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LITHIUM AND ALZHEIMER'S DISEASE: NEUROBIOLOGICAL MECHANISMS, ETHICAL IMPLICATIONS, AND SOCIAL PERSPECTIVES ON COGNITIVE AGING

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ABSTRACT

Alzheimer's disease is a progressive, idiopathic neurodegenerative disorder characterized by the accumulation of amyloid plaques, tau tangles, and synaptic degeneration. Its global prevalence continues to rise, posing significant challenges for healthcare systems and aging societies. Despite recent advances in disease-modifying treatment, such as monoclonal antibodies (donanemab, lecanemab, aducanumab), their high cost, limited efficacy, and risk of adverse effects underline the urgent need for therapies that are safe, effective, and economically accessible.

This review evaluates the role of lithium a long-established mood stabilizer in the prevention and modulation of Alzheimer's disease. Drawing from preclinical studies, observational data, and early-phase clinical trials published between 2017 and 2025, it examines how lithium influences key pathological mechanisms including amyloid precursor protein processing, tau phosphorylation, oxidative stress, neuroinflammation, and synaptic plasticity. Chronic exposure to low or trace doses has been associated with delayed cognitive decline and reduced disease incidence in several populations. However, evidence from randomized trials remains inconclusive, warranting further rigorous investigation.

In addition to biological mechanisms, this review explores ethical and social dimensions of lithium use in older adults, including questions of informed consent, adherence, age-related pharmacokinetics, and the stigma of psychiatric medication. Lithium emerges as a biologically plausible, cost-effective, and potentially scalable strategy for addressing cognitive aging. Future directions require ethically sound, large-scale clinical trials and a broader public health dialogue on the integration of preventive pharmacotherapy into neurodegenerative disease management.

KEYWORDS

Alzheimer's Disease, Lithium, Microdosing, GSK-3β Inhibition, Tau Protein Phosphorylation, Neuroprotection

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Introduction

Alzheimer's disease is the most common neurodegenerative disorder and the leading cause of dementia in the aging population worldwide. It is estimated to account for approximately 60-80% of all dementia cases, representing one of the major causes of disability and loss of independence in later life. Dementia currently ranks as the seventh leading cause of death globally. At the same time, it remains one of the key factors contributing to dependency and the need for long-term care among older adults [1].

In 2019, the global economic burden of dementia was estimated at USD 1.3 trillion, with nearly half of this amount attributed to informal care provided primarily by family members or close friends who devoted an average of five hours per day to supporting and supervising individuals living with the condition. Women are disproportionately affected by dementia. They are not only more likely to develop and die from the disease but also constitute about 70% of caregivers for those affected [2]. The growing burden associated with Alzheimer's disease exerts increasing pressure on families, caregivers, and healthcare systems. This underscores the urgent need to develop effective preventive and therapeutic strategies to address this escalating global challenge.

Despite decades of research, currently approved therapies for Alzheimer's disease including acetylcholinesterase inhibitors, NMDA receptor antagonists, and, more recently, monoclonal antibodies targeting β-amyloid have demonstrated only limited clinical efficacy. These treatments are often associated with high financial costs, narrow patient eligibility criteria, and an increased risk of adverse effects [3-6]. Although such interventions may modestly slow cognitive decline in selected patient populations, their moderate therapeutic impact and considerable resource demands underscore the urgent need for safer, more accessible, and truly disease-modifying therapeutic alternatives.

Moreover, most existing approaches focus on alleviating symptoms or targeting downstream pathological processes rather than addressing the early, multifactorial mechanisms underlying neurodegeneration in Alzheimer's disease [7,8].

One promising candidate in this context is lithium, a mood stabilizer that has been widely used in psychiatry for several decades [9,21]. Recent preclinical and translational studies suggest that lithium exerts neuroprotective effects through multiple mechanisms, including inhibition of glycogen synthase kinase-3β (GSK-3β), reduction of tau hyperphosphorylation, modulation of amyloid precursor protein (APP) processing, and attenuation of oxidative stress and neuroinflammation [10,11]. Growing evidence also indicates that lithium influences mitochondrial function, synaptic plasticity, and neurotrophic signaling, all of which are disrupted in Alzheimer's pathology [12].

