Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Lithium (pharmaceutical doses)

Evidence Summary

Small clinical trials suggest potential disease stabilization, but data are mixed. Lithium has serious safety concerns. Lower dose or novel formulations are under investigation, but efficacy is not yet known.

Neuroprotective Benefit: Small clinical trials have reported mixed results for use of lithium in dementia; the longer studies suggest disease stabilization. Epidemiological studies also are conflicting but may hint at benefit. More robust studies are needed.

Aging and related health concerns: There is some preclinical evidence suggesting potential benefit for health conditions such as stroke, but clinical evidence is lacking.

Safety: Lithium requires titration to the therapeutic range. Severe lithium toxicity can risk coma or even death. Therapeutic doses can lead to GI side effects, weight gain, tremor, and affect renal and thyroid function. Monitoring and low doses can mitigate risks.

Availability: By prescription (higher dose), in diet, or as an over-the-counter supplement (lower dose).	**Dose**: Typical psychiatric doses range between 900 and 1800 mg daily, orally; dose is titrated to achieve blood serum levels approximately between 0.4 and 1.0 mmol/L lithium, ideally between 0.6 and 0.8 mmol/L lithium. Achieving the proper dose is extremely important.	**Chemical formula:** Li **MW:** 7 g/mol 3 **Li** Lithium 6.941 Source: PubChem
Half-life: 18-36 hours	**BBB**: Penetrant.	
Clinical trials: Lithium has been tested in numerous clinical trials for different indications over decades. Some of the largest meta-analyses for lithium treatment of neurodegenerative diseases include over 1,000 patients.	**Observational studies**: Lithium has been examined in many observational studies and it is thought that hundreds of thousands of patients take lithium each year. The largest study identified in this report included over 40,000 patients, 6,900 of whom had taken lithium.	

What is it?

Lithium is a chemical element that has been widely used for decades as both an acute and chronic treatment for major psychiatric disorders (Alda et al., 2015; Hampel et al., 2019). Lithium is a first-line treatment for mood stabilization; it is approved for use in bipolar I disorder and is prescribed for managing manic and mixed episodes. It is also prescribed off-label as an adjunct therapy for major depression, for bipolar disorder without history of mania, vascular headaches, and neutropenia (NCBI StatPearls). Lithium is also thought to have specific anti-suicide effects (Alda et al., 2015). Upon ingestion, lithium spreads throughout the central nervous system, and can result in mood stabilization – typically on the order of 1 to 3 weeks, though this can vary (StatPearls). The exact mechanism of action is not clear, although lithium can modulate many aspects of cellular function in the brain, including neuronal excitability, regulation of neurotransmission, mitochondrial function, and oxidative stress, through effects on different proteins and cell signaling cascades (Malhi et al., 2013; Alda et al., 2015;

Hampel et al., 2019). It may be that lithium acts through multiple mechanisms, potentially depending on dose.

Lithium has a narrow therapeutic range and has very significant potential adverse events, leading to a black box warning. Lithium toxicity can occur at doses close to therapeutic range. Any use of prescription doses of lithium should be carefully monitored when individuals start treatment or experience side effects (NAMI).

Neuroprotective Benefit: Small clinical trials have reported mixed results for use of lithium in dementia; the longer studies suggest disease stabilization. Epidemiological studies also are conflicting but may hint at benefit. More robust studies are needed.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 9 clinical trials
- 8 observational studies
- 1 pilot study
- 7 reviews
- 1 commentary letter on a clinical trial
- Numerous preclinical studies

Amongst patients with bipolar disorder, long-term pharmaceutical use of lithium has been associated with a lower risk of dementia in several observational studies (Nunes et al., 2007; Kessing et al., 2010; Gerhard et al., 2015) and reduced measures of brain aging (reviewed in Sajatovic et al., 2013). However, other observational studies contradict the idea of protection (Dunn et al., 2005).

