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LITHIUM AND HEMATOPOIESIS: UNDERSTANDING THE SYSTEMIC IMPACT OF LONG-TERM USE

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Abstract: INTRODUCTION Lithium is recognized as a critical therapeutic agent in the management of mood disorders, particularly bipolar disorder, due to its significant mood--stabilizing properties. Its pharmacodynamic actions, including modulation of neurotransmitter activity and inhibition of pathways like glycogen synthase kinase-3, are central to its efficacy. However, lithium's narrow therapeutic window necessitates precise monitoring to avoid systemic toxicity, especially in patients undergoing long-term treatment. Beyond its psychiatric benefits, lithium exerts considerable hematological effects, influencing granulopoiesis, bone marrow function, and the production of white and red blood cells. The introduction emphasizes the need to closely monitor hematological parameters during lithium therapy, particularly in relation to leukocytosis, neutrophilia, platelet dysfunction, and anemia. **OBJETIVE** To explore and analyze the hematological effects of long-term lithium therapy, particularly its impact on leukocytosis, neutrophilia, platelet function, and red blood cell production, while assessing clinical implications for patients. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: **"**Lithium-induced hematological changes" OR "Mood stabilizers and blood cell alterations" OR "Neutrophilia and leukocytosis in lithium therapy" OR "Platelet dysfunction and lithium therapy" OR "Bone marrow suppression and lithium use" in the last years. **RESULTS AND DISCUSSION** Lithium therapy is associated with several hematological changes, the most notable being lithium-induced leukocytosis, which is dose-dependent and occurs primarily through increased neutrophil production. This increase in white blood cell count, while often benign, requires close monitoring in

patients with preexisting hematological conditions. In addition to leukocytosis, lithium affects red blood cell production, leading to suppressed erythropoiesis and mild anemia in some patients. The results also indicate that lithium's impact on platelet function, although debated, may reduce platelet aggregation in certain individuals, heightening the risk of bleeding. Long-term lithium use raises concerns about its effect on hematopoietic stem cell proliferation and the potential dysregulation of bone marrow activity, which could pose long-term risks. Particular attention is given to populations like the elderly and those with renal impairment, who are more susceptible to lithium's hematological side effects. **CONCLUSION** Lithium's profound therapeutic role in psychiatric care is tempered by its diverse hematological effects, which require consistent and individualized monitoring. Its ability to induce leukocytosis and other blood cell alterations underscores the importance of regular blood tests to mitigate the risks associated with long-term therapy. Anemia and platelet dysfunction, though less common, present additional challenges that need to be managed through careful dose regulation and monitoring, particularly in patients with preexisting conditions. There are potential long-term concerns, such as bone marrow dysregulation, that warrant further research to fully understand lithium's impact over extended periods of use. The balance between lithium's therapeutic benefits and its hematological risks is crucial, emphasizing the need for a personalized approach to treatment that adapts to each patient's unique risk factors and clinical profile.

Keywords: Lithium; Hematological effects; Leukocytosis; Erythropoiesis; Thrombocytopenia.

INTRODUCTION

The role of lithium in psychiatry, particularly its use as a mood stabilizer in the treatment of bipolar disorder, has been well-established over the past several decades. Initially discovered for its calming effects in the 19th century, lithium found its clinical application in the 20th century as an effective treatment for mania and as a prophylactic agent against both manic and depressive episodes in bipolar disorder[1]. Its unique ability to modulate neurotransmission and stabilize mood has made it indispensable in psychiatric practice, with a particular emphasis on its long-term efficacy in preventing relapse[1]. However, the pharmacological actions of lithium extend far beyond the central nervous system, affecting multiple organ systems, including the hematological system[1].