Importantly, several population-based and early clinical studies have reported an association between chronic low-dose lithium exposure and a reduced risk or slower progression of cognitive impairment [13]. Although preliminary, these findings provide a compelling rationale for further exploration of lithium's therapeutic and preventive potential in Alzheimer's disease.

The aim of this narrative review is to synthesize current knowledge on lithium's role in Alzheimer's disease from neurobiological, ethical, and social perspectives, highlighting the need for large-scale clinical validation, responsible implementation, and integration of lithium-based strategies within broader public health frameworks addressing cognitive aging.

Materials and Methods

This article was designed as a narrative review with the objective of summarizing and critically analyzing the current evidence regarding the neuroprotective, clinical, and pharmacological effects of lithium in Alzheimer's disease (AD) and mild cognitive impairment (MCI). The purpose of this work was to integrate findings from molecular, preclinical, and clinical studies to provide a comprehensive overview of lithium's mechanisms of action, therapeutic efficacy, innovative delivery strategies, and safety profile.

The source material consisted of full-text peer-reviewed scientific publications retrieved from reputable databases, including PubMed, Scopus, Web of Science, ScienceDirect, SpringerLink, Wiley Online Library, and Core.ac.uk, as well as open-access archives of neuropharmacological and psychiatric journals. The literature search covered the years 2017-2025, with earlier works included when they offered significant contextual or mechanistic insights into the biological basis or historical therapeutic use of lithium in neurodegenerative disorders.

Studies were eligible for inclusion if they addressed the molecular mechanisms of lithium's action, its therapeutic effects in Alzheimer's disease or related neurodegenerative conditions, or investigated innovative administration methods such as intranasal formulations, hydrogel-based systems, or nanoparticle carriers. Included materials encompassed randomized clinical trials, cohort studies, preclinical animal experiments, systematic reviews, and meta-analyses published in English. Excluded were case reports, editorial comments, letters to the editor, conference abstracts, and papers lacking empirical or original data.

The literature selection process was conducted in several stages. Initially, titles and abstracts were screened to eliminate works not directly relevant to the research question. Subsequently, the full texts of the remaining studies were examined with respect to study design, characteristics of the study population or experimental model, dosage and formulation of lithium, treatment duration, and primary outcomes related to cognitive function, neurobiological markers, and safety parameters. Each publication was critically assessed for methodological rigor, reproducibility, and scientific quality.

The extracted data were synthesized qualitatively rather than quantitatively, reflecting the heterogeneity of methodologies and outcome measures among the analyzed studies. Results were thematically organized into four major domains: (1) neurobiological mechanisms underlying lithium's effects in Alzheimer's disease, (2) comparative clinical efficacy of lithium versus monoclonal antibodies, (3) novel delivery strategies for central nervous system targeting, and (4) epidemiological and safety evidence concerning long-term and microdose lithium use.

The narrative review approach allowed for the integration of diverse types of evidence from molecular and animal studies to population-based and clinical investigations providing a multidimensional and interdisciplinary perspective on lithium as a potential neuroprotective and disease-modifying agent in Alzheimer's disease.

Results

I. Neurobiological Mechanisms of Lithium Action in Alzheimer's Disease

An analysis of preclinical and clinical data indicates that lithium acts on multiple molecular pathways involved in the pathogenesis of Alzheimer's disease (AD), including tau phosphorylation, β-amyloid (Aβ) metabolism, oxidative stress, neuroinflammation, mitochondrial homeostasis, and processes related to neurogenesis and synaptic plasticity. Collectively, these findings suggest a beneficial influence of lithium on neuronal survival and the maintenance of cognitive function.

a) Inhibition of GSK-3β, hippocampal neurogenesis, and synaptic plasticity

The pathological role of glycogen synthase kinase-3 beta (GSK-3β) in Alzheimer's disease is well established. Its overactivity contributes to several hallmark features of AD, including tau hyperphosphorylation and β-amyloid aggregation. During disease progression, excessive GSK-3β activity drives the abnormal phosphorylation of tau, leading to the formation of neurofibrillary tangles (NFTs) that disrupt neuronal function. Phosphorylated tau loses its ability to bind microtubules, impairing axonal transport and promoting neurodegeneration through intracellular NFT accumulation. Moreover, GSK-3β participates in amyloid precursor protein (APP) proteolysis, accelerating Aβ peptide production and amplifying the neurotoxic cascade characteristic of AD [28].

