Lithium in drinking water and suicide prevention: a review of the evidence

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Suicide is a serious public health problem worldwide, and many nations are committed to developing prevention programmes to reduce the incidence of suicide. To date, several strategies have been proposed for suicide prevention, both at the population and at the individual level, some of which may be pharmacological. In particular, a substantial amount of data show that lithium significantly reduces mortality in patients with mood disorders. Initiating from this evidence, some recent studies have investigated whether a relationship might exist between levels of lithium in drinking water and mortality rates for suicide in the general population. We have systematically reviewed all the articles published on this issue to date. The available literature indicates that higher lithium levels in drinking water may be associated with reduced risk of suicide in the general population. ***Int Clin Psychopharmacol*** **00:000–000**

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Introduction

Suicide is a serious public health problem worldwide. According to estimates from the WHO (2000), every year about one million people die by suicide in the world, although the incidence of suicides is not increasing (Hawton and van Heeringen, 2009); by 2020, the incidence is estimated at 1.5 million suicides and 10 million failed suicide attempts per year (WHO, 2000; Hawton and van Heeringen, 2009). Thus, the topic of suicide is receiving increasing attention, and many nations are committed to developing prevention programmes to reduce this ‘global epidemy’ (Hawton and van Heeringen, 2009; De Leo and Milner, 2010).

Suicide is considered a multifactorial event caused by a complex interaction between biological, genetic, psychological, social and environmental factors (Hawton and van Heeringen, 2009), but evaluation of the predictive value of risk factors is particularly difficult because of the many variables that are part of the history of each individual. However, several studies from developing and industrialized countries indicate a prevalence of mental disorders in about 90% of cases of suicide (Phillips, 2010). In particular, individuals with a mood disorder have a risk of suicide 10–20 times higher than the general population. The more parsimonious estimates of lifetime mortality for suicide in patients with a diagnosis of unipolar depression range from 2.2 to 4% (Bostwick and Pankratz, 2000; Pompili *et al.*, 2013), whereas 11% of patients with bipolar disorder committed suicide in a large 40-year follow-up (Angst *et al.*, 2002). Other psychiatric disorders in which suicide rates are higher than that in the general population include schizophrenia with a prevalence of suicide of about 5% (Hor and Taylor, 2010), borderline personality disorder with values around 5–10% (Mann, 2002; Oldham, 2006) and substance use disorders (Windfuhr and Kapur, 2011).

To date, several strategies have been proposed for suicide prevention, both at the population and at the individual level, some of which may be pharmacological. However, antidepressant use has not been consistently associated with a reduction of risk of suicide (Khan *et al.*, 2003; Fergusson *et al.*, 2005). In contrast, a substantial amount of data shows that lithium significantly reduces mortality by suicide with evidence of efficacy for both short-term and long-term treatment. The most recent quantitative review of the issue by Cipriani *et al.* (2013) analysed 32 randomized controlled trials on patients with a diagnosis of mood disorder (unipolar depression, bipolar disorder, and schizoaffective disorder) and compared efficacy data on a total of 1389 patients treated with lithium and 2069 individuals receiving placebo or other active comparators. The meta-analysis demonstrated an overall significant efficacy of lithium in preventing suicide with a highly significant reduction in rates of suicidality (odds ratio, 0.26; 95% confidence interval, 0.09–0.77). This confirms the findings of earlier reviews and meta-analyses (Tondo *et al.*, 2001; Cipriani *et al.*, 2005).

