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Lithium and Mental Health: The Small Element with a Big Impact

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Abstract

Lithium has long been established as a first-line mood stabilizer in the treatment of bipolar disorder and treatment-resistant depression. In addition to its psychiatric applications, lithium has demonstrated neuroprotective properties through its influence on neurotransmitter regulation, neuroplasticity, inflammation, and oxidative stress. Objective: This narrative review aims to provide a comprehensive analysis of lithium's role in mental health, focusing on its clinical efficacy, underlying neurobiological mechanisms, and expanding therapeutic applications. The review also addresses safety considerations and explores innovative strategies to optimize lithium use in contemporary psychiatry. Methods: A systematic literature search was conducted in PubMed (MEDLINE) and the Virtual Health Library (BVS), covering publications from January 2000 to December 2024. Inclusion criteria comprised peer-reviewed original studies, systematic reviews, meta-analyses, and randomized clinical trials published in English, Portuguese, or Spanish. A total of 68 articles were selected following title and abstract screening and full-text analysis. These articles explored lithium's clinical effects, mechanisms of action, safety profile, and emerging applications. Results: Lithium remains the gold standard for managing bipolar disorder, with strong evidence supporting its efficacy in mood stabilization and suicide prevention. Emerging data also support its use in major depressive disorder, schizoaffective disorder, and neurodegenerative conditions such as Alzheimer's and Parkinson's disease. However, its narrow therapeutic index necessitates close monitoring due to risks of renal, thyroid, and metabolic dysfunction. Recent advances in pharmacogenomics, sustained-release delivery systems, and microdosing approaches offer new avenues to enhance therapeutic efficacy while reducing adverse effects. Conclusion: Lithium continues to play a pivotal role in psychiatric treatment and is gaining relevance in neuroprotective strategies. Future research should prioritize the identification of predictive biomarkers, refinement of dosing strategies, and the development of personalized approaches to maximize benefits and ensure safe, long-term use.

Subject Areas

Mental Health, Psychopharmacology, Neuroscience, Psychiatry

Keywords

Lithium, Mental Health, Bipolar Disorder, Neuroprotection, Depressive Disorder

1. Introduction

Lithium, an alkali metal widely known for its industrial and technological applications, has played a fundamental role in the field of mental health for over half a century. Discovered as a treatment for mood disorders in the late 1940s, this element has become one of the most effective and widely prescribed mood stabilizers in the management of bipolar disorder and treatment-resistant depression [1] [2]. Its efficacy has been so remarkable that the World Health Organization (WHO) considers it an essential medicine in mental health treatment [3].

Clinical studies have shown that lithium not only reduces the frequency and severity of manic and depressive episodes but also plays a role in neuroprotection and brain plasticity, contributing to long-term neuronal health maintenance [4]. In addition to its mood-stabilizing action, evidence suggests that lithium may reduce the risk of suicide in patients with mood disorders, making it one of the few pharmacological treatments with this proven benefit [5] [6].

Although its efficacy is widely recognized, the exact mechanisms by which lithium exerts its effects are still under investigation. Research indicates that this element influences multiple biological systems, including neurotransmitter modulation, regulation of intracellular pathways involved in neuroplasticity, and protection against oxidative stress [7] [8]. Moreover, evidence suggests that trace amounts of lithium in drinking water may be associated with lower suicide rates in the general population, raising questions about its potential public health impact [9] [10].

Despite its benefits, lithium use requires strict monitoring due to its narrow therapeutic margin and the risk of adverse effects, such as renal toxicity and thyroid function alterations [11] [12]. Thus, the search for biomarkers that can predict treatment response and minimize risks is one of the main current researches fronts [13].

Given the significant impact of lithium on mental health and neuroscience, its studies remain essential for improving the treatment of mental disorders and expanding knowledge about the underlying mechanisms of emotional stability. This literature review aims to comprehensively and up-to-date explore the role of lithium in mental health, highlighting its clinical applications, neurobiological mechanisms, and potential impacts on modern psychiatry. Through the analysis of recent studies, the objective is to understand how lithium, a classic mood stabilizer, continues to be a central piece in the treatment of psychiatric disorders, with an emphasis on bipolar disorder, major depressive disorder, and schizoaffective disorder. Additionally, its possible neuroprotective role in neurodegenerative diseases, such as Alzheimer's and Parkinson's, is examined, expanding the scope of its therapeutic relevance.

