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

Serious safety risks, but doses lower than those used for bipolar disorder might avoid the safety risks while protecting against neurodegeneration especially related to tau pathology.

Neuroprotective Benefit: Possible benefit for MCI based on one clinical trial, but no benefits seen at higher doses for patients with Alzheimer's disease.

Aging and related health concerns: No compelling or consistent evidence to suggest that pharmaceutical doses of lithium benefit age-related conditions.

Safety: High doses have very severe health risks, including kidney damage. Sub-clinical pharmaceutical doses should reduce some but not all of these risks.

What is it? High doses of lithium salts are used to treat psychiatric and mood disorders such as bipolar disorder and depression. Upon ingestion, lithium spreads throughout the central nervous system, and over several weeks, reduces the symptoms of bipolar disorder in many patients. The exact mechanism of action is uncertain, although lithium can affect many aspects of cell signaling in the brain (Malhi 2013). Most likely, lithium can act through multiple mechanisms depending on the dose.

Neuroprotective Benefit: Possible benefit for MCI based on one clinical trial, but no benefits seen at higher doses for patients with Alzheimer's disease.

Types of evidence:

- 1 small randomized clinical trial in patients with mild cognitive impairment
- In bipolar patients treated with pharmaceutical doses of lithium, 4+ observational studies on the risk of dementia and biological measures of brain aging
- Randomized clinical trials that report no benefit to patients with neurodegenerative diseases like Alzheimer's (2 small trials) and ALS (at least 5 trials)
- Numerous (over 10) preclinical studies

Human research to suggest improved cognition or prevention of dementia or decline. 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 2007, Kessing 2010, Gerhard 2015) and reduced measures of brain aging (reviewed in Sajatovic 2013). However, another observational study contradicts the idea of protection (Dunn 2005). Lithium treatment can cause mental confusion in some people (Drugs.com) (Sajatovic 2013) so doctors sometimes take patients off their lithium prescription when they develop cognitive problems.

Even if lithium does protect against dementia in people with bipolar disorder, that may or may not be relevant for other people. Some studies suggest that bipolar disorder can raise the risk of dementia by itself so lithium might protect against dementia in those patients simply by treating the mood disorder.

There is less evidence about the effects of lithium on cognition in people without mood disorders. One double-blind randomized trial reported that a low pharmaceutical dose of lithium carbonate treatment for one year improved the cognitive abilities of elderly people with mild cognitive impairment. The study was too small to determine whether lithium protected against progression to Alzheimer's disease but the results were promising and lithium appeared to reduce tau phosphorylation (Forlenza 2011), a major component of Alzheimer's disease pathology. However, the conflicting evidence with respect to brain health requires further attention.

More information should be coming from the trial soon, as the report on benefits to cognition and tau phosphorylation was generated after 1 year of the trial whereas the trial was continued for an additional 1-3 years (Aprahamian, 2014). Some concerns were also raised, 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 (Forlenza 2014).

In the short-term, lithium is not likely to improve cognitive function, and at high doses, lithium can have toxic effects that lead to confusion, cognitive impairment, and other serious side effects.

Apolipoprotein E4 carriers: Unknown.

Human research to suggest benefits to patients with dementia or cognitive aging

Patients with Alzheimer's disease are unlikely to benefit from pharmaceutical doses of lithium, based on two small human trials that reported little to no benefit and substantial risks of side effects (Hampel, 2009) (Macdonald, 2008). However, one of these trials did see 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, 2009).

Mechanisms of action for neuroprotection identified from laboratory and clinical research

Laboratory studies suggest that lithium can increase the activity of stem cells and ramp up the transport of Vitamin B12 and foliate into cells, which may in turn protect the brain. Lithium can also increase the number of mitochondria (Fornai, 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 amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) (Fornai, 2008, Sarkar 2006). However, most of these mechanisms have not been validated in humans. Furthermore, early studies in animals also suggested that lithium could protect the brain against ALS, but the treatment failed to help patients (Gamez, 2013, AlzForum 2010).

