Lithium:
The Cinderella Story About a Mineral That May Prevent Alzheimer's Disease

James Greenblatt, MD and Kayla Grossman, RN

Every four seconds, someone in the world develops dementia. Worldwide, an estimated 35.6 million people already live with a form of this neurodegenerative disorder, and these numbers are on a staggering rise. The World Health Organization has projected that the number of cases of dementia will double by 2030 (65.7 million) and triple by the year 2050 (115.4 million). Already in America the most common type of dementia, Alzheimer's disease, is the sixth leading cause of death: one in three seniors passes with this type of crippling memory loss (World Health Organization, 2015).

Progressive memory loss that interferes with activities of daily living is not a normal part of aging. In fact, research is showing that cognitive decline is the result of pathophysiological processes deep within the brain that begin many years, even decades, before dementia symptoms start.

This knowledge is frightening. It brings attention to the pervasive and silent nature of these diseases. Neurodegenerative disorders have become an international public health issue with devastating medical, social and economic consequences. And yet, from the perspective of conventional medicine, relatively little is known about how to treat or stop them.

In the midst of a harrowing race to find answers, one unassuming prevention strategy has shown promise above the rest. This remedy is none other than the simple, brain-protecting mineral: lithium.

Understanding Alzheimer's Disease

Chances are you've heard of Alzheimer's disease, or you may even know someone who has suffered from it. Alzheimer's disease is a tragic neurological malady characterized by a progressive and irreparable shrinking of brain tissue. The result is a devastating decline in memory, social abilities and communication skills in sufferers, leading, eventually, to death.

In less than five percent of cases, Alzheimer's disease results from a specific genetic combination that essentially guarantees a person will develop the disease. More commonly, it is the result of a complex combination of subtle genetic, lifestyle and environmental factors that affect the brain over a lifetime. Scientists believe that Alzheimer's disease is not an acute condition, but rather the result of numerous damages that occur over the years. This slow, cumulative patterning helps to explain why most patients with Alzheimer's disease don't present with symptoms until over the age of 65.

Pathologically, Alzheimer's disease is the product of two trademark injuries or lesions that occur at the cellular level: plaques and tangles. Plaques are formed by deposits of small protein fragments called amyloid-B, or beta-amyloid, peptides. Clumps of these proteins block the synapses or spaces between brain cells or neurons. With the synapses barricaded, normal cell-to-cell signaling cannot occur and communication is essentially stopped in certain regions of the brain. Meanwhile, other lesions—called neurofibrillary tangles—develop within the neurons themselves. These tangles result from a disruption in the production of a different type of protein, called tau. Normally, tau protein filaments help to circulate nutrients and other essential supplies throughout the cell. In Alzheimer's disease, however, the strands destabilize, becoming twisted or "tangled". Without this system to circulate vital compounds, neurons starve or die, the physiological processes required for memory and learning are halted, and symptoms begin to develop.

There is now evidence to show that these damaging beta-amyloid plaques and neurofibrillary tangles may actually be a relatively common malformation in the aging human brain. New research is revealing that plaques can appear a full 30–40 years before symptoms of cognitive decline even begin to show (Langbaum et al., 2013). A recent study published in the *Journal of the American Medical Association* presented the following statistics: ten percent of healthy 50-year-olds have amyloid deposits; this figure swells to 33% by age 80, and 44% at age 90 (Visser et al., 2015). Individuals with a mental illness—specifically, patients with depression or bipolar disorder—are at an even greater risk of developing these dementia-precursors in the brain (Da Silva, Gonçalves-Pereira, Xavier, & Mukaetova-Ladinska, 2013).

Nutrition and Brain Health

Currently there are no widely accepted preventative, or even ameliorative, treatments for most dementias, including Alzheimer's disease. A swarm of clinical trials have been launched in recent years, all with the goal of finding effective pharmaceutical interventions to stop

or slow the progression of neurodegenerative disorders like Alzheimer's disease. Many of these studies failed, however. Between the years 2002 and 2012, a staggering 99.6% of studies seeking to develop drugs that could prevent, cure or alleviate Alzheimer's symptoms were either halted or discontinued (Devlin, 2013). Most of the tested drugs were making patients sicker, not better, and came with appalling side effects.

