Suicide is a serious public health problem worldwide, and many countries are committed to developing prevention programs 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. A substantial amount of data shows that lithium significantly reduces mortality in patients with mood disorders and reduction in rates of suicidality. 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. There is growing evidence that even very low lithium levels induced by routine consumption of lithium from tap water may have anti-suicidal effects both in patients with mood disorders, and in the general population.

**The objective** of this paper is to review the evidence investigating the association between suicide rates and lithium levels in drinking water.

**Methods.** Studies were identified through systematic search in PubMed. Studies were included if they investigating the relationship between the level of lithium in drinking water and suicides rates in the general population. The search in PubMed provided 35 results. After removal of 14 duplicates, of 10 reviews, and 2 opinions of the remaining 9 records were screened for eligibility.

**Results.** Seven out of nine studies found an association between trace-dose lithium and suicide rates. Studies report that lithium levels in drinking water may play a role in reducing suicide risk the general population.

**Conclusion.** The available literature indicates that higher lithium levels in drinking water may be associated with lower suicide rates.

**Key words.** Lithium, Suicide, Drinking water.

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INTRODUCTION

Suicide is among the top 20 leading causes of death globally among all ages, and accounting for approximately 800,000 deaths annually worldwide including approximately 58,000 deaths in European Union [1]. Lithuania had the highest suicide rate in the Europe in 2015 – 30.8 cases per 100,000 people (54.3 for males and 10.8 for females), accounting for over 800 deaths, or 2.1% of all deaths in the Lithuania [2]. Suicide is considered a multifactorial event caused by a complex interaction between biological, genetic, psychological, social and environmental factors [3-5], 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.

Several studies from developing and industrialized countries indicate a prevalence of mental disorders in about 90% of cases of suicide [6]. Treatment of patients with suicidal behavior is one of the most challenging tasks for healthcare professionals [7]. 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 [8, 9]. Lithium is the “gold standard” mood stabilizer against which potential mood stabilizer agents are judged [10]. A meta-analysis demonstrated an overall significant efficacy of lithium in preventing suicide with a highly significant reduction in rates of suicidality [11]. Lithium treatment reduces mortality and suicide by more than 60% in people with major depression or bipolar disorder [12]. Today, lithium carbonate is one of the most widely prescribed psychiatric drugs [13-16]. A placebo-controlled trial data showed that low doses of lithium might improve and stabilize mood quite rapidly in former drug users [17].

Although trace lithium intake doses are significantly lower than those used for the treatment of patients with psychiatric disorders [18, 19], there is growing evidence that even very low lithium levels induced by routine consumption of lithium from tap water may have anti-suicidal effects both in patients with mood disorders, and in the general population [20, 21]. One of hypotheses explaining anti-suicidal effects of low lithium levels is that long-term exposure to lithium through routinely drinking water may mitigate low absolute lithium levels [22]. Lithium is detectable at variable concentrations in drinking water throughout the world [29-32].

EFFECTS OF LITHIUM DEFICIENCY ON BEHAVIORAL PARAMETERS

As lithium deficiency in humans is unlikely, any symptoms of lithium deficiency in humans, if at all observable, would be expected to be mild and manifest themselves primarily by behavioral rather than physiological abnormalities [14]. Evidence linking low lithium intakes with altered behavior and aggressiveness in humans was reported by Dawson et al. [22, 33, 34]. These authors compared the regional mental hospital admission rates and homicide rates for 1967–1969 with the lithium concentrations in tap water samples and in urine samples obtained from 24 county sites in Texas. The highest significant inverse associations of water lithium levels were observed with first mental hospital admissions for psychosis, homicides and the arrest rates for drug use and other crimes [13]. The available experimental evidence now appears to be sufficient to accept lithium as essential; a provisional RDA for a 70 kg adult of 1,000 µg/day is suggested [14].

