
The Trace and the Dose

Lithium in Alzheimer's disease: an inhibition literature, a repletion hypothesis, and the three orders of magnitude between them

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Lithium's most-cited target is inhibited at 2 mM; the brains of patients taking it reach 0.35 mM; the endogenous lithium whose loss is now proposed to cause Alzheimer's disease sits near 0.3 μ M. Read at its own concentrations, this literature is three separate claims, and the 2025 deficiency finding is not a smaller dose of the old pharmacology but a different one. No completed trial has tested it, and none can until non-sequestered lithium is measured in a living brain.

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Abstract

Lithium occupies a peculiar position in Alzheimer’s disease. It is the oldest drug in psychiatry, the cheapest candidate disease-modifying agent in neurology, and the subject of three separate claims that are routinely presented as one: that prescribed lithium prevents dementia, that trace lithium in drinking water prevents dementia, and — since 2025 — that a deficiency of endogenous lithium helps cause Alzheimer’s disease in the first place. This paper separates those claims and reads the evidence for each at the concentration where it was actually obtained.

Ordering the literature by concentration rather than by citation count inverts the standard account. Lithium’s most-cited target, glycogen synthase kinase-3, has the *highest* measured inhibition constant of any target in the field: $K_i = 2 \text{ mM}$ [1] — above the therapeutic serum range of 0.5–1.2 mmol/L, and roughly six-fold above the $0.35 \pm 0.11 \text{ mmol/L}$ directly measured in the brains of patients taking it [2]. The targets nobody cites — inositol monophosphatase at $IC_{50} \text{ } 0.8 \text{ mM}$ [3], and the bisphosphate 3′-nucleotidase family, inhibited at frankly sub-therapeutic concentrations [4] — are the ones a patient’s brain can reach. Meanwhile the endogenous lithium whose loss is now proposed to cause the disease sits at about $0.34 \text{ }\mu\text{M}$ in normal prefrontal cortex, falling to $0.26 \text{ }\mu\text{M}$ in the disease [5]: six to eight thousand-fold below that kinase constant. The mechanism that dominates the field’s citations is therefore available at no concentration that is simultaneously tolerable and endogenous, and the authors of the deficiency paper say so themselves.

The human record is correspondingly weaker than its reputation. The “lithium halves dementia risk” figure traces to a five-study meta-analysis [6] dominated by an unadjusted prevalence comparison in 114 outpatients [7]; the most recent meta-analysis of the same literature is null [8], as is the largest cohort with a psychiatric comparator [9] and a nationwide target-trial emulation by the author of the two most-cited positive studies [10]. The drinking-water exposure–response is not monotonic — a 17% reduction above $15 \text{ }\mu\text{g/L}$ sits beside a significant 22% *increase* at $5\text{--}10 \text{ }\mu\text{g/L}$ in the same analysis [11] — and the only individual-level cohort points the other way [12]. Randomised evidence amounts to fewer than 500 patients; the one two-year trial with prespecified co-primary endpoints missed all six [13], the two trials that measured lithium’s putative target in patients found no engagement [14,15], and a potent glycogen synthase kinase-3 inhibitor was clinically negative in both Alzheimer’s disease and progressive supranuclear palsy [16,17].

Against that, the 2025 demonstration that cortical lithium is selectively reduced in mild cognitive impairment and Alzheimer’s disease, that amyloid deposits sequester it, and that dietary lithium restriction in mice reproduces amyloid, tau, microglial and myelin pathology — prevented by replacement at $4.3 \text{ }\mu\text{Eq/L}$ — is the most important result in the field in twenty years [5]. This paper argues that it is also a different *kind* of claim, and that the field has not yet noticed. Its proposed mediation is a rise in glycogen synthase kinase-3 β protein, message and Tyr216

autophosphorylation, not catalytic inhibition by mass action — which is the only way a $\mu\text{Eq/L}$ effect on that kinase can be stated without violating its K_i . Repletion physiology and inhibition pharmacology have different dose-response shapes, different eligible populations, different target-engagement biomarkers and different failure modes. Every completed trial, including every “low-dose” trial, was designed as inhibition pharmacology.

Three consequences follow. First, the existing null trials are weak evidence against the deficiency hypothesis: 54 of the 75 imaged participants in the only two-year trial were amyloid-negative [13] and therefore, on the hypothesis’s own terms, had no sink, no deficit and nothing to replete — a reading the trialists themselves offer. Second, as presently stated the hypothesis is close to unfalsifiable in the clinic, because sequestration explains failure in the amyloid-positive and sufficiency explains it in the amyloid-negative; the discriminating measurement — non-sequestered cortical or cerebrospinal-fluid lithium, never yet measured in a living person — is therefore the necessary next step. Third, the safety ceiling and the mechanistic floor are on the wrong sides of each other: the exposures tolerable in older adults ($\leq 0.4 \text{ mmol/L}$, above which 13 of 14 patients with progressive supranuclear palsy could not continue for 28 weeks) lie below the concentrations at which lithium’s classical targets are engaged, so “more lithium” is not an available reply to a null result.

The paper closes with a strength-of-evidence table across nineteen claims and ten falsifiable predictions, each paired with the experiment that would settle it.

I. One element, three claims

Lithium is the third element and the oldest drug in continuous psychiatric use. It has no known enzyme that requires it, no recommended dietary allowance, no validated status biomarker, and no recognised deficiency syndrome in human beings [18]. It is nonetheless the subject of a large and growing literature claiming that it prevents, slows, or is depleted in Alzheimer’s disease. That literature is almost always presented as one body of converging evidence. It is not. It contains three claims which differ in their exposures by four orders of magnitude, and which stand or fall on different data.

The pharmacological claim. People prescribed lithium carbonate for bipolar disorder, at serum concentrations of 0.5–1.2 mmol/L, are said to develop dementia less often than comparable patients who are not; and low “sub-therapeutic” doses, targeting 0.25–0.5 mmol/L, are said to slow decline in mild cognitive impairment. This is a claim about a drug at drug concentrations, and it is testable by randomisation. It has been tested, in fewer than 500 patients in total.

The environmental claim. Naturally occurring lithium in drinking water, at 0.5–500 µg/L — some 103–104 below the therapeutic serum range — is said to be inversely associated with dementia incidence at the population level. This is an ecological claim about an involuntary exposure, and it has never been tested by randomisation in any species at the relevant concentration.

The deficiency claim. Endogenous lithium, present in human cortex at single-digit nanograms per gram [19], is said to be a physiologically required trace element whose loss — through sequestration into amyloid deposits — is an early causal event in Alzheimer’s disease [5]. This is a claim about a nutrient, not a drug. Its natural intervention is replacement to a normal level, not dose escalation to an effect.

These three claims are frequently used to support one another. The environmental literature is cited as evidence that the pharmacological effect extends to the general population; the pharmacological literature is cited as evidence that the environmental association is causal; and both are now cited as corroboration of the deficiency hypothesis. But a mechanism that operates at 1 mmol/L is not evidence for an effect at 10 µg/L, and an association at 10 µg/L is not evidence about a drug at 1 mmol/L. The unit of analysis that makes this literature legible is not the disease, the population or the endpoint. It is the concentration.

1.1 What this paper does

This paper reads the lithium–Alzheimer literature as a function of lithium concentration, and asks of every claim: at what concentration was this demonstrated, and does any human exposure reach it? Sections 2 to 4 establish the concentration axis and locate lithium's molecular targets on it. Sections 5 to 8 examine what lithium does to amyloid, to tau, to proteostasis and to the trophic and inflammatory machinery, in each case at the concentration where the effect was shown. Sections 9 and 10 assess the human observational and randomised records. Section 11 sets out the deficiency hypothesis in detail; sections 12 and 13 argue that it is a repletion hypothesis, that it has not yet been tested as one, and that the trials usually read as refuting it do not. Section 14 addresses safety, the tolerability ceiling and the unresolved chemistry of lithium orotate. Sections 15 to 17 grade the evidence, state ten falsifiable predictions, and name the limitations of this analysis.

Two matters of nomenclature are worth fixing at the outset, because the literature's own usage obscures the argument. First, “low-dose lithium” in the clinical literature means a serum concentration of roughly 0.2–0.5 mmol/L; “microdose” means µg/day oral dosing producing serum lithium below the 0.06 mmol/L limit of detection; and “trace” or “physiological” means the endogenous µEq/L range. These are not three points on one dose–response curve — they are separated by factors of ten and a thousand respectively. Second, the cell-culture literature routinely labels 2 mM lithium “therapeutic” [20,21,22]. As a human serum concentration, 2 mmol/L is toxic. A culture result at “therapeutic” lithium is, in human terms, a result above the top of the range.

2. The concentration axis

2.1 What the brain sees

Lithium is given by mouth, measured in serum, and acts in brain. The three numbers are not the same, and the relationship between them is better characterised than most of the mechanistic literature acknowledges.

Quantitative ^7Li magnetic resonance spectroscopy in two healthy volunteers at steady state gives a brain-to-serum ratio ranging from 0.5 to 1.3 *within* subjects across 48 hours, independent of the serum concentration, with median half-lives of 28 hours in brain against 16 in serum; morning brain lithium is about 75% of the standard twelve-hour serum value [23]. A larger series puts the adult ratio at 0.92 (SD 0.36), rising with age from 0.58 (SD 0.24) in children and adolescents [24]. The most direct measurement, at 3 T in eight patients of mean age 33 taking $1,265 \pm 442$ mg/day, gives **brain lithium of 0.35 ± 0.11 mEq/L (range 0.23–0.55) at a serum concentration of 0.69 ± 0.19 mEq/L — a brain-to-serum ratio of 0.52 ± 0.16** [2], with once-daily evening dosing producing higher ratios than twice-daily administration. That cohort is young, and since the ratio rises with age

[24], an older population would be expected to sit somewhat higher. Whole-brain ^7Li imaging confirms that the distribution is heterogeneous rather than uniform [25], with white matter exceeding grey matter and the brain signal tracking the serum profile across the day [26]; roughly half to two-thirds of brain lithium is intracellular [27,28]. The standard clinical pharmacology review puts brain concentrations at about half of serum, occasionally 75–80%, and only weakly correlated with it [29].

The composite is straightforward and consequential: **at a therapeutic serum concentration of 0.5–1.2 mmol/L, human brain lithium is of the order of 0.25–0.6 mmol/L.** Every mechanistic claim about lithium in Alzheimer’s disease must be checked against that number, not against the serum value and certainly not against the culture-medium value. One further feature of the same literature will matter for safety: in patients over 50, brain lithium **ceases to correlate with serum lithium**, and it is the brain concentration, not the serum concentration, that tracks frontal-lobe dysfunction [30].

Within brain, lithium is not passively distributed. Li^+ is a substrate of the synaptosomal Na^+/H^+ antiporter, which concentrates it roughly ten-fold above a 1 mM external concentration in sodium- and potassium-free medium, with a K_m of 2.0 mM and amiloride acting as a competitive inhibitor at K_i 3.2 μM [31]. This transporter is the strongest available argument that intracellular lithium can exceed extracellular lithium, and the argument is weaker than it looks. The ten-fold accumulation required ouabain and a sodium- and potassium-free medium, and the same authors conclude that **in the steady state internal lithium sat close to the value predicted for passive distribution.** A K_m of 2.0 mM also means the transporter is nowhere near saturated at therapeutic concentrations, let alone trace ones, so the accumulation factor cannot be assumed to grow as the exposure falls.

Endogenous lithium, in the absence of any pharmaceutical exposure, is another matter altogether. Post-mortem mapping of the alkali metals across fourteen regions in forty-two neurologically normal adults aged 50 to 101 found lithium the least abundant, heterogeneously distributed, highest in caudate nucleus at 7.6 ± 4.6 ng/g with a range of 2.2 to 21.3 ng/g, lowest in brainstem and cerebellum, and apparently unchanged with age [19]. Two features of that result matter for everything downstream. Endogenous human brain lithium is in the single-digit nanograms per gram — of the order of a micromolar at most — and it varies about ten-fold between healthy people.

2.2 The four orders of magnitude

The exposures this paper must keep apart span four orders of magnitude: endogenous human brain lithium at about 0.34 μM (2.36 ng/g in prefrontal cortex, with a regional range of 2.2–21.3 ng/g) [5,19]; drinking-water lithium at 0.5–539 $\mu\text{g/L}$ across the studied populations [11,32,12]; experimental replacement in mice at 4.3 $\mu\text{Eq/L}$ [5]; rodent microdosing at 40 $\mu\text{g/kg}$, giving blood lithium below the limit of detection and brain lithium of 3.36 ng/g [33]; human microdosing at 300 $\mu\text{g/day}$, never assayed [34]; “low-dose” human trials at serum 0.17–0.5 mmol/L [13,35,36]; the therapeutic psychiatric range at serum 0.5–1.2 mmol/L and brain 0.35 mmol/L [2]; and the cell-culture literature’s “therapeutic” 2 mM and its autophagy and anti-inflammatory work at 10 mM [20,37,38].

