Standard and trace-dose lithium: A systematic review of dementia prevention and other behavioral benefits

Sivan Mauer, Derick Vergne and S Nassir Ghaemi

Aust N Z J Psychiatry published online 11 June 2014
DOI: 10.1177/0004867414536932

Review

ANZJP

Australian & New Zealand Journal of Psychiatry
1–10
DOI: 10.1177/0004867414536932

Standard and trace-dose lithium: A systematic review of dementia prevention and other behavioral benefits

Sivan Mauer[1], Derick Vergne[1,2] and S Nassir Ghaemi[1,2]

Abstract

Objective: Dementia is a major public health issue, with notably high rates in persons with mood illnesses. Lithium has been shown to have considerable neuroprotective effects, even in trace or low doses. The aim of this review is to summarize the current understanding of lithium benefits in trace or low doses in dementia prevention and for other behavioral or medical benefits.

Methods: A systematic review identified 24 clinical, epidemiological, and biological reports that met inclusion criteria of assessing lithium in standard or low doses for dementia or other behavioral or medical benefits.

Results: Five out of seven epidemiological studies found an association between standard-dose lithium and low dementia rates. Nine out of 11 epidemiological studies, usually of drinking water sources, found an association between trace-dose lithium and low suicide/homicide/mortality and crime rates. All four small randomized clinical trials of lithium for Alzheimer's dementia have found at least some clinical or biological benefits versus placebo. Only one small randomized clinical trial (RCT) of trace lithium has been conducted, assessing mood symptoms in former substance abusers, and found benefit with lithium versus placebo.

Conclusions: Lithium, in both standard and trace doses, appears to have biological benefits for dementia, suicide, and other behavioral outcomes. Further RCT research of trace lithium in dementia is warranted.

Keywords

Cognition, dementia, lithium, prevention, standard dose, trace

Introduction

Dementia is a major public health problem, rising in prevalence from 1% of the population at age 60 years to over 30% of the population by age 90 (Nunes et al., 2007), and affecting an estimated 35.6 million people worldwide, a number projected to nearly double every 20 years. Nearly 7.7 million new cases occur yearly, or about one new case every 4 seconds. Prevalence rates in Australia (9% above age 65) and Europe (6.4%) are similar, with an expected increase by one-third in the next decade (Australian Institute of Health and Welfare, 2012; Lobo et al., 2000). The estimated worldwide cost of dementia is US$604 billion (World Health Organization, 2012). There are no known preventive, or even notably ameliorative, treatments for most dementias – the most common type of which is Alzheimer's disease (AD) (Broberg et al., 2011).

A prominent risk factor of dementia is depression, which doubles the risk of dementia (da Silva et al., 2013; Kessing et al., 2008). Subjects with depression or bipolar disorder have been found to experience long-term cognitive impairment, even when in a euthymic state (Forlenza et al., 2011). Depression itself is a common illness, occurring in about

[1]Mood Disorders Program, Department of Psychiatry, Tufts Medical Center, Boston, MA, USA
[2]Tufts University School of Medicine, Boston, MA, USA

Corresponding author:
Nassir Ghaemi, Mood Disorders Program, Department of Psychiatry, Tufts Medical Center, 800 Washington Street, Box 1007, Boston, MA 02111, USA.
Email: nghaemi@tuftsmedicalcenter.org

5–10% of the population in its unipolar variety, and about 2–5% of the population in its bipolar variety (Ohgami et al., 2009).

Lithium, a very effective agent for the prevention of mania and depression, has also been shown to have considerable neuroprotective effects, far more in extent and human relevance than any other psychotropic agent (Broberg et al., 2011; Hampel et al., 2009; Helbich et al., 2012; Nunes et al., 2013; Zarse et al., 2011). Clinical studies have also demonstrated that lithium can modulate in vivo cellular cascades related to neuronal resilience and neuroprotection. Lithium treatment has been linked to increased phosphor-glycogen synthase kinase-3 beta (GSK-3B) levels and, consequently, reduced enzymatic activity in leukocytes of patients with bipolar disorder (Forlenza et al., 2011). It has also been found to induce autophagy (enhanced clearance of toxic cellular substrates) via inositol monophosphatase (IMPase) inhibition, which leads to free inositol depletion and reduced myo-inositol-1,4,5-triphosphate (IP3) levels. The induction of cellular autophagy by lithium may be a mechanism to prevent neurodegeneration (Forlenza et al., 2012; Sarkar and Rubinsztein, 2006; Sarkar et al., 2005). Phosphorylated tau (p-tau) levels are reduced with long-term lithium in mild cognitive impairment (MCI) (Forlenza et al., 2011), and the concentration of brain-derived neurotrophic factor (BDNF) is increased after only 10 weeks of lithium treatment in mild AD (Leyhe et al., 2009).

