(11)61516-x.
5. Severus E, Bauer M. Managing the risk of lithium-induced nephropathy in the long-term treatment of patients with recurrent affective disorders. *BMC Med*. 2013;11:34. doi: 10.1186/1741-7015-11-34.

6. Ferreira CAA, Guimarães HAA, Azevedo MAG, Menezes FG. Identificação dos potenciais riscos de reações adversas ao carbonato de lítio em um hospital público de Minas Gerais. *Gerais. Rev Saúde Pública SUS/MG*. 2014;2(1):43-51. Disponível em: <https://docs.bvsalud.org/biblioref/coleciona-sus/2014/34402/34402-871.pdf>.
7. Alastanos JN, Potter TG, Crouse EL. Lithium-related medication problems on nonpsychiatric inpatient medical units. *Am J Health Syst Pharm*. 2019;76(Suppl 4):S96-S101. doi: 10.1093/ajhp/zxz212.
8. Brunton LL, Hilal-Dandan R, Knollman B. Goodman & Gilman: as bases farmacológicas da terapêutica. Porto Alegre: AMGH; 2019.
9. Alsady M, Baumgarten R, Deen PM, de Groot T. Lithium in the kidney: friend and foe? *J Am Soc Nephrol*. 2016;27(6):1587-95. doi: 10.1681/ASN.2015080907.
10. Aiff H, Attman PO, Aurell M, Bendz H, Schön S, Svedlund J. The impact of modern treatment principles may have eliminated lithium-induced renal failure. *J Psychopharmacol*. 2014;28(2):151-4. doi: 10.1177/0269881113516202.
11. Aiff H, Attman PO, Ramsauer B, Schön S, Svedlund J. Cardiovascular comorbidity increases the risk for renal failure during prophylactic lithium treatment. *J Affect Disord*. 2019;243:416-20. doi: 10.1016/j.jad.2018.09.044.
12. Aprahamian I, Santos FS, dos Santos B, Talib L, Diniz BS, Radanovic M, Gattaz WF, Forlenza OV. Long-term, low-dose lithium treatment does not impair renal function in the elderly: a 2-year randomized, placebo-controlled trial followed by single-blind extension. *J Clin Psychiatry*. 2014;75(7):e672-8. doi: 10.4088/JCP.13m08741.
13. Bocchetta A, Ardaur R, Carta P, Ligas F, Sardu C, Pani A, Del Zompo M. Duration of lithium treatment is a risk factor for reduced glomerular function: a cross-sectional study. *BMC Med*. 2013;11:33. doi: 10.1186/1741-7015-11-33.
14. Chaturaka R, de Silva NL, Gunaratne R, Rajapakse S, De Silva VA, Hanwella R. Lower estimated glomerular filtration rates in patients on long term lithium: a comparative study and a meta-analysis of literature. *BMC Psychiatry*. 2014;14:4. doi: 10.1186/1471-244X-14-4.
15. Close H, Reilly J, Mason JM, Kripalani M, Wilson D, Main J, Hungin AP. Renal failure in lithium-treated bipolar disorder: a retrospective cohort study. *PLoS One*. 2014;9(3):e90169. doi: 10.1371/journal.pone.0090169.
16. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. Adverse renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder: a population-based Cohort Study. *PLoS Med*. 2016;13(8):e1002058. doi: 10.1371/journal.pmed.1002058.
17. Hayes JF, Osborn DPJ, Francis E, Ambler G, Tomlinson LA, Boman M, Wong ICK, Geddes JR, Dalman C, Lewis G. Prediction of individuals at high risk of chronic kidney disease during treatment with lithium for bipolar disorder. *BMC Med*. 2021;19(1):99. doi: 10.1186/s12916-021-01964-z.
18. Janowsky DS, Buneviciute J, Hu Q, Davis JM. Lithium-induced renal insufficiency: a longitudinal study of creatinine increases in intellectually disabled adults. *J Clin Psychopharmacol*. 2011;31(6):769-73. doi: 10.1097/JCP.0b013e31823607db.