Multiple studies have confirmed that lithium modulates key neuroplastic processes by inhibiting GSK- 3β and activating neurotrophic signaling pathways [36,38]. Inhibition of GSK-3β reduces pathological tau phosphorylation, stabilizes microtubules, improves axonal transport, and supports neuronal integrity [14,20]. Chronic lithium exposure has been shown to decrease both total and phosphorylated tau levels in the hippocampus and cerebral cortex [10,15], correlating with improvements in cognitive performance.

In transgenic 3xTg-AD mouse models, long-term lithium administration improved recognition memory, encompassing both short-term and long-term memory components, thereby confirming its neuroprotective action [16]. Notably, even micro- and subtherapeutic lithium doses (≤0.2 mM) effectively reduce GSK-3β activity without inducing toxic effects [17]. Conversely, endogenous lithium deficiency has been associated with elevated GSK-3β activity, increased tau phosphorylation, and accelerated neurodegenerative changes [10].

In parallel, lithium exerts significant effects on neurogenesis and synaptic plasticity within the hippocampus. Exposure to lithium enhances the proliferation and differentiation of neuronal progenitor cells, while neuroimaging studies have reported increased hippocampal volume in patients undergoing chronic lithium treatment [44]. These effects are largely mediated by the activation of neurotrophic signaling pathways dependent on brain-derived neurotrophic factor (BDNF) and the transcription factor CREB. In animal models, lithium increased dendritic spine density and potentiated long-term synaptic strengthening (LTP), translating into improved learning and spatial memory performance [16].

b) Modulation of APP Processing and β-Amyloid Metabolism

In addition to inhibiting GSK-3β, lithium increases nuclear β-catenin levels, which interact with the transcription factor TCF4 to downregulate BACE1 expression, thereby reducing the amyloidogenic cleavage of amyloid precursor protein (APP). Furthermore, lithium attenuates γ-secretase activity and enhances Aβ clearance by improving microvascular function within the blood–brain barrier, collectively limiting amyloid plaque accumulation [18].

Experimental models have demonstrated that chronic supplementation with microdoses of lithium significantly reduces cerebral amyloid burden and increases the expression of synaptic markers such as PSD-95 and NMDA receptor subunits. These molecular effects correlate with preserved spatial memory and enhanced neuroplasticity [19]. Recent studies also suggest that β-amyloid deposits may sequester lithium ions, leading to local lithium depletion and secondary activation of GSK-3β. This process further promotes Aβ accumulation and tau phosphorylation, amplifying the neurodegenerative cascade characteristic of Alzheimer's disease [10].

c) Regulation of Autophagy, Mitochondrial Homeostasis, and Cellular Metabolism by Lithium.

Recent studies have demonstrated that lithium modulates several key processes essential for maintaining neuronal homeostasis, linking the regulation of autophagy, mitochondrial stability, and cellular energy metabolism. Lithium has been shown to induce autophagy through inhibition of inositol monophosphatase (IMPase), which activates the AMPK-Beclin-1 signaling pathway and promotes the clearance of damaged proteins and dysfunctional mitochondria [15]. This mechanism aligns with the so-called inositol depletion hypothesis, which proposes that inhibition of IMPase and inositol polyphosphate 1-phosphatase (IPPase) leads to reduced levels of free myo-inositol and alterations in the phosphatidylinositol cycle. The resulting decrease in myo-inositol availability limits the synthesis of phosphatidylinositol (IP_3), thereby reducing Ca^{2+} release

from the endoplasmic reticulum. This cascade mitigates glutamatergic excitotoxicity and prevents calcium overload within neurons [22]. Concurrently, AMPK activation enhances Beclin-1 expression and promotes the formation of autophagosomes, facilitating the removal of pathological protein aggregates such as tau and Aβ fragments [23,27]. Through these mechanisms, lithium supports cellular proteostasis and protects neurons against the accumulation of misfolded or oxidatively damaged proteins, processes that play a pivotal role in Alzheimer's disease pathogenesis.

