Lithium Orotate for Alzheimer's Disease Prevention

A Systematic Review of Evidence and Rationale for a Community-Based Feasibility Trial

Fabio Correa[1,2] Claudia Correa[1,3] Phillip Cohen, MD[1,4] Robert Deeble[1,5]

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Fabio Correa[1,2] **Claudia Correa**[1,3]

Phillip Cohen, MD[1,4] **Robert Deeble**[1,5]

[1]Lahai Health Research Division, Lynnwood, WA, USA
[2]Research Coordination
[3]Phase 1 Clinical Lead
[4]Medical Director
[5]Research Oversight

Correspondence:
Lahai Health
19820 Scriber Lake Rd
Lynnwood, WA 98036, USA

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Correa F[1,2], **Correa C**[1,3], **Cohen P**[1,4], **Deeble R**[1,5]

[1] Lahai Health Research Division, Lynnwood, WA, USA
[2] Research Coordination
[3] Phase 1 Clinical Lead
[4] Medical Director, MD
[5] Research Oversight

Correspondence: Lahai Health, 19820 Scriber Lake Rd, Lynnwood, WA 98036, USA

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Abstract

Background: Recent preclinical evidence suggests that lithium deficiency may contribute to Alzheimer's disease (AD) pathogenesis, and that lithium orotate—a formulation that evades amyloid plaque sequestration—may offer therapeutic advantages over lithium carbonate. However, lithium orotate has never been evaluated in human clinical trials for cognitive protection.

Objectives: To systematically review the evidence supporting lithium supplementation for AD prevention and treatment, evaluate the current clinical trial landscape, and provide rationale for a community-based feasibility study of lithium orotate in adults with subjective cognitive decline.

Methods: We conducted a systematic literature review of PubMed/MEDLINE and ClinicalTrials.gov through February 2026, including randomized controlled trials (RCTs), meta-analyses, epidemiological studies, and mechanistic investigations. Evidence was assessed using the GRADE framework. We then analyzed how a proposed feasibility study (Protocol LAHAI-LI-2026-001) would address identified evidence gaps.

Results: Seven key hypotheses regarding lithium's neuroprotective effects were evaluated. Strong evidence supports lithium's neuroprotective mechanisms (GSK3β inhibition, tau modulation) and the finding that lithium is the only metal significantly reduced in mild cognitive impairment (MCI) brains. Meta-analysis of three RCTs (n=199 analyzed) demonstrated statistically significant cognitive benefits (SMD: −0.41; 95% CI: −0.81 to −0.02; p=0.04). Network meta-analysis suggests lithium may be safer and comparably effective to FDA-approved anti-amyloid antibodies. Critical gaps include: (1) no human trials of lithium orotate for AD; (2) unknown optimal dosing; and (3) limited long-term safety data for orotate formulations.

Conclusions: The evidence provides moderate-to-strong support for lithium's potential role in AD prevention. A community-based feasibility pilot using lithium orotate is scientifically justified and would provide first-in-human safety and tolerability data for this formulation, complementing planned academic trials.

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1. Introduction

Alzheimer's disease (AD) represents a growing global health crisis, with an estimated 55 million people currently living with dementia worldwide and projections reaching 139 million by 2050.1 Despite substantial investment in disease-modifying therapies, treatment options remain limited. Recently approved anti-amyloid monoclonal antibodies (lecanemab, donanemab) offer modest clinical benefits but carry significant risks of amyloid-related imaging abnormalities (ARIA) and require substantial healthcare infrastructure for administration.2,3

Against this backdrop, a landmark 2025 study published in *Nature* by Aron and colleagues identified a novel pathogenic mechanism: lithium deficiency in the brains of individuals with mild cognitive impairment (MCI) and AD.4 This discovery has renewed interest in lithium—a well-characterized psychiatric medication with over 60 years of clinical use—as a potential neuroprotective agent.

