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HIGH IMPACT REVIEW IN NEUROSCIENCE, NEUROLOGY OR PSYCHIATRY - REVIEW ARTICLE

Trace lithium and mental health

Nobuyoshi Ishii[1] · Takeshi Terao[1]

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Abstract
Lithium therapy is generally accepted as a first-line treatment for bipolar disorder, and it is also identified as one of the best augmenting options for treatment-resistant depression. Furthermore, lithium has been investigated in association with suicide, dementia and aggressiveness. In this review, we examined articles about the effects of very small amounts of lithium in treating suicide, dementia, bipolar disorder and temperament, to assess the present state of trace lithium's effect on mental state. The results indicate that trace lithium may be effective for suicide prevention but randomized, placebo-controlled trials are required to draw a definite conclusion. Indications for using trace lithium in treating such conditions as dementia, bipolar disorder and temperament are supported by very limited evidence and such effects are yet to be determined.

Keywords Lithium · Trace lithium · Suicide · Dementia · Bipolar disorder · Temperament

Introduction

Lithium, whose origin is *lithos* from Greek meaning "stone", is a soft, silvery white alkali metal and chemical element (symbol Li; atomic number 3). Lithium therapy is generally accepted as a first-line treatment for bipolar disorder, and is also indicated as one of the best augmenting options for treatment-resistant depression. Moreover, lithium has been investigated in association with suicide, dementia and aggressiveness. A network meta-analysis (Miura et al. 2014) concluded that in fact lithium seems to be the most reasonable candidate for a first-line treatment option for the long-term treatment of bipolar disorder. Another network meta-analysis (Zhou et al. 2015) showed that lithium, as well as quetiapine, aripiprazole, and thyroid hormones, was significantly more effective than placebo as an augmentation agent in treatment-resistant depression. An additional meta-analysis (Cipriani et al. 2013) demonstrated that lithium was significantly more effective than placebo in reducing the number of suicides and deaths from any cause in randomized controlled trials comparing lithium with placebo for long term treatment of mood disorders. Moreover, another meta-analysis (Matsunaga et al. 2015) indicated that lithium may have beneficial effects on cognitive performance in subjects with mild cognitive impairment and Alzheimer's dementia. Finally, a meta-analysis (Jones et al. 2011) showed that lithium was significantly better than placebo in reducing aggressive behavior. Taking into consideration these positive findings supporting the effects of lithium on various psychiatric conditions, lithium has consolidated its position as one of the most useful psychotropic drugs.

As a naturally occurring chemical element present in grains, vegetables, meat and drinking water, many people take small amounts of lithium every day. For example, grains and vegetables have 0.5–3.4 mg/kg of lithium, dairy products have 0.5 mg/kg of lithium and meat has 0.012 mg/kg (Schrauzer 2002). These amounts are very low in comparison to therapeutic lithium doses (400–1600 mg/day). Nonetheless, there is increasing evidence that these very small amounts of (trace) lithium have some effect on mental states such as suicide and dementia.

In this review, we examine several articles regarding the association of trace lithium with suicide, dementia, bipolar disorder and temperament to assess the present state of trace lithium's effect on mental state.

✉ Nobuyoshi Ishii
nobuy@oita-u.ac.jp

1 Department of Neuropsychiatry, Oita University Faculty of Medicine, Idaigaoka 1-1, Hasama-machi, Yufu, Oita 879-5593, Japan

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Trace lithium and suicide prevention

In 1990, for the first time, Schrauzer and Shrestha (1990) showed that suicide rates were 8.7 per 100,000 of population in (relatively) high lithium areas (70–160 µg/l), 14.8 in moderate lithium areas (13–60 µg/l) and 14.2 in low lithium areas (0–12 µg/l) of 27 Texas counties, roughly suggesting the inverse association between lithium levels in drinking water and suicide rates. Two decades later, Ohgami et al. (2009) reported that the lithium levels in the drinking water of 18 municipalities of Oita prefecture ranged from 0.7 to 59 µg/l, and that the standard mortality ratios (SMRs) of suicide across the 18 municipalities were significantly and negatively associated with log-transformed lithium levels ($\beta = -0.65$, $p < 0.004$) using weighting (WLS) for the number of inhabitants per municipality. By gender, the significant association was largely in males ($\beta = -0.61$, $p < 0.008$) and a non-significance was found in females ($\beta = -0.46$, $0.05 < p < 0.06$). This is, to our knowledge, the first report regarding the difference in gender responses to trace lithium, indicating that it may be inversely associated with male suicide but not female suicide.