Another question is whether lithium treatment would lower dementia risk for other populations. Bipolar disorder itself is thought to increase risk of dementia; therefore, it's unclear whether lithium is providing cognitive benefit overall, or only mitigating risk through treating the underlying mood disorder. Or, if lithium treatment is merely correlated with decreased risk that is in fact mediated through another mechanism, such as the fact that lithium treatment implies the patient is receiving medical care, or if lithium treatment is preferentially given to healthier patients. While one can address some of these limitations, such as by comparing patients who received lithium to those who received other

medications for bipolar disorder as Gerhard et al., 2015 did, it remains a caveat for these kinds of studies.

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

A 2015 systematic review and meta-analysis assessed the efficacy of lithium on cognitive function in patients with MCI or AD. The work included 3 randomized placebo controlled studies (Hampel et al., 2009, probable AD; Forlenza et al., 2011, MCI; Nunes et al., 2013, AD) and a total of 232 patients. The trials ranged in duration from 10 weeks to 15 months and included doses from 300 µg to 0.25 – 0.8 mEq/L lithium. The meta-analysis showed that the patients who received lithium had significantly less impairment than those who received placebo as measured by standard mean difference (SMD) (SMD=-0.41; 95% Ci -0.81 to 0.02, p=0.04). When they separated MCI from AD, they found that the effects were not significant in MCI (p=0.59) and were not quite significant in AD (p=0.07). They did not find any significant difference in changes in AD relevant biomarkers (total tau, phosphorylated tau, or Aβ-42). The authors also reported that the study from Nunes and colleagues had the most statistically significant results.

The trial described by Forlenza and colleagues was a randomized controlled clinical trial testing low-dose lithium or placebo in patients with MCI for up to four years and was published in multiple papers. The trial enrolled 61 physically healthy participants with MCI. In the first two years, the study was double-blinded; in the second two years, the participants were unblinded so that they could decide whether to proceed with treatment, but investigators remained blinded. Participants receiving lithium were given doses to achieve sub-therapeutic blood concentrations (0.25 to 0.5 mEq/L). The primary outcome measures were change from baseline in cognition and function as assessed by the Alzheimer's Disease Assessment scale – cognitive subscale (ADAS-COG) and Clinical Dementia Rating – Sum of Boxes (CDR-SB), measured at 12 and 24 months before patient unblinding. Secondary outcomes included change from baseline in measures of neuropsychological testing and AD-related CSF biomarkers assessed at 12 and 36 months, and conversion rate from MCI to dementia throughout the 4-year study. One note on this study is that at baseline, the placebo group was significantly older than the lithium treated group (mean age 74.8 vs. 71.6 years, respectively).

In their first paper detailing the results of 45 participants in the first year of treatment, lithium appeared to reduce tau phosphorylation and potentially mitigated cognitive decline (Forlenza et al., 2011). This portion of the study was included in the above meta-analysis. Subsequent publications raised some

concerns, including both potential long-term safety risks and decreased metabolism in the brain and hippocampus, possibly suggesting lithium toxicity to the very areas of the brain that are most at risk of Alzheimer's disease (Aprahamian et al., 2014; Forlenza et al., 2014). In 2019, the group published the results of the primary and secondary outcomes in the full sample after the entire follow-up period (Forlenza et al., 2019). In the final sample, the lithium treated group was still significantly (p=0.03) younger than placebo group; the average age in the lithium group was 71.2 (standard deviation 5.4) and in placebo group it was 74.4 (standard deviation 6.1). There were no other noted baseline differences, including no significant differences in levels of CSF Aβ, total tau, or phosphorylated tau. The average serum level of lithium was 0.39 mEq/L in the double-blind phase, and 0.41 mEq/L in the extension phase.

Overall, the researchers found that patients in the lithium group were largely cognitively and functionally stable over the course of the 2-year double-blind period, while the placebo group had mild decline that was significantly greater than the lithium group. However, the magnitude of difference was small. The table below includes the change from baseline scores on the ADAS-COG and CDR-SB for the lithium and placebo groups. The possibility that the older age of the placebo group contributed to this difference in scores cannot be ruled out.

