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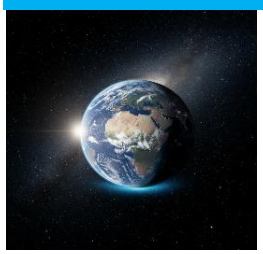

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Lithium Through Time: Past Insights, Present Applications and Future Prospects

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Abstract

Introduction and Purpose:

Lithium is a cornerstone of psychopharmacology, with expanding roles beyond psychiatry. This narrative review covers its historical evolution, current applications, and emerging uses in psychiatry, neurology, and general medicine—focusing on bipolar disorder, suicide prevention, neurodegeneration, infections, and pregnancy. The aim is to synthesize mechanistic and clinical data showing how lithium's actions (GSK-3 inhibition, neurotrophic support, anti-inflammatory effects) enable precise, safe prescribing.

Materials and Methods:

This narrative synthesis draws from recent systematic reviews, meta-analyses, and key studies on lithium's efficacy, mechanisms, and novel indications (past decade). PubMed, psychiatry/neurology journals, and public health reports were searched using terms like "lithium bipolar," "lithium suicide," "lithium neurodegeneration," prioritizing robust, clinically relevant sources.

Results:

Lithium is the gold-standard mood stabilizer (50–67% response rates, ~5-fold suicide risk reduction). Trace lithium in water links to lower suicide/dementia rates. Early data support neuroprotection in MCI/Alzheimer's, plus roles in cluster headache, infections, and perinatal mood—offset by renal/thyroid/cardiac risks needing monitoring.

Conclusions:

Lithium excels in bipolar disorder and suicide prevention, with neuroprotective, anti-inflammatory potential. Future focus: low-dose regimens, precision monitoring, digital tools.

Keywords:
Lithium; bipolar disorder; suicide prevention; neuroprotection; neurodegenerative diseases; trace lithium in water; cluster headache; pregnancy; adverse effects; therapeutic drug monitoring.

Description of the state of knowledge

Introduction

Lithium is the lightest alkali metal, characterized by a silvery sheen, high reactivity, and distinctive physical properties that set it apart from other metallic elements[1]. In clinical practice, lithium salts are regarded as first-line mood stabilizers, with robust evidence supporting their effectiveness in preventing both manic and depressive recurrences in bipolar disorder and in lowering suicide risk in patients with recurrent mood episodes[2,3]. Beyond established psychiatric indications, lithium is increasingly explored for its neuroprotective potential and possible usefulness in conditions such as mild cognitive impairment, dementia, and post-stroke recovery, indicating promising broader roles within neurology [1,4]. Its pharmacodynamic profile includes inhibition of glycogen synthase kinase-3, upregulation of neurotrophic factors, and support of neuroplastic processes, while its narrow therapeutic index necessitates strict clinical monitoring, making ongoing lithium research crucial for optimizing efficacy, enhancing safety, and reducing adverse effects[1,5].

History

Lithium's role in medicine commenced with John Cade's 1949 identification of its antimanic effects, transforming it from an experimental substance into a fundamental psychiatric treatment[1]. Initial concerns about toxicity limited its use until landmark clinical trials in Scandinavia during the 1960s and 1970s demonstrated its safety and effectiveness for preventing bipolar disorder relapse[6]. The U.S. Food and Drug Administration's approval in 1970 formalized lithium as a key psychiatric medication, with subsequent meta-analyses confirming its efficacy in minimizing mood episode recurrence[7]. More recent investigations have renewed interest in lithium's neuroprotective capabilities, supported by evidence indicating preserved cognitive function among long-term users beyond its psychiatric effects[8]. Extensive longitudinal data validate lithium's established superior efficacy in reducing suicide risk, affirming its lasting prominence in mood disorder management[6].