In response to Ohgami et al's (2009) study, Kapusta et al. (2011) and Kabacs et al. (2011) reported conflicting results. Kapusta et al. (2011) showed that lithium levels in the drinking water of 99 Austrian districts ranged from 0 to 82.3 µg/l, and that there were significantly inverse associations for the overall SMRs ($\beta = -0.22$, $p = 0.029$), females ($\beta = -0.21$, $p = 0.037$) and a non-significance for males ($\beta = -0.18$, $p = 0.083$) using WLS for the number of inhabitants per district. Overall, these results are in line with Ohgami et al's (2009) findings but show that trace lithium may be inversely associated with female suicide but not male suicide. Conversely, Kabacs et al. (2011) showed that lithium levels in the drinking water across the 47 subdivisions of the East of England ranged from 0 to 21 µg/l, and that there was no association between lithium levels in drinking water and the suicide SMRs in the 47 subdivisions of the East of England ($r = -0.054$, $p = 0.715$ for males; $r = 0.042$, $p = 0.777$ for females; $r = -0.03$, $p = 0.838$ for both genders), although they did not use WLS adjustment for the number of inhabitants per district.

Thereafter, similar papers on this subject have continued to be published. Blüml et al. (2013), a member of the Kapsuta group, investigated Texas again and reported that the lithium levels in drinking water of 226 Texas counties ranged from 2.8 to 219 µg/l, and that using Poisson regression models, lithium levels in the public water supply were significantly and inversely associated with suicide rates. Giotakos et al. (2013) reported that lithium levels in the drinking water of 34 prefectures of Greece ranged from 0.1 to 121 µg/l, and that the numbers of suicides per 100,000 of population across the 34 prefectures were significantly and inversely associated with lithium levels as a whole, though the data were not analyzed by gender. Sugawara et al. (2013) showed that lithium levels in the drinking water of 40 municipalities in Aomori prefecture ranged from 0 to 12.9 µg/l, and that the SMRs for suicide across the 40 municipalities were significantly and inversely associated with lithium levels in females ($\beta = -0.35$, $p < 0.05$) but not with lithium levels in males ($\beta = 0.14$, $p = 0.408$) using WLS.

Ishii et al. (2015) expanded the area of interest from Oita prefecture (Ohgami et al. 2009) to Kyushu island consisting of 8 prefectures including Oita prefecture, and reported that lithium levels in the drinking water of 274 municipalities of Kyushu island ranged from 0 to 130 µg/l, and that there were significantly inverse associations for the overall SMRs ($\beta = -0.175$, $p = 0.031$) and for males ($\beta = -0.228$, $p = 0.005$), but not for females ($\beta = 0.004$, $p = 0.957$) using WLS. Pompili et al. (2015) showed that lithium levels in the drinking water of 145 sites in Italy ranged from 0.11 to 60.8 µg/l, and that there were significantly inverse associations for the overall SMRs ($\beta = -0.231$, $p = 0.005$) and for females ($\beta = -0.342$, $p < 0.001$), but not for males ($\beta = -0.139$, $p = 0.095$) using WLS in 1980–1989. They also reported that there was a significantly inverse association for females ($\beta = -0.187$, $p = 0.024$), but not for the overall SMRs ($\beta = -0.055$, $p = 0.511$) or for males ($\beta = 0.009$, $p = 0.918$) using WLS in 1990–1999, and that there was a significantly inverse association for females ($\beta = -0.170$, $p = 0.041$), but not for the overall SMRs ($\beta = -0.029$, $p = 0.725$) or for males ($\beta = 0.036$, $p = 0.670$) using WLS in 2000–2011. Their findings are conflicting, but favor results for females. Shiotsuki et al. (2016) merged 35 cities of Hokkaido island and 118 cities of Kyushu island and showed that lithium levels in the drinking water of the 153 cities ranged from 0.1 to 43 µg/l, and that there was a significantly inverse association for males ($\beta = -0.225$, $p = 0.005$), but not for overall SMRs ($\beta = -0.153$, $p = 0.059$) or females ($\beta = 0.012$, $p = 0.883$) using WLS.