In this paper, we review the clinical, epidemiological, and biological literature related to whether or not lithium might have any benefit in the prevention or treatment of dementia, including AD.

Methods

This systematic review was conducted between September 2012 and August 2013 following PRISMA guidelines (Moher et al., 2009), searching the PubMed database, augmented by bibliographic cross-referencing, and use of any other sources available, including conference proceedings or abstracts from 1969 to 2013 (Figure 1).

Inclusion criteria were as follows: studies had to use the English language, include human subjects, and represent original research data. When using standard doses of lithium, studies had to examine lithium in relation to a cognitive outcome, such as minimal cognitive impairment, dementia, or other cognitive impairment. Since there are no specific studies of cognitive outcomes or dementia risk with trace lithium levels, we included any outcomes in studies of trace lithium levels to obtain a sense of whether trace lithium levels can have detectable biological or neurocognitive effects. Exclusion criteria included reviews, commentaries, case reports and studies limited to animal populations only.

In sum, we included clinical studies of lithium in humans with cognitive outcomes, and studies of trace lithium levels in humans assessing any outcome.

Key words and application of inclusion/exclusion criteria produced the following results: "Lithium AND dementia", filtered by clinical trials and human subjects, yielded 24 papers, of which 19 were excluded because six related to Huntington's chorea, four were reviews, seven were letters or case reports, and two were irrelevant (one was related to the antipsychotic risperidone, and another to depression, not dementia). "Microdose AND lithium", filtered by clinical trial, yielded one article, included in this review. "Lithium AND drinking water" yielded 35 references, of which 26 were excluded because eight were letters, seven were reviews, six involved diseases irrelevant to the focus of this review (porphyria, vascular disease, agranulocytosis, anencephaly, dental caries and thyroid levels), two were not in English, one did not assess any outcomes, one involved sodium not lithium, and one used an animal sample only. "Lithium AND suicide" yielded 318 references, which, after applying the inclusion criterion of including only trace lithium studies, led to exclusion of 311 studies because 176 did not involve trace lithium, 125 were reviews, seven were not in English, and three were letters. Using bibliographic cross-referencing from the above studies, we identified eight more studies for inclusion in this review: seven human clinical trials of lithium for cognition, and one more clinical study of trace lithium for any outcome.

Results

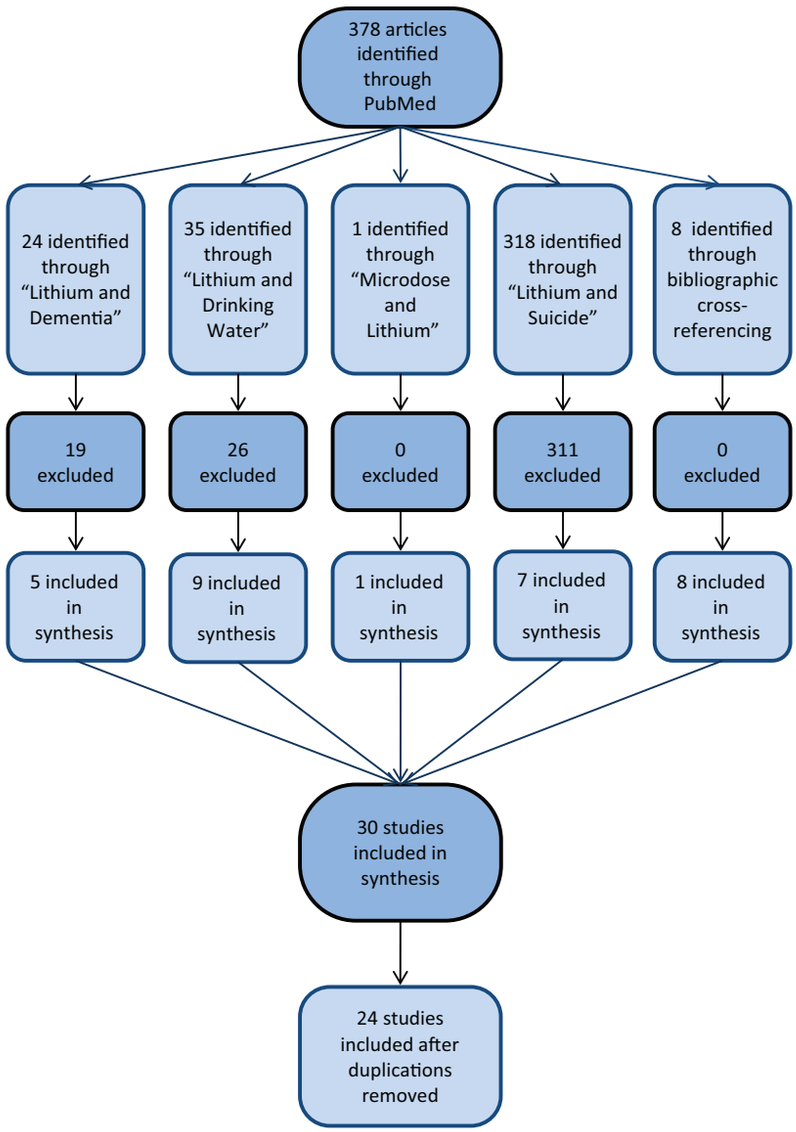
Clinical and epidemiological studies of standard lithium doses