19. Jończyk-Potoczna K, Abramowicz M, Chłopočka-Woźniak M, Strzelczuk-Judka L, Michalak M, Czekalski S Prof, Rybakowski JK Prof. Renal sonography in bipolar patients on long-term lithium treatment. *J Clin Ultrasound*. 2016;44(6):354-9. doi: 10.1002/jcu.22336.
20. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. *JAMA Psychiatry*. 2015;72(12):1182-91. doi: 10.1001/jamapsychiatry.2015.1834.
21. Kessing LV, Feldt-Rasmussen B, Andersen PK, Gerds TA, Licht RW. Continuation of lithium after a diagnosis of chronic kidney disease. *Acta Psychiatr Scand*. 2017;136(6):615-22. doi: 10.1111/acps.12820.
22. Pahwa M, Joseph B, Nunez NA, Jenkins GD, Colby CL, Kashani KB, Marin Veldic, Moore KM, Betcher HK, Ozerdem A, Cuellar-Barboza AB, McElroy SL, Biernacka JM, Frye MA, Singh B. Long-term lithium therapy and risk of chronic kidney disease in bipolar disorder: a historical cohort study. *Bipolar Disord*. 2021;23(7):715-23. doi: 10.1111/bdi.13052.
23. Rej S, Looper K, Segal M. The effect of serum lithium levels on renal function in geriatric outpatients: a retrospective longitudinal study. *Drugs Aging*. 2013;30(6):409-15. doi: 10.1007/s40266-013-0068-x.
24. Rej S, Li BW, Looper K, Segal M. Renal function in geriatric psychiatry patients compared to non-psychiatric older adults: effects of lithium use and other factors. *Aging Ment Health*. 2014;18(7):847-53. doi: 10.1080/13607863.2014.888536.
25. Tredget J, Kirov A, Kirov G. Effects of chronic lithium treatment on renal function. *J Affect Disord*. 2010;126(3):436-40. doi: 10.1016/j.jad.2010.04.018.
26. Van Alphen AM, Bosch TM, Kupka RW, Hoekstra R. Chronic kidney disease in lithium-treated patients, incidence and rate of decline. *Int J Bipolar Disord*. 2021;9(1):1. doi: 10.1186/s40345-020-00204-2.
27. Werneke U, Ott M, Renberg ES, Taylor D, Stegmayr B. A decision analysis of long-term lithium treatment and the risk of renal failure. *Acta Psychiatr Scand*. 2012;126(3):186-97. doi: 10.1111/j.1600-0447.2012.01847.x.
28. Zaidan M, Stucker F, Stengel B, Vasiliu V, Hummel A, Landais P, Boffa JJ, Ronco P, Grünfeld JP, Servais A. Increased risk of solid renal tumors in lithium-treated patients. *Kidney Int*. 2014;86(1):184-90. doi: 10.1038/ki.2014.2.
29. Clos S, Rauchhaus P, Severn A, Cochrane L, Donnan PT. Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study. *Lancet Psychiatry*. 2015;2(12):1075-83. doi: 10.1016/S2215-0366(15)00316-8.
30. Tondo L, Abramowicz M, Alda M, Bauer M, Bocchetta A, Bolzani L, Calkin CV, Chillotti C, Hidalgo-Mazzei D, Manchia M, Müller-Oerlinghausen B, Murru A, Perugi G, Pinna M, Quaranta G, Reginaldi D, Reif A, Ritter P Jr, Rybakowski JK, Saiger D, Sani G, Selle V, Stamm T,

- Vázquez GH, Veeh J, Vieta E, Baldessarini RJ. Long-term lithium treatment in bipolar disorder: effects on glomerular filtration rate and other metabolic parameters. *Int J Bipolar Disord.* 2017;5(1):27. doi: 10.1186/s40345-017-0096-2.