The gap between the first row and the last is four orders of magnitude. The gap between the first row and the row that contains lithium’s most-cited molecular target — as section 3 establishes, the 1–2 mM rung — is three.

3. Where lithium’s targets actually sit

3.1 The most-cited target has the highest Ki

The modern mechanistic literature on lithium begins with the demonstration that it inhibits glycogen synthase kinase-3 β with **a Ki of 2 mM**, and that it is not a general inhibitor of other protein kinases [1]. The companion paper of the same year showed the inhibition in intact cells, with reduced GSK-3-dependent tau phosphorylation and cytoplasmic accumulation of β -catenin and Armadillo — lithium mimicking Wnt signalling [39].

That Ki is the single most important number in this paper. Therapeutic serum lithium is 0.5–1.2 mmol/L; brain lithium measured in patients at that serum range is 0.35 ± 0.11 mmol/L [2]. **Lithium’s flagship target sits about six-fold above the concentration its own therapeutic use achieves in the organ it is prescribed to act on.** It is therefore engaged, at best, partially and at the top of a range that carries meaningful toxicity — and not directly engaged at all at any concentration below it.

The mechanism of inhibition explains why it cannot simply be dose-escalated into a clean pharmacology. Lithium is a competitive inhibitor of GSK-3 with respect to magnesium, not ATP and not substrate [40]. Kinetic dual-inhibition analysis with beryllium and ADP resolves two distinct magnesium sites, one lithium-sensitive and one lithium-insensitive that binds Mg-ATP [41]. Lithium is thus a magnesium-site poison rather than a nucleotide-pocket inhibitor, which places GSK-3 in the same pharmacological class as the lithium-inhibited, magnesium-dependent phosphomonoesterases

— a family defined structurally by a shared metal-binding motif and core [42]. No crystal structure of lithium bound to GSK-3 exists; the two-site model is an inference from kinetics. The structural account of lithium binding comes from the phosphatase branch of the family instead, where lithium is shown to occupy a key metal-activation site only after substrate or product is bound — the structural basis of uncompetitive inhibition — with mutation of the coordinating residue producing a hundred-fold change in the inhibitory constant [43].

One caveat should be entered before the comparison is pressed too hard: the 2 mM figure is an inhibition constant for a kinase and the 0.8 mM figure below is a half-inhibition concentration for a phosphatase, measured by different assays sixteen years apart, so the roughly two-and-a-half-fold gap between them is within the uncertainty of the comparison. The three-orders-of-magnitude gap that this paper turns on is unaffected, because it is a gap between millimolar and micromolar. Because the inhibition is magnesium-competitive, its potency rises as free magnesium falls, and the original authors argued that at intracellular ATP-to-magnesium ratios lithium would inhibit GSK-3 more than in vitro K_i values predict [40]. This is the load-bearing citation for the ubiquitous claim that lithium inhibits GSK-3 at therapeutic concentrations. It deserves to be named as what it is: an inference from estimated cellular magnesium, never measured directly in neurons, and never converted into an in-cell IC_{50} .

3.2 Three amplifiers, each separately evidenced

The field's answer to the K_i problem is amplification, and it is a serious answer with three independent components.

The first is the magnesium competition just described [40,41]. The second is autoregulation: inhibitory phosphorylation of GSK-3 at Ser9/Ser21 rises on lithium exposure, and this rise is a *consequence* of GSK-3 inhibition rather than a second lithium target, since it is reproduced by structurally unrelated GSK-3 inhibitors and by a peptide inhibitor [44]. Partial direct inhibition is thereby converted into a larger functional inhibition [45]. Whether the Ser9 rise requires Akt is contested: one line of work has lithium activating phosphatidylinositol-3-kinase and Akt-1 and raising inhibitory GSK-3 phosphorylation [46], while a direct test found lithium raising Ser9 phosphorylation in cells and in mouse brain **without any change in Akt phosphorylation** [47]. Genetic work places Akt as permissive rather than obligatory: strain differences in lithium response track Akt Thr308 activation, and Akt inhibition attenuates lithium's behavioural effects [48].

The third amplifier is scaffold disruption. Lithium regulates Akt/GSK-3 signalling by disrupting an Akt/ β -arrestin-2/protein phosphatase 2A complex [49], and in β -arrestin-2 knockout mice lithium fails to change Akt/GSK-3 signalling or to produce GSK-3-inhibition-like behaviour [50]. GSK-3 is itself required for that complex to form, and GSK-3 β overexpression reverses the phenotype both of lithium-treated and of Gsk3b-haploinsufficient mice [51] — which restores GSK-3 as the proximal target rather than a bystander. The genetic calibration is the most useful number in this literature: **loss of one Gsk3b allele, roughly 50% of one isoform, reproduces the behavioural and molecular effects of chronic lithium** [52]. Blocking the inhibitory serine phosphorylation

genetically, in S21A/S9A knock-in mice, produces the opposite phenotype — increased susceptibility to amphetamine hyperactivity and to stress-induced depressive behaviour [53].

Taken together these results describe lithium as a weak, partial, magnesium-competitive GSK-3 inhibitor whose functional effect is amplified by autoregulation and scaffold disruption to something like a 50% single-isoform loss. That is a defensible account at therapeutic concentrations. It is not an account that survives dilution by three orders of magnitude, and section 11 shows that the best paper on the trace rung does not attempt to make it.

3.3 The targets nobody cites are the ones the brain can reach

Inositol monophosphatase is inhibited 50% at **0.8 mM** lithium chloride, with a magnesium K_m of 1 mM, noncompetitively with respect to magnesium and uncompetitively with respect to substrate [3]. The structural work confirms the mechanism — lithium occupies a second metal site after substrate hydrolysis, trapping phosphate — and puts the therapeutically relevant range at 0.5–1.0 mM [54], on a 2.1 Å human enzyme structure [55] with a two-metal kinetic mechanism [56]. This is the lowest firm inhibition constant in the entire lithium literature, and the only classical enzyme target that a human brain at a tolerated serum concentration actually reaches. The physiological consequence proposed for it — inositol depletion, attenuated phosphoinositide signalling, and stimulus-dependent selectivity — is the inositol-depletion hypothesis [57], to which there is a pointed genetic objection: SMIT1-haploinsufficient mice have depleted brain myo-inositol with entirely normal lithium-sensitive behaviour, and SMIT1-null mice show deeper depletion with no fall in phosphatidylinositol [58]. A transport-level route to the same end exists in astrocytes, where therapeutically relevant lithium produces intracellular alkalinisation that shifts the balance between the sodium-dependent and proton-dependent inositol transporters [59].

Lower still sits a target class that the Alzheimer's literature has essentially ignored. The bisphosphate 3'-nucleotidases are members of the same lithium-inhibited phosphomonoesterase family, and are described by the authors who characterised them as inhibited **at sub-therapeutic lithium concentrations** — a family-level framing rather than a measured constant, since no inhibition constant is reported, and the more-than-eighty-fold accumulation of phosphoadenosine phosphate and the growth inhibition are yeast results [4]. In *C. elegans*, inhibition of this enzyme produces selective neuronal dysfunction [60]. BPNT2 regulates chondroitin-4-sulfation in cerebral cortex and hippocampus [61] — that is, a lithium-inhibited enzyme at sub-therapeutic concentrations controls the sulfation of a principal constituent of the perineuronal nets that sheath the interneurons whose loss shapes cortical network failure in Alzheimer's disease. Whether this matters is unknown, because nobody has looked. It is named here because any honest account of low-concentration lithium action has to acknowledge that the best-evidenced sub-therapeutic targets are not the ones the field discusses.

Table 1 — Lithium’s molecular targets ordered by the concentration at which inhibition is demonstrated, against the concentrations human tissue attains.

Target	Measured potency	Reached by human brain?	Source
BPNT1 / BPNT2 (3'-nucleotidases)	“Sub-therapeutic doses” (authors’ framing; no constant reported)	Presumed, but unquantified in brain	[4,60,61]
Inositol monophosphatase	IC ₅₀ 0.8 mM; relevant range stated as 0.5–1.0 mM	Marginally, at the top of the therapeutic range	[3,54]
Glycogen synthase kinase-3β (direct)	Ki 2 mM , Mg ²⁺ -competitive	No — above brain levels at tolerated doses	[1,40]
GSK-3 (functional, with amplifiers)	Equivalent to ≈50% loss of one Gsk3b allele	Partially, at the top of the therapeutic range	[44,50,52]
Autophagy induction via IMPase/IP₃	Induction shown at 1 mM; mechanism dissected at 10 mM	Marginally, at the top of the therapeutic range	[37]
Glial anti-inflammatory action	10 mM effective; 1 mM ineffective	No	[38]
GSK-3β level and Tyr216 state	Responds to ≈50% change in cortical Li at μEq/L	Yes — this is the endogenous range	[5]

The table states the paper’s central structural observation. The classical pharmacology of lithium is a pharmacology of the millimolar. The concentrations at which human beings are actually, chronically and involuntarily exposed to lithium — and the concentration at which the 2025 deficiency experiments operate — lie three to four orders of magnitude below it. Only the last row of the table belongs to that world, and it is not an inhibition mechanism at all.

4. The target’s disease credentials, and its clinical refutation

Before asking whether lithium engages GSK-3 in patients, it is worth asking whether GSK-3 deserves the attention. The human neuropathology is respectable. GSK-3 co-localises with neurofibrillary change and its levels are raised by about half in the Alzheimer post-synaptosomal supernatant — though the original report found **no increase in enzyme activity**, and argued that reduced

phosphatase activity made normal GSK-3 activity sufficient to hyperphosphorylate tau [62]. This distinction is routinely lost: the paper most often cited for increased GSK-3 *activity* in Alzheimer's disease reported the opposite. Neurons bearing the *active* kinase appear first in entorhinal Pre- α and spread in the Braak sequence, accumulating in pre-tangle cytoplasm [63], and the active pTyr216 pool is quantitatively raised in Alzheimer frontal cortex with somatodendritic accumulation and co-localisation with six phospho-tau epitopes the kinase generates [64]. Isoform matters: the amyloid arm of the hypothesis is assigned to GSK-3 α [65], and birds — natural GSK-3 α nulls — phosphorylate tau less, as do GSK-3 α knockout mice [66], while nearly all mouse work reports GSK-3 β . The synthesis of these strands into the GSK-3 hypothesis of Alzheimer's disease [67] remains the most coherent single-kinase account of the disease's two lesions.

It has also been tested directly, and this is the part of the record that the lithium literature tends to pass over. Tideglusib is a potent, orally available, non-ATP-competitive GSK-3 inhibitor. In a 30-patient pilot in mild-to-moderate Alzheimer's disease it produced positive trends and no significant efficacy, with asymptomatic reversible transaminase elevation in six active cases [68]. In ARGO, a 306-patient phase II trial across 55 sites, it missed its primary endpoint on every active arm, with dose-dependent reversible transaminase increase in 9–16% against 3.5% on placebo [16]. In TAUROS, 146 patients with progressive supranuclear palsy — a primary tauopathy, the cleanest available test of an anti-tau kinase mechanism — it produced no significant difference on the PSP Rating Scale or any secondary endpoint [17]. The magnetic resonance substudy of that trial is the most instructive result of the set: whole-brain atrophy progression was substantially reduced, -1.3% against -3.1% on placebo (standard errors, in a substudy of 37 patients with only 9 on placebo), with parallel reductions in cerebral, parietal and occipital rates, **and no clinical benefit whatsoever** [69].

Three inferences follow. First, GSK-3 inhibition is achievable in patients with a real inhibitor, and it does not treat Alzheimer's disease or progressive supranuclear palsy. Second, a volumetric surrogate can move handsomely while cognition does not — a warning that bears directly on the imaging claims made for lithium (section 10.6). Third, the field's response to tideglusib's failure has been to attribute lithium's promise to pleiotropy instead: lithium is held to work because it does many things at once. That may be true, but as currently stated it is unfalsifiable, and it cannot be argued in the same breath as the GSK-3 rationale that tideglusib tested and defeated.

There is one further cost of GSK-3 inhibition that the Alzheimer's literature almost never states. GSK-3 β activity is *required* for the induction of NMDA-receptor-dependent long-term depression: GSK-3 inhibitors block it, GSK-3 β activity is enhanced during long-term depression via protein phosphatase 1, and after long-term potentiation the kinase is inhibited and synapses become refractory to depression for up to an hour [70]. A chronic GSK-3 inhibitor is therefore not plasticity-neutral; it removes a physiological depotentiation mechanism. No study in this literature measures long-term depression in an Alzheimer's model under lithium.