With pharmaceutical approaches failing, many clinicians and researchers have turned to nutrition to find their answers, and an accumulating body of studies are now showing that nutrition has profound effects on brain health. The brain functions at a high metabolic rate and uses a substantial portion of total nutrient intake. It relies on amino acids, fats, vitamins, minerals and trace elements that influence both brain structure and function. Nutrition also contributes to neuron plasticity and repair, which are both key functions for mental health and wellbeing over the long term.

A collaborative research project funded by the United States National Institute on Aging recently found that individuals on a wholefoods diet rich in items like berries, leafy greens and fish are at less of a risk for Alzheimer's disease (di Fiore, 2015). Essential fatty acids such as omega-3s are also being studied at several large universities for their role in supporting brain health. Other experts have called Alzheimer's disease "type 3 diabetes", pointing to excess sugar intake as a major contributor to the disorder. The overlap between nutrition and cognitive function is becoming more widely accepted in the world of neurology.

Lithium: The Unlikely Treatment

One mineral that has shown great promise in the treatment of Alzheimer's disease is the mineral lithium, a nutrient with established benefits for the treatment of mental health disorders.

Lithium salts have been used for centuries as a popular health tonic. Over the course of history this simple mineral has been used to heal ailments as wide-ranging as asthma, gout and migraine. Lithium springs were once sought-after health destinations, visited by authors, political figures and celebrities. Throughout the 19th and into the 20th century, lithium was used as a mineral supplement to fortify a variety of foods and beverages. The third edition of the *Merck Index*, published in 1907, listed 43 different medicinal preparations containing lithium; the following year, the 1908 *Sears, Roebuck & Co Catalogue* advertised Schieffelin's Effervescent Lithia Tablets for a variety of afflictions; and in

Flynt/Bigstock.com

1929, a soft drink inventor named Charles Leiper Grigg even created a new "lithiated" beverage he called Bib-Label Lithiated Lemon-Lime Soda, now known as "7-Up". The beverage contained lithium citrate until 1950, and was originally known and marketed for its potential to cure hangovers after a night of drinking alcohol, and to lift mood.

Today lithium is still found naturally in food and water. The U.S. Environmental Protection Agency has estimated that the daily lithium intake of an average adult ranges from about 0.65 mg to 3 mg. Grains and vegetables serve as the primary sources of lithium in a standard diet, with animal byproducts like egg and milk providing the rest. Lithium has even been officially added to the World Health Organization's list of nutritionally essential trace elements alongside zinc, iodine and others (World Health Organization, 1996).

In modern medicine, lithium is most widely acknowledged for its ability to encourage mood stability in patients with affective disorders. With years of research and clinical use to back it, a substantial body of evidence now exists to show that high-dose lithium restores brain and nervous system function, right down to the molecular level. This incredible mineral is now being considered for the treatment of cognitive decline.

Scientists first became interested in the use of lithium for treating neurodegenerative disorders when they observed that bipolar patients using lithium therapy seemed to have lower rates of cognitive decline than peers on other medications. In an attempt to figure out the legitimacy of this observation, one study compared the rates of Alzheimer's disease in 66 elderly patients with bipolar disorder and chronic lithium therapy with 48 similar patients who were not prescribed the mineral. The findings in favor of lithium were staggering, with results showing that lithium treatment reduced the likelihood of developing Alzhiemer's disease to the same rate as the general elderly population: five percent of patients (3) receiving continuous lithium were diagnosed with Alzheimer's disease compared to 33% (16) in the non-lithium group (Nunes, Forlenza, & Gattaz, 2007). Two further studies in Denmark confirmed this phenomenon using different study designs, but achieving strikingly similar results. In this study series, investigators surveyed the records of over 21,000 patients who had received lithium treatment, and found that therapy was associated with decreased levels of both dementia and Alzheimer's (Kessing, Forman, & Andersen, 2010; Kessing, Søndergård, Forman, & Andersen, 2008)

