

Editorial

# Lithium in Drinking Water for Dementia and Suicide

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**Received:** May 23, 2014; **Accepted:** June 11, 2014;

**Published:** June 14, 2014

Bipolar disorder has been reported to be associated with increased risk of dementia [1,2] and the risk may increase with every new affective episodes [3] while lithium, which is the first-line agent for bipolar disorder, may reduce the risk of dementia because long-term lithium treatment significantly reduces tau phosphorylation and amyloid  $\beta$  production, increases synaptic plasticity and facilitates long-term potentiation and cell firing, most of which are due to GSK-3 inhibition [4]. Epidemiological studies revealed that continued lithium treatment was associated with reduction of the rate of dementia to the same level as that for general population [5] and the effects were not found in anticonvulsants, antidepressants, or antipsychotics [6], suggesting a specific effect of lithium. In a clinical setting, 35 patients who were 60 years or older without initial diagnosis of dementia and had previously received lithium treatment and/or were currently prescribed lithium had significantly better Mini-mental State Examination (MMSE) scores than 20 control patients [7]. Moreover, Alzheimer's disease was diagnosed in 3 of 66 (5%) elderly euthymic patients with bipolar disorder who were on chronic lithium treatment and in 16 of 48 (33%) similar patients without recent lithium treatment [8], suggesting lithium effects on dementia. Although another study showed that patients who received lithium had a higher risk of dementia compared with those who did not [9], most of these findings suggest both possibilities that lithium may directly prevent dementia via its inhibition of GSK-3 and that lithium may indirectly prevent dementia via its prophylactic effects on mood episodes [10].

As shown in Table 1, 3 placebo-controlled studies have been performed to investigate lithium effects on dementia or mild cognitive impairment. Two studies showed lithium effects on dementia [11] and

mild cognitive impairment [12] whereas another study failed to show such effects [13]. It seems likely that lithium dose is not important because the successful 2 studies used completely different doses; routine doses (150-600 mg/day titrated to target serum levels of 0.25-0.5 mmol/l) [12] and microdose (300  $\mu$ g/day, serum levels were not measured) [11], respectively. Rather, administration period may be important because successful 2 studies administered lithium for 15 months [11] and 12 months [12], respectively whereas unsuccessful study gave lithium for only 10 weeks [13]. Therefore, further studies may be required to administer lithium for 12 months or longer to detect lithium effects on dementia or mild cognitive impairment. If administrative period is 12 months or longer, lithium doses can be much lower than usual because 300  $\mu$ g/day of lithium brought about the effects [11]. This possibility may evoke an interesting idea that lithium in drinking water can prevent dementia.

In addition to lithium effects on dementia, meta-analyses [14-16] have shown anti-suicidal effects of lithium in people with mood disorders, namely major depression and bipolar disorder, but these reviews have examined only randomized controlled trials that primarily compare lithium with placebo or other drugs in long-term prophylactic treatment of mood episodes (i.e., not anti-suicidal effects) which were maintained at so-called therapeutic levels. To date, there is only one study [17] that has directly compared anti-suicidal effects (but not prophylactic effects). In this 2.5-year double-blind randomized controlled trial, patients with bipolar disorder and past suicide attempts were randomly assigned to treatment with lithium or valproate conditions but no significant difference between the two treatments was found either in time to suicide attempt or number of suicide events, failing to show anti-suicidal effects of lithium.

Interestingly, there is growing evidence from epidemiological studies that lithium in drinking water may protect against suicide. An inverse association between lithium levels in drinking water and suicide rates was first reported in the USA for 27 Texas counties [18]. In Japan, an inverse association was shown between lithium levels in drinking water and suicide rates for 18 municipalities of Oita prefecture [19] whereas another study found no association for 47 subdivisions in the East of England [20]. A nationwide Austrian study, however, found an inverse association between lithium levels in drinking water and suicide rates after adjustment of population

**Table 1:** Placebo-controlled trials investigating lithium effects on dementia or mild cognitive impairment.

Authors	Subjects and methods	Results
Nunes et al (2013) [11]	113 patients with Alzheimer's disease were randomised to receive lithium (300 $\mu$ g/day) (n=58) or placebo (n=55) in a 15-month, double-blind trial.	Lithium group showed no decreased performance in the mini-mental state examination test, in opposition to the lower scores observed for placebo group, with significant differences starting 3 months after the beginning of the treatment, and increasing progressively.
Forlenza et al (2011) [12]	45 participants with a mild cognitive impairment were randomised to receive lithium (0.25-0.5 mmol/l) (n=24) or placebo (n=21) in a 12-month, double-blind trial.	Lithium treatment was associated with a significant decrease in phosphorylated tau of cerebrospinal fluid and better performance on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) and in attention tasks.
Hampel et al (2009) [13]	71 patients with mild Alzheimer's disease were randomised to lithium treatment (0.5-0.8 mmol/l) (n=33) or placebo (n=38) in a 10-week, single-blind trial.	No treatment effect on glycogen synthase kinase-3 activity or phosphorylated tau of cerebrospinal fluid was observed. Lithium treatment did not lead to change in global cognitive performance as measured by the ADAS-Cog subscale or in depressive symptoms.

density, per capita income, proportion of Roman Catholics, as well as the availability of mental health service providers [21]. Recently, the Austrian group reconfirmed an inverse association between lithium levels in drinking water and suicide rates after adjustment of county-based population density, age, gender, race/ethnicity, median income per household, poverty and unemployment rates in Texas [22]. Very recently, 2 studies which were performed in Hirosaki prefecture of Japan [23] and in 34 prefectures of Greece [24] also reconfirmed the inverse association between lithium levels in drinking water and suicide rates.

Taking the above evidences together, further epidemiological studies are warranted to investigate the potential effects of environmental lithium in drinking water on dementia and suicide, both of which are very serious problems in the world.

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