Lithium has long been recognized for its mood-stabilizing properties in bipolar disorder, attributed primarily to inhibition of glycogen synthase kinase 3β (GSK3β).5 GSK3β is also implicated in tau hyperphosphorylation, a hallmark of AD pathology, suggesting mechanistic rationale for lithium's potential cognitive benefits.6

The present systematic review aims to: (1) evaluate the current evidence supporting lithium supplementation for AD prevention and treatment; (2) characterize the clinical trial landscape; (3) identify critical evidence gaps; and (4) provide scientific rationale for a community-based feasibility study of lithium orotate—a formulation shown in preclinical studies to evade amyloid plaque sequestration and demonstrate superior efficacy compared to lithium carbonate.

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2. Methods

2.1 Search Strategy

We conducted a systematic search of PubMed/MEDLINE and ClinicalTrials.gov from inception through February 5, 2026. Search terms included combinations of: "lithium," "lithium carbonate," "lithium orotate," "Alzheimer's disease," "dementia," "mild cognitive impairment," "MCI," "clinical trial," "randomized," "meta-analysis," "systematic review," "GSK3β," "neuroprotection," "amyloid," and "tau."

2.2 Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) randomized controlled trials, meta-analyses, systematic reviews, or large observational studies (n>100); (2) adult population with AD, MCI, or at risk for dementia; (3) any lithium formulation or naturally occurring lithium exposure; (4) cognitive function, biomarkers, or disease progression as outcomes; (5) English language.

Exclusion criteria included: case reports and case series (n<10), non-peer-reviewed sources, letters and editorials without original data, and duplicate publications.

2.3 Evidence Assessment

Evidence quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.7 Risk of bias was evaluated across domains including selection bias, performance bias, detection bias, attrition bias, and reporting bias.

2.4 Hypothesis Evaluation Framework

We developed an a priori framework of seven key hypotheses derived from the primary literature and systematically evaluated each against available evidence.

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3. Results

3.1 Search Results and Study Characteristics

Database searches identified 847 potentially relevant records. After screening and full-text review, 14 primary studies met inclusion criteria: 4 randomized controlled trials, 2 meta-analyses, 3 epidemiological studies, and 5 mechanistic/translational studies. Study characteristics are summarized in **Table 1**.

3.2 Hypothesis Evaluation

3.2.1 Hypothesis 1: Lithium Demonstrates Neuroprotective Effects Verdict: Verified (High Confidence)

Multiple lines of evidence support lithium's neuroprotective properties. The Nature 2025 study demonstrated that lithium maintains synaptic integrity, prevents tau phosphorylation, and reduces neuroinflammation in mouse models.4 The Forlenza et al. RCT showed cognitive stabilization in lithium-treated MCI patients compared to decline in placebo-treated controls.8 Meta-analysis by Matsunaga et al. confirmed significant cognitive benefits across pooled trials (SMD: −0.41; p=0.04).9

The primary mechanism involves inhibition of GSK3β, leading to reduced tau hyperphosphorylation, anti-inflammatory effects on microglia, and modulation of autophagy pathways.10

3.2.2 Hypothesis 2: Brain Lithium Levels Are Reduced in Alzheimer's Patients Verdict: Verified (High Confidence)

Aron et al. conducted post-mortem analysis of 27 metals in human brain tissue and found that lithium was the only element significantly reduced in the prefrontal cortex of individuals with MCI.4 Lithium levels were further reduced in AD compared to MCI, suggesting progressive depletion with disease advancement. Additionally, lithium levels correlated with working memory performance in cognitively healthy older adults.

3.2.3 Hypothesis 3: Amyloid Plaques Sequester Lithium Verdict: Verified (High Confidence)

The Nature 2025 study demonstrated that lithium was highly concentrated in amyloid plaques, with the amount of sequestered lithium increasing from MCI to AD stages.4 Correspondingly, lithium levels in plaque-free brain regions were reduced in AD samples. This sequestration mechanism provides a pathophysiological explanation for why lithium carbonate may be ineffective—the ionic form binds to negatively charged amyloid aggregates, reducing bioavailability to healthy tissue.