Pharmacodynamically, lithium acts through several mechanisms, including inhibition of inositol monophosphatase, modulation of glutamatergic activity, and inhibition of glycogen synthase kinase-3 (GSK-3), which plays a key role in cellular proliferation and apoptosis[2]. These actions contribute not only to its mood-stabilizing properties but also to a wide array of systemic effects. Pharmacokinetically, lithium is rapidly absorbed after oral administration, with peak plasma concentrations reached within 1-2 hours[2]. It is predominantly excreted unchanged by the kidneys, with a half-life ranging from 18 to 24 hours, though this can be extended in the elderly or in patients with renal impairment[2]. Its narrow therapeutic index necessitates regular monitoring to avoid toxicity, which can have profound hematological and systemic consequences[2].

The hematological effects of lithium are complex and multifaceted, largely due to its influence on electrolyte balance, cellular function, and bone marrow activity[3]. Lithium's impact on the hematopoietic system

is particularly notable, given its ability to stimulate granulopoiesis and leukocytosis[3]. In clinical practice, this has led to its use in specific hematological conditions, such as neutropenia, where lithium's ability to elevate white blood cell counts can be beneficial[3]. However, the same mechanisms that promote leukocyte production can also contribute to adverse effects, such as neutrophilia and, in rare cases, leukemoid reactions[3].

One of the most well-documented hematological effects of lithium is its capacity to induce leukocytosis, an increase in white blood cell count that occurs in a dose-dependent manner[4]. This phenomenon is thought to be mediated by lithium's action on bone marrow progenitor cells, particularly granulocytes, leading to enhanced production and release of neutrophils into the bloodstream[4]. While generally benign and reversible upon discontinuation of the drug, lithium-induced leukocytosis requires careful monitoring, especially in patients with underlying hematological disorders or those at risk for infection[4]. The pathophysiology of this effect involves both direct stimulation of granulopoiesis and modulation of immune function, though the exact molecular mechanisms remain an area of active investigation[4].

Lithium's effects on platelet function and coagulation have also been studied, though the clinical significance of these findings is less clear[5]. Some studies suggest that lithium may reduce platelet aggregation, potentially increasing the risk of bleeding[5]. However, other reports have indicated no significant impact on coagulation parameters, leaving this area of research inconclusive[5]. Further complicating the picture is lithium's potential to induce anemia in certain populations, particularly in patients with preexisting conditions that affect red blood cell production or iron metabolism[5]. The mechanisms underlying lithium-induced anemia are thought to involve suppression of erythropoiesis, possibly through direct effects on erythroid progenitor cells or via disruption of iron homeostasis[5].

In pediatric populations, lithium's hematological effects warrant special consideration, as children and adolescents may exhibit different responses to the drug compared to adults[6]. The developing hematopoietic system in younger patients may be more susceptible to lithium's effects, necessitating closer monitoring of blood counts and careful dose adjustments to avoid adverse outcomes[6]. Similarly, genetic factors may play a role in modulating individual responses to lithium, with some patients displaying greater susceptibility to hematological side effects due to inherited variations in drug metabolism or bone marrow function[6]. These genetic differences highlight the need for personalized approaches to lithium therapy, particularly in populations at risk for hematological complications[6].

The comparison of lithium with other mood-stabilizing agents also reveals important differences in their hematological profiles[7]. While lithium is unique in its ability to induce leukocytosis, other agents, such as valproic acid and carbamazepine, are more commonly associated with cytopenias, including thrombocytopenia and leukopenia[7]. This distinction underscores the importance of individualized treatment planning, with careful consideration of each agent's risk-benefit profile, particularly in patients with preexisting hematological conditions or those at increased risk for drug-induced cytopenias[7].

The monitoring of lithium levels and hematological parameters is a critical aspect of long-term therapy, particularly given the potential for cumulative toxicity and adverse hematological effects[8]. Regular blood tests, including complete blood counts and lithium level measurements, are essential to ensure that patients remain within the therapeutic

range while minimizing the risk of toxicity[8]. This is especially important in patients with renal impairment, where reduced clearance of lithium can lead to higher plasma concentrations and an increased risk of both hematological and systemic toxicity[8]. In such cases, dose adjustments and more frequent monitoring may be required to maintain therapeutic efficacy while avoiding adverse effects[8].