5. Amyloid: the weakest link in the chain

Lithium's effect on amyloid is usually asserted as a property. It is better described as a model-dependent phenomenon with at least four proposed mechanisms, one substantial contradiction, and one null in the model that matters most.

The founding result assigned it to the γ -secretase step: at therapeutic concentrations lithium blocks A β production without inhibiting Notch processing, and blocks A β accumulation in the brain of APP-overproducing mice, with GSK-3 α rather than GSK-3 β as the responsible isoform [65]. A second group reported inhibition of A β production at clinically relevant plasma concentrations in an APP-Swedish cell line and in PDAPP mice, reproduced by dominant-negative GSK-3 β and GSK-3 β antisense, with reduced plaque burden [71]; a third found dose-dependent reduction of secreted A β 40 and A β 42 from a C99 substrate, placing the effect at or after γ -cleavage [72]. Two further mechanisms arrive from different directions: lithium reduces APP phosphorylation and thereby A β production, with preserved dendritic structure and improved water-maze performance in hAPP mice, an effect reproduced by crossing to dominant-negative GSK-3 β [73]; and in adult *Drosophila* lithium reduces A β 42 protein without changing its message, by reducing global protein synthesis — a route that involves neither secretase nor GSK-3 [74]. A mammalian precedent for the secretase-expression arm exists in traumatic brain injury, where lithium at 1.5 mEq/kg attenuated A β load, APP accumulation and BACE1 induction [75]. Supporting biology is real: lithium activates Wnt signalling and reduces spatial-memory impairment and neurodegeneration in APP^{swe}/PSEN1 Δ E9 mice [76], and restores hippocampal neurogenesis in TgCRND8 mice [77].

Against this stands a result that any review of lithium and amyloid must adjudicate rather than omit. In CHO cells and rat cultured neurons, at a non-toxic concentration, lithium chloride **increased** A β production, through increased β -cleavage of APP generating more substrate for an unchanged γ -secretase — while the same treatment produced the canonical readouts of GSK-3 inhibition, nuclear β -catenin translocation and reduced tau phosphorylation. A bona fide GSK-3 inhibitor, SB415286, slightly *decreased* A β [78]. The finding does two things at once: it reverses the sign of the amyloid effect, and it dissociates that effect from GSK-3 entirely.

And in the one transgenic model carrying both plaques and tangles, chronic lithium reduced phospho-tau, did **not** significantly alter A β load, and did **not** improve working memory; the authors concluded that lithium would need to be combined with an anti-amyloid intervention [79].

The honest summary is that lithium's amyloid effect has been demonstrated in overexpression systems by four incompatible mechanisms, reversed in sign in one careful cell study, and absent in the most pathologically complete mouse model. It is not a settled property of the drug. This matters for section 11, because the deficiency hypothesis makes amyloid central again — but in the opposite

causal direction, as the sink that removes lithium rather than the substrate that lithium removes.

6. Tau: real, replicated, and narrower than stated

The tau arm is the strongest part of lithium's preclinical case. Lithium reduces tau phosphorylation in cultured human neurons through direct, reversible GSK-3 inhibition, and — a result worth more attention than it receives — *enhances tau binding to microtubules and promotes microtubule assembly*, which is the function the phosphorylation destroys [80]. The same year, lithium was shown to dephosphorylate tau at the Tau-1 and PHF-1 epitopes in cultured neurons and in rat brain in vivo, and to block the proline-directed hyperphosphorylation produced by phosphatase inhibition [81]. The gain-of-function counterpart is conditional GSK-3 β overexpression in adult mouse brain, which produces reduced nuclear β -catenin, somatodendritic pre-tangle tau, abnormal neuronal morphology, astrocytosis, microgliosis and apoptotic granule cells [82].

In transgenic tauopathy the phospho-tau effect reproduces, and so does an effect on aggregation. Chronic lithium decreased GSK-3-dependent phosphorylation and filamentous aggregates in triple-mutant human tau mice [83]. In mutant human tau mice, lithium produced significant GSK-3 inhibition, reduced phosphorylation at several disease-relevant epitopes, and significantly reduced aggregated insoluble tau, with a second GSK-3 inhibitor reproducing the insoluble-tau reduction and aggregated tau correlating with axonal degeneration — **but benefit only when treatment began during early tangle development** [84]. Long-term oral lithium in P301L mice improved sensorimotor scores with lower tau phosphorylation, lower soluble tau and fewer tangles, attributed to autophagy [85].

Three qualifications narrow the claim considerably, and all three are in the primary literature.

The mechanism is not only kinase inhibition. Long-term lithium at relatively low therapeutic concentrations reduced tau lesions *primarily by promoting ubiquitination*, not by inhibiting phosphorylation [86]. Seeded aggregation experiments add a conformer dependence: lithium reduced insoluble tau and p62 and raised LC3-II in cells seeded with Alzheimer-derived tau, but not with progressive supranuclear palsy or corticobasal degeneration strains [87]. Graded co-transfection work shows the functional rescue of tau-driven process outgrowth is dose-dependent and graded rather than switch-like [88] — which is the premise microdosing needs, and the only place it is directly supported.

Established tangles are arrested, not reversed. In Tg30tau mice with advanced neurofibrillary pathology, one month of gavage producing high blood concentrations reduced tau phosphorylation, Sarkosyl-insoluble tau and Gallyas-positive tangle density *back to the density present when treatment started*, and raised brain β -catenin; eight months of lithium carbonate chow from three months

of age did not alter tangle development at all [89]. Route and peak concentration mattered more than duration, and no tangle was cleared. The “full reversal of the Alzheimer-like phenotype” that circulates in this literature is a *transgene shutoff* experiment — switching GSK-3 overexpression off — not a lithium experiment [90].

Pathology reduction and cognitive benefit dissociate. In the same Tg30tau study, motor and working-memory deficits were not rescued despite the arrest of tangle formation [89]; in 3xTg-AD mice phospho-tau fell and working memory did not improve [79]. Two independent models, two demonstrations that lithium can move the lesion without moving the animal.

7. Proteostasis: two targets pulling in opposite directions

“Lithium induces autophagy” is among the most frequently repeated statements in this field, and it is usually attributed to GSK-3 inhibition. Both halves of that sentence need correction.

Lithium induces mTOR-independent autophagy by inhibiting inositol monophosphatase, depleting free inositol and lowering inositol-1,4,5-trisphosphate, thereby enhancing clearance of mutant huntingtin and α -synuclein. The demonstration is **explicit that the effect is not mediated by GSK-3 β inhibition** [37]. Two concentrations must be kept apart here, because the literature routinely conflates them. The *mechanistic dissection* — the inositol and inositol-trisphosphate dependence, and the exclusion of GSK-3 β — was performed at **10 mM lithium chloride**, chosen to match the concentration at which inositol depletion had been established, with the authors noting that their earlier protective work used 2.5–5 mM. But *autophagy induction itself* was demonstrated down to **1 mM**, which the same authors describe as approximating therapeutic levels in human beings. Induction is therefore reachable, marginally, at the top of the human therapeutic range; what is not reachable is the concentration at which the mechanism was actually established, and neither is within three orders of magnitude of endogenous brain lithium.

Worse for the simple story, the two principal targets act on proteostasis with opposite signs. GSK-3 β inhibition *activates* mTOR and thereby *attenuates* autophagy and mutant-huntingtin clearance, which is why rapamycin was added to lithium in a rationally designed combination — to cancel the brake that lithium’s own GSK-3 inhibition applies [91]. The review literature records the consequence: autophagy *down*-regulation by lithium is observed in cerebral ischaemia and Alzheimer’s models, mTOR-dependently and GSK-3 β -mediated [92].

The net autophagic effect of lithium is therefore a balance between two targets with opposite signs, occupied to different degrees at different concentrations. This yields a specific, testable and untested prediction: **the sign of lithium’s effect on autophagic flux should invert between**

the trace and therapeutic rungs, because the IMPase arm requires near-millimolar concentrations while the GSK-3-dependent brake, mediated through kinase level and activation state rather than catalytic occupancy (section 11), is available at $\mu\text{Eq/L}$. Nobody has measured autophagic flux across a lithium concentration series in neurons. It is prediction P6 in section 16.

8. Trophic, inflammatory and non-monotonic effects

8.1 What is real at or near therapeutic concentrations

Chronic lithium protects central neurons against excitotoxicity with an EC_{50} of about **1.3 mM**, requiring six to seven days of exposure — 24 hours is ineffective — by reducing NMDA-receptor-mediated calcium influx rather than down-regulating the receptor [93]. The related series puts significant protection at **0.2–1.6 mM**, maximal after six days, with NR2B tyrosine phosphorylation reduced and receptor protein unchanged [94]; the upstream kinase is Src [95], and the protection is BDNF-dependent, abolished by a Trk inhibitor or a BDNF-neutralising antibody [96]. Chronic lithium also raises Bcl-2 in frontal cortex [97], increases dentate BrdU labelling by about 25% [98], raises Wnt/ β -catenin transcripts in proportion to measured serum lithium [99], and suppresses an ischaemia-induced rise in protein phosphatase 2A activity [100]. In patients, four weeks of blinded lithium raised total brain N-acetyl-aspartate across four lobes [101].

Two features deserve emphasis. This is a *time*-dependent pharmacology as much as a concentration-dependent one — six days, not six hours. And it sits, almost without exception, at 0.2 mM and above.

8.2 The anti-inflammatory claim is a millimolar claim

Lithium is widely described as anti-inflammatory, usually with reference to GSK-3's control of microglial migration, interleukin-6 and inducible nitric oxide synthase [102,103,104]. The concentration data are unforgiving. In rat primary glia, pre-treatment with **10 mM lithium** significantly reduced lipopolysaccharide-induced TNF- α , interleukin-1 β , prostaglandin E_2 , nitric oxide, COX-2 and iNOS — and **1 mM did not** [38]. Most of the supporting microglial literature uses non-lithium GSK-3 inhibitors rather than lithium. A direct glial anti-inflammatory action of trace or microdose lithium is therefore not supported by the concentration-response data, which matters because anti-inflammatory action is one of the effects most often claimed for microdosing.

8.3 Non-monotonicity is the rule, not the exception

The sub-therapeutic literature is small, but where it has measured dose–response it has found curves that are not monotonic, and sometimes not even of consistent sign.

Long-term lithium raises intracellular BDNF by 10% in cortical and 28% in hippocampal neurons at 0.02 mM, and raises *extracellular* BDNF by 30% at 0.02 mM but by **428% at 0.2 mM** in cortical neurons — the peak of the curve lying at the intermediate concentration, not the highest [21]. Telomere length in cultured cortical neurons rises 140% at 0.02 mM, **180% at 0.2 mM**, and 120% at 2 mM, again peaking in the middle, with protection against A β 42-induced loss of viability and telomere shortening [22]. Most consequentially, a seven-day exposure series across 0.02, 0.2 and 2 mM in primary neurons found the GSK-3 β activity ratio *falling in hippocampal* but *rising in cortical* neurons at sub-therapeutic concentrations, with Akt falling in cortex and rising in hippocampus, and hippocampal neurons responding at concentrations where cortical neurons did not [20]. In *Drosophila*, lithium extends lifespan at 1–25 mM in food, optimally at 10 mM, and *shortens* it at 50–100 mM, through GSK-3/NRF-2-dependent hormesis — an explicitly biphasic curve [105]. The ecological human counterpart, an inverse correlation between tap-water lithium and all-cause mortality across eighteen Japanese municipalities with parallel lifespan extension in *C. elegans*, is frequently cited as support for trace-dose benefit [106]; it is an ecological correlation with no control for confounding.

The inference matters more than any individual number. **“Lower dose, same mechanism, fewer side effects” is not what these data show.** They show a different mechanism at a different concentration, sometimes with a different sign, sometimes in a different cell type — which is precisely why the three claims of section 1 cannot borrow evidence from one another, and why a trial at 0.17 mmol/L is not a weaker version of a trial at 0.6 mmol/L.

9. The observational record

9.1 What is actually claimed, and where the number comes from

The most widely repeated statement about lithium and dementia is that it halves the risk. The figure is an odds ratio of 0.51 (95% CI 0.36–0.72) from a meta-analysis of lithium-treated bipolar patients [6]. That analysis pooled **five** studies, and its most influential input is a cross-sectional comparison of 66 elderly euthymic bipolar patients on chronic lithium against 48 comparable patients not recently exposed, reporting Alzheimer's disease in 5% against 33% — unadjusted, prevalent rather than incident, in 114 people [7]. An effect of that magnitude from an exposure of that kind should have been treated as a signal to investigate, not as an estimate to quote. It is nevertheless the arithmetic origin of the claim.