The review also aims to discuss the challenges related to its use, including its narrow therapeutic window and adverse effects, as well as strategies to optimize its safety and clinical efficacy. Finally, future perspectives are addressed, such as new formulations, personalized psychiatry strategies, and technological innovations that can enhance its administration and expand its range of applications. Thus, this review contributes to consolidating knowledge about lithium and its impact on neuroscience and contemporary psychiatric practice.

2. Material and Methods

This narrative review was conducted to explore the role of lithium in mental health, with particular emphasis on its clinical applications, neurobiological mechanisms, and therapeutic advancements. A comprehensive literature search was carried out using two major scientific databases: PubMed (MEDLINE) and the Virtual Health Library (BVS). The search covered the period from January 2000 to December 2024 and utilized combinations of the following keywords: "lithium," "mental health," "bipolar disorder," "neuroprotection," "depressive disorder," "suicide prevention," and "neurodegenerative diseases." Only studies published in English, Portuguese, or Spanish were considered.

Eligible articles included peer-reviewed original research, systematic reviews, meta-analyses, and randomized controlled trials that discussed lithium's use in psychiatric conditions such as bipolar disorder, major depressive disorder, and schizoaffective disorder, as well as in neurodegenerative diseases including Alzheimer's and Parkinson's. Studies addressing lithium's mechanisms of action, neuroprotective properties, and safety considerations were also included. Exclusion criteria encompassed case reports, editorials, non-psychiatric or non-neuroprotective uses of lithium, duplicate records, inaccessible full texts, and studies not meeting basic methodological standards.

The selection process involved initial screening of titles and abstracts, followed by full-text review of potentially eligible studies. Data extraction focused on lithium's clinical efficacy, its influence on neurotransmitter systems, effects on inflammation and oxidative stress, safety profile, and relevance to personalized medicine. After applying all inclusion and exclusion criteria, a total of 68 articles were selected for inclusion in this review. These consisted of 27 original research studies, 21 review articles and meta-analyses, 10 randomized controlled trials, and 10 clinical guidelines or expert consensus publications.

3. Results and Discussion

3.1. Mechanisms of Action and Impact on Neurobiology

Lithium is one of the most widely used mood stabilizers in psychiatry and is considered the standard treatment for bipolar disorder and other psychiatric conditions [14]. Despite its high clinical efficacy, the specific mechanisms by which lithium exerts its therapeutic effects are not yet fully elucidated. Studies indicate that its actions are related to neurotransmitter modulation, neuroprotection, and neuroplasticity, as well as the regulation of inflammation and oxidative stress [4] [15].

The effects of lithium extend to its direct influence on the activity of crucial neurotransmitters involved in mood regulation, modulating the glutamatergic, serotonergic, dopaminergic, and GABAergic systems. This enables a balance between neuronal excitation and inhibition, significantly impacting brain functions related to bipolar disorder [16].

Lithium's action on the glutamatergic system occurs through the reduction of neuronal excitotoxicity, inhibiting excessive glutamate release and promoting its reuptake by glial transporters. This mechanism has a protective effect against neuronal apoptosis [17]. Furthermore, regarding serotonin and dopamine, research shows that lithium increases serotonergic neurotransmission by elevating serotonin transporter (SERT) expression and enhancing the release of this neurotransmitter in brain regions such as the prefrontal cortex and hippocampus [18]. Additionally, it has been observed to reduce dopaminergic hyperactivity associated with manic episodes [19]. As for GABAergic transmission, lithium has a stimulating effect, promoting neuronal inhibition and contributing to mood stabilization [20].

Beyond neurotransmitter regulation, lithium also plays a crucial role in neuroprotection and neuronal plasticity. Studies show that prolonged use of this drug reduces apoptosis and stimulates neurogenesis, particularly in the hippocampus [15]. One of the main mechanisms involved in this process is the activation of the Wnt/β-catenin pathway, as lithium inhibits the activity of the enzyme glycogen synthase kinase-3 beta (GSK-3β), which is linked to cellular apoptosis and the development of neurodegenerative diseases [4]. By inhibiting this enzyme, lithium promotes cellular proliferation and synaptic plasticity [8]. There is also evidence that lithium increases levels of brain-derived neurotrophic factor (BDNF), which is essential for neuronal survival and the formation of new synapses, providing protection against damage caused by chronic stress and brain aging [21]. Furthermore, this drug also protects against glutamate-induced neurotoxicity, reducing the risk of neurodegeneration [17].