On the basis of this clinical evidence, a few studies have directly investigated whether a relationship exists between levels of lithium in drinking water and mortality rates for suicide in the general population. Given the great theoretical as well as practical value of this question,

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Table 1 Description of the studies and summary of the main findings

References	Period, region	Number of water samples collected (number of areas)	Mean lithium levels (or range)	Results
Giotakos *et al.* (2013)	2012, Greece	149 (34 prefectures)	11.10 µg/l (SD = 21.16)	Higher lithium levels in the public drinking water were associated with lower suicide rates
Sugawara *et al.* (2013)	2008–2010, Japan	NR (40 municipalities)	0.0 − 12.9 µg/l	Statistical trend towards significance was found for the relationship between lithium levels and the average SMR among females
Blüml *et al.* (2013)	1999–2007, Texas	3123 (226 counties)	< 2.8 − 219.0 µg/l	Higher lithium levels in the public drinking water were associated with lower suicide rates
Helbich *et al.* (2013)[a]	2005–2009, Austria	6460 (99 districts)	0.0113 mg/l (SD = 0.027) (i.e. 10.3 ± 27 µg/l)	Significant negative association of lithium and suicide moderated by altitude. Lithium is negatively associated with suicide rates in lower altitude regions but is positively correlated with suicide in high-altitude regions
Helbich *et al.* (2012)[b]	2005–2009, Austria	6460 (99 districts)	0.0113 mg/l (SD = 0.027) (i.e. 10.3 ± 27 µg/l)	Higher lithium levels in the public drinking water were associated with lower suicide rates
Kabacs *et al.* (2011)	2006–2008, East of England	47 (six counties, 47 subdivisions)	< 1 − 21 µg/l	No association between lithium levels in drinking water and suicide rates
Kapusta *et al.* (2011)	2005–2009, Austria	6460 (99 districts)	0.0113 mg/l (SD = 0.027) (i.e. 10.3 ± 27 µg/l)	Higher lithium levels in the public drinking water were associated with lower suicide rates
Ohgami *et al.* (2009)	2002–2006, Japan, Oita Prefecture	NR (18 municipalities)	< 0.7 − 59 µg/l	Higher lithium levels in the public drinking water were associated with lower suicide rates
Schrauzer and Shrestha (1990)	1978–1987, Texas	NR (27 counties)	0 − 160 µg/l	Higher lithium levels in the public drinking water were associated with lower suicide rates (but only in those counties with lithium levels in the water ranging from 70 to 160 µg/l)

NR, not reported; SMR, standardized mortality ratio.
[a,b]Same original data sets as in Kapusta *et al.* (2011) but different statistical analyses.

we considered a review of the available literature on the issue worthwhile.

Method of literature search

We conducted a systematic computerized literature search through MEDLINE/PubMed (*http://www-ncbi-nlm-nih-gov.proxy.unibs.it/pubmed*) and EMBASE (*http://www.embase.com.proxy.unibs.it*) databases for all articles published in English, investigating the relationship between the level of lithium in drinking water and suicides rates in the general population. We used the following keywords to generate a list of potentially useful studies: ([lithium] AND [drinking water] OR [public water]) AND ([suicide] OR [mortality rates]). The search was performed until December 2013. All the reference lists within the selected studies were also reviewed to check for other references not found in the systematic search.

Results

The studies available to date on the relationship between the level of lithium in drinking water and suicides in the general population and the main results obtained are presented in Table 1.

The first study, conducted by Schrauzer and Shrestha (1990), examined the levels of lithium in drinking water in 27 different counties in Texas between 1978 and 1987. The counties were classified into the high (mean lithium content, 123 ± 25 µg/l; range, 70–160 µg/l), medium (mean lithium content, 35 ± 15 µg/l; range, 13–60 µg/l) and low (mean lithium content, 5 ± 4 µg/l; range, 0–12 µg/l) level groups according to the lithium content in the municipal water supplies. County suicide mortalities were taken from annual US vital statistics handbooks issued by the Department of Health and Human Services (1978 and 1987). The authors reported suicide rates per 100 000 population as follows: 8.7 in the (relatively) high lithium area, 14.8 in the moderate lithium area and 14.2 in the low lithium area. A statistically significant difference in the suicide rate in the population groups defined according to mean water lithium levels was detected ($P < 0.005$); rates of death by suicide over the period investigated were lower in counties with higher lithium levels.