The same meta-analysis established the other essential number: bipolar disorder itself carries an odds ratio for dementia of 2.96 (2.09–4.18) [6]. The most recent synthesis puts it at 3.13 (2.40–4.09), or 2.60 (1.76–3.85) excluding overlapping populations, with heterogeneity of $I^2 = 99.8\%$ and the explicit conclusion that the evidence is *uncertain* [107]; independent estimates cluster at 2.3–2.4 [108,109]. **The confounder is larger than the claimed effect.** Every pharmacological estimate in this literature is a small contrast extracted from inside a much larger one.

9.2 The direction of the association depends on the comparator

Read chronologically, the pharmacological literature is not a cumulative case but an argument about controls.

The earliest primary-care case-control study found lithium users at *higher* risk of dementia, adjusted OR 1.8 (1.1–2.8), with risk rising with the number of prescriptions [110]. The first Danish register study — routinely cited as showing lithium protects — reported a dementia rate ratio of **1.47 (1.22–1.76)** in anyone who had ever purchased lithium against a general-population comparator; the protective claim rests on a *within-exposed* contrast, in which the rate in continuing users fell to general-population levels [111], and on a companion analysis within bipolar disorder in which the rate fell after the second prescription relative to the first, with no such decrease for anticonvulsants, antidepressants or antipsychotics [112]. A US Medicaid cohort with anticonvulsants as a negative control found an effect only in the highest exposure band, HR 0.77 (0.60–0.99), with nothing below it [113].

The single most instructive study is a Taiwanese nested case-control analysis of 63,347 Alzheimer cases. In the general population, lithium use carried an adjusted OR for Alzheimer's disease of **1.79 (1.34–2.38)**; restricted to patients with bipolar disorder, the same exposure gave **1.36 (0.89–2.09)**

— **null, with no trend by duration or dose** [114]. The apparent direction of the lithium–dementia association is thus a function of whether the comparison group has the illness for which lithium is prescribed.

Modern designs have not resolved this so much as narrowed the range. The most-cited recent cohort, in a UK secondary-care mental-health population, reported dementia HR 0.56 (0.40–0.78) and Alzheimer HR 0.55 (0.37–0.82) — on 548 exposed patients and 53 events, with protection apparently present at **one year or less** of exposure, which is too short for disease modification and therefore a marker of bias rather than biology [115]. A Korean cohort found higher dementia risk with valproate and with dual therapy, and no clear lithium effect [116]. Against this, the two best-controlled European analyses are null: a Finnish cohort of 9,698 people with at least three consecutive years of lithium dispensations found dementia HR 1.15 (99% CI 0.99–1.33) against a psychiatric comparator [9], and a nationwide Danish target-trial emulation of sustained lithium against lamotrigine and valproate over ten years found no systematic difference for any physical outcome including dementia [10] — the latter authored by the investigator whose earlier register studies supply the field’s two most-cited positive results. Recent federated-network analyses with active comparators cluster at HR 0.69–0.82 [117,118], and a Medicare target-trial emulation of progression in already-impaired patients reports RR 0.87 (0.78–0.99), though it remains a preprint [119]. One propensity-matched analysis reporting RR 0.49 rests on 103 events with an absolute Alzheimer incidence one to two orders of magnitude below expectation for the age band, implying gross under-coding [120].

The meta-analytic record is contradictory rather than cumulative. Three syntheses of essentially one literature report OR 0.51 [6], RR 0.66 [121] and **OR 0.94 (0.77–1.24) overall with 0.90 (0.71–1.15) within bipolar disorder — null** [8]. The null one is the most recent and the least cited. Narrative reviews of the same material range from cautiously favourable [122,123] to a review that grades each study, reports the graded ones as supporting lithium, and nonetheless finds the number of studies “substantially small” and the standard-dose evidence insufficient to establish efficacy for dementia prevention [124].

9.3 Four biases, all pointing the same way

The standard defence of the protective reading is that confounding by indication biases *toward* the null, so the estimates are conservative [115]. That argument holds only if the bipolar–dementia association is causal rather than prodromal, and the evidence says much of it is prodromal. The association is strongest in patients with bipolar disorder of less than five years' duration or onset after age 70 [109]; in the psychiatric–dementia literature generally, pooled estimates are **stronger in studies with shorter follow-up** — demonstrated for depression, where the pooled relative risk falls from 2.15 below eight years to 1.46 beyond fifteen, the signature of reverse causation, though bipolar disorder was not pooled or stratified in that analysis [125]; and first psychiatric diagnoses rise steeply in the years immediately before a dementia diagnosis, peaking in the final year [126]. When mid-life psychiatric exposure is required to precede dementia by at least ten years, the associations persist but attenuate with age [127]. If incipient cognitive impairment causes lithium to be stopped or never started — and every clinician knows it does — then protopathic bias generates a spurious protective association of exactly the observed size and direction.

Three further biases act the same way. **Healthy-adherer bias** afflicts every study defining exposure as continued or sustained use [111,112,113,9]: the clearest symptom is the low-dose target-trial emulation that reported dementia HR 0.38 (0.24–0.60) alongside an all-cause mortality HR of 0.56 (0.39–0.80) over two years on 94 events — a drug that appears to halve two-year mortality in people over 60 is describing who receives it, not what it does, as the authors themselves state [128]. **Competing risk of death** is modelled almost nowhere, although bipolar disorder carries a mortality HR of about 1.5 [109]. And **surveillance bias** cuts the other way — lithium mandates three-monthly bloods and specialist contact, which should *increase* dementia ascertainment — so its presence makes the null results harder to dismiss, not easier. The general methodological point, that confounding by indication and by disease severity dominate psychotropic pharmacoepidemiology, is well established [129].

Finally, one large cohort raises the opposite possibility. In 501,233 UK Biobank participants, bipolar disorder carried a dementia HR of 2.52 (2.00–3.19), and mediation analysis suggested that **up to two-thirds of the bipolar–neurodegeneration association may be mediated by bipolar-related medications, lithium among them** [130]. Mediation analysis cannot separate drug from illness severity, and the result deserves no more credence than the positive ones. It deserves no less, either, and it is absent from most reviews.

9.4 Drinking water: an ecological literature with a non-monotonic curve

The environmental claim rests on a different design with different failure modes. The anchor study is a Danish nested case-control analysis of 73,731 dementia cases and 733,653 controls, with individual residence histories linked to municipal water measurements. Its headline is an incidence rate ratio of **0.83 (0.81–0.85)** above 15.0 µg/L against a 2.0–5.0 µg/L reference. Its second finding, almost never quoted, is an incidence rate ratio of **1.22 (1.19–1.25)** at 5.1–10.0 µg/L, with 0.98 (0.96–1.01) in between [11]. That is not a dose-response; it is a curve that crosses unity twice. The absolute difference in median exposure between cases and controls was about 0.7 µg/L. The authors state that confounding by everything else that varies with municipality of residence cannot be excluded, and the published correspondence pressed the point [131].

The replications do not settle it. The Texan county-level analysis most often cited as confirmation reports $r = -0.20$ ($P = 0.01$) between log water lithium and the change in Alzheimer mortality, which **loses significance after adjustment for obesity and type 2 diabetes combined ($P = 0.07$)** — by the authors' own analysis, with lithium also inversely correlated with obesity and diabetes prevalence [32]; its companion paper's abstract contradicts itself on whether rural counties had more or less lithium [132]. A Japanese analysis of 808 municipalities found an inverse association with Alzheimer prevalence **in women only** [133]. The newest and largest study, county-level US water lithium against the Medicare dementia population, is directionally supportive with a prevalence ratio of 0.965 (0.950–0.981) and an incidence rate ratio of 0.958 (0.939–0.978) — effect sizes of three to four percent, within reach of residual county-level confounding — alongside *higher* mortality among people with dementia in high-lithium counties [134].

Most importantly, the only individual-level cohort points the other way. Linking 37,597 members of the Scottish Mental Survey of 1932 to water-lithium measurements at 285 sites, with 3,605 incident dementias, found an increased risk in women, highest in the second quartile at HR 1.17 (1.04–1.32), and nothing in men; the authors concluded their results do not support an association [12]. Scottish water lithium averages 1.45 µg/L, an order of magnitude below Danish levels, so the exposure range is truncated — but a truncated range cannot produce a positive association in the harmful direction by truncation alone.

One further result undercuts the entire ecological design from below. In a Portuguese biomonitoring study, urinary lithium correlated only weakly with drinking-water lithium ($\rho = 0.174$) [135] — so municipal water concentration, the exposure variable every study in this section uses, is a poor proxy for how much lithium anyone actually absorbed. The methodological verdict on this body of work is also available from within it. A meta-analysis of water lithium and neuropsychiatric outcomes across 2,678 regions and 113 million people found the expected inverse association with suicide, and also found $I^2 \approx 81\%$ and Egger's test $P = 0.013$ — **demonstrable publication bias** — while noting that dementia could not be quantitatively analysed at all for lack of data [136,137]. Subsequent reviews of the five available dementia studies remain favourable [138] or frankly qualitative [139], and the question has already reached the clinical advice columns [140].

Table 2 — The human observational record at a glance: the estimate depends on the comparator and the design.

Design class	Best examples	Estimate	Reading
Unadjusted prevalence, psychiatric clinic	[7]	5% vs 33% AD	Origin of the “halving” claim; 114 patients
General-population comparator	[111,114,110]	RR 1.47; OR 1.79; OR 1.8	Direction is <i>harmful</i> — confounding by indication
Within-bipolar, active comparator	[114,9,10]	OR 1.36 (ns); HR 1.15 (ns); no difference	Null in the best-controlled designs
Within-bipolar, exposure-graded	[113,112]	HR 0.77 top band only	Effect only where healthy-adherer bias is strongest
Modern active-comparator networks	[117,118,119]	HR 0.69–0.82 (risk ratios 0.66–0.87)	Partly “valproate harm”; consistent, modest
Highly selected low-dose users	[128]	HR 0.38 with mortality HR 0.56	Healthy-user signature, authors concur
Meta-analyses	[6,121,8]	OR 0.51 / RR 0.66 / OR 0.94 (ns)	One literature, opposite conclusions
Ecological water lithium	[11,134]	IRR 0.83 above 15 µg/L, 1.22 at 5–10 ; PR 0.965	Non-monotonic; 3–4% in the largest study
Individual-level water lithium	[12]	HR 1.17 in women, null in men	The only individual-level cohort is contrary

The honest summary is that long-term lithium use in bipolar disorder is associated with modestly lower recorded dementia incidence, with a defensible effect range of about **HR 0.8–0.9 shrinking toward 1.0** in the designs that best control indication, adherence and comparator choice; that none of it is evidence about people without a mood disorder; and that the environmental literature remains an ecological inference with a curve that changes sign inside its own exposure range.

10. The randomised record

10.1 Everything ever randomised

Total randomised exposure to lithium for cognitive outcomes in mild cognitive impairment and Alzheimer's disease is **under 500 patients** — less than a single arm of one anti-amyloid phase III trial. The record consists of: a 22-patient open feasibility study in which 14 discontinued after a mean of 16 weeks, with no difference in deaths, dropouts or MMSE change [141]; a 71-patient, 10-week, single-blind trial whose co-primary endpoints were CSF phospho-tau and lymphocyte glycogen synthase kinase-3 activity, both null, with no effect on any secondary measure including ADAS-Cog ($P = .11$) [14]; a 45-patient single-centre trial in amnesic mild cognitive impairment at 0.25–0.5 mmol/L for 12 months, reporting a decrease in CSF phospho-tau at $P = 0.03$ [35], extended to 61 patients over two years double-blind plus two single-blind, reporting stability against decline on placebo and an increase in CSF A β 42 at 36 months [142]; a microdose trial at 300 μ g/day for 15 months in about 113 patients — the randomised total cannot be confirmed from the retrievable record — reporting MMSE stability with separation claimed from three months [34]; a 77-patient, 12-week trial for agitation [36]; and one two-year trial with prespecified co-primary endpoints, LATTICE [13].

10.2 LATTICE: the best-designed trial, and its result

LATTICE randomised 83 people aged 60 or over with mild cognitive impairment to lithium carbonate or placebo for two years at a single site, with six prespecified co-primary outcomes: delayed verbal recall, visual memory, a preclinical Alzheimer cognitive composite, hippocampal volume, cortical grey-matter volume and BDNF [13,143]. **None met its threshold.** The best result was a difference in verbal-recall decline of 0.69 points per year (1.42 on placebo against 0.73 on lithium; 95% CI 0.01–1.37; $P = .05$). Hippocampal and cortical volumes declined in both arms with no treatment-by-time interaction. Serious adverse events occurred in 29% on lithium against 23% on placebo; diarrhoea, tiredness and tremor were roughly doubled. An independent Bayesian re-expression of the published data puts a 96.5% posterior probability of benefit on the verbal-recall outcome — and concludes that the trial supports an **inconclusive** interpretation [144].