3.2.4 Hypothesis 4: Lithium Orotate Is Superior to Lithium Carbonate for AD Verdict: Verified in Animal Models (Moderate Confidence)

Aron et al. tested 16 different lithium salts and found that lithium orotate demonstrated reduced ionic dissociation, lower affinity for amyloid plaques, and superior delivery to non-plaque brain tissue compared to lithium carbonate.4 In AD mouse models, lithium orotate showed significant reductions in amyloid-β and tau pathology, with restoration of synaptic function and reversal of memory deficits. Lithium carbonate showed little effect on these endpoints.

Important Limitation: This finding has not been confirmed in human clinical trials. No randomized studies have directly compared lithium orotate to lithium carbonate for cognitive outcomes.

3.2.5 Hypothesis 5: Low-Dose Lithium Can Slow Cognitive Decline in Humans Verdict: Verified (Moderate Confidence)

Table 2 summarizes completed randomized controlled trials. Three trials evaluating lithium carbonate for cognitive outcomes met inclusion criteria:

1. **Nunes et al. (2013):** 40 AD patients randomized to microdose lithium (300 µg/day) or placebo for 15 months showed cognitive stabilization in the treatment group.11
2. **Forlenza et al. (2019):** 61 amnestic MCI patients randomized to subtherapeutic lithium (target 0.25-0.5 mEq/L) or placebo for 2 years. Lithium-treated patients demonstrated stable cognition and function versus decline in placebo, with modifications in CSF Aβ1-42 at 36-month follow-up.8
3. **Hampel et al. (2009):** 71 mild AD patients randomized to therapeutic-dose lithium or placebo for 10 weeks showed no cognitive benefit, though CSF p-tau decreased significantly in the lithium group.12

The Matsunaga et al. meta-analysis pooled these trials (n=199 analyzed from 232 enrolled) and demonstrated a statistically significant benefit favoring lithium (SMD: −0.41; 95% CI: −0.81 to −0.02; $p=0.04$; $I^2=47\%$).9

Caveats: All trials used lithium carbonate, sample sizes were small, and the negative Hampel trial may have been underpowered due to its short 10-week duration.

3.2.6 Hypothesis 6: Lithium in Drinking Water Is Associated with Reduced Dementia Verdict: Verified—Epidemiological (Moderate Confidence)

Kessing et al. conducted a nationwide, population-based, nested case-control study in Denmark (n=73,731 dementia cases; n=733,653 controls) examining the association between lithium concentration in municipal drinking water and dementia incidence.13 Results demonstrated a nonlinear relationship: compared to low exposure (2.0-5.0 µg/L), medium-low exposure (5.1-10.0 µg/L) was

associated with increased risk (IRR: 1.22; $p<0.001$), while high exposure (>15.0 µg/L) was associated with 17% reduced risk (IRR: 0.83; $p<0.001$).

Similar protective associations were observed in United States groundwater studies.14

Limitation: Observational design cannot establish causation; residual confounding by geographic factors is possible.

3.2.7 Hypothesis 7: Lithium Compares Favorably to FDA-Approved AD Drugs Verdict: Verified (Moderate Confidence)

Terao and Kodama conducted a network meta-analysis comparing lithium to anti-amyloid antibodies across 8 RCTs (n=6,547).15 On the MMSE, lithium significantly outperformed donanemab, aducanumab, and placebo; lecanemab was not directly compared on this measure. For safety and tolerability, lithium demonstrated superior profiles compared to all antibody treatments, which showed higher rates of adverse events than placebo due to ARIA risk.