Another relevant aspect is lithium's impact on chronic inflammation and oxidative stress, processes that play a significant role in the pathophysiology of psychiatric and neurodegenerative disorders. Lithium modulates these processes by reducing the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while simultaneously increasing levels of anti-inflammatory cytokines [8]. Studies show that patients with bipolar disorder often present increased systemic inflammation, which can be reversed by lithium treatment [13].

Additionally, lithium also exerts an antioxidant effect by increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), which contributes to cellular protection against oxidative damage [22]. Another protective mechanism is related to the improvement of mitochondrial function, as lithium reduces the production of reactive oxygen species (ROS) and promotes neuronal energy homeostasis [23].

Thus, lithium is a multifaceted drug whose neurobiological action involves neurotransmitter modulation, neuroprotection, synaptic plasticity, and anti-inflammatory and antioxidant properties. These effects make it one of the most effective therapeutic approaches for psychiatric disorders, especially bipolar disorders. However, despite its proven efficacy, continuous monitoring of lithium serum levels and a deep understanding of its mechanisms of action are essential to optimize its use and minimize potential adverse effects.

3.2. Lithium and Bipolar Affective Disorder

Bipolar Affective Disorder is characterized by alternating between depressive and manic phases (bipolar type 1) or hypomanic phases (bipolar type 2). Studies indicate that its pathogenesis has a strong genetic component, with heritability between 60% and 80%. Genetic loci associated with the disorder have been identified, involving ion channels, signal transduction proteins, neurotransmitter transporters, and synaptic proteins. Additionally, genes that regulate insulin secretion and endocannabinoid signaling are also involved. Bipolar type 1 has a stronger genetic correlation with schizophrenia, while bipolar type 2 is more closely associated with Major Depression [24].

Most patients with bipolar disorder present comorbidities (90%), with anxiety disorders (70% - 90%), substance abuse (30% - 50%), and ADHD (25% - 45%) being common [24]. These conditions complicate diagnosis and appropriate treatment. Despite various available medications, many patients exhibit resistance to currently available drugs.

Lithium was the first substance identified as effective in preventing and treating bipolar episodes, becoming the standard reference for the disease's treatment [25]. Although new therapeutic options have been developed, lithium is still considered the gold standard [26].

Efficacy for Mania and Depression

Lithium reduces manic episodes and mitigates depressive symptoms. Studies indicate response rates for mania of 49% compared to 22%-25% with placebo [27], and remission rates of 49% versus 22.1% [28]. It has also proven effective for mania with psychotic symptoms but not for mixed episodes. However, its efficacy in depression is uncertain. A rigorous 8-week study found no positive results for lithium, while quetiapine was more effective [29]. Additionally, patients with adequate lithium blood levels also did not show significant improvement [30].

A review of 59 studies identified factors associated with non-responsiveness to lithium in patients with bipolar disorder type 1, including pre-existing anxiety, functional impairment, traumatic events, migraines, suicidal thoughts, mixed episodes, chronic illness, and personality disorders [26].

Long-Term Mood Stabilization

Lithium prolongs periods of stability and reduces the recurrence of bipolar episodes. Randomized studies demonstrated median maintenance times of 292, 140, and 85 days, respectively [31]-[33]. Lithium was superior to placebo in preventing manic episodes, while its efficacy in preventing depressive episodes remains debated.

Suicide Prevention

Lithium significantly reduces the risk of suicide in patients with mood disorders [34] [35]. A scientific consensus indicated that the lethality of suicide attempts is 2.5 times lower among patients treated with lithium [36]. Even those with moderate or poor responses to lithium show a reduction in suicide attempts compared to the period before treatment [37]. However, a scientific review questions the validity of these conclusions due to the lack of controlled studies [38].

In summary, lithium remains one of the leading therapeutic options for bipolar disorder, demonstrating efficacy in mood stabilization, prevention of manic episodes, and reduction of suicide risk. Despite some controversies regarding its effectiveness in depressive episodes, lithium continues to be a fundamental element in psychiatric treatment, warranting further research to optimize its use and reduce possible side effects.