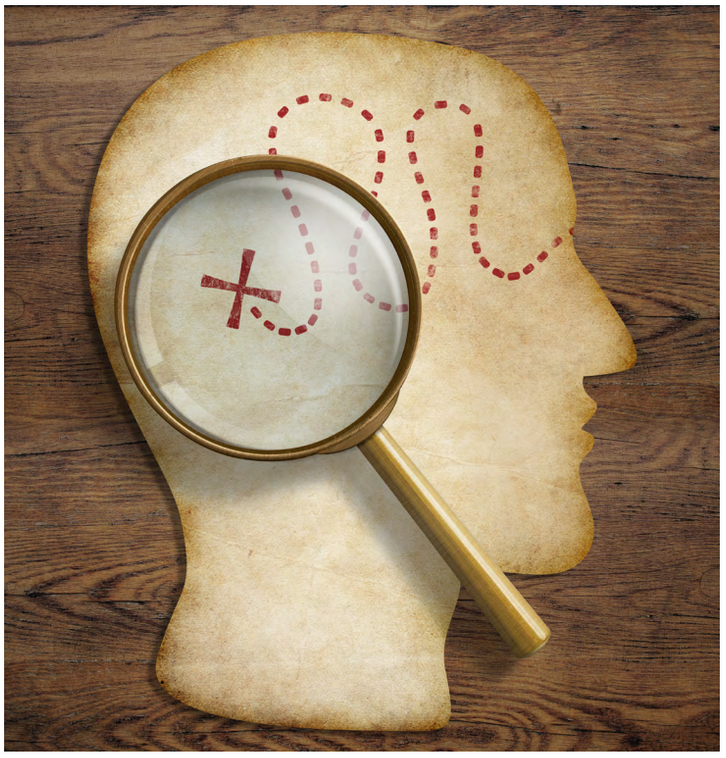
Unfortunately, the first clinical trials testing lithium with dementia patients proved disappointing. Researchers attempted to fit lithium into the same diagnostic treatment framework used by drug companies in the beginning—that is, testing the therapy on patients who already had fully developed Alzheimer's. However, at this point, the damage to the brain was simply too great to turn around.

One small, open-label study looked at low-dose lithium use in 22 Alzheimer's patients over the course of one year (Macdonald et al., 2008). While researchers concluded that prescription lithium salts were relatively safe in this population, there were no observed cognitive benefits. The small baseline sample size coupled with a high discontinuation rate may have been to blame for these discouraging results. It may also have been too late for lithium to make a difference in these advanced stages of illness.

Another multi-center, single-blind study looked at the use of lithium sulfate in participants with mild Alzheimer's disease over a 10-week period (Hampel et al., 2009). They too failed to find significant effects of lithium treatment on cognitive performance or related biomarkers. One major issue with this trial was the length of observation—it likely takes months, not weeks, to see substantial cognitive shifts in patients.

A group led by Forlenza et al. (2011) sought to correct for these initial design flaws. Focus was shifted away from the post-diagnosis period and settled on prevention. This unique study attempted to determine whether long-term lithium treatment could stop Alzheimer's disease from occurring in high-risk individuals. Forty-five participants with mild cognitive impairment (MCI), a precursor to Alzheimer's, were randomized to receive lithium or a placebo. Over the 12-month trial,

Romario Ien/Bigstock.com



lithium dosages were kept at sub-therapeutic levels (150mg to 600mg daily) to minimize potential side effects. At the conclusion of the study, researchers discovered that those in the lithium group had a decreased presence of destructive tau proteins when compared to pre-study levels. This finding came in stark contrast to the tau levels of the placebo group, which had increased steadily over the course of the study. What's more, the lithium group showed improved performance on multiple cognitive scales. Overall tolerability of lithium was deemed good as patients reported limited side effects, and the adherence rate to treatment was an impressive 91%. Researchers concluded that lithium had a significant disease-modifying impact on preventing dementia and Alzheimer's disease when initiated early on in the disease progression.

The Promise of Low-Dose Lithium

Additional testing has found that lithium can be effective when used at low-doses or supplemental levels similar to those found naturally in water and foods, and the studies are beginning to show that the benefits of pharmaceutical lithium (used at an average of 600–1200 mg daily) can be achieved with much smaller and safer doses (between 1–20 mg). When lithium is used at these low or nutritional doses, the risks of side effects plummet.