As seen in Table 1, three case–control studies, three retrospective cohort studies, and one prospective cohort study, ranging in sample size from 22 to almost 20,000 subjects and a follow-up of 1–10 years, have been published. Five of seven studies found an association between lithium use and low dementia rates.

The only prospective study, with up to 26 years' outcome data in a mood disorder population from Zurich, found a major decrease in dementia with lithium treatment (77% reduction in odds ratio) (Angst et al., 2007). Of the three retrospective studies (Kessing et al., 2008, 2010; Terao et al., 2006), all of them found benefit. The notable benefit in the Danish bipolar samples (Kessing et al., 2008, 2010) may suggest, as with the Zurich study, special effectiveness for dementia prevention in mood disorders, as opposed to the general population.

Two out of three case–control studies showed no benefit with lithium (Dunn et al., 2005; Macdonald et al., 2008); both studies were in non-mood disorder samples. One case–control study found notable benefit with lithium

Figure 1. Flow chart depicting steps in the systematic review of articles.



(Nunes et al., 2007); unlike the others, it was limited to a bipolar sample.

Epidemiological studies of trace lithium doses

For trace lithium levels with any outcome, we identified 11 epidemiological studies, many conducted by geology specialists (Table 2). Sample sizes were often large (5 million in one study, 8 million in another), including regions such as over two dozen Texas counties (Dawson et al., 1970; Schrauzer and Shrestha, 1990), the entire state of North Carolina (Voors, 1972), the 100 largest American cities, or 99 districts in Austria. In all cases, water levels were tested for lithium availability. Outcomes often involved major behavioral abnormalities (such as suicide, homicide, psychiatric admissions, crimes) or some medical illnesses (such as cardiovascular disease), or overall mortality. Suicide was the most commonly measured outcome.

Nine of 11 studies found an association between higher levels of trace lithium in drinking water and beneficial clinical, behavioral, legal, and medical outcomes. The most commonly assessed outcome – suicide – was reduced in four of five studies.

The major risk in epidemiological studies is confounding bias (Agabegi and Stern, 2008; Ely, 1992; Ghaemi, 2009), which is best addressed by regression modeling and other forms of matching for confounding factors (Ghaemi, 2009). The two most valid studies in this group (Blüml

Table 1. Clinical and epidemiological studies of standard doses of lithium for cognition or dementia.

Study	Design	*n*	Length of follow up	Sample	Results	Comments
Dunn et al., 2005	Nested case–control	9954 cases, 9973 controls	10 years	General practice research database, all age >60	Increased dementia rate in those on lithium	Adjusted for a few limited confounding variables. No lithium levels or doses reported. Duration of treatment with lithium consistent with confounding effect of mood disorder as risk factor for dementia.
Terao et al., 2006	Controlled retrospective cohort study	36 current or past lithium-treated patients; 21 age- and sex-matched controls	Mean length of lithium tx: 4 years ± 4 years	University clinic outpatients, age >60, without dementia	Cognitive function (MMSE) was improved in lithium group versus controls	Very small sample size
Nunes et al., 2007	Case–control	114: 66 lithium; 48 no lithium	Mean length of lithium tx: 6 years	Elderly euthymic BD, age 68.2 ± 5 years	5% dementia with lithium vs 33% without lithium	Sample related only to BD
Angst et al., 2007	Prospective controlled cohort study	406 bipolar and unipolar mood disorder patients	25 years	Outpatient cohort from Zurich followed prospectively for 20 years	Lithium reduced risk of dementia in all subjects, especially in BD (OR 0.23, 95% CI 0.06–0.89)	Longest prospective data available on this topic
Kessing et al., 2008	Retrospective observational cohort study	16,238 patients	10 years	Denmark national prescription database	Dementia diagnosis was reduced to general population levels with long-term lithium, but not anticonvulsant use	Second largest sample size analyzed on this topic
Macdonald et al., 2008	Case–control	322: 22 AD/ lithium and 300 comparison group with AD	1 year	Patients with a diagnosis of probable or possible AD of mild to moderate severity (MMSE range 12–24); >60 years	There was no difference in death, drop outs or change in MMSE between those receiving lithium and comparison group	High drop-out rate (54.5%)
Kessing et al., 2010	Retrospective observational cohort study	4856	10 years	Denmark national prescription database	50.4% were exposed to lithium; 36.7% were exposed to an anticonvulsant; 88.1% to antidepressants; and 80.3% to antipsychotics	Largest sample size of patients with BD analyzed in this topic
				Patients with main diagnosis of manic or mixed episode or BD	Continued use of lithium was associated with decreased rate of dementia	