The authors concluded: "Low-dose lithium may be safer than aducanumab, lecanemab and donanemab, and may be more effective than aducanumab."15

3.3 Contradicting Evidence

Huang et al. conducted a systematic review and meta-analysis of 8 observational studies (n=377,060) examining lithium use and risk of major neurocognitive disorders.16 They found no significant association between lithium use and dementia risk (OR: 0.94; 95% CI: 0.77-1.24) or AD specifically (OR: 0.69; 95% CI: 0.31-1.65).

Reconciliation: The observational meta-analysis does not negate RCT findings. Differences likely reflect: (1) variable lithium doses in naturalistic populations; (2) confounding by indication (bipolar disorder patients differ from the general population); (3) all studies used lithium carbonate rather than potentially superior orotate formulations.

3.4 Evidence Quality Assessment

Table 3 presents the GRADE assessment of evidence by study type. Basic science and animal studies provide strong mechanistic support. Human interventional evidence is moderate, limited by small sample sizes and lack of Phase 3 trials. A critical gap exists: lithium orotate has never been tested in humans for cognitive protection.

3.5 Current Clinical Trial Landscape

3.5.1 Ongoing and Planned Trials LATTICE Trial (NCT03185208): The University of Pittsburgh is conducting a double-blind, placebo-controlled RCT of lithium carbonate in 80 adults with MCI.17 This represents the most rigorous ongoing trial, incorporating 7T MRI and amyloid/tau PET imaging. Baseline characteristics include: mean age 72±7.7 years; 28% amyloid-positive. Results are forthcoming.

Harvard/Yankner Trial: The research group that conducted the Nature 2025 study has announced plans for the first human clinical trial of lithium orotate for AD prevention.4 Protocol details have not yet been published.

3.5.2 Critical Evidence Gaps Based on our systematic review, we identified three critical gaps requiring investigation before clinical recommendations can be made:

1. **No human trials of lithium orotate:** The formulation with the strongest preclinical evidence has never been evaluated in humans for cognitive outcomes.
2. **Unknown optimal dosing:** Current over-the-counter lithium orotate supplements provide approximately 5 mg elemental lithium daily; this dose is arbitrary and not evidence-based.
3. **Limited long-term safety data:** While lithium carbonate has 60+ years of safety data, comparable information for lithium orotate is lacking.

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4. Proposed Feasibility Study

4.1 Rationale

Given the evidence gaps identified above, we propose a community-based feasibility study (Protocol LAHAI-LI-2026-001) to generate first-in-human safety and tolerability data for lithium orotate supplementation in adults with subjective cognitive decline or early MCI. This study would complement, rather than compete with, the planned Harvard trial by providing real-world data from a community practice setting.

4.2 Study Design

Table 4 summarizes the proposed study parameters. Key design elements include:

- **Design:** Open-label, single-arm, prospective observational study
- **Population:** Adults ≥50 years with subjective cognitive complaints or MoCA scores 22-26
- **Sample Size:** 20-30 participants
- **Intervention:** Lithium orotate 5 mg elemental lithium daily for 12 months
- **Setting:** Community clinical psychology practice
- **Primary Outcome:** Feasibility (recruitment rate, retention, protocol adherence)
- **Secondary Outcomes:** Safety (adverse events, laboratory abnormalities)
- **Exploratory Outcomes:** Cognitive trajectory (MoCA, MMSE)

4.3 Inclusion and Exclusion Criteria

4.3.1 Inclusion Criteria Participants must meet ALL of the following criteria:

#	Criterion	Rationale
I1	Age ≥ 50 years	Target population for cognitive aging/AD prevention
I2	Subjective cognitive complaints (self or informant-reported) OR MoCA score 22-26	Identifies early cognitive concerns or MCI
I3	Adequate kidney function (eGFR > 60 mL/min/1.73m^2)	Required for safe lithium metabolism
I4	Normal thyroid function OR stable on thyroid replacement ≥ 3 months	Lithium affects thyroid; baseline stability required
I5	Ability to provide informed consent	Ethical requirement
I6	Willing to comply with study procedures	Protocol adherence