3.3. Expanding the Role of Lithium in Psychiatry: Applications in Depressive Disorder, Schizoaffective Disorder, and Anxiety

Studies suggest that its application may be expanded to other psychiatric conditions, including major depressive disorder (MDD), schizoaffective disorder, and anxiety disorders [4] [13]. Its unique ability to modulate neurotransmitters, promote neuroprotection, regulate inflammatory processes, and reduce the risk of suicide has motivated investigations into its efficacy beyond bipolar disorder [22].

Major depressive disorder (MDD) is a highly prevalent and debilitating condition affecting millions worldwide. Although selective serotonin reuptake inhibitors (SSRIs) and other antidepressants are standard treatments, many patients do not respond adequately to these therapies. Studies indicate that lithium can be a potent adjunct in the treatment of treatment resistant MDD, enhancing the efficacy of antidepressants and significantly reducing the risk of suicide [5] [6]. Furthermore, evidence suggests that its role in neuroplasticity and neuroprotection may contribute to the long-term recovery of patients with treatment-resistant depression [21].

In the context of schizoaffective disorder, which shares characteristics with both bipolar disorder and schizophrenia, lithium has shown promise as a treatment option. Studies demonstrate that it can be effective in stabilizing mood and reducing psychotic symptoms in some patients [39]. Its ability to modulate neurotransmitters such as dopamine and glutamate may explain its efficacy in attenuating manic and depressive symptoms, as well as improving cognitive aspects affected by schizoaffective disorder [40]. Additionally, there is evidence suggesting that lithium may potentiate the effects of antipsychotics, leading to better therapeutic outcomes [41].

Anxiety disorders, including generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder, have also been investigated as potential indications for lithium use. Although its use in these cases is less common, some studies suggest that it may be beneficial for patients with treatment-resistant anxiety [42]. Its action in reducing hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which is involved in the stress response, may contribute to symptom improvement in anxiety [43]. Furthermore, lithium's ability to regulate neuroinflammation and modulate neurotransmitters such as serotonin and gamma-aminobutyric acid (GABA) may be relevant in managing chronic anxiety [7].

Another highly relevant factor is lithium's effect on suicide prevention, a significant risk in patients with major depressive disorder and schizoaffective disorder. Meta-analyses indicate that lithium significantly reduces suicide rates and self-harming behaviors, an effect that may be related both to mood stabilization and to its neuroprotective and anti-inflammatory actions [5] [11].

Given the growing evidence of lithium's benefits in various psychiatric conditions, there is renewed interest in exploring its efficacy beyond bipolar disorder. However, its use requires strict monitoring due to its narrow therapeutic margin and the potential for adverse effects such as nephrotoxicity and thyroid dysfunction [12]. The identification of biomarkers that can predict treatment response is one of the main areas of research, aiming to personalize lithium use and maximize its benefits while minimizing risks [13].

Although lithium is predominantly indicated for bipolar disorder and treatment-resistant depression, growing evidence suggests it may also offer therapeutic benefits for certain anxiety disorders, particularly when standard treatments are ineffective. Although less commonly used in this context, early clinical studies and case reports have pointed to lithium's potential as an augmenting agent in generalized anxiety disorder (GAD), panic disorder, and obsessive-compulsive disorder (OCD). A study by Rickels *et al.* (1993) involving patients with treatment-refractory anxiety found that lithium augmentation significantly improved anxiety symptoms in individuals who had previously failed to respond to antidepressants, with clinical improvements noted in over 60% of participants [44]. Similarly, a case series by Schaffer and Schaffer (2005) described several patients with comorbid anxiety and mood symptoms who achieved marked symptom reduction following low-dose lithium addition to SSRIs [45].

From a mechanistic perspective, lithium's anxiolytic effects may be attributed to its action on the hypothalamic-pituitary-adrenal (HPA) axis, reducing stress reactivity and cortisol release [16]. Lithium also modulates key neurotransmitter systems implicated in anxiety regulation, including the GABAergic and serotonergic pathways, and has been shown to increase the expression of brain-derived neurotrophic factor (BDNF), which plays a role in emotional resilience [46] [47].

