

# A Negative Association Between Lithium in Drinking Water and the Incidences of Homicides, in Greece

Orestis Giotakos · George Tsouvelas · Paul Nisianakis · Vera Giakalou ·  
Alexandros Lavdas · Charalampos Tsiamitas · Katsaris Panagiotis ·  
Vasilis Kontaxakis

Received: 3 September 2014 / Accepted: 11 December 2014  
© Springer Science+Business Media New York 2015

**Abstract** The purpose of the present study was to evaluate the association between lithium levels in the public water supply and incidences of homicide in Greece. A total of 149 samples of drinking water were collected from 34 out of 52 prefectures, and data for homicides were taken from *National Statistic Service of Greece* (Hellenic Statistical Authority - EL.STAT). The average lithium level was 11.10 µg/l (SD=21.16). The results indicate that there is a tendency for lower mean number of homicides in the prefectures with high levels of lithium in drinking water ( $R^2=0.054$ ,  $\beta=-0.38$ ,  $p=.004$ ). Considering the results of our previous study, which showed an inverse association between the lithium levels in drinking water and the incidence of suicide, homicide, rape, and drug abuse, we suggest that natural lithium level intake may influence impulsiveness, a factor that mediate to the manifestation of both suicidality and aggressiveness.

**Keywords** Trace element · Lithium · Drinking water · Homicide · Impulsivity · Mood disorders · Molecular pathway · Neurotoxins

## Introduction

Lithium is widely used in pharmacological doses for the treatment of bipolar disorder and helps in the prevention of suicidal behavior as well as the reduction of impulsive aggression in patients with mood disorders [1–4]. An ecological study of Schrauzer and Shrestha [5] has shown an inverse association between the lithium levels in drinking water and the incidence rates of suicide, homicide, and rape. The purpose of the present study was to evaluate the association between lithium levels in the public water supply and homicide rates in Greece and

---

O. Giotakos  
Psychiatric Department, 414 Military Hospital of Athens, Athens,  
Greece  
e-mail: info@obrela.gr

G. Tsouvelas  
Department of Psychology, National and Kapodistrian University of  
Athens, Athens, Greece  
e-mail: tsouvelasgiorgos@gmail.com

P. Nisianakis  
Center of Biological Research of Armed Forces, Athens, Greece  
e-mail: p.nisianakis@ergastiria.gr

V. Giakalou (✉)  
Medical Department, Molecular Neuroscientist, Specifar-Actavis  
Pharmaceuticals, Athens, Greece  
e-mail: v.giakalou@specifar.gr

A. Lavdas  
EURAC Research, Bozen, Italy  
e-mail: Alexandros.Lavdas@eurac.edu

C. Tsiamitas  
Kapodistrian University of Athens, Athens, Greece

K. Panagiotis  
Pharmacovigilance Department - PLRP, Specifar-Actavis  
Pharmaceuticals, Athens, Greece  
e-mail: p.katsaris@specifar.gr

V. Kontaxakis  
Department of Psychiatry, National and Kapodistrian University of  
Athens, Athens, Greece

present it in the context of our current knowledge on the effects of lithium intake.

## Method

A total of 149 samples of drinking water were collected during 2012 from 34 out of the 51 prefectures of Greece. A team of researchers undertook the collection of drinking water from both rural and urban areas of these prefectures. Lithium levels were analyzed by inductively coupled plasma mass spectrometry (ICP-MS) [6]. Data for homicides, from 34 prefectures of Greece, were taken from the *National Statistic Service of Greece* (Hellenic Statistical Authority - EL.STAT) for the period of 2007–2011. The index of homicides was the mean of homicides per prefecture in Greece. Analyses were performed with the IBM Statistical Package for Social Sciences 20.

## Results

The average lithium level, as evidenced by the raw values for the 34 prefectures of Greece, was 11.10  $\mu\text{g/l}$  (SD=21.16). Four regressions (linear, exponential, inverse, linear weighted for prefecture population) were performed between lithium levels in drinking water as independent variable and mean number of homicides for the period of 2007–2011 as dependent variable (see Table 1 and Fig. 1). Table 1 displays the correlation between the variables, the standardized regression coefficients ( $\beta$ ), the  $R$ ,  $R^2$  and the adjusted  $R^2$ .  $R$  for regression was significantly different from zero in the case of linear ( $F(1, 147)=8.338, p=.004$ ) and exponential regression ( $F(1,147)=6.327, p=.013$ ), and 95 % confidence limits were calculated. Linear regression interprets the largest proportion of variance explained relative to the exponential and inverse regression analyses. However, the coefficient  $\beta$  of inverse regression analysis is shown to be higher than all other regressions. A negative correlation was observed between lithium levels in drinking water and homicides even after controlling for

population per prefecture.  $R$  for regression, after weighted for prefecture population, was not significantly different from zero ( $F(1,147)=2.399, p=.124$ ), but nevertheless, still a negative tendency was observed between lithium levels and homicide (see Table 1).