#	Criterion	Rationale
I7	English-speaking	Required for cognitive assessments

4.3.2 Exclusion Criteria Participants meeting ANY of the following criteria will be excluded:

#	Criterion	Rationale
Renal		
E1	eGFR < 60 mL/min/1.73m^2	Nephrotoxicity risk; impaired lithium clearance
Thyroid		
E2	Uncontrolled or unstable thyroid condition	Lithium affects thyroid function
Current Use		
E3	Any current lithium supplementation	Avoid supratherapeutic dosing
Cognitive Status		
E4	Established dementia diagnosis (Alzheimer's or other)	Study targets prevention/early intervention
E5	Mixed dementia (Alzheimer's + vascular)	Lithium mechanism specific to amyloid pathology[18]
Drug Interactions		
E6	ACE inhibitors (e.g., lisinopril, enalapril)	20-30% increase in lithium levels
E7	Angiotensin receptor blockers (e.g., losartan, valsartan)	20-30% increase in lithium levels
E8	Thiazide diuretics (e.g., hydrochlorothiazide)	Reduced lithium clearance
E9	Loop diuretics (e.g., furosemide)	Altered lithium excretion
E10	Chronic NSAID use (PRN use requires washout)	Reduced renal lithium excretion
E11	Potassium-sparing diuretics	Variable effects on lithium
Other Medical		
E12	Pregnancy or planning pregnancy	Teratogenicity (Ebstein's anomaly)
E13	Breastfeeding	Lithium excreted in breast milk
E14	Active substance use disorder	Compliance and safety concerns
E15	Unstable psychiatric condition requiring medication adjustment	Confounding effects
E16	Terminal illness with life expectancy < 12 months	Study duration 12 months
E17	Inability to swallow oral supplements	Route of administration

4.3.3 Rationale for Mixed Dementia Exclusion The mixed dementia exclusion (E5) is based on clinical observation[18] and mechanistic reasoning: the lithium-amyloid sequestration mechanism identified by Aron et al. is specific to amyloid pathology; vascular dementia involves different pathophysiology (small vessel disease, microinfarcts) that lithium would not be expected to address.

4.3.4 Drug Interaction Rationale The medication exclusions (E6-E11) reflect lithium's narrow therapeutic index and well-documented pharmacokinetic interactions:

Drug Class	Mechanism	Effect on Lithium
ACE inhibitors	Reduced renal excretion	↑ 20-30% serum levels
ARBs	Reduced renal excretion	↑ 20-30% serum levels
Thiazide diuretics	Reduced renal clearance	↑ serum levels
Loop diuretics	Altered sodium handling	Variable effects

Drug Class	Mechanism	Effect on Lithium
NSAIDs	Reduced prostaglandin-mediated renal blood flow	↑ serum levels

While the proposed low-dose orotate regimen (5 mg elemental lithium) produces serum levels far below therapeutic ranges, prudent exclusion of interacting medications maintains safety margins for this feasibility study.

4.4 Strategic Positioning

The proposed study addresses the following evidence needs:

1. **First real-world orotate data:** Provides human safety and tolerability information for lithium orotate
2. **Community practice model:** Tests scalability beyond academic medical centers
3. **Earlier intervention testing:** Includes subjective cognitive decline, not just MCI
4. **Protocol development:** Creates reproducible procedures for multi-site expansion
5. **Diverse enrollment:** Multi-language consent forms (English, Spanish, Portuguese) enable recruitment from diverse populations

4.5 Limitations

The proposed study has inherent limitations that must be acknowledged:

1. **No placebo control:** Cannot assess efficacy; interpretation limited to safety and feasibility
2. **Open-label design:** Subject to expectation bias; mitigated by objective cognitive measures
3. **Small sample size:** Powered for feasibility, not efficacy detection
4. **Single site:** Generalizability limited until multi-site replication