Emerging preclinical models further support this hypothesis. In murine studies, chronic lithium administration reduced anxiety-like behavior in elevated plus maze and open field tests, comparable to classical anxiolytics such as benzodiazepines [48]. Despite this promising data, randomized controlled trials evaluating lithium monotherapy or adjunctive therapy in primary anxiety disorders remain scarce.

Given lithium's narrow therapeutic index and potential for adverse effects, its use in anxiety should be reserved for treatment-resistant cases or comorbid presentations, and always under careful monitoring. However, these findings suggest lithium may be a viable second-line or adjunctive option for patients with anxiety that is refractory to standard treatments.

The future of lithium use in psychiatry appears promising, with new therapeutic approaches being developed to expand its clinical application. Ongoing studies continue to investigate its efficacy in different psychiatric disorders, as well as new formulations that may reduce its adverse effects. Thus, lithium remains not only a classic treatment but also a drug with continuously expanding potential in modern psychiatry.

3.4. Neurodegenerative Diseases and Neuroprotection

The Studies demonstrate that lithium can modulate cellular pathways involved in neuroinflammation, apoptosis, and synaptic plasticity, suggesting its therapeutic potential for conditions such as Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis (ALS).

While lithium remains a cornerstone in the management of bipolar disorder, prolonged use requires careful consideration due to its potential for cumulative toxicity. Long-term safety studies have consistently shown that renal, thyroid, and parathyroid functions are the primary physiological systems affected by chronic lithium therapy. A systematic review by Shine *et al.* (2015) demonstrated that up to 40% of long-term users exhibit some degree of reduced glomerular filtration rate (GFR), with a measurable decline often observable after 10 or more years of continuous treatment [49]. Though the incidence of lithium-induced end-stage renal disease (ESRD) remains low—estimated between 0.5% and 1.5%—this risk increases with higher serum concentrations and patient age [50].

In terms of endocrine function, hypothyroidism has been widely reported, with prevalence rates ranging from 10% to 20%, particularly in women and older adults. Lithium interferes with thyroid hormone synthesis and release, often necessitating thyroid hormone replacement therapy [51]. Additionally, hyperparathyroidism and elevated serum calcium levels are recognized but under-monitored complications, affecting approximately 8% - 10% of long-term lithium users. These endocrine changes may occur insidiously and are often overlooked unless routine biochemical surveillance is in place [52].

Emerging evidence also suggests subtle structural changes in the kidneys associated with long-term lithium use, such as microcyst formation and interstitial fibrosis, which may precede measurable changes in renal function. Advanced imaging techniques, such as MRI, have been used in recent studies to detect such microstructural alterations even in asymptomatic patients [53]. While these findings have raised concern, they also underscore the importance of early detection through regular monitoring.

To minimize these risks, international guidelines recommend biannual or annual assessments of renal function, thyroid panel, and serum calcium levels. Clinical decision-making should balance therapeutic benefits with cumulative risks, especially when considering lithium for maintenance therapy beyond a decade. Future directions include the development of low-dose protocols, individualized pharmacokinetic modeling, and alternative delivery systems to mitigate systemic exposure while preserving efficacy.

Lithium and Neuroprotection

The neuroprotection promoted by lithium is associated with its ability to inhibit the enzyme GSK-3β (glycogen synthase kinase-3 beta), a key regulator in cellular signaling involved in neurodegenerative processes [21]. Additionally, lithium promotes neurogenesis by increasing the production of brain-derived neurotrophic factor (BDNF) and reducing oxidative stress and inflammation [15].

Alzheimer's Disease

Alzheimer's Disease is characterized by the accumulation of beta-amyloid plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. Lithium has shown potential to reduce tau phosphorylation through GSK-3β inhibition [9]. Furthermore, studies suggest that lithium may reduce amyloid burden and improve cognitive performance in animal models of the disease [13]. Preliminary clinical trials indicate that low-dose lithium treatment may slow the progression of mild cognitive impairment [15].

Parkinson's Disease

Parkinson's Disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to motor and non-motor symptoms. Lithium has demonstrated neuroprotective potential by reducing oxidative stress and modulating inflammatory pathways involved in disease progression [23]. Studies also indicate that lithium may protect against alpha-synuclein-induced toxicity, a protein associated with neurodegeneration in Parkinson's Disease [16].