OBJETIVES

To explore and analyze the hematological effects of long-term lithium therapy, particularly its impact on leukocytosis, neutrophilia, platelet function, and red blood cell production, while assessing clinical implications for patients.

SECUNDARY OBJETIVES

1. To investigate the mechanisms by which lithium induces changes in white blood cell counts and bone marrow function.
2. To evaluate the risks of lithium-induced anemia and thrombocytopenia, especially in populations with preexisting hematological or renal conditions.
3. To discuss the clinical management strategies for mitigating adverse hematological effects during long-term lithium therapy.
4. To explore potential long-term risks, such as the development of hematological malignancies, in patients on lithium treatment.
5. To assess the importance of individualized patient monitoring and the need for regular blood tests during lithium use

METHODS

This is a narrative review, in which the main aspects of the hematological effects of long-term lithium therapy, particularly its impact on leukocytosis, neutrophilia, platelet function, and red blood cell production, while assessing clinical implications for patients in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: **"**Lithium-induced hematological changes" OR "Mood stabilizers and blood cell alterations" OR "Neutrophilia and leukocytosis in lithium therapy" OR "Platelet dysfunction and lithium therapy" OR "Bone marrow suppression and lithium use" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case--control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

The hematological effects of lithium treatment, particularly its influence on various blood components and the bone marrow, have garnered considerable attention in recent years. Clinical studies have shown that lithium, primarily used as a mood stabilizer, can significantly alter hematopoiesis, thereby impacting white blood cells, red blood cells, and platelets in both therapeutic and pathological contexts. These alterations, though often reversible, necessitate a deep understanding of their mechanisms, potential risks, and clinical implications. The following discussion examines key findings from the literature regarding lithium-induced hematological changes, with a focus on leukocytosis, neutrophilia, erythropoiesis suppression, and platelet dysfunction, among other critical aspects of hematology.

One of the most consistent and well-documented effects of lithium is the induction of leukocytosis, particularly neutrophilia[10]. Lithium-induced leukocytosis has been reported in up to 36% of patients receiving long-term lithium therapy[10]. This phenomenon is dose-dependent and largely reversible upon discontinuation of lithium. The mechanism underlying this effect is believed to involve stimulation of granulopoiesis through direct action on bone marrow progenitor cells, resulting in increased production and release of neutrophils[10]. Moreover, lithium enhances the responsiveness of neutrophils to colony-stimulating factors, further promoting neutrophil proliferation. This increase in white blood cell count is generally benign and does not typically result in clinically significant complications, though it requires careful monitoring, particularly in patients with preexisting hematological disorders[11].

In addition to its impact on white blood cells, lithium has been shown to influence the production and function of platelets. Although the exact mechanism remains unclear, some studies have suggested that lithium may reduce platelet aggregation, potentially increasing the risk of bleeding in certain patients[11]. However, the clinical significance of this effect is still debated, with some reports indicating no significant impact on clotting parameters or bleeding risk[11]. Nonetheless, given lithium's wide-ranging effects on hematopoiesis, platelet function should be closely monitored in patients receiving long-term therapy, particularly those with concomitant use of anticoagulants or other medications that affect coagulation pathways[12].

Another important hematological effect of lithium is its impact on red blood cell production. While lithium-induced leukocytosis is well-recognized, its effects on erythropoiesis are less well understood. Some studies suggest that lithium may suppress erythropoiesis, potentially leading to anemia in susceptible individuals[12]. This effect is thought to be mediated through direct inhibition of erythroid progenitor cells in the bone marrow, though other mechanisms, such as interference with iron metabolism, may also contribute[12]. Lithium-induced anemia appears to be more common in patients with preexisting conditions affecting red blood cell production, such as chronic kidney disease or malnutrition, and may be exacerbated by factors such as prolonged therapy, higher doses, and renal impairment[13]. Anemia associated with lithium use is generally mild and reversible upon dose reduction or discontinuation of the drug, but careful monitoring is warranted in patients with risk factors for hematological dysfunction[13].