tx: treatment; MMSE: Mini Mental State Examination; BD: bipolar disorder; OR: odds ratio; CI: confidence interval; AD: Alzheimer's disease.

Table 2. Epidemiological studies of trace amounts of lithium.

Study	Design	*n*	Length of follow up	Sample	Results	Comments
Voors, 1970	Observational epidemiological	Not provided	Not provided	The 100 largest American cities, varying lithium water levels assessed versus heart mortality	Lower cardiovascular mortality rates in high lithium cities ($r = -0.21$ to -0.43, depending on sex and race). Results corrected for age, sex, race and hardness of water (effects of other trace minerals). Lower overall mortality rates also seen ($r = -0.06$ to -0.22, depending on sex and race). Best results were seen in white males, and worst results in non-white females.	Trace lithium was associated with decreased overall mortality, with a major effect through cardiovascular mortality, corrected for age, sex, race, and other mineral content in water.
Dawson et al., 1970	Observational epidemiological	Not provided	Fall and summer of 1968	26 randomly selected counties in state of Texas	Lithium was found in measurable quantities in the drinking water of 22 of 27 county seats in Texas state. The incidence of patients' first admission and prevalence of readmission as well as the diagnosis of psychosis, neurosis and personality disorders was inversely proportional to the lithium content of their residential drinking water (0–160 µg/l).	First study about lithium in drinking water and mental hospital admission
Voors, 1972	Observational epidemiological	5 million	1965–1970	The population of North Carolina	The lithium concentration in drinking water in North Carolina ranged from zero to 0.85 mg/l. The incidence of patients' first admission and prevalence of readmission, as well as the diagnosis of neurosis and personality disorders, was inversely proportional to the lithium content of their residential drinking water.	Instead of direct assessment of lithium level in drinking water, an index was used as the product of the concentration of potassium and calcium carbonate, based on the rationale that a chemical relation exists between sodium, potassium and lithium.
Oliver et al., 1976	Observational epidemiological	384	1 year	384 individuals in Washington County, MD, who had been randomly selected	Lithium's effect did not appear to be beneficial at these levels (0–32 ppb)	75% of patients were in the low level lithium range
Schrauzer and Shrestha, 1990	Observational epidemiological	Not provided	1978–1987	27 Texas counties, 1978–1987, varying lithium water levels assessed versus suicide, homicide, rape, robbery, burglary, theft, substance abuse arrests	All assessed behavior was lower in high-lithium counties	Trace lithium correlates with a generalized benefit for behavior, as expressed in suicidal, violent, criminal, or impulsive acts. These correlations were not accounted for by income.

(Continued)

Table 2. (Continued)