Research showed that lithium as a substance occurring naturally in food and drinking water may exert positive effects on mental health [26]. Although natural lithium intake doses are significantly lower than those used for the treatment of patients with psychiatric disorder [18, 19], there is growing evidence that even very low lithium levels induced by routine consumption of lithium from tap water may have anti-suicidal effects both in patients with mood disorders, and in the general population [27, 28]. One of hypotheses explaining anti-suicidal effects of low lithium levels is that long-term exposure to lithium through routinely drinking water may mitigate low absolute lithium level [22]. Lithium is detectable at variable concentrations in drinking water throughout the world [29-32].

ANTISUICIDAL EFFECT OF LITHIUM

Dietary source of lithium

Lithium is a trace element widely distributed on Earth [25, 26]. Because of its similarity with sodium and potassium, lithium easily crosses all biological barriers, meaning that it shows almost complete oral absorption and a uniform distribution in body fluids [25]. Mobilized by weathering processes, lithium is transported into soils, from which it is taken up by plants and enters the food chain. Lithium was detected in human organs and fetal tissues already in the late 19th century, leading to early suggestions of possible specific functions in the organism [13, 26].

The study reported that dietary lithium which has received scant attention is found in grains and vegetables and to some extent animal derived foods [14]. Lithium is found in variable amounts in foods; primary food sources are grains and vegetables; in some areas, the drinking water also provides significant amounts of the element. Human dietary lithium intakes depend on location and on the type of foods consumed and vary over a wide range. Lithium was detected in human organs and fetal tissues already in the late 19th century, leading to early suggestions as to possible specific functions in the organism. However, it took another century until evidence for the essentiality of lithium became available. In studies conducted from the 1970 to the 1990, rats and goats maintained on low-lithium rations were shown to exhibit higher mortalities as well as reproductive and behavioral abnormalities. In human defined lithium deficiency diseases have not been characterized, but low lithium intakes from water supplies were associated with increased rates of suicides, homicides and the arrest rates for drug use and other crimes [13]. The available experimental evidence now appears to be sufficient to accept lithium as essential; a provisional RDA for a 70 kg adult of 1,000 µg/day is suggested [14].

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Mechanistic considerations of lithium

Lithium acts on mood and suicidality via complex interactions with the serotonergic system [35] and to decrease cerebral level of tryptophan and serotonin [32, 36]. The research shows that the important role testosterone plays in the regulation of mood and behavior, therefore it is a potentially important marker for suicide risk in an already at-risk population [37].

The biochemical mechanisms of action of lithium appear to be extraordinarily complex, multifactorial and strongly intercorrelated with the functions of other elements, drugs, enzymes, hormones, vitamins, growth and transforming factors. Although these were mostly observed at pharmacological levels, they could also occur at nutritional levels, accounting for the unusually broad activity spectrum of lithium [38]. However, lithium has been shown to enhance folate and B12 transport into cells [37], the transport of these factors is inhibited in lithium deficiency and can be restored by lithium supplementation. Since vitamin B12 and folate also affect mood-associated parameters, the stimulation of the transport of these vitamins into brain cells by lithium may be cited as yet another mechanism of the antidepressive, mood elevating and antiaggressive actions of lithium at nutritional dosage levels. Recognition of the intercorrelated nature of all biological actions of lithium may result in improved therapeutic concepts. Thus, the joint administration of lithium with vitamin B12 and folate may prove more effective than lithium or the vitamins alone [4, 39]. The fact that embryonal lithium concentrations are the highest during early fetal development suggests that it is specifically needed [24, 40, 41].

METHODS

The electronic search strategy on PubMed database was conducted from the date of inception of the studies in the databases to October 2016. The following keyword combinations were used: “suicide” AND “lithium in drinking water”, or “lithium in public water”. Using the keyword combinations described above, the search in PubMed provided 35 results. Studies were included if they published in English, and investigating the relationship between the level of lithium in drinking water and suicides rates in the general population. After removal of 14 duplicates, of 10 reviews, of 2 opinions of the remaining 9 records were screened for eligibility.