Mechanisms of Lithium Action

Lithium affects many cell signaling pathways, helping cells resist stress, improve signal transmission, and reduce brain inflammation through wide-ranging effects. Recent reviews see lithium as a broad controller of enzymes, receptors, and gene activity, unlike drugs that target just one thing. It blocks GSK-3 by competing with magnesium and adding phosphate to serine sites. This limits cell death, fixes daily rhythms, and aids healthy synapse changes. As a result, it strengthens β-catenin groups, boosts growth factors, and calms inflammation, supporting steady mood and brain protection. It also blocks enzymes that break down inositol, lowering its levels. This restores normal phosphatidylinositol and G-protein signals. Lithium raises BDNF and activates TrkB receptors. This promotes new neurons in the hippocampus and protects mitochondria from oxygen damage and energy shortages[1]. It cuts inflammation by blocking NF-κB and adjusting microglia. It also tweaks AMPA receptors to steady overactive brain networks[9]. Changes in histones, DNA methylation, and microRNAs boost brain flexibility and explain why responses to treatment vary[10]. Current views describe lithium as a versatile brain regulator. It treats psychiatric symptoms and may slow some brain diseases[1].

Application

Lithium serves as the primary medication in long-term management of bipolar disorder, demonstrating markedly superior treatment results for preventing relapses and maintaining

mood stability compared to other mood-regulating drugs. Current research shows that lithium produces therapeutic benefits in approximately two-thirds of patients, most of whom achieve symptom stabilization following each treatment period[7]. This medication possesses distinctive properties in reducing suicidal behavior among bipolar patients, outperforming other treatments such as valproate in lowering self-harm incidents according to extensive clinical reviews[11]. Lower doses of lithium may provide protective effects on brain cells, including reduced neurodegeneration and decreased inflammatory markers, even without reaching standard therapeutic blood levels[12]. Maintaining serum concentrations between 0.6-0.8 mmol/L achieves a balance between therapeutic effectiveness and reduced adverse effects, requiring regular blood tests to monitor kidney and thyroid function[8]. Stopping lithium treatment due to declining kidney function substantially increases the risk of mood episode relapse, highlighting the necessity for individualized clinical decision-making[13]. Expert consensus recognizes that lithium remains underutilized despite strong evidence of its effectiveness in everyday clinical practice, often due to incorrect assumptions regarding safety and side effect profiles[8]. Extended-release formulations improve treatment adherence and patient comfort by reducing peak blood levels, thereby minimizing side effects such as tremor, increased urination, and digestive disturbances[7].

Bipolar Disorder Treatment

Lithium constitutes a primary mood stabilizer in bipolar disorder management, exhibiting substantial efficacy in mitigating acute manic episodes and forestalling relapses during protracted maintenance therapy. Empirical data reveal that approximately 66% of patients attain clinically significant symptom alleviation during manic or depressive episodes, with over 50% achieving remission per therapeutic cycle[7]. Lithium demonstrably prolongs euthymic intervals and diminishes recurrence rates among individuals with bipolar disorder. It confers a distinctive advantage by substantially reducing suicide attempts in high-risk cohorts, corroborated by extensive clinical evidence. Systematic monitoring of serum concentrations effectively mitigates renal and thyroid liabilities, rendering severe adverse events infrequent in routine clinical contexts. Extended-release formulations enhance therapeutic adherence and tolerability by attenuating peak-trough fluctuations that precipitate tremors or gastrointestinal disturbances[8].

Anti-suicidal action of lithium.