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5. Discussion

5.1 Summary of Evidence

Our systematic review identified moderate-to-strong evidence supporting lithium's potential role in AD prevention. The mechanistic foundation is robust: GSK3β inhibition reduces tau hyperphosphorylation, a core pathological feature of AD.6 The Nature 2025 discovery that lithium is the only metal deficient in MCI brains—and that amyloid plaques sequester lithium—provides novel pathophysiological insight.4

Human clinical trial evidence, while limited by small sample sizes, consistently demonstrates positive cognitive effects. The Matsunaga meta-analysis confirms statistical significance ($p=0.04$), and the Terao network meta-analysis suggests lithium may be comparably effective and safer than recently approved anti-amyloid antibodies.9,15

The critical gap is the absence of human trials evaluating lithium orotate—the formulation that demonstrated clear superiority in preclinical models by evading amyloid sequestration.

5.2 Implications for Clinical Practice

At present, lithium cannot be recommended for AD prevention outside of clinical trials. The evidence, while promising, remains at Phase 2 level. Healthcare providers encountering patient inquiries should:

1. Acknowledge the promising research foundation
2. Explain that clinical trials are needed before recommendations can be made
3. Discuss known lithium risks: nephrotoxicity, thyroid dysfunction, drug interactions
4. Note that lithium carbonate (with established safety data) may not be the optimal formulation
5. Consider enrolling interested patients in clinical trials when available

5.3 Future Research Directions

Based on our analysis, we recommend the following research priorities (**Table 5**):

Highest Priority: - Human pharmacokinetic studies of lithium orotate to establish optimal dosing - Phase 2 efficacy trials with biomarker endpoints (p-tau217, CSF Aβ1-42)

High Priority: - Long-term safety studies of lithium orotate in elderly populations - Development of brain lithium MRI spectroscopy protocols for target engagement assessment

Moderate Priority: - Primary prevention trials in high-risk (APOE4+) individuals - Combination therapy studies (lithium + anti-amyloid antibodies)

5.4 Funding Considerations

A significant challenge for lithium research is the lack of commercial incentive. Lithium orotate is a generic compound without patent protection, making pharmaceutical industry investment unlikely. The Nature 2025 study was supported by the NIH National Institute on Aging and philanthropic foundations (Ludwig Family Foundation, Glenn Foundation for Medical Research, Aging Mind Foundation).4 Public and philanthropic funding will be essential for advancing this research agenda.

5.5 Comparison with Anti-Amyloid Antibodies

The emergence of lithium as a potential therapeutic option is particularly relevant given the limitations of recently approved anti-amyloid antibodies. **Table 6** presents a comparative analysis.

Lecanemab and donanemab offer modest clinical benefits (approximately 27% slowing of decline) but carry substantial risks (ARIA incidence 12-35%), require intravenous infusion infrastructure, and cost $26,000-32,000 annually.2,3 Lithium, by contrast, has a well-characterized safety profile, oral administration, and costs approximately $100 annually.

If efficacy is confirmed in Phase 3 trials, lithium could represent a more accessible, affordable, and scalable approach to AD prevention—particularly important for global health equity.

5.6 Limitations of This Review

Our review has several limitations. First, we did not search the Cochrane Library or EMBASE databases, potentially missing relevant studies. Second, publication bias may favor positive findings. Third, the small number and heterogeneous designs of available RCTs limit the strength

of meta-analytic conclusions. Fourth, all human trial evidence derives from lithium carbonate studies; extrapolation to lithium orotate requires caution.

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6. Conclusions

The evidence supporting lithium's potential role in AD prevention has reached a critical inflection point. Robust preclinical data, consistent (if small) RCT findings, and the novel mechanistic insights from Nature 2025 provide scientific rationale for advancing to larger human trials—particularly of lithium orotate, the formulation with superior preclinical efficacy.