RESULTS

The selected 9 papers reported studies published between 1990 and 2016 in different countries. The studies available to date on the relationship between the level of lithium in drinking water and suicide and the main results obtained are presented in Table 1.

The first reported a negative association between lithium levels in tap water and suicide rates in Texas Schrauzer and Shrestha [13]. Using data from 27 Texas counties for the period 1978–1987, it is found that the incidence rates of suicide, homicide, and rape were significantly higher in counties whose drinking water lithium levels ranging from 70 to 160 μg/L.

These results were replicated in two studies by Ohgami et al. [22] and by Kapusta et al. [4], one from Japan and one from Austria concluded that areas with higher lithium levels in the drinking water had lower suicide rates. They found that lithium levels were significantly and negatively associated with suicide standardized mortality ratio averages for the period 2002-2006 and suggested that even very low levels of lithium in drinking water may play a role in reducing suicide risk within the general population. Kapusta et al. [4] evaluated the association between local lithium levels in drinking water and suicide mortality at district level in Austria. The overall suicide rate as well as the suicide mortality ratio were inversely associated with lithium levels in drinking water and remained significant after sensitivity analyses and adjustment for socioeconomic factors.

However, Kabacs et al. [31], did not prove this association between lithium in drinking water and suicide rates across the East of England. The analyses of the data showed that there was no correlation between lithium levels in drinking water and suicide mortality rates in the 47 subdivisions of the East of England. This negative result could in part be explained by methodological weaknesses of the study, for example, sociodemographic or socioeconomic characteristics were not included.

Giotakos et al. [20] reported lower suicide rates in prefectures with high levels of lithium in drinking water. Analyses were conducted with respect to lithium levels in 34 prefectures of Greece from both rural and urban areas. The results indicate that there is a tendency for lower suicide rates in the prefectures with high levels of lithium in drinking water.

Confirmation of the association between levels of lithium in drinking water and suicide rate comes from study published by Blüml et al. [42], which analyzed of 226 counties in Texas between 1999–2007. This study modeled the response of the county-level rate of suicide using both a linear and Poisson rate regression adjusted for county-based population density, lithium levels, age, sex, race/ethnicity, median income per household, poverty and unemployment rates. Results showed that lithium levels were significantly associated with suicide rates.

A recent study in Italy by Pompili et al. [43] found that lithium levels in tap water and local suicide rates were not significantly inversely related. Based on lithium concentrations and analyzed suicide data at the community level, and including the following covariates: totally mountainous areas, highly urbanized, and geographic location, were reported that suicide rates were not statistically significantly correlated with lithium levels.

The research group around Kapusta and colleagues [4] published a second study, Helbich et al. [44], on the same data set as that describe previously, using a more refined statistical model based on the analysis of geospatial epidemiological data and lithium prescription. Previous studies have assumed that the lithium in drinking water originated from natural sources alone. They have not considered whether lithium prescribed to patients may have accumulated via waste water in groundwater aquifers after urinary excretion and interplay with natural lithium [21]. The results showed that lower lithium concentrations in the ground and drinking water might be responsible for higher suicides rates even after adjustment of lithium prescriptions.

The most recently published study on the issue, Shiotsuki et al. [45], evaluated the association between lithium levels in the public water supply and suicide rates suicide after adjustment of
of meteorological factors. The results suggest that trace lithium is inversely associated with male but not female suicide after adjustment of meteorological factors. Gender differences has been observed that lithium decreases an impulsive aggressive behavior, which decrease suicide rates among men by reducing impulsivity and aggression [46].

**CONCLUSIONS**

The suicide protective property of trace lithium was confirmed with a positive effect almost all studies. However, better understanding of how higher levels of lithium in the drinking water can help in the prevention of suicide is required. It is still not clear what amount of lithium in drinking water can provide an independent protective effect for suicide. In particular, more research is needed to understand how lithium levels in the public drinking water supply correlate with blood lithium levels. Also, drinking water is not the only dietary source of lithium. According to the US Environment Protection Agency, some grains and vegetables are even richer in lithium than drinking water [14]. Further studies could contribute to preventive strategies in the community and could explain the neurobiological mechanisms of the anti-suicidal effects of lithium and suicidal behavior. This may indicate a relatively practical way to have an impact on the epidemiology of suicide and public health at the county level.