Two features of the trial matter more than its verdict, and both are quantitative. The mean achieved serum lithium among completers was **0.17 (SD 0.13) mEq/L** at a mean dose of 195 mg/day — the lowest measured exposure of any lithium trial in this field. And of the 75 participants imaged for amyloid, **21 were amyloid-positive and 54 were amyloid-negative**. Section 12 argues that these two numbers, taken with the deficiency hypothesis, make LATTICE a much weaker test than it appears.

10.3 The mechanism has never been demonstrated in a patient

Two trials measured lithium's putative target in human beings. The 10-week Alzheimer trial made lymphocyte glycogen synthase kinase-3 activity a co-primary endpoint and found no effect [14]. A dose-escalation pilot in mild cognitive impairment, taking patients to 400 mg/day and a mean serum lithium of 0.415 mmol/L, found **no difference in glycogen synthase kinase-3 biomarkers between patients and controls and no significant effect of chronic lithium on the robust markers** — with 6 of 11 participants withdrawing during titration [15]. A third attempt does not even reach the tally: LATTICE planned glycogen synthase kinase-3 activity as an additional biomarker outcome, and the assays failed quality control and could not be assessed [13]. Set beside tideglusib's clinical failure at unambiguous target engagement [16,17], the position is uncomfortable: the mechanism has not been shown to be engaged by lithium in a patient, and when it is engaged by a better drug, nothing happens.

The trophic claims fare no better under direct test. The proposition that low-dose lithium raises BDNF in Alzheimer's disease traces to a post hoc subset of the negative 10-week trial, in which the cognitive benefit was **inversely** correlated with serum lithium concentration [145]; the companion substudy found no effect on GDNF and a *negative* correlation between serum lithium and CSF GDNF [146]. Since then, BDNF was unchanged in the 12-week agitation trial [147] and null as a co-primary outcome in LATTICE [13].

10.4 The behavioural indication is separate, and also negative on its primary endpoint

Lithium for agitation in Alzheimer's disease was tested in a four-site, 12-week, double-blind trial at a target serum of 0.2–0.6 mmol/L, with final concentrations of about 0.3 mmol/L (0.28 in non-responders, 0.35 in responders; no overall mean is reported). The primary outcome, neuropsychiatric-inventory agitation and aggression, improved in both arms with a between-group difference of 0.7 (95% CI –1.4 to 2.7, $P = 0.53$) [36]. Response by the composite secondary definition was 31.6% against 17.9% ($P = 0.26$). One result stands out: moderate or marked improvement on the clinical global impression occurred in 10 of 38 on lithium and **0 of 39** on placebo ($P < 0.001$) — an unadjusted secondary endpoint with a zero cell, in a trial that missed its primary. Exploratory analyses favoured lithium for delusions and irritability, and the effect was greater in patients with high mania-scale scores. The honest reading, which is the authors' own, is that lithium may act on mania-like phenomena in dementia rather than on agitation generically. The attempted replication in frontotemporal dementia enrolled 16 of a planned 60 and produced a median change of exactly 0.0 in both arms [148].

10.5 What the meta-analyses say now

The pooled estimate that established the field’s optimism came from 3 trials and 199 patients: SMD -0.41 (-0.81 to -0.02), $P = 0.04$, $I^2 = 47\%$, with **no** effect on any CSF biomarker [149]; its first author’s later meta-analysis concluded that glycogen synthase kinase-3 inhibitors are ineffective as a class [150]. The current and most complete synthesis — 6 randomised trials, 394 patients, searched to April 2025, with frequentist and Bayesian analyses — finds **no significant benefit on the MMSE (mean difference -1.61 , 95% CI -4.11 to 0.88), mixed memory results, and no consistent benefit for function, neuropsychiatric symptoms or CSF biomarkers** — though in the same sentence it reports an ADAS-Cog difference of -1.82 (-3.05 to -0.60) that excludes zero and favours lithium, with high heterogeneity on both estimates [151]; a parallel review notes attenuated deterioration in 3 of 4 dementia-spectrum trials, particularly beyond 12 months [152]. Two widely quoted supports do not bear their weight: a meta-analysis of “lithium and disease modification” comprises 32 studies of which 29 are animal [153], and the claim that lithium outperforms the anti-amyloid antibodies rests on indirect comparisons of roughly 200 lithium patients against thousands of antibody patients on the MMSE — with CDR-Sum of Boxes, the endpoint regulators used, favouring only donanemab and lecanemab [154,155]. An older meta-analysis of mood stabilisers as adjuncts favoured placebo [156], and a 2026 systematic review finds long-term low-dose lithium inconsistent in its effects on amyloid deposition and on cognition, while reporting that it does reduce phospho-tau [157].

10.6 The imaging case is weaker than its citation record

“Lithium grows grey matter” derives from a two-page research letter reporting increased grey-matter volume after four weeks [158], whose companion paper reported increased N-acetyl-aspartate across four lobes [101]. The randomised test of the inference is decisive and rarely cited alongside it: in 31 healthy men randomised to lithium or placebo for 11 days, voxel-based morphometry showed increased grey matter ($P = .001$) while registration-based whole-brain atrophy measurement (SIENA) showed no change ($P = .23$), and lithium significantly *reduced* grey-matter T1 relaxation ($P = .008$) — **the volumetric signal is plausibly an MR contrast artefact rather than tissue growth** [159]. The hippocampal literature is cross-sectional and confounded [160,161]; the one randomised maintenance comparison found its only significant treatment-by-time effect in *white* matter [162]; and the largest dataset, an ENIGMA mega-analysis of 2,664 patients and 4,065 controls, finds medicated patients with *smaller* subcortical volumes, lithium’s contribution being to weaken a negative antiepileptic–hippocampus association rather than to enlarge anything [163]. Tideglusib’s PSP substudy supplies the matching caution from the other direction: atrophy progression more than halved, clinical outcomes unchanged [69].

10.7 Cognitive harm is better established than cognitive benefit

At therapeutic concentrations lithium mildly impairs the cognition of the people who take it. A meta-analysis of 12 studies and 539 subjects at a mean trough of 0.80 mEq/L found significant impairment of immediate verbal learning and memory (effect size 0.24, 95% CI 0.05–0.43) and of creativity (0.33, 0.02–0.64), with psychomotor slowing of 0.62 (0.27–0.97) among affective-disorder patients, and **no cognitive improvements** [164]. In 30 healthy volunteers randomised for three weeks at about 0.8 mmol/L, lithium reduced the practice and learning effect on repeated testing [165]. Randomised trials in bipolar disorder show no consistent cognitive effect in either direction [166], and a 2026 synthesis finds an increased risk of confusional states when lithium is combined with electroconvulsive therapy [167]. This is a small effect at a concentration well above what any prevention trial proposes. It is nonetheless the better-replicated cognitive effect of lithium in human beings.

10.8 Tolerability is what has actually killed lithium in neurodegeneration

Table 3 — Lithium in neurodegenerative disease, ordered by achieved or targeted serum concentration. Tolerability fails before efficacy can be tested.

Serum Li (mmol/L)	Study	Population	Outcome
Not measurable (300 µg/day)	Microdose trial [34]	AD, n = 113	MMSE stable; never replicated; no biomarker
0.17 (SD 0.13)	LATTICE [13]	MCI, n = 83, 2 years	All 6 co-primaries missed ; verbal recall P = .05
0.25–0.5 (target)	Forlenza [35,142]	aMCI, n = 45→61	CSF p-tau (2011); CSF Aβ42 at 36 mo (2019)
0.28–0.35	Lit-AD [36]	AD + agitation, n = 77	Primary negative (difference 0.7, –1.4 to 2.7)
0.33–0.61	Dose-finding pilot [15]	MCI, n = 11	No GSK-3 engagement ; 54% withdrawal
0.4 (mean)	Feasibility study [141]	AD, n = 22	14/22 discontinued; no MMSE difference
0.42 (median)	FTD trial [148]	FTD, n = 16 of 60 planned	Median NPI change 0.0 in both arms
0.4–0.8	ALS trials [168,169,170]	ALS, n = 84 / 133 / 214	All null; one showed faster decline [171]
0.2–0.4 vs 0.4–0.8	ALS dose-finding [172]	ALS, n = 171	Stopped by monitoring committee; 68% discontinued

Serum Li (mmol/L)	Study	Population	Outcome
0.5–0.8	Ataxia trial [173]	SCA3, n = 62	Primary null; safe
0.5–0.8 (mean 0.68)	10-week AD trial [14]	AD, n = 71	GSK-3 and all CSF biomarkers null
0.6–1.0	HIV cognitive impairment [174,175]	n = 66, 24 weeks	Primary null; every biomarker null
Therapeutic (escalating to 1.0–1.2)	PSP/CBD pilot	PSP/CBD, n = 17	1 of 14 tolerated ≥0.4 for 28 weeks; 13 stopped early
Therapeutic	MSA trial [176]	MSA	Stopped by monitoring committee for excess AEs

Three neurodegenerative populations could not take the drug at all. In progressive supranuclear palsy and corticobasal degeneration, an open-label escalation study made the ability to complete 28 weeks at 0.4 mEq/L or above its primary endpoint: one of fourteen achieved it, and thirteen stopped early for intolerability, with no CSF tau values ever reported. That trial has never been published in a journal; its results exist only as a registry posting (ClinicalTrials.gov NCT00703677), which is itself worth noting — the single human attempt to give lithium at anti-tau concentrations to patients with a primary tauopathy is absent from the literature that cites lithium as an anti-tau agent. In multiple system atrophy the trial was stopped by its data monitoring committee for significantly more trial abandonment and more adverse events on lithium [176]. In amyotrophic lateral sclerosis, a dose-finding trial was stopped with 68.4% of 171 patients discontinuing overall and more than 30% dropping out at each of the two target levels, including the sub-therapeutic 0.2–0.4 mEq/L arm [172].

The pattern in Table 3 is the crux of the clinical problem, and it is the mirror image of Table 1. **The trials that report good tolerability are precisely those that held serum lithium at or below about 0.4 mmol/L — and those are the trials with the least effect. The trials that reached concentrations at which lithium’s classical targets are engaged could not keep their patients on the drug.** The mechanistic floor lies above the tolerability ceiling. “Give more lithium” is therefore not an available response to a null trial in an elderly population, which means the field’s only remaining move is to argue that less is enough — and that is the claim section 11 examines.

10.9 The calibrating failure

The lithium literature has one fully resolved precedent, and it should be read before any new enthusiasm. In 2008, a randomised but single-blind, non-placebo-controlled study of 16 patients given lithium plus riluzole against 28 given riluzole alone reported that no lithium-treated patient died in 15 months, against 29% mortality in controls, with marked attenuation of functional decline [177]. Four independent randomised trials followed: one stopped for futility with HR 1.13 [168]; one stopped by its monitoring committee with 68% discontinuation [172]; one null on survival at 12 and 16 months [169]; and one phase III trial of 214 patients with 50% against 59% alive at 18 months, adjusted OR 0.71 (0.40–1.24) [170]. A historical-control study found decline **faster** on lithium [171], an individual-patient meta-analysis of 518 participants gave HR 1.0 (0.7–1.4) with a single exploratory pharmacogenetic interaction — a survival benefit confined to patients homozygous for the C allele at *UNC13A* — that was taken forward into a confirmatory randomised trial [178,179]; a later meta-analysis confirmed the null [180]. **That confirmatory trial has now failed.** The lithium arm of the MAGNET platform (ClinicalTrials.gov NCT06008249) was terminated after its planned interim analysis showed no survival benefit against placebo, announced in October 2025, with 88 patients randomised across ten centres and no publication. The last surviving positive signal in the ALS lithium literature has been prospectively refuted, which closes the arc completely. The pilot that started it all carries a published erratum. The Alzheimer's evidence currently rests on pilots of comparable fragility, and the honest inference is not that lithium will fail in dementia as it failed in ALS — it is that a field which has already made this mistake once should recognise the shape of it.

II. The deficiency hypothesis

In 2025 the question changed. A study of post-mortem human brain and blood, with mechanistic follow-up in mice, proposed that lithium is a physiologically required trace element in the brain, that it is depleted in Alzheimer's disease through sequestration into amyloid deposits, and that restoring it to endogenous concentrations prevents pathology in three mouse models [5]. Because this paper is the reason the field is moving, it is set out here in detail — and then, in sections 12 and 13, taken seriously enough to be criticised.