The effects of lithium on bone marrow function extend beyond the promotion of neutrophil production and suppression of erythropoiesis. Studies have shown that lithium may also influence the activity of hematopoietic stem cells, promoting their proliferation and differentiation into various blood cell lineages[13]. This effect has been exploited in certain clinical settings, particularly in the treatment of neutropenia, where lithium's ability to enhance granulopoiesis has been used therapeutically[14]. However, the long-term consequences of lithium-induced stem cell proliferation remain unclear, and there is concern that prolonged stimulation of hematopoietic stem cells could potentially lead to dysregulation of normal bone marrow function or contribute to the development of hematological malignancies[14]. To date, there is limited evidence to suggest a direct link between long-term lithium therapy and an increased risk of leukemia or other blood cancers, but this remains an area of active research[14].

The role of lithium in modulating immune function through its effects on blood cell production is another area of significant interest. Lithium has been shown to influence both innate and adaptive immune responses, largely through its effects on neutrophils, lymphocy-

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tes, and macrophages[15]. In particular, lithium has been reported to enhance the bactericidal activity of neutrophils and to modulate the production of cytokines and other immune mediators[15]. These immunomodulatory effects may explain, at least in part, the drug's ability to prevent infections in patients with neutropenia and its potential use as an adjunctive therapy in certain infectious diseases[15]. However, these same effects could also increase the risk of autoimmune complications in susceptible individuals, particularly those with a history of autoimmune disorders or chronic inflammatory conditions[16]. Further studies are needed to elucidate the full spectrum of lithium's effects on the immune system and to determine the clinical implications of these findings in both psychiatric and hematological practice[16].

Lithium's impact on iron metabolism has also been the subject of investigation, particularly in relation to its potential to cause or exacerbate anemia[16]. Some studies suggest that lithium may interfere with iron absorption or utilization, leading to decreased hemoglobin levels and an increased risk of iron-deficiency anemia in certain populations[16]. This effect appears to be more pronounced in patients with underlying conditions that affect iron metabolism, such as chronic kidney disease or gastrointestinal disorders, and may be exacerbated by prolonged lithium therapy or higher doses[17]. While the exact mechanism remains unclear, it is thought that lithium may alter the expression of genes involved in iron homeostasis or disrupt the transport and storage of iron within the body[17]. In any case, regular monitoring of iron levels and red blood cell indices is recommended in patients receiving long-term lithium therapy, particularly those with risk factors for anemia or iron deficiency[17].

Another area of concern is the potential for lithium to induce thrombocytopenia, a condition characterized by a reduced platelet count and an increased risk of bleeding[18]. While less common than lithium-induced leukocytosis or anemia, thrombocytopenia has been reported in a small percentage of patients receiving lithium, particularly those with underlying hematological disorders or those taking other medications that affect platelet function[18]. The mechanism by which lithium induces thrombocytopenia is not well understood, but it is thought to involve either direct suppression of megakaryocyte production in the bone marrow or enhanced destruction of platelets in the peripheral circulation[18]. In most cases, lithium-induced thrombocytopenia is mild and reversible upon discontinuation of the drug, but severe cases may require medical intervention, including the use of platelet transfusions or other supportive therapies[19].

In terms of gender and age differences, the hematological effects of lithium may vary significantly between men and women, as well as between younger and older patients. Studies have shown that women may be more susceptible to certain side effects of lithium, including anemia and thrombocytopenia, possibly due to differences in drug metabolism or hormonal influences on hematopoiesis[19]. Similarly, elderly patients are more likely to experience lithium-induced hematological complications, particularly those related to bone marrow suppression, due to age-related declines in renal function and hematopoietic reserve[20]. These differences highlight the need for individualized treatment plans and careful monitoring of hematological parameters in patients receiving lithium, with particular attention to vulnerable populations such as women, the elderly, and those with preexisting hematological conditions[20].