Recently, Liaugaudaite et al. (2017) showed that lithium levels in the drinking water of nine cities of Lithuania ranged from 0.48 to 35.53 µg/l, and that there was a significantly inverse association for the overall SMRs ($\beta = -0.911$, $p = 0.001$) and for males ($\beta = -0.965$, $p < 0.001$), but not for females ($\beta = 0.150$, $p = 0.700$) with log-transformed lithium levels using WLS. Knudsen et al. (2017) reported that lithium levels in the drinking water of 275 municipalities in Denmark ranged from 0.6 to 30.7 µg/l, and surprisingly that there was an increasing suicide rate by increasing lithium levels. These two studies had similar locations and lithium ranges but opposite findings.

Trace lithium and dementia prevention

Epidemiological studies revealed that continued lithium treatment was associated with reduction in the rate of dementia to the same level as that for the general population (Kessing et al. 2008) and that these effects were not found in anticonvulsants, antidepressants, or antipsychotics (Kessing et al. 2010), suggesting a specific effect of lithium for dementia. In a clinical setting, 35 patients who were 60 years or older and without an initial diagnosis of dementia and who had previously received lithium treatment and/or were currently prescribed lithium, had significantly better Mini-Mental State Examination (MMSE) scores than 20 control patients who were lithium therapy naïve (Terao et al. 2006). 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 (Nunes et al. 2007), suggesting lithium effects for dementia prevention. Hampel et al. (2009) randomized 71 patients with mild Alzheimer's disease to lithium treatment (0.5–0.8 mmol/l) ($n = 33$) or placebo ($n = 38$) in a 10-week, single-blind trial, and reported that no treatment effect on glycogen synthase kinase-3 activity or phosphorylated tau of cerebrospinal fluid was observed, and that lithium treatment did not lead to any change in global cognitive performance as measured by the ADAS-Cog subscale, or in depressive symptoms. On the other hand, Forlenza et al. (2011) randomized 45 participants with a mild cognitive impairment to receive lithium (0.25–0.5 mmol/l) ($n = 24$) or placebo ($n = 21$) in a 12-month, double-blind trial, and showed that 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.

As for the effects of trace lithium on dementia, Nunes et al. (2013) randomized 113 patients with Alzheimer's disease to receive lithium (300 μg/day) ($n = 58$) or placebo ($n = 55$) in a 15-month, double-blind trial. They reported that the lithium group showed no decreased performance in MMSE scores, in opposition to the lower scores observed for the placebo group, with significant differences starting 3 months after the beginning of the treatment, and increasing progressively. This suggests the efficacy of a micro-dose lithium treatment in preventing cognitive loss, reinforcing its therapeutic potential to treat AD using very low doses. Kessing et al. (2017a, b) examined Danish population-based registers and drinking water samples from 151 waterworks supplying approximately 42% of the Danish population, and showed that lithium levels in the drinking water ranged from 0.6 to 30.7 μg/l, and that lithium exposure was statistically significantly different between patients with a diagnosis of dementia (median 11.5 μg/l, interquartile range 6.5–14.9 μg/l) and controls who were selected from a random sample (10 controls from the age- and sex-matched to each patient with dementia) that consisted of 1,500,000 persons in the Danish population that was registered on January 1, 1995, and alive and did not have dementia at the index date of the patient (median 12.2 μg/l, interquartile range 7.3–16.0 μg/l; $p < 0.001$).

Trace lithium and bipolar disorder

Kessing et al. (2017a, b) showed that the median of the average lithium exposure did not differ between cases with a diagnosis of mania/bipolar disorder (12.7 μg/l; interquartile range (IQR) 7.9–15.5 μg/l) and ten age- and gender-matched controls from the Danish population ($N = 140{,}311$) (12.5 μg/l, IQR 7.6–15.7 μg/l, $p = 0.2$) and that the incidence rate ratio of mania/bipolar disorder did not decrease with higher long-term lithium exposure overall, or within age categories (0–40, 41–60 and 61–100 years of age). They suggested that higher long-term lithium exposure from drinking water was not associated with a lower incidence of bipolar disorder.