Study	Design	*n*	Length of follow up	Sample	Results	Comments
Ohgami et al., 2009	Observational epidemiological	1,206,174	2002–2006	Population of 18 municipalities of Oita Prefecture with a range of lithium in drinking water (0.7–59 μg/l) from 2002 to 2006	There was a significant, negative correlation between suicide rates and lithium levels in the drinking water.	Lack of control for confounding variables (e.g. economic, psychosocial features)
Zarse et al., 2011	Observational epidemiological	1,206,174	2006	Population of 18 municipalities of Oita Prefecture with a range of lithium in drinking water (0.7–59 μg/l) from 2002 to 2006. The authors also exposed *C. elegans*, a roundworm commonly used for anti-aging studies, to comparable concentrations of lithium and quantified mortality during the process.	Tap water Li+ was inversely associated with overall mortality. LiCl shown to extend lifespan of roundworm model. In humans, they found an inverse correlation between drinking water Li+ concentration and all-cause mortality in 18 Japanese municipalities.	Secondary analysis of the above study.
Kapusta et al., 2011	Observational epidemiological	8.3 million	2005–2009	6460 water samples were analyzed from households in 99 districts of Austria; average population per district 88,813	Lithium levels in drinking water inversely associated with suicide rates	The only study to assess lithium present directly from household tap-water source
Kabacs et al., 2011	Observational epidemiological	5.7 million	2006–2008	Eastern countries of England	No correlation between lithium levels in drinking water and suicide	Lithium levels were much lower than other studies, thus the hypothesis of benefit at high levels could not be tested
Helbich et al., 2012	Observational epidemiological	8.3 million	2005–2009	6460 water samples were analyzed from households in 99 districts of Austria, average population per district 88,813	Lower suicide rates with higher lithium levels ($r = -0.26$)	Regression modeling corrected for population density, per capita income, Roman Catholic prevalence, unemployment rate, psychiatrist density, psychotherapist density, general practitioner density. In the final model, the main predictors were being Roman Catholic (coefficient = 0.004), psychiatrist density (coefficient = −0.04), and lithium level (coefficient = −4.84). As seen, lithium effects were 100 times more protective than psychiatrist density.
Blüml et al., 2013	Observational epidemiological	Not provided	1999–2007	3123 water samples from 226 Texas counties	Lower suicide rates with higher lithium levels (rate ratio for fractional polynomial model: 0.88 for 100 μg/l)	Poisson and linear regressions models adjusted for county-based population density, median income per household, poverty and unemployment rates

ppb: parts per billion.

et al., 2013; Helbich et al., 2012) conducted regression models adjusting for potential confounding factors, such as economic factors like poverty, unemployment, and social factors (e.g. religious denomination prevalence and psychiatrist density). A third study (Voors, 1970) matched for age, sex, race, and mineral content in water. All of these studies, which corrected for at least some statistical confounding factors, found notable benefit with lithium for suicide prevention and mortality. Another report which found a suicide benefit with lithium did not correct for other confounding factors but is the only study to assess lithium presence directly in household water-tap sources (Kapusta et al., 2011).

In both negative studies (Kabacs et al., 2011; Oliver et al., 1976), most water samples had low levels of lithium; thus, benefits of high trace lithium levels may not have been detectable.

In the other positive studies, two, which assessed psychiatric admission rates, found consistent association with lower hospitalization in areas with high lithium water levels (Dawson et al., 1970; Voors, 1972), two found decreased overall mortality (with specific benefit for cardiovascular mortality in one study) (Voors, 1970; Zarse et al., 2011), and another study found a range of behavioral benefits including lowered crime and homicide rates (Schrauzer and Shrestha, 1990).

Randomized clinical trials (RCTs) of dementia or cognitive symptoms

Four RCTs, ranging from 6 to 15 months in 27–113 subjects, have been conducted to assess lithium's effects on cognitive impairment or dementia. Benefits were seen on at least some clinical or biological parameters in all four studies. The impression has been given that this literature is negative (Tariot and Aisen, 2009) because the first published RCT (Hampel et al., 2009) reported a negative result for its primary outcome (GSK-3 biological activity at 6-month follow-up). However, the same study reported benefit with another biological outcome (BDNF levels) (Leyhe et al., 2009) and there was a decrease in worsening of clinical cognitive symptoms in that elderly MCI population: using the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog), exactly twice as many lithium- than placebo-treated subjects, 28.6% vs 14.3%, had notable cognitive improvement (ADAS-Cog improved >4 points). This benefit is not statistically significant, but given the small sample size, type II error is not improbable. The effect size is notable: using confidence intervals (CIs), we recalculated these data to find a twofold benefit with lithium (risk ratio = 2.0, lower CI 0.64, upper CI 6.20), with probability of positive benefit being more likely above than below the null value.

The other three positive studies included a 6-month study of glial cell line-derived neurotrophic factor (GDNF) expression in Alzheimer's dementia (Straten et al., 2011), and two studies of about 1 year in duration finding prevention of worsening of cognitive functions compared to placebo (Nunes et al., 2013), as well as other biological benefits (reduction in p-tau in lithium-treated subjects) (Forlenza et al., 2011).