11.1 The human observation

Prefrontal cortex from the Religious Orders Study and Rush Memory and Aging Project was assayed by inductively coupled plasma mass spectrometry for **27 metals**, with pre-cleaned vessels, ultra-trace digestion, indium internal standards, digestion blanks, duplicate runs on consecutive days correlating above $r = 0.99$, spike recovery of 91–105%, and **double-blinded sample relabelling**. Of the 27 metals, **lithium alone was significantly reduced in both mild cognitive impairment and Alzheimer's disease**, and it carried the lowest adjusted P value of any metal. Total cortical lithium fell from 2.362 ± 1.233 ng/g in people without cognitive impairment to 1.903 ± 1.033 in mild cognitive impairment and 1.798 ± 1.008 in Alzheimer's disease — reductions of 19.4% and 23.8%, one-way ANOVA $F(2,345) = 9.44$, $P = 1.0 \times 10^{-4}$. The cortex-to-serum ratio fell by 28.6% and 37.4% respectively, $F(2,282) = 12.49$, $P = 6.3 \times 10^{-6}$. **Serum lithium did not differ between groups, and cerebellar lithium did not differ** — the deficit is compartmental and regional, not systemic. A second, independent cohort of frozen frontal cortex showed a 52.2% reduction, and two further sample sets — 60 cases re-analysed in a different university laboratory, 48 processed by an alternative dry-weight digestion protocol — reproduced the direction. The normal range is wide: 0.52–6.00 ng/g in the unimpaired, consistent with earlier normative mapping [19].

11.2 Sequestration, and the bioavailable pool

The proposed mechanism of the deficit is physical capture. Laser-ablation mass spectrometry with amyloid immunostaining of adjacent sections found lithium concentrated within A β plaques in **every** case, with a plaque-to-non-plaque ratio rising from 2.24 ± 0.20 in mild cognitive impairment ($n = 7$) to 3.53 ± 0.82 in Alzheimer's disease ($n = 5$) — twelve cases in all, which is the sample the most novel claim in this literature rests on. Biochemical fractionation gives the number that matters most: lithium in the **plaque-free cortical fraction fell to $49.2 \pm 31.9\%$ of the unimpaired mean ($n = 42$; $P = 1.14 \times 10^{-5}$)** — the bioavailable pool is halved, roughly twice the loss measured in unfractionated tissue. Lower non-plaque lithium correlated with worse episodic memory, semantic memory and global cognition across the whole ageing population, and more strongly within Alzheimer cases, where the episodic-memory correlation reaches $r = 0.540$ ($P = 0.0047$) while semantic memory does not remain significant. In J20 mice the same enrichment appears in deposits at 12 months but **not at 3 months, before deposition** — the temporal control the claim requires. In vitro, lithium binds synthetic A β 42 fibrils and oligomers saturably, with a high-affinity component inside the physiological concentration range.

This yields a feed-forward loop rather than a linear cause: deposits trap lithium, lithium-deficient microglia clear amyloid less efficiently, and more deposits form. It is the most novel and most internally consistent element of the hypothesis. It is also, as section 12 argues, the element that makes the hypothesis hardest to falsify.

11.3 The depletion experiments

The causal claim rests on removal, which is the stronger design. A chemically defined diet with **92% of its lithium removed** and the other 26 metals unchanged produced serum lithium at $10.85 \pm 6.73\%$ of control (-89%) and cortical lithium at about half of control in both triple-transgenic and ageing wild-type mice. The consequences were: increased hippocampal amyloid burden, detectable after **five weeks** and progressive, including raised A β 42 in **non-transgenic** ageing mice; **three- to four-fold increases in phospho-tau** at Ser202 and Ser396/404; pro-inflammatory microglia marked by CD68, GPNMB and LPL, releasing more IL-6, TNF and chemokines on stimulation and with **significantly reduced A β 42 uptake and degradation**; loss of dendritic spines, synaptophysin, PSD-95, myelin basic protein, oligodendrocytes and axons, with thinner sheaths and an elevated g-ratio; and impaired learning and memory with clean motor and visual controls. Single-nucleus sequencing after five weeks showed coordinated changes across six cell types, with synaptic and myelination programmes down and neurodegeneration programmes up, overlapping human Alzheimer datasets and, in microglia, the GPNMB+ disease-associated state and Alzheimer GWAS genes.

Within its own frame this is a strong experiment. Lithium restriction in a mouse produces, within weeks, a multi-cell-type phenotype resembling the disease — including in animals carrying no human transgene at all.

11.4 The mechanism, and the paradox its authors concede

Lithium deficiency raised **total glycogen synthase kinase-3 β protein and its mRNA** in CA1 neurons, oligodendrocytes and microglia, raised the activating pTyr216 modification, lowered the pSer9-to-total ratio, and lowered nuclear β -catenin in three cell types. **Inositol was unchanged** — the classical pharmacological target was not engaged. Two structurally unrelated glycogen synthase kinase-3 inhibitors reversed the phenotype in vivo and restored microglial amyloid uptake in vitro.

The authors then state the problem plainly: the reported inhibition constant of the lithium–GSK-3 β interaction is millimolar, which makes direct inhibition an unlikely mechanism at the low micromolar concentrations of endogenous brain lithium. Their data answer it by relocating the mechanism: **endogenous lithium does not inhibit the kinase catalytically, it holds down the kinase's expression level and activation state**. That is a regulatory relationship, not an occupancy relationship, and it is the single most important conceptual move in the recent literature — because it is the only formulation in which a fall from 0.34 to 0.26 μ M in cortical lithium — a change of some 0.08 μ M — can act on a target whose K_i is 2 mM without violating mass action.

It is also, at present, a description rather than a mechanism. No sensor, transcriptional pathway or signalling step is identified that would allow a sub-micromolar change in lithium to set the expression level of a kinase. And the mechanistic rescue is pharmacological — two inhibitors, one of them at 50 mg/kg daily for 14 days — with **no genetic manipulation of Gsk3b** in the deficiency model.

11.5 Replacement, and what the salt actually does

The replacement arm produced the result that has driven the public reception of this work. Sixteen lithium salts were screened by conductivity; lithium orotate, the least conductive, was carried forward. Given in drinking water at **4.3 μ Eq/L — about 30 μ g of elemental lithium per litre** — it prevented amyloid and phospho-tau accumulation in the prevention window, reduced hippocampal plaque burden to $42.7 \pm 24.8\%$ of vehicle in established pathology ($P = 0.0018$) and CA1 phospho-tau density to $32.6 \pm 30.1\%$, reduced plaque burden by about 64% in aged J20 mice ($P = 1.8 \times 10^{-8}$), restored synaptic and myelin markers, lowered total and pTyr216 GSK-3 β , and largely reversed memory deficits in triple-transgenic and aged wild-type animals. Equimolar lithium carbonate, and sodium orotate as an anion control, did not.

The pharmacology behind that contrast is more subtle than the headline. **Total serum and hippocampal lithium did not differ significantly between the two salts**. What differed was distribution: the plaque-to-non-plaque ratio was 2.44 ± 0.62 on carbonate against 1.35 ± 0.52 on orotate in triple-transgenic mice, and 5.67 ± 1.18 against 2.56 ± 1.19 in J20 mice, while the **non-plaque bioavailable pool was restored to 89.6–93.5% of wild-type by orotate and to 45.6–54.8% — that is, not at all — by carbonate**. The claim is not that orotate delivers more lithium; it is that orotate delivers lithium that amyloid does not take. Long-term dosing did not change blood urea nitrogen, creatinine or thyrotropin in three cohorts.

Three cautions belong with these numbers. The in vitro affinity difference underlying the claim is about two- to two-and-a-half-fold in the low concentration range (EC₅₀ 35.0 against 13.98 µEq/L for oligomers; 3.74 against 1.93 for fibrils); across the full 0–500 µEq/L range it **vanishes for oligomers** (160.7 against 155.2 µEq/L) while persisting at 1.6-fold for fibrils (158.3 against 99.6) — so the paper’s own text, which describes carbonate as the higher-affinity salt across a broad range, overstates in one direction just as a flat “the difference vanishes” would overstate in the other. The vehicle group in the pivotal 9-to-18-month rescue experiment comprised three animals. And the J20 result quoted above comes from a different, later window — 17 to 22 months — with the paper’s own text rounding the reduction to about 70%.

12. Repletion is not inhibition

12.1 Two different pharmacologies

If the deficiency hypothesis is right, then lithium in Alzheimer’s disease is not a drug with a weak target. It is a nutrient with a set-point. The distinction is not semantic; the two framings differ in every respect that matters for designing a trial.

Table 4 — Inhibition pharmacology against repletion physiology: the same molecule under two theories.

	Inhibition pharmacology	Repletion physiology
Operative concentration	0.4–1.2 mmol/L serum	≈0.3 µM brain; a 1.3–1.5-fold increment in intake
Dose–response	Monotonic up to toxicity	Saturating at normal; no benefit above sufficiency
Who can respond	Anyone with the target	Only the deficient
Target engagement marker	Serum lithium; kinase activity	Non-sequestered brain or CSF lithium
Expected effect of more drug	More effect, then toxicity	No further effect, then toxicity
Meaning of a null trial	Wrong target, or too little drug	Enrolled replete patients, or failed to replete
Mechanism at the target	Catalytic inhibition, Mg2+ site	Kinase expression and Tyr216 state
Correct comparator	Placebo	Placebo plus lithium status at baseline

Every completed human trial in this field belongs to the left-hand column. Each titrated to a serum concentration, monitored serum, enrolled patients by clinical phenotype without regard to lithium status, and interpreted its result as a statement about a dose. That is the appropriate design for a weak kinase inhibitor. It is the wrong design for a nutrient, in the same way that a trial of iron in unselected anaemic patients is the wrong design for iron-deficiency anaemia — and would, run that way, return a null.

12.2 The null trials do not test the hypothesis they are read as refuting

LATTICE is now routinely cited as evidence against low-dose lithium in mild cognitive impairment. Under repletion logic it is close to uninformative, for two reasons that are in its own published numbers.

First, **54 of the 75 imaged participants were amyloid-negative, against 21 amyloid-positive** [13,143]. On the deficiency hypothesis, the cortical lithium deficit is produced by sequestration into amyloid deposits [5]. A participant without amyloid has no sink, and therefore — by the hypothesis's own mechanism — no deficit to correct. Nearly three-quarters of the trial population was, on the theory being tested, ineligible to benefit.

Second, the amyloid-positive stratum is where a repletion effect should have appeared, and it is where the numbers are. Randomisation was stratified by amyloid status, and among completers the effect sizes were **Hedges' $g = 0.74$ for verbal memory, 0.82 for hippocampal volume and 0.81 for hippocampal percentage change in the amyloid-positive group, against 0.32, 0.09 and 0.12 in the amyloid-negative** [13]. Those are medium-to-large effects in a stratum of 21, which is to say: exactly what an underpowered subgroup looks like whether the effect is real or not, but a three-fold separation in the predicted direction on three separate measures.

This reading is not an outside reinterpretation. The trialists state it themselves, noting that their predominantly amyloid-negative sample “may have diluted treatment effects” and that exploratory analyses suggested larger effects in amyloid-positive participants [13].

The same argument applies, with less force, to the older trials: none measured amyloid status at entry at all, and none measured lithium status in any compartment. The 10-week trial [14] was too short for any disease-modifying mechanism; the 12-week agitation trial [36] tested a behavioural endpoint; the microdose trial [34] measured no serum lithium and has never been replicated.

12.3 And that is the problem

The preceding argument is a defence of the deficiency hypothesis against a body of null trials. It is also, read carefully, an indictment of it — because the same reasoning can absorb any future result.

Consider the available explanations for a negative trial under the hypothesis as currently stated. If the patients were amyloid-negative, they were replete and had nothing to gain. If they were amyloid-positive, their plaques sequestered the lithium given — which is the published explanation for

why carbonate failed where orotate worked [5]. If the dose was low, it was insufficient; if the dose was high, it was the wrong pharmacology, “approximately 1,000 times the endogenous level”, and may have driven the amyloid-binding rather than the bioavailable pool. **Every cell of the outcome table has an explanation available in advance.** A hypothesis in that position is not yet wrong; it is not yet testable, which is a different and more urgent problem.

What would make it testable is a measurement rather than an argument: the concentration of **non-sequestered lithium in the living brain, or a validated proxy for it in cerebrospinal fluid.** That quantity is the hypothesis’s own definition of the operative variable, it is the quantity the human observation is built on, and it has never been measured in a living person. Every claim in the hypothesis becomes falsifiable once it exists: whether low bioavailable lithium precedes amyloid or follows it; whether oral lithium — in any salt — raises it; whether raising it changes anything.