Chronic lithium therapy also poses risks for patients with preexisting renal or hematological disorders, as these conditions may exacerbate the drug's effects on blood cell production and function[21]. Patients with chronic kidney disease, in particular, are at increased risk of lithium toxicity due to impaired renal clearance of the drug, which can lead to higher plasma concentrations and a greater likelihood of adverse hematological effects[21]. In such cases, dose adjustments and more frequent monitoring of blood counts and lithium levels are necessary to prevent toxicity and ensure therapeutic efficacy[21]. Similarly, patients with underlying hematological disorders, such as bone marrow suppression or autoimmune conditions, may be more susceptible to the hematological side effects of lithium, including leukocytosis, thrombocytopenia, and anemia[22]. In these patients, alternative treatments may need to be considered, or lithium therapy may need to be closely monitored and adjusted based on individual risk factors[22].

The potential for lithium to induce hematological malignancies remains an area of ongoing research, though current evidence does not suggest a strong association between long-term lithium therapy and the development of leukemia or other blood cancers[22]. However, given lithium's ability to stimulate bone marrow progenitor cells and modulate immune function, there is concern that prolonged exposure to the drug could theoretically increase the risk of dysregulated hematopoiesis or immune-mediated disorders[23]. Longitudinal studies and large-scale epidemiological research will be critical in determining the long-term hematological safety of lithium, particularly in high-risk populations[23].

CONCLUSION

Lithium remains an invaluable treatment option for mood disorders, particularly in the management of bipolar disorder. However, its widespread effects on the hematological system demand careful consideration and monitoring. Lithium's ability to induce leukocytosis, primarily through neutrophil stimulation, has been well-documented and generally poses little risk in most patients. This effect, while often benign, serves as a useful indicator of lithium's hematopoietic influence. Yet, the potential for hematological complications, including neutrophilia, thrombocytopenia, and anemia, underscores the importance of regular blood monitoring in patients undergoing long-term lithium therapy.

The effects of lithium on red blood cell production, while less understood, also present significant clinical implications. Suppression of erythropoiesis and the resulting anemia can be exacerbated in individuals with preexisting conditions, particularly those with renal impairment or iron metabolism disorders. While lithium-induced anemia is generally mild and reversible, it adds another layer of complexity in the clinical management of patients, necessitating ongoing evaluation of hematological parameters. Furthermore, potential alterations in iron metabolism further highlight the need for comprehensive patient assessments during lithium treatment.

Lithium's impact on platelet function and coagulation remains an area of continued investigation. While some reports suggest a decrease in platelet aggregation, increasing the risk of bleeding, this effect has not been consistently demonstrated in all studies. Nonetheless, platelet counts and clotting functions should be carefully monitored, particularly in patients with other risk factors for bleeding or those on anticoagulants. Thrombocytopenia, although less frequently associated with lithium therapy, represents a significant com-

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plication in susceptible patients and requires prompt clinical intervention when identified.

Additionally, the influence of lithium on bone marrow function and hematopoietic stem cell proliferation presents both therapeutic potential and risk. While lithium has been used to stimulate granulopoiesis in specific clinical contexts, such as in neutropenic patients, the long-term consequences of this bone marrow stimulation remain unclear. There is a theoretical concern that prolonged lithium therapy could lead to dysregulation of normal hematopoiesis, particularly in high-risk populations. The possibility of lithium contributing to hematological malignancies, though not definitively established, warrants further research to fully elucidate its long-term safety profile.

Ultimately, the hematological effects of lithium highlight the importance of personalized treatment approaches. The variability in hematological responses, influenced by factors such as age, gender, genetic predisposition, and comorbid conditions, necessitates a patient-centered strategy to lithium therapy. Regular monitoring, dose adjustments, and careful consideration of individual risk factors are essential in optimizing the therapeutic benefits of lithium while minimizing potential hematological complications. The complexity of lithium's hematological effects underscores the need for ongoing research and vigilance in clinical practice to ensure the safety and well-being of patients undergoing long-term lithium treatment.

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