Although unrelated to cognitive outcomes, we have included the only RCT of trace lithium in humans in Table 3, since it confirms most of the epidemiological data in Table 2 indicating that, indeed, trace lithium levels can have important biological and neuropsychiatric effects. In the only RCT on the topic (Schrauzer and De Vroey, 1994), trace lithium levels improved mood substantially more than placebo in former substance abusers.

Discussion

This systematic review finds that most studies on lithium in standard doses showed notable cognitive benefits or effectiveness in dementia prevention. Epidemiological studies are numerous, large, and replicated. Most RCTs show clear biological or clinical benefits as well. Further, trace lithium levels are associated rather consistently in epidemiological studies with a range of medical and behavioral benefits, especially decreased mortality and suicide; these trace behavioral effects have been confirmed in the only RCT using trace lithium levels.

In sum, standard doses of lithium may have cognitive benefits for dementia prevention, and, although trace levels have not been studied for that outcome, trace lithium levels may have a range of other medical/behavioral benefits.

This systematic review of the literature supports the need for more attention to lithium, in standard and trace doses, for potential benefit in dementia prevention. This literature represents a formidable amount of pilot data supportive of possible, or even probable, benefit with lithium for dementia prevention. Extensive research, in both time and funding, has been conducted with putative dementia prevention interventions involving complex mechanisms, often related to apoE4 gene mechanisms or effects on neurofibrillary tangles and plaques. The simple intervention of lithium, even at low or trace doses, has been mostly ignored in dementia clinical trial research. This literature review would suggest that renewed attention should be given to the potential of lithium as a preventive intervention for dementias.

Based on initial signals of prediction of response in these epidemiological and randomized studies, it may be that lithium would yield preferential benefits in dementia prevention in persons with mood disorders, at standard or possibly trace levels, and that such benefit may not involve improvement in cognitive function but rather prevention of further decline.

In this respect, it may also be relevant that recent research suggests that the dementia process likely begins biologically at least a decade before the first clinical signs,

Table 3. Randomized clinical trials (RCTs) of lithium for dementia or cognitive symptoms.[a]

Study	Design	*n*	Length of follow up	Sample	Results	Comments
Schrauzer and Shrestha, 1994[a]	Trace lithium versus placebo	24	4 weeks	Former substance abuse patients (heroin and methamphetamine)	Improvement in mood based on self-rated scales	First RCT of trace lithium effects on human beings showed evidence of mood benefit
Hampel et al., 2009	Single-blind, placebo-controlled, multicenter	71	6 months	Patients, aged 50–85, with mild AD, MMSE score ≥21 and ≤26, enrolled at six memory clinics in Germany, 10-week study	No treatment effect on GSK-3 activity vs placebo	Very short duration. Benefits with lithium vs placebo seen in ADAS-Cog scores (although not statistically significant, with high false-negative probability).
Leyhe et al., 2009	Single-blind, placebo-controlled, parallel-group, multicenter	27	6 months	Subgroup analyzed of above study, assessing BDNF[a] levels	BDNF levels increased with lithium vs placebo	Biomarker benefits are seen with BDNF in the same study that reputed no biomarker benefits with GSK-3
Forlenza et al., 2011	Double-blind, placebo-controlled	45	1 year	Outpatient participants with a MCI all aged >59, followed for 12 months	Significant decrease of p-tau of lithium-treated group. This group also performed better on cognitive assessment and attention tests (CDR, ADAS-Cog) than placebo.	Contradicts prior negative study which was much shorter (Hampel et al., 2009)
Straten et al., 2011	Single blinded, placebo-controlled	27	6 months	27 (13 lithium and 14 patients placebo)	Findings indicated beneficial effects of lithium treatment might reduce necessity of enhanced GDNF expression in early AD	First prospective randomized study describing the impact of lithium in GDNF
Nunes et al., 2013	Lithium microdose versus placebo	113	15 months	Mild AD treated with 300 µg/day of lithium	Lithium group had no further worsening of MMSE, while placebo group worsened	Second RCT of trace lithium confirms benefits in cognition

[a]One RCT was included despite assessments only in mood outcomes, not cognition, because it involves trace lithium.
MMSE: Mini Mental State Examination; AD: Alzheimer's disease; GSK-3: glycogen synthase kinase 3; ADAS-Cog: Alzheimer's Disease Assessment Scale – cognitive subscale; BDNF: brain-derived neurotrophic factor; MCI: mild cognitive impairment; p-tau: Tau protein; CDR: Clinical Dementia Rating; GDNF: glial cell line-derived neurotrophic factor.

with the largest biological changes occurring within the fifth decade of life. During this age threshold about 40% of individuals at high risk for AD (e.g. apoE4 carriers) have senile plaques, despite the absence of clinical signs of dementia (Schrauzer and De Vroey, 1994). Thus, true biological prevention may need to begin in individuals before even the earliest clinical phase of dementia.