Lithium is well established as a highly effective treatment for reducing suicidal behavior in patients with recurrent mood disorders. Its use is associated with lower rates of suicide attempts and completed suicides compared to patients not on lithium therapy. The antisuicidal benefits of lithium are linked to its ability to modulate neurotransmission, stabilize mood, and decrease impulsivity. Neuroprotective and anti-inflammatory effects further enhance its protective role. Owing to strong clinical evidence, lithium remains a frontline option in suicide prevention strategies for mood disorders[14]. Lithium demonstrates remarkable efficacy in mitigating suicidal ideation and self-destructive behaviors among bipolar patients, with substantial evidence documenting reductions in suicide mortality and attempts across longitudinal clinical investigations[11]. The protective mechanisms against suicidal acts represent among the most rigorously examined therapeutic advantages in psychiatric pharmacology, with data indicating a 50-80% decrease in self-harm risk when compared to competing mood-regulating pharmaceuticals in individuals experiencing recurring affective disturbances. Lithium surpasses rival therapeutic agents including divalproex and lamotrigine in curtailing suicidal outcomes, especially among bipolar patients demonstrating antecedent self-harm incidents[14]. The biological underpinnings of lithium's protective actions involve diverse neurochemical cascades, particularly inhibition of glycogen synthase kinase-3 (GSK-3), producing anti-inflammatory consequences and reduction of behavioral traits including aggression and impulsivity implicated in suicidal phenomena[15]. Lithium's capacity to suppress inflammatory activation and attenuate dysphoric affect, psychomotor agitation, and behavioral impulsivity appears instrumental to its shielding capacity against suicide attempts, especially during depressive and admixed affective episodes in bipolar illness[14].

Lithium in Neurodegenerative Diseases

Lithium is recognized as a key treatment for bipolar disorder, with extensive analysis confirming its ability to reduce mood episode recurrence. Its effects operate through multiple neurobiological mechanisms including regulation of neurotransmitter systems and enhancement of neuroprotection[1]. A central element of its function is the inhibition of glycogen synthase kinase-3 (GSK3), which influences neuronal survival and signaling pathways implicated in neurodegenerative and psychiatric conditions[1,16].

In the context of Alzheimer’s disease, lithium shows promise by modifying harmful processes such as tau protein phosphorylation and amyloid precursor metabolism. This leads to reduced synaptic dysfunction and cognitive decline. It also acts to reduce neuroinflammation and oxidative damage while supporting neurotrophic factors, suggesting potential disease-modifying effects beyond symptom control[16].

Recent research also highlights lithium’s role in synaptic homeostasis and regulation of microRNA expression, mechanisms that may underpin its efficacy across various brain disorders. Despite its benefits, lithium requires close monitoring due to its narrow therapeutic range and risk of toxicity. Ongoing studies aim to better define its molecular targets to improve therapeutic strategies and expand its clinical use[1].

Antiviral and Antimicrobial Properties

Lithium compounds show growing promise against resistant infections, extending their role beyond psychiatry. For instance, a lithium derivative from salicylic acid and nitrogen compounds strongly fights multidrug-resistant Acinetobacter baumannii. It stops bacterial growth and breaks biofilms using oxidative damage and membrane disruption[17]. Lithium chloride also limits Marek's disease virus in chicken cells by reducing replication and boosting interferon-beta. Similar effects occur against porcine parvovirus in early infection[18,19].
Early COVID-19 observations suggested lithium carbonate helps by lowering inflammation, raising white blood cells, and improving immune balance[20]. Lithium in laser-treated calcium phosphate materials controls Staphylococcus bacteria and Candida fungi without harming human cells[21]. These effects likely come from GSK-3 blockade, reactive oxygen species, and immune changes, pointing to lithium's potential against infections [17].

Cluster Headaches

Cluster headache is one of the most serious primary headache disorders, defined by repeated episodes of intense one-sided pain around the eye that typically last between 15 minutes to 3 hours per attack[22]. Despite having recognizable symptoms, cluster headache is often not

correctly diagnosed, with patients waiting an average of approximately 10.43 years from first symptoms to proper identification[23]. The chemical basis of cluster headache involves problems with multiple neurotransmitter systems, including higher levels of histamine and increased release of neuropeptides called calcitonin gene-related peptide (CGRP) and substance P, especially when attacks are occurring[24]. Deep brain stimulation that targets specific areas of the hypothalamus has become a promising treatment approach, showing significant reductions in how often attacks happen, how severe they are, and how long they last in patients with chronic cluster headache that does not respond to other treatments[25]. Verapamil and lithium are the most proven medications for preventing cluster headaches, while newer medications that target CGRP show promising results in early studies[26].