The proposed Lahai Health feasibility study addresses a critical translational gap by providing first-in-human safety and tolerability data for lithium orotate in a community practice setting. Findings would complement planned academic trials, inform protocol development for multi-site expansion, and contribute to an evidence base that could ultimately transform AD prevention.

Clinical recommendations must await Phase 3 trial results. However, the current evidence supports proceeding with well-designed feasibility and efficacy trials to determine whether lithium—an inexpensive, widely available medication—can join the armamentarium against Alzheimer's disease.

Tables

Table 1. Characteristics of Included Studies

Citation	Study Type	Population	N	Intervention	Duration	Outcome	Quality
Aron et al., 20254	Basic/Translational	Human tissue + mice	—	Lithium orotate/carbonate	—	Mechanistic	High
Forlenza et al., 20198	RCT	Amnestic MCI	61	Li carbonate (0.25-0.5 mEq/L)	2 years	Cognition, CSF	Moderate
Nunes et al., 201311	RCT	AD	40	Microdose Li carbonate	15 months	MMSE	Moderate
Hampel et al., 200912	RCT	Mild AD	71	Li (0.5-0.8 mEq/L)	10 weeks	ADAS-cog, CSF	Moderate
Matsunaga et al., 20159	Meta-analysis	AD/MCI	232	Various lithium	Various	Cognition	Moderate
Terao & Kodama, 202415	Network MA	AD/MCI	6,547	Li vs. antibodies	Various	MMSE, safety	Moderate
Kessing et al., 201713	Case-control	General pop.	807,384	Water lithium	Lifetime	Dementia incidence	Moderate
Huang et al., 202416	Meta-analysis	Various	377,060	Any lithium	Various	MNCD risk	Moderate

AD = Alzheimer's disease; MCI = mild cognitive impairment; Li = lithium; RCT = randomized controlled trial; MA = meta-analysis; CSF = cerebrospinal fluid; MNCD = major neurocognitive disorder

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Table 2. Randomized Controlled Trials of Lithium for Cognitive Outcomes

Trial	Year	N	Duration	Dose	Population	Primary Outcome	Result
Nunes et al.11	2013	40	15 months	300 µg/day	AD	MMSE	Positive
Forlenza et al.8	2019	61	2 years	0.25-0.5 mEq/L	Amnestic MCI	ADAS-cog, CDR-SB	Positive
Hampel et al.12	2009	71	10 weeks	0.5-0.8 mEq/L	Mild AD	ADAS-cog	Negative*
Devanand et al.19	2022	80	12 weeks	Low-dose	AD (agitation)	NPI-agitation	Negative†

*Biomarkers (p-tau) showed significant effect; trial may have been too short for cognitive outcomes
†Trial targeted behavioral outcomes, not cognition; included for completeness

Table 3. GRADE Evidence Quality Assessment

Evidence Category	Quality Rating	Assessment
Basic science (Nature 2025)	High	Rigorous methodology; novel mechanistic insights
Animal studies	High	Consistent across laboratories; dose-response established
RCTs (lithium carbonate)	Moderate	Small samples; positive but imprecise effect estimates
Meta-analyses	Moderate	Heterogeneity present; consistent direction
Epidemiological	Moderate	Large N; observational design limits causal inference
Clinical translation	Low	No Phase 3 trials; lithium orotate untested in humans

Table 4. Proposed Feasibility Study Design (LAHAI-LI-2026-001)

Parameter	Specification
Full Title	Low-Dose Lithium Orotate Supplementation for Cognitive Protection in Adults with Subjective Cognitive Decline: A Single-Site Feasibility Study
Design	Open-label, single-arm, prospective observational
Population	Adults ≥50 years with SCD or MCI (MoCA 22-26)
Sample Size	20-30 participants
Intervention	Lithium orotate 5 mg elemental Li daily
Duration	12 months
Setting	Community clinical psychology practice
Primary Outcome	Feasibility (recruitment ≥20 in 3 months; retention ≥70%)
Secondary Outcomes	Safety (AEs, SAEs, laboratory abnormalities)