It is worth recording that the first registered lithium orotate trial in Alzheimer’s disease makes precisely this its central mechanistic question: whether oral lithium orotate raises cerebrospinal-fluid lithium against placebo over nine weeks in 40 patients with biomarker-confirmed early disease (ClinicalTrials.gov NCT07459959, not yet recruiting at the time of writing). The field’s next real datum is a pharmacokinetic one.

12.4 Independent replication is missing, and two human measurements point the other way

As of September 2026 **no other group has published post-mortem brain lithium in Alzheimer’s disease against controls.** The four replications supporting the human observation — second cohort, second laboratory, second digestion protocol, plaque fractionation — are internal to the same report [5], and the journal’s own follow-up is a supportive commentary rather than a challenge [181]. (A two-page laboratory-medicine letter on endogenous lithium levels and Alzheimer’s disease has since appeared, but its content could not be retrieved for this review and it may or may not contain original measurements [182].) The absence has a technical explanation as well as a historical one: ultra-trace inductively coupled plasma mass spectrometry with pre-cleaned vessels is a recent capability, and the neutron-activation methods that carried trace-element neuropathology for decades cannot see lithium at all — which is why the question went unasked rather than answered in the negative. The appropriate response is therefore neither scepticism nor assent but a second brain bank. The precedent is not encouraging on magnitudes: the nearest prior claim of an essential-metal deficiency in Alzheimer brain, a pan-cerebral copper reduction to 53–70% of control [183], reappears in the 2025 metallomics as a 9.6% reduction — the two datasets agree on direction and disagree by a factor of five on size.

Three further human measurements complicate the picture. In 187 aluminium-plant workers, **higher** plasma lithium was associated with **worse** cognitive scores [184]; a larger 2026 study of 455 workers — from the same institution and the same industrial setting, so an extension rather than an independent replication — reports the same direction, with lithium among the metals its mixture model names as contributing to impairment [185]. In a pilot of 60 people, faecal lithium was

significantly **higher** in cognitive impairment [186]. And an earlier serum metallomic study found lithium discriminating impaired from unimpaired subjects without distinguishing mild cognitive impairment from dementia [187]. One measurement points the hypothesis's way from outside Alzheimer's disease: blood lithium was lower in 45 patients with spinocerebellar ataxia type 3 than in 44 controls [188]. None of these measures the compartment the hypothesis is about; none can be dismissed on that ground alone.

12.5 “Deficiency” is a word the evidence has not yet earned

Lithium is not a recognised essential element for human beings. There is no defined deficiency syndrome, no validated status biomarker and no nutritional reference standard; the regulatory and review literature places it, at best, as a **candidate beneficial trace element** [18,189]. The animal basis is older and thinner than its citation record suggests: the founding review proposes a provisional intake of 1,000 µg/day while stating that lithium-deficiency diseases have not been characterised in humans [190]; the best-indexed rodent deprivation study found decreased aggression and a circadian phase delay with growth unchanged [191]; other work reports immune and thymic changes [192] and tissue depletion in a diabetic hamster model [193]. Human “status” biomarker work is essentially one group's scalp-hair series [194,195], and no hair or nail lithium study in dementia exists. What *is* established, by physical methods independent of the 2025 report, is that endogenous brain lithium is spatially structured rather than passively distributed, with white matter exceeding grey matter [196,197] — a regulated distribution being the strongest prior argument for a physiological role, and the reason the question was worth asking in the first place [198].

Three quantitative tensions remain. The claimed pathogenic shortfall — 24% of total cortical lithium, 0.34 µM to 0.26 µM — is small against an **eleven-fold range in healthy brains** (0.52–6.00 ng/g) and against regional variation of the same magnitude [19]. The mouse depletion, 92% removal of dietary lithium, is not a state any human occupies. And the human deficit is measured in brains already full of plaques, with sequestration into those plaques offered as its cause — so in the tissue examined, the deficit is partly *downstream* of the pathology it is proposed to cause.

13. Reading the dose: the gap nobody has closed

There is a third problem, and it is arithmetic rather than conceptual.

The mouse rescue was achieved with drinking water containing 30 µg of elemental lithium per litre, on top of a diet containing 103 ng/g. For a mouse drinking 4–5 mL and eating 3–4 g daily, that is roughly 0.12–0.15 µg/day added to 0.31–0.41 µg/day already present: **a 1.3-to-1.5-fold**

increase in total lithium intake, or about 4–5 µg/kg/day. Straight milligram-per-kilogram scaling to a 70 kg human gives about 0.3 mg of elemental lithium daily; allometric scaling gives about 0.025 mg.

Now place the human exposures beside it. LATTICE delivered about 195 mg of lithium carbonate daily — roughly 36 mg of elemental lithium, or 0.5 mg/kg/day, **some 100-fold above the mouse dose on a weight basis**, a discrepancy the deficiency hypothesis's proponents have themselves invoked to explain the null. And the first registered lithium orotate trial titrates to 720 mg of lithium orotate daily, about 28–31 mg of elemental lithium (NCT07459959) — **the same order of magnitude as the trial whose dose is said to have been a hundred-fold too high**.

This is the practical crux of the whole field, and it forks. Either the operative human dose is two orders of magnitude below anything yet given, in which case no trial to date — including every “low-dose” and “microdose” trial — has tested repletion, and the effect must survive in a species whose lithium handling, plaque burden and dietary intake all differ from the mouse's. Or the doses now being planned are low-dose *pharmacology* wearing the vocabulary of repletion, in which case they inherit every safety obligation of chronic lithium in older adults and none of the protection that “physiological” implies. The two positions are frequently held simultaneously. The field's flagship advocacy review, published in *JAMA Psychiatry* after LATTICE reported, invokes the repletion hypothesis, calls for a prospective trial of low-dose lithium orotate in mild cognitive impairment, and in the same argument specifies “low-dose lithium (approximately 0.3 mM)” as the neurotrophic exposure [199] — a serum concentration some two orders of magnitude above the repletion dose computed here, and one that carries the thyroid and renal thresholds of section 14. They are not compatible.

The remaining possibility deserves naming: that repletion and low-dose pharmacology are the same intervention at different points on a non-monotonic curve — which the preclinical data positively encourage, given peak effects at intermediate concentrations for BDNF secretion and telomere maintenance [21,22], opposite-signed kinase responses in cortical and hippocampal neurons at the same sub-therapeutic concentration [20], and frank hormesis in the one organism where the full curve has been measured [105]. Independent evidence that *sub-psychiatric* lithium can move brain kinase activity exists — 10 mg/kg/day in drinking water reduced prefrontal glycogen synthase kinase-3 activity in mice [200] — but that dose is some 2,000-fold above the “physiological” one on a weight basis, which locates it firmly in the pharmacological column.

14. Safety, the ceiling, and the salt



14.1 The harms are ordinary, quantified, and concentrated in the population being proposed for treatment

Lithium's toxicity profile is among the best characterised in medicine. Meta-analysis of 385 studies gives a urinary concentrating defect of about 15% of maximum, clinical hypothyroidism at OR 5.78 (2.00–16.67), calcium raised by 0.09 mmol/L, parathyroid hormone by 7.32 pg/mL, and renal replacement therapy in 0.5% of patients, with glomerular filtration rate reduced by a non-significant 6.22 mL/min — on which the authors' own conclusion is that there is little evidence of clinically significant renal impairment in most patients and that the risk of end-stage failure is low [201]. Laboratory-linkage data give adjusted hazard ratios of 1.93 for stage 3 chronic kidney disease, 2.31 for hypothyroidism and 1.43 for raised *total* calcium — adjusted calcium was null — with harms appearing early and concentrated at above-median lithium concentrations [202]. Hyperparathyroidism runs at about 4% against 0.5% in healthy populations, with multiglandular disease in half of cases and calcium insufficiently monitored in practice [203]; against active comparators, lithium carries higher rates of kidney, thyroid and calcium abnormalities and lower rates of substantial weight gain [204,205].

Three findings bear directly on a prevention indication in older people. Renal harm is **concentrated in exactly that group**: in a cohort of 6,360 bipolar patients, ever-use of lithium carried a renal-failure hazard ratio of 2.5 (1.6–4.0), with patients aged 50 and over at particular risk and a number needed to harm of 44 [206]. The decline is exposure-dependent and, crucially, **does not reverse on stopping**: in a ten-year prospective cohort, median decline was 0.79 mL/min/1.73 m² per year, 59% declined faster than the general-population mean, decline tracked duration and mean serum concentration, and trajectories did not change in the 20% who discontinued [207]. And the thresholds are lower than “low-dose” advocacy implies: in a population cohort of incident bipolar disorder, the serum concentrations above which hypothyroidism and stage 3 chronic kidney disease became detectable were **approximately 0.50 and 0.59 mEq/L** [208] — inside the range some Alzheimer proposals target. Longer-term cohorts confirm gradual decline from the first year, with about a third of patients treated 10–29 years showing evidence of chronic renal failure though only 5% severe [209]; a recent meta-analysis finds a large cross-sectional eGFR gap with a small annual rate difference and non-significant hard outcomes [210]. The mechanisms — vasopressin resistance, aquaporin-2 down-regulation, tubulointerstitial injury with microcysts — are well worked out [211,212,213]. One of them is worth a sentence of its own: of the four mechanisms proposed for the nephrotoxicity, **the first is altered glycogen synthase kinase-3 signalling** [214]. If that is right, the therapeutic target and the toxicity target are the same protein, and the therapeutic index cannot be widened by improving selectivity for it.

In older adults specifically, four further facts should govern any prevention proposal. Lithium clearance falls with age, and recommended maintenance doses for patients over 60 are about three-fifths those for patients under 40 [29]. Serum lithium **does not predict brain lithium** in people over 50, and it is brain lithium that tracks frontal dysfunction [30] — while in the same population higher brain lithium also tracks higher N-acetyl-aspartate and higher myo-inositol [215],

so the compartment that carries the benefit carries the harm. Toxicity occurs at nominally therapeutic concentrations, with neurotoxicity the commonest manifestation among reported cases at a mean age of 71 [216] — including lithium neurotoxicity presenting as dementia and missed for 18 months because serial serum levels were in range [217]. And of the drugs an older person may buy unsupervised, **non-steroidal anti-inflammatories independently raise serum lithium** [218]. The current authoritative review of 8,808 older adults on lithium finds practice concentrations of 0.47–0.67 mmol/L, harm signals from 0.82, overt toxicity from 1.20, and endorses age-specific target ranges that most laboratories still do not report [219]; at the low targets proposed for prevention, assay imprecision is itself a material fraction of the target [220]. The one reassuring direction is bone: fractures were *less* frequent on lithium than on other mood stabilisers, HR 0.66 (0.44–0.98) [221].

Finally, “trace lithium is inert” is not established. In 202 Andean women with high environmental exposure, urinary lithium was inversely associated with free thyroxine and positively with thyrotropin [222]. That exposure is far above any supplement dose, so the finding bounds rather than refutes microdose safety — but it shows that non-pharmacological lithium is not biologically silent, which is, after all, the premise of the deficiency hypothesis.

14.2 The orotate question

Lithium orotate carries the weight of the replacement claim, and its pharmacology is not settled.

The historical record is genuinely two-sided. In 1978, rats given lithium orotate had higher serum and brain lithium than those given carbonate, with brain concentrations about three-fold higher at 24 hours [223]. In 1979 that experiment was repeated with renal measurements added: lithium was again higher — in serum, kidney and heart, brain not being among the tissues assayed — **together with markedly reduced glomerular filtration rate, urine flow and renal lithium clearance**, which the authors took to account for the higher concentrations, concluding that it seemed inadvisable to use lithium orotate in patients [224]. Both experiments used single intraperitoneal injections, with orotate given as a slurry against carbonate in solution — a route-and-formulation confound that bears directly on the question of whether any orotate advantage is a property of the molecule. An independent series found **no difference** in uptake, distribution or excretion between orotate, carbonate and chloride, with the one reproducible orotate-specific difference being more slowly developing polyuria [225]. The modern case for the salt is a mouse behavioural study reporting an approximately ten-fold potency difference, abolished by organic-anion transport inhibitors, with carbonate but not orotate producing polydipsia in both sexes, raised creatinine in males and raised thyrotropin in females over 14 days [226]; its authors' earlier review frames the superiority of orotate explicitly as a proposal rather than a finding [227].