Evidence pointing to the usefulness of low-dose lithium has come primarily from epidemiological studies conducted by geology specialists and other professionals. Eleven different studies have looked at lithium levels in the drinking water from various regions throughout the globe: twenty-four counties in Texas, the 100 largest American cities and 99 districts in Austria have been considered, alongside other locations in Greece and Japan (Dawson, Moore, & McGanity, 1970; Giotakos, Nisianakis, Tsouvelas, & Giakalou, 2015; Kabacs, Memon, Obinwa, Stochl, & Perez, 2011; Kapusta et al., 2011; Schrauzer & Shrestha, 1990; Sugawara, Yasui-Furukori, Ishii, Iwata, & Terao, 2013). Lithium levels in the water in these areas have been compared to rates of behavioral issues (including psychiatric admissions, suicide, homicide and crimes), medical illnesses and overall mortality. Collectively the studies have analyzed outcomes in well over 10 million subjects. In 9 of the 11 studies, a positive association between high lithium levels and beneficial behavioral, legal and medical outcomes was observed. In each of the negative studies, levels of lithium were likely too low to yield any significant health effects (Mauer, Vergne, & Ghaemi, 2014).

These studies have spurred interest in the clinical applications of low-dose lithium, although trials have been slow coming. Because lithium is a naturally occurring mineral and is not patentable (and therefore not profitable), little financial backing has been put towards the cause. Recently, however, in one highly-regarded study published in the journal *Current Alzheimer's Research*, a scant 0.3 mg of lithium was administered to Alzheimer's patients once daily for 15 months (Nunes et al., 2013). Those receiving lithium demonstrated stable cognitive performance scores throughout the duration of the study, while those in the control group suffered progressive declines. Moreover, three months into the study, the seemingly impossible happened: the lithium treatment cohort began showing increasing mini-mental status scores.

Additional high-quality trials using low-dose lithium are essential, especially in the realm of dementia and cognitive decline.

Key Neuroprotective Mechanisms

There is now clear scientific evidence to suggest not only that lithium protects the brain, but also how it does so. Lithium ions (at both high and low concentrations) have been shown to modify key cellular cascades that increase neuronal viability and resilience. Most prominently, lithium disrupts the key enzyme responsible for the development of the amyloid plaques and neurofibrillary tangles associated with Alzheimer's disease. This enzyme is called glycogen synthase kinase-3 (GSK-3), a serine/threonine protein kinase that normally plays a major role in neural growth and development. In the healthy brain, GSK-3 is very important—it helps to carry

out the synaptic remodeling that drives memory formation.

In Alzheimer's disease, however, GSK-3 becomes hyperactive in the areas of the brain that control cognition and behavior, including the hippocampus and frontal cortex. When revved-up in this way, GSK-3 phosphorylates, or activates, amyloid-B and tau proteins within the neurons. Eventually, these proteins accumulate and create the signature plaques and neurofibrillary tangles that disrupt brain function and result in symptoms of cognitive decline. Lithium works as a direct GSK-3 inhibitor to prevent this overexpression, halting inappropriate amyloid production and the hyper phosphorylation of tau proteins before they become problematic (Hooper, Killick, & Lovestone, 2008; Wada, 2009).

In addition to protecting the brain from the development of plaques and tangles, lithium has been shown to repair existing damage brought on by the Alzheimer's disease pathogenesis. For example, lithium ions encourage the synthesis and release of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), which in turn stimulate the growth and repair of neurons (Leyhe et al., 2009). Patients on lithium have been found to have significantly higher gray-matter volumes in the brain, hinting that lithium has powerful stimulatory effects on neurogenesis. One study has even directly demonstrated that damaged nerve cells exposed to lithium respond with increases in dendritic number and length (Dwivedi & Zhang, 2014).

Conclusion

Alzheimer's and dementia have become modern health problems of epidemic proportions. Nonetheless, relatively few pharmacological solutions have been discovered for preventing, treating and reversing associated cognitive decline. As conventional treatment approaches falter, clinicians and researchers have been turning more and more to natural alternatives. It has become increasingly evident that nutrition is a key factor when it comes to brain health.

Evidence suggests that the mineral lithium, in particular, may play a major role in shifting the pathophysiological cascade associated with dementia and Alzheimer's disease. In clinical studies, long-term lithium therapy has been found to decrease the problematic plaques and tangles leading to symptoms of cognitive decline. This powerful mineral acts by inhibiting damaging enzymes and stimulating the release of protective

alexraths/Bigstock.com

neurotrophic factors in the brain.