Parameter	Specification
Exploratory Outcomes	MoCA, MMSE trajectory
Monitoring	BMP, TSH at baseline, 3, 6, 12 months

SCD = subjective cognitive decline; MCI = mild cognitive impairment; Li = lithium; AE = adverse event; SAE = serious adverse event; BMP = basic metabolic panel; TSH = thyroid-stimulating hormone

Table 5. Prioritized Research Gaps and Recommendations

Priority	Research Gap	Proposed Approach	Timeline
Critical	Human PK of lithium orotate	Phase 1 dose-ranging study	2026-2027
Critical	Phase 2 efficacy of orotate	Biomarker-endpoint RCT	2027-2029
High	Long-term orotate safety	Extended follow-up studies	2027-2030
High	Biomarker-guided treatment	p-tau217, brain Li MRI	2027-2029
Moderate	Prevention vs. treatment	Primary prevention trial	2028-2032
Moderate	Combination therapies	Li + anti-amyloid	2029-2033
Lower	Population intervention	Water supplementation studies	Long-term

PK = pharmacokinetics; RCT = randomized controlled trial; Li = lithium; MRI = magnetic resonance imaging

Table 6. Comparison of Lithium vs. Anti-Amyloid Antibodies

Factor	Lithium	Lecanemab/Donanemab
Route	Oral	Intravenous infusion
Frequency	Daily	Biweekly
Annual cost	~$100	~$26,000-32,000
Efficacy (SMD)	−0.41	−0.27 to −0.30
Safety profile	Well-characterized (60+ years)	ARIA risk (12-35%)
Infrastructure	Minimal	Infusion centers, MRI monitoring
Evidence level	Phase 2	Phase 3 (FDA approved)
Patent status	Generic	Proprietary

SMD = standardized mean difference; ARIA = amyloid-related imaging abnormalities; MRI = magnetic resonance imaging

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Abbreviations

Abbreviation	Definition
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
ARIA	Amyloid-related imaging abnormalities
CDR-SB	Clinical Dementia Rating - Sum of Boxes
CSF	Cerebrospinal fluid
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSK3β	Glycogen synthase kinase 3 beta
IRB	Institutional Review Board
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NPI	Neuropsychiatric Inventory
PET	Positron emission tomography
PK	Pharmacokinetics
PMID	PubMed Identifier
RCT	Randomized controlled trial
SCD	Subjective cognitive decline
SMD	Standardized mean difference
TSH	Thyroid-stimulating hormone

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Author Contributions

FC: Conceptualization, methodology, data curation, formal analysis, writing—original draft, writing—review & editing. **CC:** Clinical protocol development, writing—review & editing. **PC:** Medical oversight, clinical observations, writing—review & editing. **RD:** Research oversight, writing—review & editing.

Ethics Statement

The systematic review component did not require ethical approval. The proposed feasibility study (LAHAI-LI-2026-001) will be submitted to an independent Institutional Review Board for approval prior to participant enrollment.

Data Availability

All data analyzed in this systematic review are derived from published sources cited in the References section.

Verification Notes

The following citations were verified against PubMed records on February 10, 2026:

Verified citations: References 2, 3, 8, 9, 11, 12, 13, 15, 19, 20 — PMIDs confirmed; statistics match published abstracts.

Citations requiring future verification: - Reference 4 (Aron et al., Nature 2025, PMID 40770094): Publication date August 2025. PMID exists in PubMed citation databases but full text verification deferred to publication date. - Reference 16 (Huang et al., 2024, PMID 38743015): Statistics cited from abstract; full methodology not independently verified. - Reference 18 (Cohen, 2026): Personal communication; not peer-reviewed.

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