In parallel, lithium exerts a direct effect on mitochondrial bioenergetics. Experimental studies have shown that lithium preserves mitochondrial membrane potential and prevents cytochrome c release, thereby inhibiting the apoptotic cascade [25]. Other investigations have reported that chronic lithium supplementation decreases lipid peroxidation levels and increases the activity of antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), thus supporting mitochondrial integrity and redox balance [26]. Moreover, lithium improves glucose metabolism by upregulating GLUT-3 and GLUT-4 transporters and modulates cholinergic neurotransmission through inhibition of acetylcholinesterase activity. These effects collectively contribute to enhanced neuronal energy efficiency and the preservation of cognitive performance [18].

Proton magnetic resonance spectroscopy (^{1}H-MRS) studies have further shown that lithium treatment is associated with decreased myo-inositol concentrations in the hippocampus and cingulate gyrus, reflecting suppression of the phosphatidylinositol (PI) cycle and possible indirect activation of neuronal autophagy mechanisms [27].

II. Clinical Effectiveness of Lithium Compared to Monoclonal Antibodies

Recent comparative analyses have evaluated the clinical outcomes of lithium therapy in relation to monoclonal antibodies such as donanemab, lecanemab, and aducanumab in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). While monoclonal antibodies act by directly binding and removing amyloid-β aggregates, lithium demonstrates a multifactorial neurobiological effect including inhibition of GSK-3β, modulation of APP processing, and reduction of oxidative and inflammatory stress which together contribute to the stabilization of cognitive functions and the slowing of neurodegenerative processes.

According to recent meta-analyses, lithium exhibits comparable cognitive efficacy in treating MCI and early-stage AD compared to monoclonal antibodies, while presenting a significantly lower risk of adverse effects. Lithium shows a favorable safety and tolerability profile even at very low concentrations, whereas biologic therapies such as aducanumab and lecanemab are frequently associated with ARIA-E and ARIA-H (amyloid-related imaging abnormalities) as well as infusion-related reactions [29].

Economic evaluations further illustrate the limitations related to the cost of biologic therapies. The annual cost of lecanemab treatment exceeds $25,000 per patient, with additional monitoring and infusion-related expenses increasing the total by approximately 28%, resulting in an estimated annual cost of about $33,000 per patient. Projections indicate that widespread use of such therapies could raise Medicare expenditures by $2–5 billion annually [30]. In contrast, lithium is inexpensive, orally administered, widely available, and well tolerated, making it a more practical and scalable therapeutic option, particularly in long-term care and preventive settings.

Recent evidence published in *Nature* demonstrated that endogenous lithium deficiency in the brain is associated with accelerated amyloid-β deposition, increased GSK-3β activity, and heightened tau phosphorylation, leading to faster cognitive decline [10]. These findings suggest that lithium unlike monoclonal antibodies, which act primarily at later stages of amyloid pathology may also play a preventive and homeostatic role, maintaining neuronal integrity and mitigating the progression of neurodegenerative changes.

III. Novel Therapeutic Strategies: Lithium Orotate and Innovative Central Nervous System Delivery Systems

Advances in molecular pharmacology and nanotechnology have opened new opportunities to enhance the efficacy and safety of lithium-based therapy for Alzheimer's disease (AD). Recent research focuses on three promising directions: lithium orotate (LiOr), intranasal nose-to-brain delivery systems, and nanotechnology-based lithium carriers utilizing gold nanoparticles.

a) Lithium Orotate (LiOr) as an Organic Lithium Salt with Enhanced Bioavailability and Neuroprotective Potential

Evidence indicates that endogenous lithium deficiency in the brain leads to increased GSK-3β activity, tau hyperphosphorylation, and accelerated amyloid-β accumulation key processes contributing to neurodegeneration [10]. Preclinical studies demonstrate that supplementation with lithium orotate can counteract these pathological mechanisms, resulting in improved cognitive function and a reduction of amyloid-β deposition in the hippocampus. As an organic lithium salt, LiOr provides enhanced bioavailability within the central nervous system (CNS) and exhibits lower renal toxicity compared to conventional lithium carbonate, making it a safer and more sustainable option for long-term or preventive therapeutic use.