31. Schoot TS, Molmans THJ, Grootens KP, Kerckhoffs APM. Systematic review and practical guideline for the prevention and management of the renal side effects of lithium therapy. *Eur Neuropsychopharmacol.* 2020;31:16-32. doi: 10.1016/j.euroneuro.2019.11.006.
32. Ott M, Stegmayr B, Salander Renberg E, Werneke U. Lithium intoxication: Incidence, clinical course and renal function - a population-based retrospective cohort study. *J Psychopharmacol.* 2016;30(10):1008-19. doi: 10.1177/0269881116652577.
33. Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: a literature review of approaches to clinical management and risk stratification. *BMC Nephrol.* 2018;19(1):305. doi: 10.1186/s12882-018-1101-4.
34. Castro VM, Roberson AM, McCoy TH, Wiste A, Cagan A, Smoller JW, Rosenbaum JF, Ostacher M, Perlis RH. Stratifying risk for renal insufficiency among lithium-treated patients: an Electronic Health Record Study. *Neuropsychopharmacology.* 2016;41(4):1138-43. doi: 10.1038/npp.2015.254.
35. Pottegård A, Hallas J, Jensen BL, Madsen K, Friis S. Long-term lithium use and risk of renal and upper urinary tract cancers. *J Am Soc Nephrol.* 2016;27(1):249-55. doi: 10.1681/ASN.2015010061
36. Ozerdem A, Ceylan D, Targitay B. The relationship between lithium and cancer proliferation: a case-based review of the literature. *Curr Drug Metab.* 2018;19(8):653-62. doi: 10.2174/1389200219666180430095933
37. Gong R, Wang P, Dworkin L. What we need to know about the effect of lithium on the kidney. *Am J Physiol Renal Physiol.* 2016;311(6):F1168-F1171. doi: 10.1152/ajprenal.00145.2016.
38. Yamane MT, Machado VK, Osternack KT, Mello RG. Simulação realística como ferramenta de ensino na saúde: uma revisão integrativa. *Rev Espac Saude.* 2019;20(1):87-107. doi: 10.22421/15177130-2019v20n1p87
39. Minay J, Paul R, McGarvey D, Savage G, Stevenson M, Fogarty D, Mulholland C, Kelly C. Lithium usage and renal function testing in a large UK community population; a case-control study. *Gen Hosp Psychiatry.* 2013;35(6):631-5. doi: 10.1016/j.genhosppsych.2012.10.016
40. Enderle J, Klink U, di Giuseppe R, Koch M, Seidel U, Weber K, Birringer M, Ratjen I, Rimbach G, Lieb W. Plasma Lithium Levels in a General Population: a Cross-Sectional Analysis of Metabolic and Dietary Correlates. *Nutrients.* 2020;12(8):2489. doi: 10.3390/nu12082489.
41. Dastych M, Synek O, Gottwaldová J. Impact of long-term lithium treatment on renal function in patients with bipolar disorder based on novel biomarkers. *J Clin Psychopharmacol.* 2019;39(3):238-42. doi: 10.1097/JCP.0000000000001030.
42. Paton C, Adroer R, Barnes TR. Monitoring lithium therapy: the impact of a quality improvement programme in the UK. *Bipolar Disord.* 2013;15(8):865-75. doi: 10.1111/bdi.12128.
43. Paul R, Minay J, Cardwell C, Fogarty D, Kelly C. Meta-analysis of the effects of lithium usage on serum creatinine levels. *J Psychopharmacol.* 2010;24(10):1425-31. doi: 10.1177/0269881109104930.
44. Kirkham E, Skinner J, Anderson T, Bazire S, Twigg MJ, Desborough JA. One lithium level >1.0 mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database. *BMJ Open.* 2014;4(11):e006020. doi: 10.1136/bmjopen-2014-006020.
45. Licht RW, Grabenhenrich LB, Nielsen RE, Berghöfer A; International Group for the Study of Lithium (IGSLi). Lithium and renal tumors: a critical comment to the report by Zaidan et al. *Kidney Int.* 2014;86(4):857. doi: 10.1038/ki.2014.178.

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