### Table 1. Summary of studies investigating the anti-suicidal effects of lithium as a trace element in drinking water

<table>
<thead>
<tr>
<th>References</th>
<th>Measurement</th>
<th>Number of samples (no. of areas)</th>
<th>Adjusted for</th>
<th>Mean lithium levels</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiotsuki et al. 2016/Japan</td>
<td>Li level in drinking water</td>
<td>153 samples</td>
<td>Annual total sunshine, annual mean temperature, annual total rainfall, annual total snowfall</td>
<td>3.8 µg/L (SD ± 5.3; 0.1–43)</td>
<td>Lithium is inversely associated with male but not female suicide after adjustment of meteorological factors.</td>
</tr>
<tr>
<td>Helbich et al. 2015/ Austria</td>
<td>Li level in drinking water</td>
<td>6460 lithium measures of 99 districts</td>
<td>Population density, per capita income, proportion of Roman Catholics, density of psychiatrists per 10 000 population, the number of general practitioners, the density of psychotherapists per 10 000 people</td>
<td>11.3 µg/L (SD ± 27)</td>
<td>Suicide rate, SMR inversely associated with Li levels even after adjustment of meteorological factors.</td>
</tr>
<tr>
<td>Pompili et al. 2015/ Italy</td>
<td>Li level in drinking (tap) water</td>
<td>145 samples</td>
<td>Population size, mountainous area, highly urbanized, geographic location</td>
<td>5.28 µg/L (0.11–60.8 µg/L)</td>
<td>Lithium concentrations and local suicide rates were not significantly inversely related.</td>
</tr>
<tr>
<td>Blüml et al. 2013/ Texas</td>
<td>Li level in public water</td>
<td>3123 lithium water samples, 226 counties</td>
<td>Population density, age, gender, race/ethnicity, median income per household, poverty and unemployment rates</td>
<td>2.8–219 µg/L</td>
<td>Higher lithium levels in the public drinking water were associated with lower suicide rates.</td>
</tr>
<tr>
<td>Giotakos et al. 2013/Greece</td>
<td>Li level in drinking water</td>
<td>149 water samples from 34 prefectures</td>
<td>Population density</td>
<td>11.10 µg/L (SD ± 21.16; 0.1–121)</td>
<td>Tendency for lower suicide rates in the prefectures with high levels of lithium in drinking water.</td>
</tr>
<tr>
<td>Kabacs et al. 2011/UK East of England</td>
<td>Li level in drinking (tap) water</td>
<td>47 samples from 47 subdivisions</td>
<td>No</td>
<td>&lt;1–21 µg/L</td>
<td>No association between lithium levels in drinking (tap) water and mortality from suicide.</td>
</tr>
<tr>
<td>Kapusta et al. 2011/Austria</td>
<td>Li level in drinking water</td>
<td>99 districts</td>
<td>Population density, per capita income, proportion of Roman Catholics, mental health service providers</td>
<td>11.3 µg/L (SD ± 27)</td>
<td>Higher natural lithium concentrations in drinking water are associated with lower suicide mortality rates.</td>
</tr>
<tr>
<td>Ohgami et al. 2009/ Japan</td>
<td>Li level in drinking water</td>
<td>18 municipalities of Oita Prefecture</td>
<td>Population size</td>
<td>0.7–59 µg/L</td>
<td>Even very low levels of lithium in drinking water may play a role in reducing suicide risk within the general population.</td>
</tr>
<tr>
<td>Schrauzer and Shrestha 1990/ Texas</td>
<td>Li level in drinking water</td>
<td>27 counties</td>
<td>Population density</td>
<td>0–160 µg/L</td>
<td>Low lithium intakes from water supplies were associated with increased rates of suicides.</td>
</tr>
</tbody>
</table>
REFERENCES