These results were replicated in a study conducted by Ohgami *et al.* (2009) in Japan. The authors examined lithium levels in tap water in the 18 municipalities of Oita Prefecture (study population, 1 206 174) from 2002 to 2006. Lithium levels in the tap water suppliers of each municipality were measured using ion chromatography or mass spectroscopy. If the lithium levels of drinking water were measured at multiple water suppliers in the same municipality, the mean value was calculated. The lithium levels ranged from 0.7 to 59 µg/l. By taking differences in sex and age distribution of individual municipality populations into account, the standardized mortality ratio

(SMR) of suicide was calculated for each municipality. Because of greater differences in population size across the 18 municipalities, weighted least squares regression analysis adjusted for the size of each population was used to investigate the association between lithium levels in drinking water and SMRs. The study demonstrated an inverse correlation between levels of lithium in drinking water and mortality rates for suicide in this region of Japan ($\beta = -0.65$, $P < 0.004$). The association remained significant in male individuals ($\beta = -0.61$, $P < 0.008$), but only a marginal significance was found in female individuals ($\beta = -0.46$, $0.05 < P < 0.06$).

Researchers from the University of Vienna conducted another study to evaluate the association between local lithium levels in drinking water and suicide mortality in Austria (Kapusta *et al.*, 2011). A nationwide sample of 6460 lithium measurements was examined for association with suicide rates per 100 000 population and with suicide SMR across all 99 Austrian districts. Mortality data were taken from the Census Officer of the Austrian population for 2005–2009. The average number of water samples per district was 65.3 (range, 1–312). The mean lithium level in Austrian drinking water was 0.0113 mg/l (SD = 0.027) (i.e. 11.3 ± 27 μg/l). The analyses were performed with a multivariate linear regression that considered the contribution of social and economic confounding factors known to influence suicide mortality in Austria (population density, per capita income, proportion of Roman Catholics as well as the availability of mental health service providers). The overall suicide rate ($R^2 = 0.15$, $\beta = 70.39$, $t = 74.14$, $P = 0.000073$) as well as the suicide SMR ($R^2 = 0.17$, $\beta = 70.41$, $t = 74.38$, $P = 0.000030$) were inversely associated with lithium levels in drinking water and remained significant after sensitivity analyses and adjustment for socioeconomic factors.

In a study conducted in England by Kabacs *et al.* (2011), lithium levels in tap water were measured in the 47 subdivisions of the East of England and were correlated with the respective suicide SMR for each subdivision. Drinking (tap) water samples were obtained from publicly accessible sources (restaurants, public toilets, pubs, cafeterias, and petrol stations), and lithium levels were measured using inductively coupled plasma mass spectrometry. SMRs for suicide from 2006 to 2008 for the 47 subdivisions of the East of England were taken from the NHS Clinical and Health Outcome Knowledge Base. Lithium levels in drinking water ranged from less than 1 to 21 μg/l across the 47 subdivisions. The analyses were conducted using Pearson's correlation coefficient (r) and bivariate scatter plots to investigate the association between lithium levels in drinking water and suicide SMRs. The analyses of the data showed that there was no correlation between lithium levels in drinking water and 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). Similarly, the bivariate scatter plots showed no association between lithium levels in drinking water and suicide SMRs. However, this negative result could in part be explained by methodological weaknesses of the study, such as the small number of samples taken and the narrow range of lithium concentrations observed in the 47 regions surveyed, which was significantly lower than those recorded in the studies by Schrauzer and Shrestha (1990) (70–160 μg/l) and Oghami *et al.* (2009) (0.7–59 μg/l).