Assessment	Lithium, mean (standard deviation)	Placebo, mean (standard deviation)	*P*
CDR-SB	-0.22 (0.9)	0.53 (1.8)	<0.05
ASAS-COG	0.83 (1.1)	1.8 (1.9)	<0.05

The researchers also assessed conversion from MCI to dementia. In the lithium group, 5 (16%) patients converted, whereas 9 (30%) of the placebo group did; this result was not statistically significant (p=0.06). The study also reported that between 12 and 36 months, the lithium group showed an increase in CSF levels of Aβ, largely driven by those with higher CSF Aβ at baseline; the authors speculated that this could potentially reflect Aβ clearance. There were no reported changes in tau or phosphorylated tau; the preliminary results reported in Forlenza et al., 2011 were ultimately not borne out in the full study size or time.

The other studies covered in the meta-analysis are discussed in the 'Human research to suggest benefits to patients with dementia' section.

A retrospective cohort study in the UK used electronic health records from community and mental health services to assess the incidence of dementia in individuals 50 years and older who were cognitively intact at baseline and had been exposed to lithium compared to those who did not have lithium exposure. Up to 15 years of follow-up data were available for patients, and the study excluded patients who had less than a year of follow-up data. The study comprised 29,618 patients; 548 of them had lithium exposure as determined by a lithium prescription and/or bloodwork indicative of lithium prescription. The exposed and non-exposed groups had several differences at baseline; the exposed group was statistically more likely to be married, cohabiting, or in civil partnership – typically protective against dementia – but also were more statistically likely to be smokers and had other co-morbidities associated with increased risk of dementia such as hypertension, depression, bipolar disorder, diabetes, and/or hyperlipidemia. In the exposed cohort, 53 of 548 (9.7%) of patients were diagnosed with dementia; 36 (6.8%) with AD and 12 (2.6%) with vascular dementia (VD). In the unexposed cohort, 3,244 of 29,070 (11.2%) were diagnosed with dementia; 2,276 (8.1%) with AD and 698 (2.6%) with VD.

After controlling for factors including sociodemographic factors, smoking status, other medications, and co-morbidities, lithium use was associated with a significant lower incidence of dementia (HR= 0.56; 95% CI 0.40 to 0.78), a lower incidence of AD (HR 0.55, 95% CI 0.37 to 0.82) and a lower incidence of VD (HR 0.36, 95% CI 0.19 to 0.69) as compared to no lithium exposure. This statistical significance was observed for short term (less than 1 year) and long term (greater than 5 years) of lithium exposure. While it was not possible to draw firm dose-response conclusions in this study due to sample size, their data suggest that longer durations might be associated with more significantly lower incidence of dementia. The authors caveat that their results, which were robust to sensitivity analyses, are based on a small group exposed to lithium and also represented a specific subset of the population seeking mental health services. The population of their study had an overall higher incidence of dementia, which is to be expected, but makes it less clear how their results might apply to the general population without bipolar disorder or other mental health diagnoses (Chen et al., 2022). The finding that lithium prescriptions for patients with a psychiatric disorder such as bipolar disorder are associated with lower incidence of dementia echoes findings in other observational studies, such as Nunes et al., 2007, Kessing et al., 2010, and Gerhard et al., 2015, some of which had a larger sample size. Gerhard et al., 2015, for instance, comprised almost 42,000 patients with bipolar disorder, 6,900 of whom were prescribed lithium, all using Medicaid claims in the US. Observational studies of individuals with bipolar disorder are subject to limitations as discussed briefly in the introduction to this section of the report.

Epidemiological work also hints at a protective effect of lithium against dementia, though the findings are not without controversy. Lithium is a natural element and can be found in rocks, soil, and ground water in varying concentrations in different geographic regions. Several studies have investigated whether there are any associations between lithium concentration in drinking water and neurological conditions. A study of 73,731 patients with dementia and 733,653 age- and sex-matched controls in Denmark found that people diagnosed with dementia had a statistically significantly lower exposure to lithium in their drinking water (Kessing et al., 2017). Another study assessed the relationship between trace levels of lithium in drinking water and change in AD mortality. They found that changes in AD mortality were significantly inversely correlated with increased trace lithium levels (Fajarado et al., 2018).