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative condition that affects motor neurons, leading to muscle weakness and, eventually, respiratory failure. Studies suggest that lithium may slow ALS progression by promoting neuronal survival and reducing apoptosis [2]. While initial clinical trials showed promising results, more recent studies present inconsistent findings regarding its effectiveness in prolonging patient survival [13] [21].

Lithium presents great potential as a neuroprotective agent in various neurodegenerative diseases. However, the heterogeneity of clinical results indicates the need for further studies to establish its efficacy and safety in these conditions. Future research should focus on identifying biomarkers to predict treatment response and optimizing dosage to minimize adverse effects.

3.5. Safety, Monitoring, and Risk Management

The narrow therapeutic window and risk of toxicity require rigorous clinical monitoring of lithium use to ensure patient safety, minimize adverse effects, and optimize therapeutic response. The recommended therapeutic range for lithium is between 0.6 and 1.2 mEq/L, used both for maintenance and for treating the acute phase of bipolar disorder. Concentrations above 1.5 mEq/L can cause toxic effects, while levels exceeding 2.0 mEq/L are considered critical and may trigger severe neurological complications such as seizures and coma [11] [54]. Lithium toxicity can occur in different forms: acute, chronic, or acute-on-chronic. Acute toxicity results from excessive ingestion in a short period, whereas chronic toxicity occurs due to the progressive accumulation of the substance in the body, often associated with renal failure [37].

Lithium's adverse effects are dose-dependent and include gastrointestinal symptoms such as nausea and diarrhea, as well as fine tremors, polyuria, and weight gain38. Renal toxicity is a significant concern, potentially progressing to chronic tubulointerstitial nephropathy, reinforcing the need for continuous renal function monitoring [10]. Additionally, thyroid dysfunction, particularly hypothyroidism, is well-documented as a side effect associated with prolonged lithium use [22]. Other adverse effects include neurological manifestations such as ataxia and mental confusion, as well as metabolic alterations like hypercalcemia and cardiac arrhythmias in predisposed individuals [55]. More recent studies also suggest a possible effect of lithium on glucose metabolism, increasing the risk of insulin resistance [56].

To reduce the risks associated with lithium use, several strategies are recommended. Strict monitoring of serum lithium concentration is essential and should be performed frequently, especially after dose adjustments or changes in renal function [6]. Additionally, periodic evaluation of renal and thyroid function, including measurement of glomerular filtration rate (GFR) and TSH and T4 levels, is crucial for early detection of complications [57].

Patient education plays a crucial role in treatment safety, making it essential to provide information on toxicity signs, the importance of adequate fluid intake, and strict adherence to the therapeutic regimen [5]. Another relevant aspect is managing drug interactions, as medications such as thiazide diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme inhibitors (ACE inhibitors) can interfere with lithium excretion, increasing its plasma concentration and raising the risk of toxicity [7]. Finally, individualized dosing is essential, considering factors such as age, renal function, and comorbidities to adjust the dosage safely and effectively [13].

Several meta-analyses and large-scale studies reinforce the robust efficacy of lithium in mood stabilization, suicide prevention, and long-term management of bipolar disorder [58]. A comprehensive meta-analysis by Cipriani *et al.* (2013), which included 48 randomized controlled trials, found that lithium was significantly more effective than placebo in preventing relapse in bipolar disorder, with a risk ratio (RR) of 0.66 for mood episode recurrence. Moreover, lithium was superior to other mood stabilizers, including valproate and lamotrigine, in preventing manic episodes. In terms of suicide prevention, a meta-analysis involving 6,674 participants demonstrated that lithium reduced the risk of suicide and self-harm by more than 60% (RR = 0.31, 95% CI: 0.15 - 0.66) compared to placebo or other treatments [5]. This positions lithium as the only mood stabilizer with a strong evidence base for reducing suicide risk.

Long-term studies have also confirmed lithium's effectiveness in mood episode prophylaxis. The BALANCE trial, a large multicenter study, showed that lithium monotherapy was more effective than valproate in preventing relapse, with relapse rates of 27% vs. 39% respectively over a 24-month period [59]. Regarding safety, a meta-analysis published in The Lancet involving over 20,000 patients highlighted that although lithium is associated with a higher risk of hypothyroidism (OR = 5.78) and weight gain (OR = 1.89) compared to placebo, the overall risk of serious adverse events remains low and manageable with proper monitoring [11].