Lithium ions have been found to operate efficiently at low doses, mimicking those found in nutritional sources. At these sub-pharmaceutical levels, lithium has been shown to be a beneficial and safe neuroprotective therapy across age groups and with minimal side effects.

The safety profile of low-dose lithium is particularly attractive, as prevention strategies for dementia are most effective when started early and continued for long periods of time. The dangerous plaques and tangles involved in Alzheimer's disease begin up to 40 years before the appearance of symptoms. What's more, 10% of healthy 50-year-olds already have amyloid deposits developing in the brain tissues. Thus, for optimal effectiveness, steps to protect the brain must be taken at a much younger age than previously thought.

When started early, low-dose lithium may be the key intervention to prevent cognitive decline. But first, we must move past the stigma that surrounds it. As psychiatrist Anna Fels (2014) wrote in her recent article for *The New York Times*, "One could make a case that lithium is the Cinderella of psychotropic medications, neglected and ill-used" (para 18). Lithium is the single most proven substance to keep neurons alive, and yet it continues to be viewed in the public mind as a dangerous and scary drug. Lithium is found readily in our environment, food, water, and each and every cell in the human body. It is time we change the conversation around one of nature's most effective and powerful neuroprotective remedies.

References

Da Silva, J., Gonçalves-Pereira, M., Xavier, M., & Mukaetova-Ladinska, E. B. (2013). Affective disorders and risk of developing dementia: Systematic review. *The British Journal of Psychiatry, 202*, 177–186. doi:10.1192/bjp.bp.111.101931

Dawson, E. B., Moore, T. D., & McGanity, W. J. (1970). The mathematical relationship of drinking water lithium and rainfall to mental hospital admission. *Diseases of the Nervous System, 31*(12), 1–10.

Devlin, H. (2015, July 22). Scientists find first drug that appears to slow Alzheimer's disease. *The Guardian*. Retrieved from http://www.theguardian.com/science/2015/jul/22/scientists-find-first-drug-slow-alzheimers-disease

Di Fiore, N. (2015). Diet may help prevent Alzheimer's: MIND diet rich in vegetables, berries, whole grains, nuts [Rush University Medical Center]. Retrieved from: https://www.rush.edu/news/diet-may-help-prevent-alzheimers

Dwivedi, T., & Zhang, H. (2014). Lithium-induced neuroprotection is associated with epigenetic modification of specific BDNF gene promoter and altered

apoptotic-regulatory proteins. *Frontiers in Neuroscience, 8*, 1–8. doi:10.3389/fnins.2014.00457

Fels, A. (2014, September 13). Should we all take a bit of lithium? *The New York Times*.

Retrieved from http://www.nytimes.com/2014/09/14/opinion/sunday/should-we-all-take-a-bit-of-lithium.html

Forlenza, O. V., Diniz, B. S., Radanovic, M., Santos, F. S., Talib, L. L., & Gattaz, W. F. (2011). Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: Randomized controlled trial. *The British Journal of Psychiatry, 198*, 351–365. doi:10.1192/bjp.bp.110.080044

Giotakos, O., Nisianakis, P., Tsouvelas, G., & Giakalou, V. V. (2015). Lithium in the public water supply and suicide mortality in Greece. *Biological Trace Element Research, 156*, 376–379. doi:10.1007/s12011-013-9815-4

Hampel, H., Ewers, M., Bürger, K., Annas, P., Mörtberg, A., Bogstedt, A., . . . Basun, H. (2009). Lithium trial in Alzheimer's disease: A randomized, single-blind, placebo- controlled, multicenter 10-week study. *The Journal of Clinical Psychiatry, 70*(6), 922–931.

Hooper, C., Killick, R., & Lovestone, S. (2008). The GSK3 hypothesis of Alzheimer's disease. *Journal of Neurochemistry, 104*(6), 1433–1439.