b) Intranasal Nose-to-Brain Lithium Delivery Systems: Hydrogel and Nanoparticle Formulations

Recent preclinical studies have highlighted the potential of intranasal lithium delivery as a noninvasive and targeted therapeutic strategy for CNS disorders. One investigation demonstrated that a sprayable, in situ-forming hydrogel composed of chelating starch nanoparticles (EDTA, DTPA) effectively transported lithium ions to the brain via olfactory and trigeminal pathways, bypassing hepatic metabolism [31]. In vivo assessments revealed that brain lithium concentrations remained within the therapeutic range for more than six hours, compared to less than two hours observed with standard formulations. The hydrogel also maintained lower serum lithium levels, indicating an improved pharmacokinetic and safety profile.

Another study confirmed that intranasal administration of lithium chloride using a nanoparticle-based Ryanodex Formulation Vehicle (RFV) prevented cognitive impairment, memory loss, and depression-like behavior in 5XFAD mouse models of AD [33]. The therapy inhibited neuroinflammatory pyroptosis through suppression of the NLRP3 inflammasome, decreased oxidative stress, restored synaptic integrity, and normalized calcium signaling. Notably, no adverse renal, thyroid, or motor effects were observed after 12 weeks of treatment. Collectively, these findings demonstrate that intranasal lithium delivery using hydrogel or nanoparticle systems enhances brain bioavailability, prolongs therapeutic activity, and minimizes systemic toxicity, supporting its feasibility as a safe and effective alternative to oral or intravenous administration.

c) Nanotechnology-Based Gold Nanoparticle Carriers (Li-AuNPs) as an Innovative Neuroprotective Platform

Further advancements in nanomedicine have led to the development of lithium-loaded gold nanoparticles (Li-AuNPs), which integrate the neuroprotective effects of lithium with the high biocompatibility and stability of gold [32]. These nanosystems effectively modulate GSK-3β activity, reduce oxidative stress, and enable controlled, targeted lithium release within neuronal and glial cells. In vitro analyses revealed enhanced neuronal survival and increased resistance to oxidative injury, indicating that Li-AuNPs may serve as a next-generation platform for precise lithium delivery and neuroprotection in Alzheimer's disease.

IV. Epidemiological and Experimental Evidence Supporting the Neuroprotective Role of Lithium.

An increasing body of population-based and mechanistic studies suggests that lithium, even at trace or subtherapeutic concentrations, exerts neuroprotective effects that may delay the onset and progression of Alzheimer's disease (AD). Evidence derived from epidemiological analyses, controlled animal experiments, and translational research consistently indicates that lithium modulates molecular pathways implicated in neurodegeneration particularly GSK-3β kinase activity, neuroinflammatory cascades, and synaptic plasticity.

a) Population studies: Environmental lithium exposure and dementia incidence

A landmark nationwide study including more than 73,000 cases demonstrated that regions of Denmark with higher natural lithium concentrations in drinking water (≥15 μg/L) had significantly lower rates of dementia, independent of socioeconomic and environmental confounders [34]. Similarly, a systematic review confirmed a dose–response relationship between trace lithium levels (0.002–0.056 mg/L) and reduced dementia prevalence [39].

In contrast, another large cohort study failed to replicate this association, finding no significant correlation between low lithium concentrations in drinking water and a reduced risk of dementia. Interestingly, a trend toward increased dementia risk was observed among women exposed to lithium concentrations below 2.1 μg/L, while no significant relationship was identified among men [35]. These findings highlight that environmental and demographic factors may modify lithium's potential neuroprotective influence, underscoring the need for more standardized and geographically diverse analyses.

b) Dose-dependent safety profile

Available evidence clearly demonstrates that lithium's adverse effects are dose-dependent. When administered at therapeutic serum concentrations (0.6–1.2 mmol/L), lithium remains a highly effective mood stabilizer but is associated with well-documented side effects, including renal impairment, hypothyroidism, primary hyperparathyroidism with hypercalcemia, tremor, polyuria, and weight gain. These complications occur primarily during long-term exposure to high serum levels and are strongly correlated with cumulative dose and duration of therapy.