Lithium Treatment in Pregnancy and Postpartum Period

Lithium is a recognized treatment to prevent mood episode relapse in pregnant and postpartum women with bipolar disorder despite inherent risks. Pregnancy-induced physiological changes such as increased glomerular filtration necessitate dose adjustments and frequent lithium blood level monitoring, especially in the third trimester. To minimize neonatal harm, lithium dosage reduction by 30-50% or temporary discontinuation 1–2 days before childbirth is commonly recommended, with resumption within 12 hours postpartum. Lithium crosses the placenta freely, exposing the fetus to maternal blood levels at birth; this may cause transient neonatal symptoms like decreased muscle tone[27]. Although first-trimester exposure correlates with a slight risk of congenital heart defects, newer evidence suggests risks are lower than previously estimated, supporting continuation when clinical benefit outweighs risk[28,29]. Lithium use may slightly increase premature delivery and neonatal hospital readmission risks, yet links to preeclampsia, gestational diabetes, or low birth weight remain inconclusive[28]. Early postpartum maintenance of therapeutic lithium levels is vital due to heightened relapse risk and post-delivery kidney function changes. Breastfeeding while on lithium requires careful risk-benefit assessment due to possible lithium passage in breast milk. Overall, lithium remains critical for bipolar disorder management during pregnancy and the perinatal period, contingent on close supervision and monitoring[26].

Adverse effects of lithium

Although lithium offers substantial therapeutic value in managing bipolar disorder, its profile includes multiple side effects demanding vigilant clinical supervision and informed patient discussions. Progressive renal parenchymal damage stands out as a primary long-term concern, affecting 10-40% of individuals on extended therapy, particularly beyond 10-20 years of exposure. Nephrogenic diabetes insipidus, characterized by pronounced polyuria and polydipsia, emerges in 20-40% of users, often compromising daily quality of life. Thyroid dysfunction, manifesting as hypothyroidism or glandular enlargement, impacts roughly 20-30% of patients due to lithium's disruption of hormone biosynthesis and secretion. Cognitive impairments like memory deficits and slowed cognition frequently erode patient well-being, prompting treatment discontinuation[30]. Cardiac irregularities, including arrhythmias and myocarditis, necessitate baseline and ongoing evaluations, especially in vulnerable populations[31]. Overdose scenarios heighten risks of profound conduction blocks and life-threatening dysrhythmias, particularly among elderly patients with comorbidities [32].

Monitoring Lithium Therapy and Safety

Therapeutic monitoring of lithium is essential for safe treatment, requiring regular serum concentration assessments to maintain levels within the therapeutic window[1]. Standard practice involves measuring lithium levels 10–14 hours post-dose, targeting concentrations between 0.6–1.2 mEq/L based on clinical indication and individual factors[1,34]. Electronic health record–integrated reminder systems improve compliance with monitoring schedules, reducing risks of subtherapeutic levels or toxic accumulation[35]. Periodic assessments every 3–6 months following dose stabilization allow early detection of adverse effects and therapy adjustment[1].

Recent evidence indicates that lower serum lithium concentrations—as low as 0.4–0.6 mEq/L—may provide therapeutic benefits while reducing toxicity risks, particularly in older adults or those with renal impairment. Individualized dosing strategies optimize the risk-benefit profile[34]. Comprehensive monitoring encompasses evaluation of renal function, thyroid status, and metabolic parameters to detect lithium-related complications. Patient education regarding hydration, dietary sodium consistency, and medication adherence fosters optimal outcomes[1].