The research group around Kapusta and colleagues published a second study (Helbich *et al.*, 2012) on the same data set as that described previously, using a more refined statistical model based on the analysis of geospatial epidemiological data. This confirmed a significant inverse correlation between mortality rates for suicide and lithium concentrations in drinking water (geographic weighted regression analysis, $P < 0.005$). A third study by the same group (Helbich *et al.*, 2013) investigated the impact of lithium in drinking water on suicide with respect to altitude. The results showed that lithium levels were negatively significantly associated with altitude. The authors speculated that lower lithium concentrations in the ground and drinking water might be responsible for higher suicide rates in high-altitude areas ($\rho = -0.64$, $P < 0.001$).

Confirmation of the association between levels of lithium in drinking water and suicide rate comes from a recent study published by Blüml *et al.* (2013), which analysed counties in Texas between 1999 and 2007. In total, 3123 water samples from public wells were analysed for dissolved lithium and averaged for 226 counties. The mean lithium levels in the counties ranged from 2.8 to 219.0 μg/l (0.000403 – 0.0315 mmol/l). Crude and age-adjusted suicide mortality rates (1999–2007) per 100 000 for 254 Texas counties were taken from the Texas Department of Health. The authors modelled the response of the county-level rate of suicide in Texas using both a linear and a Poisson rate regression adjusted for county-based population density, lithium levels, age, sex, race/ethnicity, median income per household, poverty, and unemployment rates. Lithium levels were significantly associated with age-adjusted suicide rates in the weighted model ($P = 0.02$). Moreover, mean lithium levels were statistically significant in all Poisson models (rate ratio for the fractional polynomial model, 0.88 for 100 μg/l; 95% confidence interval, 0.84 – 0.93), with the suicide rate ratio as a function of the change in the mean lithium level for the Poisson regression model with fractional polynomials.

A recent study by Sugawara *et al.* (2013) evaluated the association between lithium levels in tap water and suicide SMR in 40 municipalities in Aomori Prefecture in Japan (study population, 1 373 339). Lithium levels in the tap water supplies of each municipality were measured using inductively coupled plasma mass spectrometry. The lithium levels in drinking water ranged from 0 to 12.9 μg/l. In total, the average suicide SMR in Aomori Prefecture was 123 (range, 96–186) for male individuals and 105 (range, 72–152) for female individuals. Weighted least squares regression analysis, adjusted for the size of each population, was used to investigate the association between lithium levels and SMRs. After adjusting for confounders (the number of medical institutions per 10 000 people and the unemployment rate), a statistical trend was found for the relationship between lithium levels and the average SMR among female individuals ($\beta = -0.37$, $P < 0.10$) but not among male individuals ($\beta = 0.12$, $P = 0.597$).

The most recent study on the issue (Giotakos *et al.*, 2013) evaluated the association between lithium levels in the public water supply and prefecture-based suicide rates in Greece. Analyses were conducted with respect to lithium levels analysed by inductively coupled plasma mass spectrometry in 149 samples from 34 prefectures in Greece. A database of suicides by sex for the period from 1999 to 2010 at the prefecture level was provided by the Greek Statistic Authority. The average number of samples per prefecture was 4.72 (range, 1–17). The average lithium level was 11.10 μg/l (range, 0.1 – 121 μg/l). A linear regression analysis was conducted to test the prediction of suicides per 100 000 residents by lithium values in drinking water. The results indicated lower suicide rates in the prefectures with higher levels of lithium in the drinking water ($P < 0.05$).

Discussion

Although not numerous, these studies are surprisingly consistent in demonstrating a highly significant inverse correlation between lithium levels in drinking water and suicide rates. This may indicate a relatively practical way to have an impact on the epidemiology of suicide and public health at the county level. However, better understanding of how higher levels of lithium in the water can help in the prevention of suicide is required.