Not all groups have come to the same conclusions. Mental health diagnosis rates can vary significantly based on regional resource availability and demographics, and there are other confounding factors when comparing geographic region and incidence of diagnosis. Parker et al., 2018 published results of a study of medical claims from over 4 million adults in the US. The authors report no significant association between groundwater lithium levels and incidence of dementia or bipolar disorder after they adjusted for demographics and health care resources in the United States. Similar controversy exists with whether increased groundwater lithium levels are associated with decreased incidence of suicide or not (Eyre-Watt et al., 2021).

An ongoing study (NCT03185208) is assessing whether treatment with lithium can delay or prevent conversion from MCI to AD. For further information, please see the 'Research Underway' section.

Human research to suggest benefits to patients with dementia:

The efficacy of lithium for patients with AD or other dementias is not yet clear. Some evidence points to potential for benefit. A 15 month study of 113 patients with AD randomized patients to either a microdose of lithium (300 µg) or placebo, and the only outcome measure was cognitive function as assessed by MMSE. Participants were established patients and thus had cognitive testing as measured by MMSE once every 6 months in the year before the trial. During the trial, they were assessed by MMSE once every three months. The patients had relatively similar MMSE scores and trends before the trial began. During the trial, the treated group's MMSE scores stayed stable, whereas the placebo group's MMSE scores significantly declined in comparison (Friedman test, $p<0.001$) (Nunes et al., 2013).

Other studies have not replicated these results but have their own caveats. Hampel et al., 2009 describes a randomized controlled trial of 71 participants with mild AD randomized to either placebo or lithium treatment with a target serum level of 0.5 to 0.8 mmol/L lithium. The trial lasted for 10 weeks, consisting of a 6-week titration period followed by a 4-week maintenance phase. The trial was single-blind; participants were not aware of their assignment, but investigators were not blinded. The primary outcome measures were levels of CSF phosphorylated tau and GSK3 activity in blood. Secondary outcome measures included CSF levels of total tau, Aβ, and cognitive assessments including ADAS-COG and MMSE. There were no statistically significant differences between groups on any measures, though there was a non-significant trend (p=0.11), with 28% of Li-treated patients vs 15% of controls exhibiting a clinically-significant improvement in their cognitive scores (Hampel et al., 2009).

Macdonald et al., 2008 reports on a small open-label study of 22 patients with mild to moderate AD for up to 1 year. Patients were started at a dose of 100 mg daily and titrated to a steady state of between 0.3 and 0.8 mmol/L lithium. While there was no placebo group, the authors compared the participants in this trial to matching participants in another ongoing trial of AD patients; the patients in both studies had been recruited through the same process and had very similar clinical assessments. Only 8 patients completed the trial. There were two deaths, neither thought to be related to lithium treatment. The other 12 patients discontinued for a variety of reasons; 3 were due to apparent side effects, the others due to other illness, consent withdrawal, inability of care home to guarantee correct dosage administration, or other non-lithium-related reason. There was no difference in deaths, discontinuations, or change in cognitive score between the lithium treated group and the comparison group; however, the already small study became very small by the end of treatment.

A 2024 systematic review and meta-analysis assessed the comparative efficacy, tolerability, and acceptability of lithium and three anti-amyloid therapies: donanemab, lecanemab, and aducanumab in patients with MCI and AD. The analysis included 89 patients from two studies on lithium, both described above: Nunes et al., 2013 and Forlenza et al., 2019. The authors report mixed results: that lithium was significantly more effective than the three anti-amyloid drugs when looking at changes on MMSE; that all four drugs outperformed placebo but were not significantly different from one another on ADAS-COG; and that lithium was not significantly better than placebo on CDR-SB whereas donanemab and lecanemab both performed better than placebo. Whether these results speak to perhaps different benefits of the drugs (e.g. on functional performance vs. memory) or speak only to the very small size of the lithium trials and the preliminary results thereof is not yet known (Terao & Kodama, 2024).