## Discussion

A systematic tendency was observed in Greece for the negative association between homicides and lithium levels. When a linear regression analysis weighted by population was conducted, the results did not find a robust relationship between these two variables. After controlling for population, a negative association between our variables was also observed, but the proportion of the variance explained fell from 4.7 to 0.9 %.

Lithium, as a natural trace element, is washed out by rain from rocks and from the soil, dissolving in ground water and reaching the food chain via drinking water. In some regions, its concentrations may reach up to 5.2 mg/l, corresponding to a natural daily intake of lithium of up to 10 mg/l [7]. The biochemical mechanisms of action of lithium are considered to be connected with the functions of several enzymes, hormones, and vitamins, as well as with growth and transforming factors [8].

In animals, lithium upregulates neurotrophins, including brain-derived neurotrophic factor (BDNF), nerve growth factor, neurotrophin-3 (NT3), as well as receptors to these growth factors in the brain. Lithium has been reported to be beneficial in animal models of brain injury, stroke, amyotrophic lateral sclerosis, spinal cord injury, and Alzheimer's, Huntington's, and Parkinson's diseases. It stimulates proliferation of stem cells, including bone marrow and neural stem cells in the subventricular zone, striatum, and forebrain. Lithium also remarkably protects neurons against glutamate, seizures, and apoptosis due to a wide variety of neurotoxins [9].

In humans, lithium treatment has been associated with humoral and structural evidence of neuroprotection, such as increased expression of antiapoptotic genes, inhibition of cellular oxidative stress, synthesis of brain-derived neurotrophic factor

**Table 1** Four regression analyses of levels of lithium in drinking water on the mean number of homicides for years 2007–2009 per prefecture

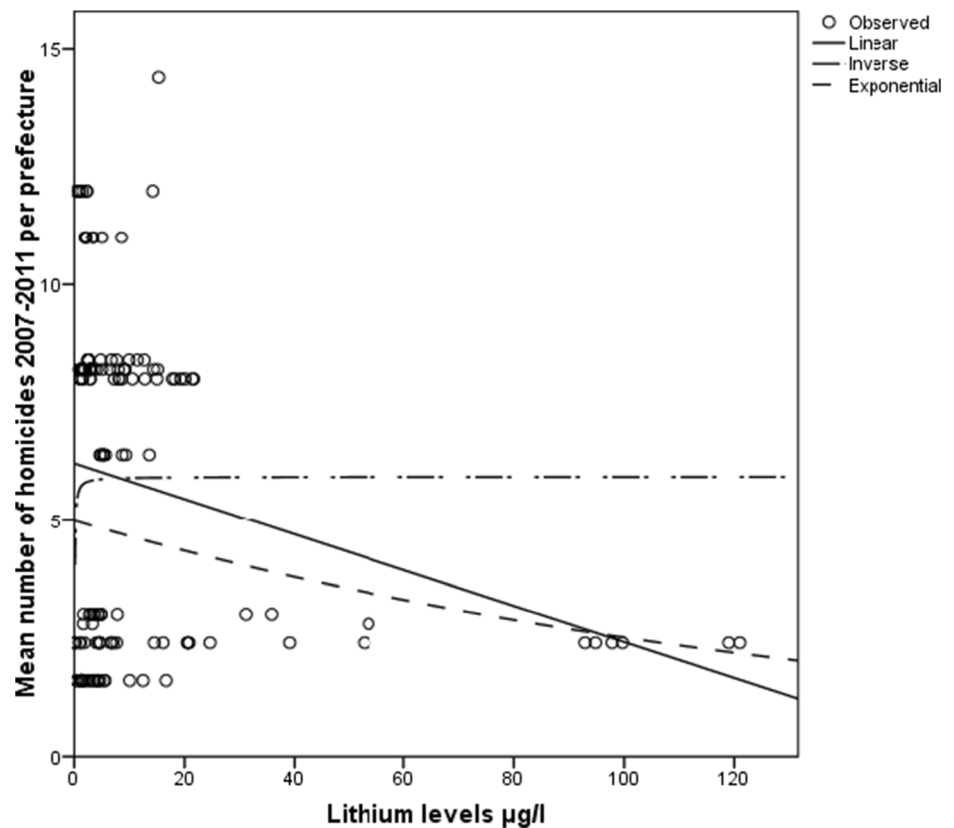
	Predictor	Correlation homicides	$\beta$	$R$	$R^2$	Adjusted $R^2$
Linear	Lithium in drinking water	-.232**	-.038**	.232	.054	.047
Inverse	Lithium in drinking water	-.102	-.249	.102	.010	.004
Exponential	Lithium in drinking water	-.041*	-.007*	.203	.041	.035
Linear weighted by population per prefecture	Lithium in drinking water	-.200 <sup>a</sup>	-.127	.127	.016	.009