Many of the potential mechanisms of action described above could theoretically protect against both Alzheimer's disease and ALS. However, lithium might also specifically protect against Alzheimer's and related dementias by protecting against pathology of tau proteins by reducing the activity of the enzyme glycogen synthase kinase-3 beta (Noble, 2005, Engel, 2008). 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, 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 2011) but a higher dose trial in Alzheimer's patients did not yield the same results (Hampel, 2009).

Aging and related health concerns: No compelling or consistent evidence to suggest that pharmaceutical doses of lithium benefit age-related conditions.

Types of evidence:

- 2 cross-sectional studies on telomere length in bipolar patients treated with Lithium
- Several lifespan studies in worms and flies

Long-term use of pharmaceutical lithium has been correlated in bipolar patients with longer leukocyte telomere length (Squassina, 2016, Martinsson, 2013) although it can also cause serious risks including kidney damage.

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, 2016) although low doses of lithium have increased lifespan in several (Castillo-Quan, 2016, Zarse 2011, Tam 2014) but not all studies (Zhu, 2015) (see Lithium microdosing report).

Safety: High doses have very severe health risks, including kidney damage. Sub-clinical pharmaceutical doses should reduce some but not all of these risks.

To avoid serious side effects, lithium treatment must be monitored closely by an experienced healthcare professional and the dose must be tailored to the individual. Safety risks are generally higher at higher doses but risk of side effects at a given dose varies across individuals.

One clinical trial treated elderly patients with a low drug dose of lithium (Forlenza 2011), less than half the dose typically used for bipolar disorder. Although the low-dose was well-tolerated by the elderly patients, with very 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 (Aprahamian, 2014). Decreased metabolism in key brain areas was also seen (Forlenza 2014).

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. 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, 2011, McKnight, 2012). The risks of lithium treatment are particularly high in people with renal (kidney) or cardiovascular disease, dehydration, 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 www.drugs.com and www.mayoclinic.org.

Sources and Dosing:

Drug prescriptions of lithium typically take the form of lithium carbonate formulated into oral treatments of capsules, solutions, syrups, tablets, or extended release tablets. The dose depends on the age of the patient and how the drug has been formulated. Typically, the lowest possible dose is prescribed and then adjusted to achieve a certain range of lithium levels in the patients' blood serum, while carefully monitoring for side effects. Higher doses raise the risk of dangerous side effects. It can take about a week of evenly-repeated dosing to achieve a steady-state of lithium in the serum (Heim, 1994).

Typically, doses between 900-1200 milligrams per day of lithium carbonate are used to achieve a blood serum concentration between 0.6 and 1.2 mEq/L to treat bipolar disorder (more info at Drugs.com). In one small clinical trial in elderly people with memory impairment but no mood disorders, some benefits were seen with a slightly lower dose, roughly 150 to 450 milligrams per day to achieve blood serum levels of 0.25-0.5 mEq/L (Forlenza 2011). The lithium ion makes up slightly less than 20% of lithium carbonate's mass so a 900 milligram dose contains roughly 169 milligrams of lithium ions while a 150 milligram dose contains about 28 milligrams of lithium ions.

Some side effects (e.g. psoriasis) may be decreased with myoinositol supplements but it's unclear whether this would also block some of the neuroprotective properties of lithium, such as increased autophagy. Myoinositol is a dietary supplement that can improve insulin signaling. The relationship between myoinositol and lithium is complex with conflicting clinical data.

Lithium is also sold as over-the-counter supplements in far lower doses of lithium orotate or lithium aspartate.

Research underway: According to Forlenza, results are expected soon from an extension of the 2-year clinical trial of lithium in mild cognitive impairment. Co-crystals of lithium, such as lithium salicylate,

might perhaps yield a safer pharmacokinetic profile that avoids the spike in lithium common with available lithium salts (Smith 2014).

Search terms:

- Pubmed: lithium with aging, dementia, Alzheimer, safety, cognitive
- AlzForum: Lithium
- NIH Reporter: lithium