The potential benefit of trace lithium for dementia can be connected to the existence of basic science evidence on lithium's neuroprotective effects. Both animal and human studies show that lithium has a range of potent neuroprotective and neuroplastic effects (Bearden et al., 2007; Chen et al., 2000; Gould and Manji, 2005; Manji et al., 1999; Moore et al., 2000; Rowe and Chuang, 2004). In animal studies, when lithium has been compared at lower versus higher concentrations, neuronal viability seems to be enhanced with any concentration of lithium. Although standard lithium concentrations of 0.6–0.8 have the most benefit for enhancing neuronal viability, even 'low' levels of 0.2–0.4 have that benefit, compared to placebo (Hashimoto et al., 2002). Trace levels of lithium would be undetectable in standard blood tests, which generally do not measure lithium levels below 0.2. But, in some of the available animal research, even concentrations below 0.2 lead to enhanced neuronal viability (Hashimoto et al., 2002).

This basic neuroscience evidence, combined with the many clinical studies on the biological activity of trace lithium, would support clinical research on trace lithium prevention of dementia. If effective, such trace dosing would likely be much more tolerable than standard lithium levels, especially in aging populations, thus making this intervention more feasible from a public health standpoint. In summary, this review of the literature suggests that this promising avenue of intervention for perhaps the most devastating neuropsychiatric condition, dementia, should be explored more intensively.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Declaration of interest

In the past 12 months, Dr Ghaemi has received a research grant from Takeda Pharmaceuticals. Neither he nor his family hold equity positions in pharmaceutical corporations. Dr Sivan Mauer and Dr Derick Vergne declare no conflicts of interest.

References

Agabegi SS and Stern PJ (2008) Bias in research. *American Journal of Orthopedics* 37: 242–248.

Angst J, Gamma A, Gerber-Werder R, et al. (2007) Does long-term medication with lithium, clozapine or antidepressants prevent or attenuate dementia in bipolar and depressed patients? *International Journal of Psychiatry in Clinical Practice* 11: 2–8.

Australian Institute of Health and Welfare (2012) *Dementia in Australia*. Cat. no. AGE 70. Canberra: AIHW.

Bearden C, Thompson PM, Dalwani M, et al. (2007) Greater cortical gray matter density in lithium-treated patients with bipolar disorder. *Biological Psychiatry* 62: 7–16.

Blüml V, Regier MD, Hlavin G, et al. (2013) Lithium in the public water supply and suicide mortality in Texas. *Journal of Psychiatric Research* 47: 407–411.

Broberg K, Concha G, Engström K, et al. (2011) Lithium in drinking water and thyroid function. *Environmental Health Perspectives* 119: 827–830.

Chen G, Rajkowska G, Du F, et al. (2000) Enhancement of hippocampal neurogenesis by lithium. *Journal of Neurochemistry* 75: 1729–1734.

Da Silva J, Gonçalves-Pereira M, Xavier M, et al. (2013) Affective disorders and risk of developing dementia: Systematic review. *The British Journal of Psychiatry* 202: 177–186.

Dawson EB, Moore TD and McGanity WJ (1970) The mathematical relationship of drinking water lithium and rainfall to mental hospital admission. *Diseases of the Nervous System* 31: 811–820.

Dunn N, Holmes C and Mullee M (2005) Does lithium therapy protect against the onset of dementia? *Alzheimer Disease and Associated Disorders* 19: 20–22.

Ely JW (1992) Confounding bias and effect modification in epidemiologic research. *Family Medicine* 24: 222–225.

Forlenza OV, de Paula VJ, Machado-Vieira R, et al. (2012) Does lithium prevent Alzheimer's disease? *Drugs & Aging* 29: 335–342.

Forlenza OV, Diniz BS, Radanovic M, et al. (2011) Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: Randomised controlled trial. *The British Journal of Psychiatry* 198: 351–356.

Ghaemi SN (2009) *A Clinician's Guide to Statistics and Epidemiology in Mental Health: Measuring Truth and Uncertainty*. New York: Cambridge University Press.

Gould TD and Manji HK (2005) Glycogen synthase kinase-3: A putative molecular target for lithium mimetic drugs. *Neuropsychopharmacology* 30: 1223–1237.