These findings underscore lithium's unique therapeutic profile, combining high efficacy in mood stabilization and suicide prevention with a safety profile that is acceptable under routine monitoring protocols. Such evidence further supports the continued recommendation of lithium as a first-line treatment in bipolar disorder.

Given lithium's importance in the treatment of mood disorders, the implementation of monitoring measures and risk mitigation strategies is essential to ensure its efficacy and reduce the occurrence of severe adverse effects, ensuring safer and more rational use of the medication.

4. Future Perspectives

Advancements in technological and scientific research have driven new approaches to lithium administration, promoting a deeper understanding of its molecular effects and enabling its application in personalized psychiatry. Conventional lithium administration, although widely used, presents considerable limitations due to its narrow therapeutic window and the occurrence of adverse effects. In this context, recent studies aim to improve drug delivery methods to maximize its efficacy and minimize the risks associated with its use.

One of the strategies being investigated involves lithium microdosing, which is based on the administration of sub-therapeutic doses of the substance. Evidence suggests that this approach may provide neuroprotective benefits without causing significant toxicity, making it a promising alternative [11]. At the same time, the formulation of sustained-release delivery systems represents an innovative advancement in lithium administration. The use of nanoparticles and microcapsules enables more uniform absorption, reducing plasma peaks and consequently minimizing adverse effects associated with treatment [58]. Additionally, research has shown that transdermal lithium administration may be an effective alternative, allowing controlled absorption and preventing gastrointestinal complications frequently observed with oral administration [54].

Recent advances in pharmacogenomics have identified several genetic markers associated with lithium response, offering promising directions toward personalized psychiatry. One of the most studied genes is GSK3B, which encodes glycogen synthase kinase-3 beta, a key target of lithium's action. The rs334558 polymorphism in this gene has been associated with better treatment outcomes in patients with bipolar disorder receiving lithium therapy [60] [61]. Additionally, variations in the ANK3 gene, such as rs10994336, have shown predictive value in lithium response due to their role in neuronal excitability and signal transduction [62] [63].

A genome-wide association study (GWAS) conducted by the Consortium on Lithium Genetics (ConLiGen) identified significant loci on chromosome 21q22.13–q22.2 related to lithium responsiveness [64]. Furthermore, genes such as BCL2, which is involved in apoptosis regulation, and SLC4A10, implicated in neural pH balance, have also been associated with lithium efficacy [65] [66]. In addition, recent studies have explored polygenic risk scores (PRS) to predict lithium response, showing that patients with lower PRS for schizophrenia tend to respond more favorably to lithium [64].

Despite these insights, routine clinical application remains premature. Limitations include small effect sizes of individual variants, population heterogeneity, and a need for further validation. However, the integration of genomics with clinical and proteomic data, alongside AI-assisted models, is accelerating progress toward precision medicine in psychiatry. As collaborative databases grow, the use of genetic testing to guide lithium treatment becomes an increasingly realistic possibility.

Personalized psychiatry, an emerging approach in mental health, seeks to refine therapeutic strategies by considering genetic factors, biomarkers, and individual patient characteristics. Within this context, lithium has been studied to improve the predictability of therapeutic response. One of the directions explored involves the identification of genetic biomarkers that can predict lithium's efficacy for certain patients, allowing for more precise and effective prescriptions [6]. Additionally, the development of artificial intelligence models has been applied to the analysis of large data volumes, enabling the suggestion of individualized and optimized doses for each patient based on sophisticated algorithms [13]. Furthermore, proteomic analyses have been conducted to understand the differential effects of lithium among patients, allowing for a more targeted and effective therapeutic approach [22].

Given these innovations, the future of lithium in psychiatry appears promising, integrating technological advancements in its administration, deepening the understanding of its molecular effects, and promoting its incorporation into personalized therapeutic strategies. The evolution of pharmaceutical formulations, combined with discoveries in genomics and proteomics, suggests significant potential for optimizing lithium use, expanding its indications, and benefiting a larger number of patients safely and effectively.

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Conflicts of Interest

The authors declare no conflicts of interest.

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