An ongoing study is examining the efficacy of Nanolithium (NP03), a microdose of lithium that is encapsulated in microemulsions and is administered buccally, in patients with AD (NCT05423522). NP03

also has an Orphan Drug designation for treatment of Huntington's disease. See 'Research Underway' for more information.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Lithium can affect a dizzying array of cellular activities, many of which may have benefits for neurological health; it is therefore not clear which mechanism(s) may mediate neuroprotection. Some of the most prominent current theories focus on the neuromodulatory actions of lithium.

One of the most prominent and best supported mechanistic theories of the neuromodulatory action of lithium– specifically in the context of AD and other related dementias – is via lithium's inhibitory effects on glycogen synthase kinase 3 (GSK3) (Noble et al., 2005; Engel et al., 2008; Chiu & Chuang, 2011; Wilson et al., 2017; Snitow et al., 2021; Chatterjee & Beaulieu, 2022; Ruiz & Eldar-Finkelman, 2022). There are two very similar isoforms of GSK3, GSK3α and GSK3β. Unless otherwise specified, GSK3 will refer to both enzymes. GSK3 has over 100 targets and is involved in a wide range of activities including energy metabolism, inflammation, circadian rhythm, development, gene regulation through proteins like CREB, and cell survival. GSK3 inhibition can also lead to increases in BDNF levels. GSK3 inhibitors are an active area of research for a variety of diseases. GSK3 is thought to act on amyloid β precursor protein (APP), modulate activity of both β- and γ-secretases, two enzymes that also affect APP processing. GSK3 is also thought to directly phosphorylate tau. Inhibiting GSK3 therefore leads to reduction of tau phosphorylation and corresponding tau tangle load as well as reduction of Aβ load. Inhibition of GSK3 may have other neuroprotective roles, such as promoting neurogenesis. Often, the effects seen in preclinical research rely on doses that are not easily achieved in the patients but, in this case, low pharmaceutical doses of lithium (for example 0.5 mmol/L) would be expected to inhibit the enzyme (Sutherland & Duthie, 2015). One pilot clinical trial reported that the phosphorylation of tau proteins (a potential driver of Alzheimer's disease) was reduced by one year of treatment with a low pharmaceutical dose of lithium, roughly 150 to 450 milligrams of lithium carbonate daily to achieve blood serum levels of 0.25-0.5 mEq/L (Forlenza et al., 2011) but a higher dose trial in Alzheimer's patients did not yield the same results (Hampel et al., 2009); Forlenza and colleagues also did not report significant tau reduction in their full dataset (Forlenza et al., 2019). GSK3 may also phosphorylate α-synuclein (Snitow et al., 2021). Reflecting the hypothesis that lithium treatment acts at least in part through GSK3, an ongoing RCT evaluating whether lithium can delay or help the conversion from MCI to dementia is testing change in GSK3β activity in their participants over the course of the trial (NCT03185208).

There are many other potential mechanisms of action of lithium. As reviewed by Alda, 2015 and Hampel et al., 2019, among others, lithium affects ion dynamics and membrane potential, therefore modulating neuronal excitability. It is thought that lithium can more directly affect neurotransmission, such as through affecting membrane transporters and receptors and neurotransmitter synthesis. The effects of lithium on glutamatergic transmission, for instance, is one potential route of neuroprotection. Lithium can modulate a number of molecules involved in cellular signaling cascades, including inositol monophosphate, cAMP and cGMP, and nitric oxide (NO). Some groups have found evidence that lithium can improve mitochondrial function and decrease oxidative stress, potentially in part through affecting NA-K ATPase. Lithium may affect regulation of calcium levels in neurons, which can have wide-ranging downstream impacts.

Laboratory studies have shown a variety of potential effects of lithium. Some work has suggested that lithium can increase the activity of stem cells and ramp up the transport of Vitamin B12 and folate into cells, which may in turn protect the brain. Lithium can also increase the number of mitochondria (Fornai et al., 2008), and increase autophagy, a process by which cells get rid of dysfunctional or unnecessary parts including the aggregated proteins associated with Alzheimer's, Parkinson's, Huntington's disease, and ALS (Fornai et al., 2008; Sarkar & Rubinsztein, 2006). Lithium treatment has reduced levels of pro-inflammatory cytokines and markers of oxidative stress (Wilson et al., 2018). In preclinical models, lithium has also been suggested to potentially improve blood brain barrier (BBB) integrity and/or mitigate damage to the BBB, possibly through its anti-inflammatory effects (Taler et al., 2021; Almeida et al., 2022; Song et al., 2022).