Contraindications

Lithium therapy has specific contraindications requiring careful clinical evaluation[35]. Severe renal impairment (glomerular filtration rate <30 mL/min/1.73m²) is an absolute contraindication due to lithium accumulation and nephrotoxicity risk[1]. Significant cardiac conduction abnormalities, such as advanced atrioventricular block, represent important contraindications as lithium may worsen these conditions. History of lithium-induced nephrogenic diabetes insipidus or severe hypersensitivity reactions precludes re-exposure [35]. Uncontrolled hyponatremia poses a contraindication, as sodium depletion increases lithium retention and toxicity[1]. Untreated thyroid disease warrants caution given lithium's thyroid effects[35].

Pregnancy, particularly first trimester, requires careful consideration due to potential teratogenic risks[7]. Acute dehydration or conditions causing volume depletion may necessitate temporary discontinuation. Concurrent medications including ACE inhibitors, NSAIDs, and thiazide diuretics reduce lithium clearance and elevate toxicity risks[36]. Expert consensus emphasizes comprehensive pre-treatment evaluation encompassing renal function, cardiac assessment, and baseline laboratory parameters[35].

Environmental Lithium Levels and Mental Health Statistics

Natural lithium found in drinking water represents an important area of research, with studies showing connections between lithium exposure in water supplies and lower rates of suicide, dementia, and other mental health problems in communities where this occurs[4]. Higher amounts of lithium in groundwater have been shown to be linked with reduced suicide death rates in different regions and population studies, suggesting that the community may be protected against suicide through this natural exposure[2]. Small amounts of lithium in public water systems, ranging from 0.002 to 0.25 mg/L, appear to be enough to provide brain protection, with research showing that this exposure connects to lower rates of dementia and death in people living in these areas[37]. The way lithium works in the body involves stopping a specific enzyme called glycogen synthase kinase-3 (GSK-3) and reducing brain inflammation at low doses, which may explain why communities with lithium in their water have fewer cases of dementia[4].

New Directions in Lithium Research and Applications

Contemporary lithium research extends beyond psychiatric applications, exploring therapeutic potential in neurodegenerative diseases[4]. Evidence demonstrates lithium's promise in Alzheimer's disease through GSK-3 inhibition and modulation of tau phosphorylation, potentially slowing cognitive decline. These neuroprotective mechanisms expand understanding of lithium's clinical utility beyond mood stabilization[16].

Translational studies reveal lithium's multifaceted effects on cellular signaling, oxidative stress reduction, and neuroinflammation, suggesting broader applications across neurological conditions. Lithium enhances mitochondrial function, promotes neurogenesis, and modulates microRNA expression influencing neuronal survival[1].

Personalized medicine approaches identify biomarkers predictive of lithium response and toxicity susceptibility, enabling individualized treatment optimization. Novel lithium formulations and delivery systems are under investigation to improve tolerability and reduce adverse effects[4]. Clinical trials examining lithium in amyotrophic lateral sclerosis, Parkinson's disease, and traumatic brain injury reflect the expanding investigative landscape[1].

These developments position lithium as a multi-target agent addressing diverse pathophysiological mechanisms, warranting continued rigorous investigation in precision psychiatry and neurology[4,16].

Conclusion

Lithium is a versatile therapeutic agent primarily used as a mood stabilizer in bipolar disorder, effectively preventing mood episodes and reducing suicide risk via multiple molecular mechanisms including GSK-3β inhibition and neurotrophic support. Beyond psychiatry, it shows promise in neuroprotection, anti-inflammation, and as an adjunct antiviral and antibacterial agent. Its clinical use in conditions like cluster headaches and pregnancy necessitates careful monitoring because of its narrow therapeutic window. Advances in precision medicine and monitoring technologies aim to optimize lithium’s safety and efficacy. Future research will focus on enhancing formulations, validating new therapeutic roles, and deepening understanding of lithium’s molecular targets, ensuring its lasting importance in medicine.

Disclosures

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