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 (Microdoses)

Evidence Summary

A clinical trial suggests slowed cognitive decline in Alzheimer's patients; likely safe.

Neuroprotective Benefit: A pilot trial in Alzheimer's patients and laboratory evidence suggest protection from decline in Alzheimer's patients.

Aging and related health concerns: Low doses are associated with lifespan extension in flies, but there is no compelling evidence indicating a role for anti-aging activity in humans.

Safety: Doses below 5 mg/day are considered safe, but high doses are associated with toxicity, such as kidney damage.

What is it? Lithium is a highly reactive, light metal commonly found in drinking water and foods. Regions with fresh water, such as river basins, often contain higher concentrations of lithium. The concentration of lithium in local drinking water influences the levels in a person's urine (Callan, 2013). High doses of lithium carbonate are commonly used to treat bipolar disorder and have severe long-term health risks but low dose supplements of other lithium salts are widely available.

Neuroprotective Benefit: A pilot trial in Alzheimer's patients and laboratory evidence suggest protection from decline in Alzheimer's patients.

Types of evidence:

- No clinical research on dietary or supplement doses of lithium in patients without dementia
- 1 small randomized clinical trial in patients with Alzheimer's disease
- 1 preclinical study using a microdose of lithium in rodents; Numerous preclinical studies using higher doses

Human research to suggest improved cognition or prevention of dementia or decline. None except for trial in dementia patients (below) although some evidence exists for pharmaceutical doses of lithium in mild cognitive impairment or in bipolar patients (see Lithium pharmaceutical doses report).

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

A small "microdose" treatment with lithium was reported in 2013 to have slowed cognitive decline in Alzheimer's patients over 15 months in a double-blind clinical trial from Brazil (Nunes 2013). , However, since this was a pilot trial it is not yet known whether this cognitive effect was large enough to improve patients' lives or their ability to function. The quality of the trial is difficult to gauge because unusually little information was provided on the methods and participants. It is noteworthy that microdose (0.3 mg per day in the form of lithium carbonate or lithium gluconate) was found to have such benefits when larger doses have had varying but limited success in patients with Alzheimer's disease or mild cognitive impairment. Follow-up studies are needed to confirm these results.

Mechanisms of action for neuroprotection identified from laboratory and clinical research

It is unknown whether these effects reported in laboratory animals and test tubes, often with higher doses, will have similar effects in humans.

Lithium may 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 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 ALS (Fornai, 2008 Sarkar 2006). Lithium might also specifically protect against Alzheimer's and related dementias by reducing tau phosphorylation through the enzyme glycogen synthase kinase-3 beta (Noble, 2005, Engel, 2008).

There is currently little to no evidence that these effects take place in humans. Only one preclinical study in mice has directly looked at the effects of a microdose of lithium (Nunes, 2015). Moreover, despite promising early studies in animals that drug doses of lithium could treat the disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), the treatment failed to help patients in clinical trials (Gamez, 2013, AlzForum 2010).

Aging and related health concerns: Low doses are associated with lifespan extension in flies, but there is no compelling evidence indicating a role for anti-aging activity in humans.

Types of evidence:

- 1 low-quality epidemiology study on lithium levels in tap water
- Several lifespan studies in worms and flies

One low-quality study reported that Japanese people living in areas with relatively high content of lithium in tap water had lower overall rates of death than similar people living in areas with relatively low content of lithium in tap water (Zarse 2011). However, this study has not yet been replicated or tested in other groups of people. It is very possible that the positive results are due not to lithium but to some other shared feature of the Japanese communities living in certain regions that happen to have high lithium content in the water. Long-term use of pharmaceutical lithium have been correlated in bipolar patients with longer leukocyte telomere length (Squassina, 2016, Martinsson, 2013).

Lifespan or healthspan extension has not been reported in mammals at any dose. In worms and flies, low doses of lithium have been reported to increase lifespan in several (Castillo-Quan, 2016, Zarse 2011, Tam 2014) but not all studies (Zhu, 2015). The most extensive of these studies was a report from Linda Partridge's lab that, while high doses of lithium chloride (e.g. 50-100 mM) shortened lifespan, low doses (e.g. 1-25mM) extended lifespan in males and females even when given late in life or when given

transiently in early life. No loss of fecundity was seen and the effect seemed to be more pronounced on high fat/high sugar diets. The suggested mechanism of action was not autophagy but rather inhibition of GSK3β leading to NRF2 activation (Castillo-Quan, 2016). In contrast, autophagy has been suggested as a primary mechanism of action in other invertebrate lifespan studies on lithium (e.g. Tam 2014).