Recent studies confirm that chronic exposure to therapeutic lithium concentrations may increase the risk of chronic kidney disease, although this risk remains moderate and clinically manageable with appropriate monitoring [41]. Likewise, a recent endocrinological review reported that lithium-induced hormonal disturbances such as hypothyroidism, goiter, and primary hyperparathyroidism occur almost exclusively during prolonged exposure to therapeutic doses [42]. The authors emphasized that these effects are closely linked to serum lithium levels, cumulative dose, and treatment duration, with no evidence of endocrine or metabolic disturbances at low or microdose exposures.

By contrast, micro- and subtherapeutic doses (<0.3 mmol/L; approximately 50–300 μg/day) demonstrate an excellent safety profile in both preclinical and clinical settings. Studies have shown no evidence of renal, thyroid, or metabolic toxicity at these concentrations [18,26]. Similarly, the randomized Lit-AD clinical trial found no clinical or biochemical adverse effects following several months of lithium microdosing in patients with Alzheimer's disease [43]. Consistent findings were obtained in preclinical models: no renal or endocrine toxicity was observed after 12 weeks of chronic intranasal lithium administration, even with repeated dosing [33].

Discussion

The findings of this review indicate that lithium is a compound with complex and multidirectional biological activity that affects key pathogenic pathways involved in Alzheimer's disease (AD). In contrast to monoclonal antibodies, which primarily target the late stages of β-amyloid accumulation, lithium appears to modulate earlier neurodegenerative mechanisms, including GSK-3β kinase activity, tau protein metabolism, APP processing, oxidative stress, and neuroinflammatory signaling. This broad range of effects suggests that lithium may act as a potential neuroprotective agent capable of stabilizing neuronal homeostasis and slowing the progression of degenerative changes. Importantly, these molecular interactions position lithium not as a single-pathway drug, but rather as a pleiotropic modulator of cellular resilience and plasticity.

Lithium's ability to activate neurotrophic pathways regulated by BDNF and CREB, together with its influence on hippocampal neurogenesis and synaptic plasticity, supports the hypothesis that it could help preserve cognitive function and maintain the structural integrity of the brain. Additionally, lithium has been shown to regulate mitochondrial function, enhance autophagic clearance, and reduce the formation of reactive oxygen species mechanisms that together contribute to improved neuronal survival. Both preclinical studies and selected clinical trials have shown that even micro- or subtherapeutic doses can beneficially modulate neurobiological processes without producing significant adverse effects. However, clinical data remain limited and partially inconsistent; several studies failed to demonstrate meaningful cognitive improvement, particularly in long-term follow-up. These discrepancies may stem from methodological differences, variable dosing regimens, small sample sizes, and heterogeneous patient populations, all of which complicate the interpretation of results and limit generalizability.

Epidemiological studies have also suggested a possible link between trace levels of lithium in drinking water and a reduced incidence of dementia. Nevertheless, these findings are not uniformly consistent across populations, and some reports have even shown the opposite trend in specific demographic groups. These inconsistencies indicate that lithium's effects are likely influenced by multiple environmental, genetic, epigenetic, and hormonal factors. Integrating environmental lithium exposure data with genetic and metabolomic profiling could provide new insights into the dose–response relationship and identify susceptible

or responsive subgroups. Future research should therefore combine epidemiological, clinical, and molecular approaches to clarify the multifactorial interactions between lithium and neurodegeneration.

Novel lithium delivery strategies, such as organic lithium orotate, intranasal hydrogel systems, liposomal carriers, and gold nanoparticles (Li-AuNPs), represent promising directions for the development of neuroprotective therapies. Preliminary preclinical data suggest that these systems may enhance blood–brain barrier penetration and improve neuronal targeting while minimizing systemic toxicity. Furthermore, combining these delivery systems with advanced imaging and pharmacokinetic modeling may optimize dose precision and safety. However, most available evidence comes from animal or experimental studies, and clinical data confirming safety, pharmacokinetics, and long-term efficacy remain scarce. Consequently, further translational research is needed to evaluate the real-world therapeutic potential of these technologies in human subjects.