Dependent variable: mean prefecture number of homicides (period 2007–2011), (method enter)

\* $p < .05$ ; \*\* $p < .01$

<sup>a</sup> Partial correlation controlling for prefecture population

**Fig. 1** Scatterplot between the mean number of homicides for 2007–2011 per prefecture and lithium levels in microgram per liter



(BDNF), cortical thickening, increased grey matter density, and hippocampal enlargement. Such a wide range of intracellular responses may be secondary to two key effects, that is, the inhibition of glycogen synthase kinase-3 beta (GSK3 $\beta$ ) and inositol monophosphatase (IMP) by lithium [10]. Lithium acts through multiple pathways to inhibit GSK3 beta. This enzyme phosphorylates and inhibits nuclear factors that turn on cell growth and protection programs, including the nuclear factor of activated T cells (NFAT) and WNT/beta-catenin [9].

Lithium salts have a well-established role in the treatment of major affective disorders. Neuroimaging studies in humans have demonstrated that chronic use is associated with cortical thickening, higher volume of the hippocampus and amygdala, and neuronal viability in bipolar patients on lithium treatment. Chronic lithium intake is associated with a reduced risk of Alzheimer's disease in subjects with bipolar disorder, while chronic lithium treatment at subtherapeutic doses can reduce cerebral spinal fluid phosphorylated tau protein [11]. Therefore, lithium treatment may yield disease-modifying effects in AD, both by the specific modification of its pathophysiology via inhibition of overactive GSK3 $\beta$  and by the unspecific provision of neurotrophic and neuroprotective support [10]. Additionally, recent *in vivo* and *in vitro* studies indicate that lithium is able to ameliorate ethanol-induced neuroapoptosis. Lithium is an inhibitor of GSK3 which has recently been identified as a mediator of ethanol neurotoxicity [12].

There is increasing evidence from ecological studies that lithium levels in drinking water are inversely associated with suicide mortality [13–16], while some studies have shown that lithium is effective on the treatment of aggression and impulsivity, even as a low-dose supplementation [4, 17, 18]. The present study showed an inverse association between the lithium levels in drinking water and the incidence of homicides. These results are in accordance with that of the abovementioned ecological study of Schrauzer and Shrestha [5], which showed an inverse association between the lithium levels in drinking water and the incidence rates of suicide, homicide, and rape. The present study is an extension of a previous study that showed an inverse association between the lithium levels in drinking water and the incidence of suicide in Greece [16]. We suggest that intake of natural lithium levels may influence impulsiveness levels, which is a factor that mediate the manifestation of both suicidality and aggressiveness. Evidence from both basic and clinical researchers supports that lithium may decrease impulsivity. Based on findings that lithium inhibits both GSK3 isoenzymes, Jiménez et al. [19] analyzed the potential impact of genetic variants located at the GSK3 $\alpha$  and  $\beta$  genes on impulsivity levels. They found that genetic variability at GSK3 $\beta$  gene was associated with increased impulsivity in bipolar patients. Furthermore, a recent meta-analysis

[20] in 48 randomized control trials comparing lithium with placebo or active drugs in a long-term treatment for mood disorders found that lithium is an effective treatment for reducing the risk of suicide in people with mood disorders, and the authors suggested that impulsivity might be a mechanism mediating the antisuicidal effect. Finally, the present results pose the question of whether the prospect of adding lithium to drinking water is realistic, weighing the benefits and potential risks [21–24].

**Acknowledgments** The authors would like to acknowledge the following:



PHARMACEUTICALS, for the collection of water samples.

- *Center of Biological Research of Armed Forces, 414 Hospital of Athens*, for the analysis of water samples.
- *National Statistic Service of Greece* (Hellenic Statistical Authority - EL.STAT), for its contribution in providing the database regarding homicides in Greece during 2007–2011 at the prefecture level.
- *Tsouvelas George* who is supported by a grant from “Alexander S. Onassis” Public Benefit Foundation for doctoral studies.
- *Nissiannakis Paul*, Chemist, MSc, Center of Biological Research of Armed Forces, 414 Military Hospital of Athens.
- *Giakalou Vera-Varvara*, Molecular Neuroscientist, as the corresponding author for bibliography research (Medline, PubMed literature search) regarding the investigation on the role of lithium and for her contribution of rewriting the manuscript according to the Editor’s guidance and instructions according to BTER for submission criteria.
- *Lavdas, Alexandros A*, MSc, PhD, Neuroscientist, Senior Researcher at EURAC, Italy, for bibliography research and his recommendations.