The chemistry objection is now formally published. No study has demonstrated a stable lithium orotate species in physiological fluids; acid–base chemistry predicts protonation and dissociation in the stomach, so what is absorbed is lithium ion plus orotic acid; oral pharmacokinetics of the two salts are comparable; and carbonate is itself neuroprotective at very low doses [228]. If that critique holds, the

in vivo distribution difference at matched total lithium requires an explanation other than the molecule — an orotate-anion effect on transport being the leading candidate [226]. Clinical pharmacology reviews of lithium formulation do not include orotate in the recognised landscape at all [229]. Nor is orotate the only engineered salt making this argument: a lithium salicylate–proline cocrystal has completed a phase 1/2 study in Alzheimer’s disease (NCT05363293) and a head-to-head brain and plasma pharmacokinetic comparison against lithium carbonate using ^7Li spectroscopy (NCT06921590), with its sponsor reporting higher brain lithium than carbonate. That is formally the same claim as the orotate claim, on a better-controlled human design — but the evidence is so far a registry posting and a sponsor statement, the programme is commercial, and its scientific precursor was retracted [230]. It should be watched rather than cited.

The safety file is thin in a way that matters for a decades-long prevention indication. Modern toxicology is one 28-day rat study with a no-observed-adverse-effect level of 400 mg/kg/day plus a negative genotoxicity battery [231] — but lithium’s characteristic harms take years, not weeks. Human data amount to case reports (an overdose of an internet supplement producing serum lithium of 0.40 mEq/L and mild symptoms [232]; a patient whose “lithium” was an over-the-counter orotate product with serum lithium below 0.05 mmol/L [233]), a professional warning letter [234], and uncontrolled historical series that cannot support any inference [235,236]. The only human imaging study of a supplement-dose orotate product — nine healthy men, 5 mg/day, adherence self-reported — reports detectable brain lithium but states a concentration range (“approximately 10–60 mM”) implausible by three orders of magnitude against a therapeutic brain concentration of about 0.35 mM, almost certainly a unit error for micromolar [237].

Meanwhile the market has moved ahead of the evidence. Surveys of 211 over-the-counter lithium users find lithium aspartate 10 mg daily the commonest product, with perceived cognitive benefit widely reported and **side effects and withdrawal phenomena more prevalent than anticipated** [238]; qualitative work finds three-quarters of users reporting perceived cognitive improvement [239]. Lithium orotate is sold as a dietary supplement in the United States and classified as a prescription drug in Canada. The senior author of the deficiency paper has stated publicly that he does not recommend taking lithium orotate, because the dose range and human toxicity profile are undetermined. That is the correct position, and it should be quoted wherever this work is discussed, because the predictable consequence of a “deficiency” framing is unsupervised supplementation in the population least able to tolerate lithium and most likely to be taking an interacting drug.

15. Strength of evidence

Table 5 — Nineteen claims, graded. “Strong” means replicated in human beings by more than one group with concordant designs; “moderate” means consistent human evidence with one serious design limitation; “weak” means single-study, indirect, or contradicted; “contested” means credible evidence on both sides.

Claim	Strength	Basis	Principal objection
Lithium inhibits GSK-3 at concentrations the brain reaches	Weak	Ki 2 mM vs brain 0.35 mM [1,2]	Requires three amplifiers; never measured in human brain
Lithium inhibits IMPase at therapeutic concentrations	Strong	IC ₅₀ 0.8 mM, structure and kinetics [3,54]	Downstream inositol-depletion hypothesis genetically challenged [58]
GSK-3 is dysregulated in Alzheimer brain	Moderate	Active pTyr216 pool raised [64,63]	Total activity not raised in the founding study [62]
GSK-3 inhibition treats Alzheimer's disease	Refuted	Tideglusib negative, n = 306 [16] and PSP n = 146 [17]	—
Lithium reduces tau phosphorylation in vivo	Strong	Multiple models, multiple groups [81,84,83]	Not exclusively kinase-mediated [86]
Lithium reverses established tangles	Refuted	Arrest only, at high peak concentrations [89]	“Reversal” is transgene shutoff [90]
Lithium lowers amyloid	Contested	Four mechanisms reported [65,71,73,74]	Raised via β -cleavage [78]; null in 3xTg [79]
Lithium's pathology effects deliver cognitive benefit in models	Weak	Some models [76,85]	Dissociation in two models [79,89]
Lithium induces autophagy	Moderate	Induction at 1 mM, mechanism at 10 mM [37]	Unreachable below the therapeutic range; GSK-3 arm opposes it [91]
Lithium is anti-inflammatory in glia	Weak	10 mM effective, 1 mM not [38]	Concentration unreachable

Claim	Strength	Basis	Principal objection
Sub-therapeutic lithium has neuronal effects	Moderate	BDNF and telomere effects at 0.02–0.2 mM [21,22]	Non-monotonic; region-dependent sign [20]
Lithium use lowers dementia incidence in bipolar disorder	Weak-to-moderate	Consistent direction, HR 0.66–0.87 [117,118]	Null with psychiatric comparators [9,10]; null meta-analysis [8]
Lithium halves dementia risk	Refuted as stated	OR 0.51 from 5 studies [6]	Driven by 114 unadjusted patients [7]
Water lithium is inversely related to dementia	Weak	IRR 0.83 >15 µg/L [11]; PR 0.965 [134]	Non-monotonic (IRR 1.22 at 5–10 µg/L); contrary individual-level cohort [12]; publication bias [136]
Low-dose lithium slows cognitive decline in MCI/AD	Weak	One positive single-centre trial [35,142]	Six co-primaries missed [13]; negative meta-analysis [151]
Lithium engages GSK-3 in patients	Refuted	Two trials, no engagement [14,15]	—
Lithium raises BDNF in patients	Refuted	Post hoc subset only [145]	Null in two direct tests [147,13]
Cortical lithium is reduced in MCI and AD	Moderate	Blinded ICP-MS, 27 metals, internal replications [5]	No independent replication; cross-sectional; contrary plasma and faecal data [184,185,186]
Lithium deficiency causes Alzheimer pathology	Moderate in mice, untested in humans	92% dietary depletion reproduces the phenotype [5]	No human ante-mortem measure; sequestration makes the human deficit partly downstream
Lithium orotate evades amyloid sequestration	Weak	Distribution difference at matched total Li [5]	No stable species demonstrated in vivo [228]; affinity difference 2–2.5×
Low-dose lithium is safe in older adults	Contested	Renal function preserved to 4 years [240]	More AEs, diabetes and arrhythmia in the same trial; thyroid/CKD thresholds ≈0.5 mEq/L [208]; harm irreversible [207]

16. Ten predictions, and the experiment that settles each

P1. Independent post-mortem metallomics will reproduce a reduction in cortical lithium in Alzheimer's disease, but smaller than 24%. *Experiment:* pre-registered ultra-trace ICP-MS in two independent brain banks, with dry-weight normalisation, agonal-state and medication covariates, and blinded relabelling. *Falsified if* no reduction appears, or if it does not survive adjustment for terminal illness and renal function. The precedent for magnitude shrinkage on replication is copper [183,5].

P2. Bioavailable (non-plaque) cortical lithium will separate cases from controls better than total cortical lithium. *Experiment:* paired fractionation and laser-ablation mapping in the same cases, with the plaque-free pool as the primary variable. *Falsified if* total lithium performs as well; the hypothesis's central quantity would then be redundant.

P3. Cerebrospinal-fluid lithium will be measurable at endogenous concentrations and will correlate with amyloid burden, not with serum lithium. *Experiment:* high-sensitivity ICP-MS on CSF from an amyloid-PET-characterised cohort, alongside the ⁷Li imaging whose feasibility and acceptability in patients is now being established [241]. This is the enabling measurement for everything else in this list, and it does not yet exist.

P4. Oral lithium will raise total brain lithium without restoring the non-sequestered pool in amyloid-positive patients. *Experiment:* the registered lithium orotate trial's CSF endpoint, stratified by amyloid burden; ideally with ⁷Li imaging. *Falsified if* CSF or non-plaque lithium rises equally regardless of amyloid load — which would also dissolve the orotate rationale.

P5. Lithium orotate and lithium carbonate will prove pharmacokinetically indistinguishable in human plasma, and any orotate advantage will be a transport phenomenon, not a molecular one. *Experiment:* analytical speciation of plasma after each salt, plus organic-anion-transporter inhibition in a model system [228,226]. A registered head-to-head ⁷Li comparison of an engineered lithium cocrystal against carbonate (NCT06921590) has already run the human half of this design for a different salt; its published result will be the first real test.

P6. The sign of lithium's effect on autophagic flux will invert between endogenous and therapeutic concentrations. *Experiment:* flux measurement across a 0.1 μ M–2 mM series in human neurons, with IMPase and GSK-3 arms separated pharmacologically and genetically [37,91].

P7. In a repletion-designed trial, benefit will be confined to patients who are lithium-deficient at baseline, and the dose-response will saturate. *Experiment:* a trial enriched for amyloid positivity, stratified by a validated lithium-status measure, with at least three

doses spanning two orders of magnitude and repletion — not serum concentration — as the target-engagement endpoint. Absent P3, this trial cannot be run.

P8. Cognitive benefit at sub-therapeutic concentrations will not be mediated by BDNF. *Experiment:* a mediation analysis in any trial that shows a cognitive effect at all; the direct tests so far point this way [145,147,13].

P9. Genetic reduction of Gsk3b will reproduce lithium repletion in the deficiency model, and lithium repletion will fail in its absence. *Experiment:* conditional Gsk3b manipulation crossed into the dietary-depletion paradigm, in place of small-molecule rescue [5,52].

P10. Chronic lithium at any dose that raises cerebrospinal-fluid lithium measurably will produce a detectable renal signal within five years in people over 70. *Experiment:* a prevention trial powered for eGFR slope as a co-primary safety endpoint, given exposure-dependent and apparently irreversible decline [207,206] and thresholds near 0.5 mEq/L [208].

17. Limitations of this analysis

This is a reading of published evidence, not new data, and it inherits that literature's gaps. Several quantitative claims in the older mechanistic papers could not be checked against stated concentrations, because those numbers appear only in print methods; where a concentration is described here as “therapeutic” or “clinically relevant” without a figure, that is the primary source's own wording. Effect sizes for the two Brazilian mild-cognitive-impairment reports [35,142], the achieved serum concentration in the feasibility study [141], and the randomised total of the microdose trial [34] are not retrievable from the published records, and are reported here as such. The deficiency hypothesis is assessed on one paper and its supplementary data; no independent replication exists yet, and this analysis would need revision if one appears. Dose translation between mouse and human is performed here by both milligram-per-kilogram and allometric scaling, neither of which is reliable for an ion whose renal handling, dietary intake and tissue distribution differ between the species. Two areas are treated only in passing: lithium's actions on the bisphosphate 3'-nucleotidases and thereby on chondroitin sulfation [4,61], which may matter and is unstudied in this context; and the ⁷Li imaging literature, whose sensitivity at endogenous concentrations is the rate-limiting technical question behind half the predictions above. Finally, one retracted paper circulates in the lithium-formulation literature and is excluded here; readers assembling their own bibliography on alternative lithium salts should check its status [230].

18. Conclusion

The lithium literature in Alzheimer's disease is three literatures, and its confidence comes from reading them as one. Separated, each is weaker and more interesting than the composite.

The pharmacological claim is modest and probably partly artefactual: an association of about HR 0.8–0.9 inside bipolar disorder, shrinking toward unity in the designs that control indication and adherence, resting on a mechanism that has never been demonstrated in a patient and that failed when tested with a better drug. The environmental claim is an ecological inference whose exposure–response changes sign inside its own range and whose only individual-level cohort points the other way. And the deficiency claim — the interesting one — is a genuinely new proposition supported by one careful laboratory: that endogenous lithium is physiologically necessary, that amyloid takes it, and that the bioavailable pool, not the total, is what tracks cognition.

The three-order-of-magnitude gap between the concentration at which lithium's classical targets are engaged and the concentration at which it is endogenously present is not a detail to be waved at. It is the reason the deficiency hypothesis had to relocate the mechanism from catalytic inhibition to the expression and activation state of a kinase; it is the reason no completed trial has tested that hypothesis; and it is the reason the field's habitual reply to a null result — more drug, longer exposure — is unavailable here, because the tolerability ceiling in older adults lies below the mechanistic floor.

What follows is not pessimism but sequence. The next necessary result is not a trial; it is a measurement. Until non-sequestered lithium can be measured in a living brain or its cerebrospinal fluid, a repletion hypothesis cannot be tested, a repletion dose cannot be chosen, and every negative trial will be answerable by an argument rather than by data. A hypothesis that can explain any outcome is not a strong hypothesis; it is one whose decisive experiment has not been built yet. Building it is cheap by the standards of this disease, and it would settle in one cohort what twenty-five years of dose-guessing has not.

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