Theoretically, lithium could protect against aging through the mechanisms of action described above for neuroprotection.

Safety: Doses below 5 mg/day are considered safe, but high doses are associated with toxicity, such as kidney damage.

Lithium derived from food, water, and low-dose dietary supplements (below 5 mg/day) are typically considered safe. Higher doses have serious health risks whether obtained from supplements or pharmaceutical drugs (Balon, 2013). Side effects of lithium include damage to the thyroid and parathyroid glands, weight gain, kidney damage, and possibly risks to unborn children in pregnant women. Toxicity to the brain, while rare, can occur.

Although lower doses typically cause fewer problems, the dose that is "safe" varies across individuals. Many common drugs can interact with lithium and, in some cases, change the levels of lithium that are considered safe (Drugs.com). Such drugs include common antidepressants, over-the-counter anti-inflammatory drugs (NSAIDs like Celebrex), caffeine, theophylline, and anti-hypertensive medications (Grandjean & Aubry 2009, D'Souza, 2011, McKnight, 2012). Older people must be careful, particularly if they use multiple medications or have health conditions that interact with lithium. Even without these interactions, the same dose of lithium will often lead to much higher levels in the body in older adults (Rej, 2014). The risk of lithium toxicity is particularly high in people with renal (kidney) or cardiovascular disease, dehydration, sodium depletion, or if they take diuretics or haloperidol.

How to use:

Lithium is commonly found in drinking water and various foods, with dietary intake estimated at 0.6 to 3.1 milligrams per day in the United States in 1985 (Schrauzer, 2002). Lithium supplements are sold as pills, liquid capsules, solutions, and syrups of lithium orotate or lithium aspartate. Prescribed medications, in contrast, typically use lithium carbonate or lithium citrate. In all of these cases, the lithium ion is the active ingredient.

Lithium orotate supplements are often sold in doses of 5 to 10 milligrams of lithium ion in pills that might contain 120 mg of lithium orotate itself (in other words, a given pill might contain 5 milligrams of lithium and 115 mg of orotate).

Lithium orotate supplements are often touted as "safer, "natural," or more effective at reaching the brain than other lithium salts. A German physician, Hans Nieper, heavily promoted the use of lithium orotate, believing that lithium would remain bound to the orotate until it reached its target tissues (i.e. the brain). This claim does not appear to be backed by evidence. In one study from the 1970's, injection with lithium orotate versus lithium carbonate did result in higher levels in the brain of rats (Kling, 1978). However, this study used a high-dose preparation of lithium orotate that probably impaired kidney function and led to slower secretion of lithium from the body (Smith, 1979). In other words, lithium orotate did not better penetrate the brain but simply accumulated in brain and body because the kidney failed to remove it quickly. In contrast, when equivalent doses of lithium ion were injected into rats as either lithium orotate, lithium carbonate, or lithium chloride, the resulting levels of lithium across the body and brain were very similar (Smith, 1976).

Lithium orotate has been virtually unstudied by scientists over the last 40 years but, given the number of supplements sold and the personal experiences described on internet forums, it seems likely that these supplements are safe in most people and might even help some individuals. However, the popular claim that lithium orotate penetrates the brain better than lithium carbonate has no scientific basis.

Just as large doses of lithium from lithium carbonate can cause toxicity, large doses of lithium orotate can cause toxicity. At least one case has been documented of lithium toxicity from a mega-dose of 18 pills of lithium orotate, equivalent to 82.7 milligrams of the lithium ion (Pauze 2007). For comparison, 82.7 milligrams is lower than the amount of lithium obtained in standard pharmaceutical doses of lithium carbonate.

Research underway: None known on microdoses of lithium although several studies are underway for pharmaceutical doses of lithium. 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's, safety, cognitive
- AlzForum: Lithium
- NIH Reporter: Microdose, lithium

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