Trace lithium and temperament

Matsuzaki et al. (2017) performed a stepwise multiple regression analysis and revealed that hyperthymic temperament scores of non-clinical residents in Sapporo, Obihiro, Takaoka, Koshigaya, and Oita cities were significantly and positively associated with lithium levels in drinking water (0.1–43.0 μg/l). Using the same subjects, Ishii et al. (2017) performed a multiple regression analysis via the forced entry method and revealed that depressive temperament scores were significantly and negatively associated with lithium levels in drinking water. Although the results seem to be different depending on the method of the multiple regression analysis, both a positive association with hyperthymic temperament scores and a negative association with depressive temperament scores consistently show the effects of trace lithium on upregulation in mood and thinking associated with temperament.

Discussion

As shown in Table 1, two studies (Kabacs et al. 2011; Knudsen et al. 2017) had the narrower ranges of lithium levels in drinking water. Apart from Sugawara et al.'s study (2013), it seems likely that this narrowness of the

Table 1 The relationship between lithium levels in drinking water, suicide rate, and gender difference

Authors	Region	Range of lithium levels in drinking water (μg/l)	Crude association with suicide rate	Gender difference
Schrauzer and Shrestha (1990)	Texas in USA	0–12 (A), 13–60 (B), 70–160 (C)	C < A, B	N/A
Ohgami et al. (2009)	Oita in Japan	0.7–59	Significantly inverse association	Males but not females
Kapusta et al. (2011)	Austria	0–82.3	Significantly inverse association	Females but not males
Kabacs et al. (2011)	East England	0–21	No association	
Blüml et al. (2013)	Texas in USA	2.8–219	Significantly inverse association	N/A
Giotakos et al. (2013)	Greece	0.1–121	Significantly inverse association	N/A
Sugawara et al. (2013)	Aomori in Japan	0–12.9	Significantly inverse association	Females but not males
Ishii et al. (2015)	Kyushu in Japan	0–130	Significantly inverse association	Males but not females
Pompili et al. (2015)	Italy	0.11–60.8	Significantly inverse association	Females but not males
Shiotsuki et al. (2016)	Hokkaido and Kyushu in Japan	0.1–43	Significantly inverse association	Males but not females
Liaugaudaite et al. (2017)	Lithuania	0.48–35.53	Significantly inverse association	Males but not females
Knudsen et al. (2017)	Denmark	0.6–30.7	No association	

ranges precluded the authors from finding a significantly inverse association. Other studies had wider ranges and found an association, which seems to be closer to the truth. Therefore, at least in regards to suicide, relatively higher lithium levels (though much lower levels than therapeutic ones) may be associated with lower suicide rates. With regard to gender differences, Table 1 shows that four studies found a significantly inverse association with lithium levels in drinking water only in males (male response to trace lithium) whereas three studies found an association only in females (female response to trace lithium). Therefore, the gender difference effect is yet to be determined.

Nonetheless, Kanehisa et al. (2017) investigated the lithium levels of 199 lithium therapy-naïve patients including 31 patients with suicide attempts, 21 patients with self-harm, and 147 control patients. There was a significant difference ($p = 0.043$) between the three groups, whereby patients with suicide attempts had significantly lower lithium levels than control patients ($p = 0.012$) in males but not females. This is consistent with male responses to trace lithium. Sher (2015) suggested one possibility that higher levels of lithium in drinking water decreases suicide rates among men by reducing impulsivity and aggression, and another possibility that lithium reduces suicidality in men by decreasing testosterone levels. Therefore, in our opinion, trace lithium may be effective for suicide prevention particularly in males as opposed to females. This should be investigated in randomized, placebo-controlled trials in the future.

As for dementia, bipolar disorder, and temperament, at the moment a very limited number of studies have investigated the effects of trace lithium. Therefore, any conclusion cannot be established, though further studies are warranted.

In conclusion, trace lithium may be effective for suicide prevention but randomized, placebo-controlled trials are required to draw a definite conclusion. Other indications for using trace lithium in the treatment of such conditions as dementia, bipolar disorder, and temperament, have very limited supporting evidence and the effects are yet to be determined.

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