Kabacs, N., Memon, A., Obinwa, T., Stochl, J., & Perez, J. (2011). Lithium in drinking water and suicide rates across the East of England. *The British Journal of Psychiatry, 198*, 406–7. doi:10.1192/bjp.bp.110.088617

Kapusta, N. D., Mossaheb, N., Etzersdorfer, E., Hlavin, G., Thau, K., Willeit, M., . . . Leithner-Dziubas, K. (2011). Lithium in drinking water and suicide mortality. *The British Journal of Psychiatry*, *198*, 346–350. doi:10.1192/bjp.bp.110.091041

Kessing, L. V., Forman, J. L., & Andersen, P. K. (2010). Does lithium protect against dementia? *Bipolar Disorders, 12*, 87–94. doi:10.1111/j.1399-5618.2009.00788.x

Kessing, L. V., Søndergård, L., Forman, J. L., & Andersen, P. K. (2008). Lithium treatment and risk of dementia. *Archives of General Psychiatry, 65*, 1331–1335. doi:10.1001/archpsyc.65.11.1331

Langbaum, J. B., Fleisher, A. S., Chen, K., Ayutyanont, N., Lopera, F., Quiroz, Y. T., . . . Reiman, E. M. (2013). Ushering in the study and treatment of preclinical Alzheimer disease. *Nature Reviews: Neurology, 9*, 371–381. doi:10.1038/nrneurol.2013.107

Leyhe, T., Eschweiler, G. W., Stransky, E., Gasser, T., Annas, P., Basun, H., & Laske, C. (2009). Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's disease. *Journal of Alzheimer's Disease, 16*, 649–656. doi:10.3233/JAD-2009-1004

Macdonald, A., Briggs, K., Poppe, M., Higgins, A., Velayudhan, L., & Lovestone, S. (2008). A feasibility and tolerability study of lithium in Alzheimer's disease. *International Journal of Geriatric Psychiatry, 23*, 704–11. doi:10.1002/gps.1964

Mauer, S., Vergne, D., & Ghaemi, S. N. (2014). Standard and trace-dose lithium: A systematic review of dementia prevention and other behavioral benefits. *The Australian and New Zealand Journal of Psychiatry, 48*, 809–818. doi:10.1177/0004867414536932

Nunes, M. A., Viel, T. A., & Buck, H. S. (2013). Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. *Current Alzheimer Research, 10*(1), 104–107.

Nunes, P. V., Forlenza, O. V., & Gattaz, W. F. (2007). Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *The British Journal of Psychiatry, 190*, 359–60.

Schrauzer, G. N., & Shrestha, K. P. (1990). Lithium in drinking water and the incidences of crimes, suicide and arrests related to drug addiction. *Biological Trace Element Research, 25*(2), 105–113.

Sugawara, N., Yasui-Furukori, N., Ishii, N., Iwata, N., & Terao, T. (2013). Lithium in tap water and suicide mortality in Japan. *International Journal of Environmental Research and Public Health, 10*, 6044–6048. doi:10.3390/ijerph10116044

Visser, P. J., Jansen, W. J., Ossenkoppele, R., Knol, D. L., Tijms, B. M., Scheltens, P., Verhey, F. R., . . . Zetterberg, H. (2015). Prevalence of cerebral amyloid pathology in persons without dementia. *JAMA, 313*, 1924–1938. doi:10.1001/jama.2015.4668

Wada, A. (2009). Lithium and neuropsychiatric therapeutics: Neuroplasticity via glycogen synthase kinase-3B, B-catenin and neurotrophin cascades. *Journal of Pharmacological Sciences*, 110(1), 14–28.

World Health Organization. (1996). *Trace elements in human nutrition and health*. Retrieved from http://www.who.int/nutrition/publications/micronutrients/9241561734/en/

World Health Organization. (2015, March). *Dementia*. Retrieved from http://www.who.int/mediacentre/factsheets/fs362/en/

Author notes

James M. Greenblatt, MD, currently serves as the Chief Medical Officer and Vice President of Medical Services at Walden Behavioral Care in Waltham, Massachusetts. He is also an Assistant Clinical Professor of Psychiatry at Tufts University School of Medicine. An acknowledged integrative medicine expert, Dr. Greenblatt has lectured throughout the United States on the scientific evidence for nutritional interventions in psychiatry and mental illness.

Kayla Grossmann, RN, works as a nurse advocate and freelance writer specializing in integrative health research and practice. She supports several large organizations in the field by contributing to their ongoing educational initiatives and clinical programming.

Find out more about their upcoming book and work at www.lowdoselithium.org