Although these mechanisms sound promising, it is discouraging to note that most of these mechanisms have not been validated in humans. Early studies in animals also suggested that lithium could protect the brain against amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) but the treatment failed to help patients (Gamez et al., 2013, AlzForum).

APOE4 interactions:

It is not yet known whether APOE alleles have differential interactions with lithium treatment.

Aging and related health concerns: There is some preclinical evidence suggesting potential benefit for health conditions such as stroke, but clinical evidence is lacking.

Types of evidence:

- 1 systematic review and meta-analysis
- 2 cross-sectional studies on telomere length in bipolar patients treated with Lithium
- Several lifespan studies in worms and flies

Several lifespan studies in worms and flies Long-term use of pharmaceutical lithium have been correlated in bipolar patients with longer leukocyte telomere length (Squassina et al., 2016; Martinsson et al., 2013) although it can also cause serious risks including kidney damage. A low drug dose of lithium for 2 years in patient with mild cognitive impairment was reported to increase the risk of diabetes, weight gain, arrhythmia, and possibly hypothyroidism although it was, in general, well-tolerated (Aprahamian et al., 2014).

Lifespan or healthspan extension has not been reported in mammals at any dose. In worms and flies, high doses of lithium have shortened lifespan (Castillo-Quan et al., 2016) although low doses of lithium have increased lifespan in several (Castillo-Quan et al., 2016; Zarse et al., 2011; Tam et al., 2014) but not all studies (Zhu et al., 2015). For more discussion of these results in worms and flies, check out the parallel report on microdoses of lithium.

There are some hints of potential benefits of lithium in the context of vascular injury, atherosclerotic plaque formation, or stroke, though clinical data only exists for the latter, and that clinical data is sparse. The hypothesis is that these effects are mediated by lithium's anti-inflammatory, anti-apoptotic, and/or antioxidant actions; careful human studies are needed to test this hypothesis (Almeida et al., 2022; Chen et al., 2022).

Safety: Lithium requires titration to the therapeutic range. Severe lithium toxicity can risk coma or even death. Therapeutic doses can lead to GI side effects, weight gain, tremor, and affect renal and thyroid function. Monitoring and low doses can mitigate risks.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 3 clinical trials

- 3 observational studies
- 1 commentary on an observational study
- 2 professional resources pages
- 2 reviews
- # laboratory studies

Too-high doses of lithium can cause lithium toxicity. Signs of lithium toxicity are "obvious and can be identified and managed easily", but ignoring these signs can be fatal. Symptoms of mild lithium toxicity often include nausea, vomiting, lethargy, tremor, and fatigue. Moderate toxicity symptoms include confusion, agitation, delirium, tachycardia, and hypertonia. Severe lithium toxicity can manifest as coma, seizures, hyperthermia, and hypotension, and can lead to brain damage or death. Below is a table of the serum lithium levels typically associated with each grade of toxicity, expressed in units of mEq/L lithium (NCBI StatPearls).

Grade of Toxicity	Associated Serum Lithium Level
Mild	1.5 to 2.5 mEq/L
Moderate	2.5 to 3.5 mEq/L
Severe	More than 3.5 mEq/L

Common side effects in patients with psychiatric disorders include gastrointestinal side effects like nausea and diarrhea, excessive thirst and urination, weight gain, exacerbation of psoriasis, and hand tremor. Vomiting is reported to be an infrequent side effect and is typically associated with toxicity; tremor, on the other hand, is reported to be common as an adverse event, with toxicity-related tremors typically being more irregular, widespread, and severe, and are usually accompanied by other signs of toxicity. Lithium, especially long-term use of lithium, can affect the kidneys as well as the thyroid and parathyroid gland, and individuals should discuss monitoring with their physician. Cognitive impairment has also been reported by patients, though it is very difficult to disentangle the effects of lithium vs. the effect of other drugs in use and the underlying disorder itself (Gitlin et al., 2016). Drugs.com has a further list of possible side effects.