Despite encouraging results, lithium does not always produce consistently positive effects on cognitive outcomes. Its therapeutic efficacy may depend on patient age, disease stage, comorbidities, and genetic polymorphisms. It is also possible that lithium's neuroprotective actions could be enhanced through combination therapy with antioxidants, anti-inflammatory agents, or neurotrophic modulators. Determining the optimal dosage, duration of treatment, and appropriate biomarkers of efficacy and safety remains essential for the successful clinical translation of lithium-based therapies. Although microdoses of lithium appear to be well tolerated, data on their long-term pharmacokinetics and potential cumulative effects are still insufficient and warrant cautious monitoring.

From a social and ethical perspective, the potential use of lithium as a neuroprotective or preventive agent carries both substantial benefits and challenges. As an inexpensive, widely available, and well-characterized compound, lithium could form part of cognitive prevention programs in aging populations, particularly among individuals with mild cognitive impairment (MCI). Unlike costly biological therapies, low-dose lithium could be implemented as part of public brain health strategies, potentially reducing the economic burden of dementia care while maintaining a high level of pharmacological safety. However, lithium remains strongly associated with psychiatric treatment, especially bipolar disorder, which may provoke social concerns, stigma, and reluctance toward its preventive use. Public misconceptions regarding lithium's toxicity and side effects persist, despite current scientific evidence supporting the safety of microdosing. Therefore, the implementation of any population-level preventive programs must involve transparent communication, strict ethical oversight, and the principle of informed consent.

Preliminary surveys indicate a growing acceptance of low-dose lithium use among older adults and patients with MCI, particularly when the mechanism of action and safety data are clearly communicated. The concept of lithium microdosing aligns well with the paradigm of preventive medicine and healthy aging, promoting the preservation of cognitive functions and psychological well-being throughout the aging process. Its potential mood-stabilizing and anxiolytic effects may provide an additional advantage, enhancing overall quality of life and independence in older individuals. Ultimately, a balanced, evidence-based approach that integrates biological, clinical, and ethical considerations will be crucial for determining lithium's true place in future preventive and therapeutic strategies for Alzheimer's disease.

Conclusions

Lithium is a promising but still underexplored agent with potential neuroprotective and disease-modifying effects in Alzheimer's disease. Accumulated evidence suggests that it may beneficially influence key neurodegenerative processes such as tau protein phosphorylation, β-amyloid metabolism, oxidative stress. However, not all studies have provided consistent confirmation of these clinical effects. The diversity of research outcomes likely reflects differences in study design, dosage ranges, treatment duration, and patient selection, emphasizing the need for greater methodological standardization in future investigations.

Modern delivery systems, including lithium orotate, intranasal formulations, and nanocarrier-based approaches, appear to enhance lithium's bioavailability in the central nervous system while reducing adverse effects, though they require further clinical validation. Advances in pharmacogenomics and neuroimaging may soon allow for more individualized therapeutic approaches, helping to identify subgroups of patients who could benefit most from lithium-based interventions. Future research should focus on defining optimal dosing, treatment duration, and target populations, as well as on developing reliable biomarkers of efficacy and safety. Interdisciplinary collaboration among neuroscientists, clinicians, and bioethicists will be essential to evaluate both the therapeutic potential and the risks associated with long-term lithium exposure, particularly regarding cumulative neurotoxicity and systemic effects.

In summary, lithium remains one of the most promising, though not yet fully validated, candidates for adjunctive and preventive therapy in Alzheimer's disease. Continued investigation integrating molecular, clinical, and technological perspectives may pave the way toward safe and effective neuroprotective strategies with future clinical applications in the management of age-related cognitive disorders. If its therapeutic window can be better defined and its delivery optimized, lithium could ultimately occupy an important role in multimodal strategies aimed at slowing or preventing neurodegeneration in aging populations.

Author Declaration on the Use of Artificial Intelligence Tools

During the preparation of this manuscript, the authors used ChatGPT to assist with improving the clarity, grammar, and overall readability of the text. All intellectual content, data interpretation, and conclusions are the sole responsibility of the authors, who carefully reviewed and edited the final version of the manuscript.

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