The neurobiological basis for the antisuicidal effects of lithium, even at plasma levels usually considered as therapeutic (0.6–1.0 mmol/l), remains largely unknown. From a clinical perspective, it has been hypothesized that lithium may exert its antisuicidal effects by reducing relapses of mood disorder, but additional mechanisms should also be considered based on the evidence. First, lithium therapy is not as effective in the acute phase of depressive episodes as other antidepressants (NICE, 2009; Cipriani *et al.*, 2011), which, in turn, do not seem to have similar antisuicidal efficacy (Khan *et al.*, 2003; Fergusson *et al.*, 2005; Gunnell *et al.*, 2005; Hammad *et al.*, 2006). Second, there is evidence of a reduction in the risk of suicide in patients treated with lithium even among those whose primary mood symptoms had responded inadequately to lithium (Cipriani *et al.*, 2013). Thus, clinical and epidemiological data suggest that lithium may have specific effects against suicide, which are at least partially independent of its mood-stabilizing action. In contrast, the antisuicidal effect of lithium might possibly be related to its antiaggressive effects, which have been shown in various species, populations and settings, such as animals, inhabitants of nursing homes for the elderly, mentally handicapped individuals, children and adolescents with hyperactive, hostile and aggressive behaviour, and hyperaggressive inmates of correction units and prisons (Müller-Oerlinghausen and Lewitzka, 2010).

Neurobiological mechanisms that might be involved in the antisuicidal effects of lithium include decreased impulsivity and hostile or aggressive behaviour (Cipriani *et al.*, 2013). Such an effect may be mediated by enhanced functioning of the central serotonin system (Hughes *et al.*, 2000). In contrast, several more recent studies suggest that lithium also has stimulating effects on neurogenesis (Wada, 2009; Nciri *et al.*, 2013), which in turn may be related to its different clinical effects.

The studies reviewed here present lithium concentrations in drinking water as milligrams or micrograms per litre of pure lithium element. This is not directly comparable with the absolute or molar weight of lithium contained in salts (i.e. carbonate, citrate, sulphate, or other lithium salts) delivered for treatment. Although the amount of pure lithium ion is always relevant, the weight is different – for example, 1 mmol of pure lithium corresponds to 6.94 mg, but 1 mmol of lithium presented as lithium carbonate corresponds to 36.9 mg of the compound.

Moreover, the amount of lithium found in drinking water is much lower than the dose of lithium salts considered therapeutic in humans. The mean lithium concentration in drinking water reported in the studies reviewed is in the range of 0.01 mg/l; this would require thousands of litres to match the amount of lithium present, for instance in a single 300 mg tablet of lithium carbonate.

Explication of the findings that even the very low levels of lithium provided in drinking water may reduce the risk of suicide is, at present, only speculative. It is possible, although unlikely, that the low levels of lithium such as those found in drinking water can bring about significant mood-stabilizing effects and reduce the risk of suicide in mood disorders not yet clinically defined by this mechanism. In contrast, it could be speculated that even very low but long-lasting lithium exposure can enhance neurotrophic mechanisms, neuroprotective factors and/or neurogenesis, which may account eventually for a reduced risk of suicide (Kovacsics *et al.*, 2009: Wada, 2009; Kapusta *et al.*, 2011). It must also be taken into account that drinking water is not the only dietary source of lithium. According to the US Environment Protection Agency, for instance, some grains and vegetables are even richer in lithium than drinking water. Moreover, the daily intake of lithium element, independent from the type of compound and vehicle containing it, may oscillate between 650 and 3100 μg in adults. This means that drinking water may be only a partial contributor to lithium consumption in humans (Schrauzer, 2002; Kabacs *et al.*, 2011).

Whether high lithium concentrations in drinking water has unwanted, adverse effects on human health must also be addressed. In particular, more research is needed to understand how lithium in tap water may affect thyroid function, pregnant women and foetuses *in utero* (Chandra and Babu, 2009; Kabacs *et al.*, 2011).

If confirmed by further, more focused, prospectively designed studies, the effect of sufficient levels of lithium in drinking water in reducing suicide risk in the general population could contribute to preventive strategies in the community and allow the neurobiological mechanisms of the antisuicidal effects of lithium and suicidal behaviour to be further elucidated.

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Conflicts of interest

There are no conflicts of interest.

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