The side effect profile in older adults without a psychiatric diagnosis, whether cognitively intact or with some degree of cognitive impairment, is an important question. One clinical trial treated elderly patients with a low drug dose of lithium, less than half the dose typically used for bipolar disorder, and published results in several papers. In their first paper covering 45 participants for 1 year, the authors report similar rates of adverse events in lithium and placebo groups, with no standout concerns (Forlenza et al.,

2011). A follow up paper reported more in-depth safety outcomes for 61 total participants after four years of lithium treatment. Although the low dose was well-tolerated by the elderly patients with few reported side effects, some red flags were raised including increased incidence of diabetes, arrhythmia, significant weight gain, and possibly hypothyroidism, although no difference was seen in kidney function, gastritis, or dyslipidemia. There were significantly more adverse events in the lithium group as compared to placebo, especially when looking at adverse events that interfered with daily functioning (Aprahamian et al., 2014). Decreased metabolism in key brain areas was also reported (Forlenza et al., 2014). In total, 52 of the 61 participants completed the double-blind stage of the trial, one of whom experienced clinical symptoms of lithium toxicity (mean serum levels of lithium in the study were approximately 0.4 mEq/L). Of the double-blind phase completers, 40 finished the extension study. There was no statistically significant difference in reason for discontinuation or withdrawal between groups (Forlenza et al., 2019).

A 2022 study assessed the use of lithium for symptoms of agitation and/or aggression in patients with AD. The randomized controlled double-blinded study enrolled 77 patients and randomized to either placebo or lithium doses of 150 to 600 mg daily to achieve a serum lithium level of 0.2 to 0.6 mmol/L. Dosing lasted for 12 weeks. The authors report that there were no significant differences in rates of serious adverse events between groups, nor any significant difference in incidence of specific adverse events between the two groups. There was a trend towards increase gait instability in patients receiving lithium (p=0.055) and potentially a trend towards changes in thyroid hormone levels in the lithium group, though the latter was potentially confounded by prior history of thyroid disease (Devanand et al., 2022).

A small pilot study of 11 patients with MCI assessed biomarkers and safety of lithium treatment for 9 weeks; doses started at 100 mg daily, and steadily increased to 400 mg daily. Of the 11 patients, 4 withdrew due to reported side effects, though there was no association between lithium blood concentration and withdrawal. No serious adverse events were reported. Six of the 11 patients reported side effects, and those of moderate or severe intensity included: metallic taste, dry mouth, nausea, decreased concentration, insomnia, or confusion. Feeling drowsy or lethargic was the most commonly reported adverse event overall (Duthie et al., 2019).

Drug interactions:

Lithium may interact with at least 708 drugs; of these interactions, 177 are major interactions, 489 are moderate, and 42 are minor. Notable interactions include but are not limited to buspirone, fentanyl, St. John's wort, tramadol, tryptophan, antidepressants and antipsychotics, and MAO inhibitors (Drugs.com).

Common drugs like over-the-counter anti-inflammatory drugs (for example, celecoxib/Celebrex or indomethacin), caffeine, theophylline, antidepressants, anti-hypertensive medications, and others can interact with lithium and change the dose of lithium that might be safe or effective (Grandjean & Aubry; 2009; D'Souza et al., 2011; McKnight et al., 2012). Older people are much more vulnerable, with higher serum levels in response to the same dose and with risks from interactions with comorbidities and other drugs. The risks of lithium treatment are particularly high in people with renal or cardiovascular disease, hypothyroidism, previous neuroleptic malignant syndrome, seizures, dehydration (including diarrhea and excessive sweating), sodium depletion, or if they take diuretics or haloperidol.
More information on lithium side effects and interactions with medications, alcohol, and food can be found at Drugs.com and www.mayoclinic.org.