**Conflict of Interest** The authors do not have financial or nonfinancial competing interests in publishing this article.

## References

1. Cade JFJ (1949) Lithium salts in the treatment of psychotic excitement. *Med J Aust* 2:349–352
2. Sheard MH (1975) Lithium in the treatment of aggression. *J Nerv Ment Dis* 160:108–118
3. Rapoport SI, Basselin M, Kim HW, Rao JS (2009) Bipolar disorder and mechanisms of action of mood stabilizers. *Brain Res Rev* 61(2): 185–209
4. Fazel S, Zetterqvist J, Larsson H, Långström N, Lichtenstein P (2014) Antipsychotics, mood stabilisers, and risk of violent crime. *Lancet* 384(9949):1206–1214
5. Schrauzer GN, Shrestha KP (1990) Lithium in drinking water and the incidences of crimes, suicides and arrests related to drug addictions. *Biol Trace Elem Res* 25:105–113
6. Stefansson A, Gunnarsson I, Giroud N (2007) New methods for the direct determination of dissolved inorganic, organic and total carbon in natural waters by reagent-free ion chromatography and inductively coupled plasma atomic emission spectrometry. *Anal Chim Acta* 582: 69–74
7. Helbich M, Leitner M, Kapusta N (2012) Geospatial examination of lithium in drinking water and suicide mortality. *Int J Health Geogr* 11(19):1–8
8. Schrauzer GN (2002) Lithium: occurrence, dietary intakes, nutritional essentiality. *J Am Coll Nutr* 21:14–21
9. Young W (2009) Review of lithium effects on brain and blood. *Cell Transplant* 18(9):951–975
10. Forlenza OV, de Paula VJ, Machado-Vieira R, Diniz BS, Gattaz WF (2012) Does lithium prevent Alzheimer’s disease? *Drugs Aging* 29(5):335–342
11. Diniz BS, Machado-Vieira R, Forlenza OV (2013) Lithium and neuroprotection: translational evidence and implications for the treatment of neuropsychiatric disorders. *Neuropsychiatr Dis Treat* 9:493–500
12. Luo J (2010) Lithium-mediated protection against ethanol neurotoxicity. *Front Neurosci* 28:4–41
13. Ohgami H, Terao T, Shiotsuki I, Ishii N, Iwata N (2009) Lithium levels in drinking water and risk of suicide. *Br J Psychiatry* 194:464–465
14. Kabacs N, Memon A, Obinwa T, Stochl J, Perez J (2011) Lithium in drinking water and suicide rates across the East of England. *Br J Psychiatry* 198:406–407
15. Kapusta ND, Mossaheb N, Etzersdorfer E, Hlavín G, Thau K, Willeit M, Prashak-Rieder N, Sonneck G, Leithner-Dziubas K (2011) Lithium in drinking water is inversely associated with suicide mortality. *Br J Psychiatry* 198:346–350
16. Giotakos O, Nisianakis P, Tsouvelas G, Giakalou V (2013) Lithium in the public water supply and suicide mortality in Greece. *Biol Trace Elem Res* 156:376–379
17. Schrauzer GN, de Vroey E (1994) Effects of nutritional lithium supplementation on mood: a placebo-controlled study with former drug users. *Biol Trace Elem Res* 40(1):89–101
18. Fierro AA (1988) Natural low dose lithium supplementation in manic-depressive disease. *Nutr Perspectives* 10–11
19. Jiménez E, Arias B, Mitjans M, Goikolea JM, Roda E, Ruiz V, Pérez A, Sáiz PA, Paz García-Portilla M, Burón P, Bobes J, Vieta E, Benabarre A (2014) Association between GSK3 $\beta$  gene and increased impulsivity in bipolar disorder. *Eur Neuropsychopharmacol* 24(4): 510–8. doi:10.1016/j.euroneuro.2014.01.005
20. Cipriani A, Hawton K, Stockton S, Geddes JR (2013) Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 27(346):f3646
21. Klemfuss H, Schrauzer GN (1995) Effects of nutritional lithium deficiency on behavior in rats. *Biol Trace Elem Res* 48(2):131–139
22. Schrauzer GN, Shrestha KP, Flores-Arce MF (1992) Lithium in scalp hair of adults, students, and violent criminals. *Biol Trace Elem Res* 34(2):161–176
23. Müller-Oerlinghausen B, Felber W, Berghöfer A, Lauterbach E, Ahrens B (2005) The impact of lithium long-term medication on suicidal behavior and mortality of bipolar patients. *Arch Suicide Res* 9:307–319
24. Zarse K, Terao T, Tian J, Iwata N, Ishii N, Ristow M (2011) Low-dose lithium uptake promotes longevity in humans and metazoans. *Eur J Nutr* 50(5):387–389