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

Hashimoto R, Hough C, Nakazawa T, et al. (2002) Lithium protection against glutamate excitotoxicity in rat cerebral cortical neurons: Involvement of NMDA receptor inhibition possibly by decreasing NR2B tyrosine phosphorylation. *Jounal of Neurochemistry* 80: 589–597.

Helbich M, Leitner M and Kapusta ND (2012) Geospatial examination of lithium in drinking water and suicide mortality. *International Journal of Health Geographics* 11: 1–19.

Kabacs N, Memon A, Obinwa T, et al. (2011) Lithium in drinking water and suicide rates across the East of England. *The British Journal of Psychiatry* 198: 406–407.

Kapusta ND, Mossaheb N, Etzersdorfer E, et al. (2011) Lithium in drinking water and suicide mortality. *The British Journal of Psychiatry* 198: 346–350.

Kessing LV, Forman JL and Andersen PK (2010) Does lithium protect against dementia? *Bipolar Disorders* 12: 87–94.

Kessing LV, Søndergård L, Forman JL, et al. (2008) Lithium treatment and risk of dementia. *Archives of General Psychiatry* 65: 1331–1335.

Leyhe T, Eschweiler GW, Stransky E, et al. (2009) Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's disease. *Journal of Alzheimer's Disease* 16: 649–656.

Lobo A, Launer LJ, Fratiglioni L, et al. (2000) Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 54 (11 Suppl 5): S4–S9.

Macdonald A, Briggs K, Poppe M, et al. (2008) A feasibility and tolerability study of lithium in Alzheimer's disease. *International Journal of Geriatric Psychiatry* 23: 704–711.

Manji H, Moore G and Chen G (1999) Lithium at 50: Have the neuroprotective effects of this unique cation been overlooked? *Biological Psychiatry* 46: 929–940.

Moher D, Liberati A, Tetzlaff J, et al. (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine* 6: e1000097.

Moore G, Bebchuk J and Hasanat K (2000) Lithium increases *N*-acetylaspartate in the human brain: In vivo evidence in support of bcl-2's neurotrophic effects? *Biological Psychiatry* 48: 1–8.

Nunes MA, Viel TA and Buck HS (2013) Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. *Current Alzheimer Research* 10: 104–107.

Nunes P, Forlenza O and Gattaz W (2007) Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *The British Journal of Psychiatry* 190: 359–360.

Ohgami H, Terao T, Shiotsuki I, et al. (2009) Lithium levels in drinking water and risk of suicide. *The British Journal of Psychiatry* 194: 464–465; discussion 446.

Oliver S, Comstock G and Helsing K (1976) Mood and lithium in drinking water. *Archives of Environmental Health* 31: 92–95.

Rowe M and Chuang D (2004) Lithium neuroprotection: Molecular mechanisms and clinical implications. *Expert Reviews in Molecular Medicine* 6: 1–18.

Sarkar S and Rubinsztein DC (2006) Inositol and IP3 levels regulate autophagy: Biology and therapeutic speculations. *Autophagy* 2: 132–134.

Sarkar S, Floto RA, Berger Z, et al. (2005) Lithium induces autophagy by inhibiting inositol monophosphatase. *The Journal of Cell Biology* 170: 1101–1111.

Schrauzer GN and De Vroey E (1994) Effects of nutritional lithium supplementation on mood. A placebo-controlled study with former drug users. *Biological Trace Element Research* 40: 89–101.

Schrauzer GN and Shrestha KP (1990) Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. *Biological Trace Element Research* 25: 105–113.

Straten G, Saur R, Laske C, et al. (2011) Influence of lithium treatment on GDNF serum and CSF concentrations in patients with early Alzheimer's disease. *Current Alzheimer Research* 8: 853–859.

Tariot PN and Aisen PS (2009) Can lithium or valproate untie tangles in Alzheimer's disease? *Journal of Clinical Psychiatry* 70: 219–221.

Terao T, Nakano H, Inoue Y, et al. (2006) Lithium and dementia: A preliminary study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 30: 1125–1128.

Voors A (1970) Lithium in the drinking water and atherosclerotic heart death: Epidemiologic argument for protective effect. *American Journal of Epidemiology* 92: 164–171.

Voors A (1972) Drinking-water lithium and mental hospital admission in North Carolina. *North Carolina Medical Journal* 33: 597–602.

World Health Organization (2012) *Dementia: A Public Health Priority*. Geneva: World Health Organization.

Zarse K, Terao T, Tian J, et al. (2011) Low-dose lithium uptake promotes longevity in humans and metazoans. *European Journal of Nutrition* 50: 387–389.