Research underway:

There are currently 73 ongoing studies registered on clinicaltrials.gov that involve lithium in some way. Many of these studies merely mention lithium as a component of a medical device such as a battery. Of the studies testing lithium as an intervention, many focus on treatment of psychiatric conditions like bipolar disorders. Five studies involve lithium as a treatment for cognition in some way.

NCT05423522 is a currently recruiting randomized controlled trial of NanoLithium (NP03). NP03 is an encapsulated version of lithium that has a transmucosal route of administration, which allows for very low dose lithium to be given. In this study, participants receive buccal doses of 3 mL (1.8 mg) lithium or matching placebo once daily. The first phase of the study will be double-blinded and last for 12 weeks; the second phase will be an optional open-label extension for 36 weeks. The primary outcome measure is change in neuropsychiatric score as assessed by the NPI-12. Secondary outcome measures include a variety of safety assessments, measures of cognitive and daily functioning, and biomarkers, including FDG PET, inflammatory markers, and AD markers.

NCT03185208 is an ongoing prevention study known as LATTICE to assess whether treatment with lithium can delay or prevent conversion from MCI to dementia. The randomized controlled double-blinded study enrolled 80 adults 60 years and older with MCI who were able to receive Aβ PET scans at baseline. Participants were randomized to either lithium carbonate or placebo. Those receiving lithium will start at 150 mg dose and titrated up to a dose that results in steady blood levels of 0.6 and 0.8 mEq/L; the placebo group will also receive sham dose increases to ensure appropriate blinding.

Participants will receive doses of study drug for 2 years. The primary outcomes of the study are change in cognitive function, change in biomarkers (BDNF and GSK-3β), and change in brain volume measures as assessed by MRI. Other outcome measures include measures of brain integrity and levels of CSF p-tau. This study is predicted to be completed in mid-2024.

NCT06008249 is an ongoing platform study of the efficacy of different drugs for treatment of ALS. This specific trial arm is assessing whether lithium carbonate may be safe and effective in a specific subgroup of ALS patients: those with a specific polymorphism of the *UNC13A* gene. The study plans to enroll 171 patients. The patients will be randomized to either placebo or lithium carbonate. Patients in the active treatment group will start taking 400 mg once daily and will be titrated up to two or three doses daily depending on plasma lithium levels; the target range is between 0.4 and 0.8 mmol/L lithium. Placebo patients will also receive sham dose adjustments to maintain blinding. Participants will receive lithium for up to 2 years. Outcome measures include overall survival or survival to respiratory insufficiency, measures of daily functioning and disease progression, quality of life, neuropsychiatric symptoms, safety, and tolerability.

NCT05126238 is an ongoing study that seeks to assess whether prophylactic administration of lithium before carotid artery surgery can reduce the risk of postoperative neurocognitive disorders. The study plans to enroll 500 patients who are undergoing carotid artery surgery. The participants will receive doses of 300 mg lithium in the 2 days prior to surgery, as well as 3 doses of 300 mg lithium the day of surgery, or matching placebo. The outcome measures will include frequency of postoperative cognitive events such as postoperative delirium and agitation, as well as other measures like frequency of strokes, cardiac arrest and death, hospital stay length, mortality, and other adverse events. The study will also assess serum biomarkers such as tau, GFAP, and neurofilament light.

NCT06051240 plans to examine whether treatment with lithium can mitigate or prevent cognitive decline after brain radiotherapy in 84 pediatric patients. The study will randomize pediatric patients at least 5 years of age to either 42 mg (6 mmol) lithium or matching placebo. Participants will be dose escalated to a target serum level of 0.5-1.0 mmol/L lithium. They will receive treatment for 6 months, and then be followed for up to 7 years to assess long-term outcomes. The outcome measures include measures of cognition, feasibility, adverse events, and assessments of white matter integrity through MRI.

Search terms:

Pubmed, Google: lithium

- Dementia, Alzheimer's, stroke

Websites visited for lithium

- Clinicaltrials.gov
- Examine.com
- Geroprotectors: C. elegans; human
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma