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The Association Between Lithium in Drinking Water and Incidence of Suicide Across 15 Alabama Counties

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Abstract. *Background:* Recent studies have shown that lithium may be effective at reducing suicide at low doses, such as those found in drinking water. *Aims:* The purpose of this study was to compare suicide rates with natural lithium levels in the drinking water of various Alabama counties. *Method:* Five drinking water samples from each of 15 Alabama counties were collected. Lithium levels were measured in triplicate using an inductively coupled plasma emission spectrophotometer and compared with suicide rate data for the period 1999–2013. Age, gender, and poverty were evaluated as potential confounding variables. *Results:* The average measured lithium concentrations ranged from 0.4 ppb to 32.9 ppb between the counties tested. The plot of suicide rate versus lithium concentration showed a statistically significant inverse relationship ($r = -.6286$, $p = .0141$). Evaluation of male-only suicide rate versus lithium concentration data also yielded significant results; however, the female-only rate was not significant. Age standardized suicide rates and poverty when individually compared against lithium levels were also found to be statistically significant; unexpectedly, however, poverty had a parallel trend with suicide rate. *Conclusion:* Lithium concentration in drinking water is inversely correlated with suicide rate in 15 Alabama counties.

Keywords: suicide, lithium, epidemiology, community mental health

Lithium, as the lightest metal of the periodic table, has several unique properties that lend it to even more unique applications. These uses range from lightweight alloys for the wings of planes to the high-powered batteries that make portable technology possible (Atkins, Overton, Rourke, Weller, & Armstrong, 2010). Undoubtedly, lithium's most fascinating applications come from its effects on the brain. Currently, lithium is used as a treatment for bipolar disorder and major depressive disorder. Several meta-analyses (Baldessarini et al., 2006; Cipriani, Hawton, Stockton, & Geddes, 2013; Cipriani, Pretty, Hawton, & Geddes, 2005; Guzzetta, Tondo, Centorrino, & Baldessarini, 2007) have found that, in addition to its mood-stabilizing effects in these patients, lithium treatment results in a reduction in the risk of suicide. Effective treatment for reduction of suicidal behavior in patients with schizophrenia or schizoaffective disorder is notoriously difficult, with only one drug, clozapine, approved for this indication by the Food and Drug Administration (American Foundation for Suicide Prevention, 2016). Thus, the results of these studies are quite significant.

Another unique property of lithium is that, as a naturally occurring element, it is found at varying levels within our water supply. This fact, combined with the results of the aforementioned research, has led to the completion of a number of ecological studies. These studies observed the relationship between natural lithium levels in drinking water and suicide rates. Studies completed in Texas (Blüml et al., 2013; Schrauzer & Shrestha, 1989), Japan (Ishii et al., 2015; Ohgami, Terao, Shiotsuki, Ishii, & Iwata, 2009; Shiotsuki et al., 2016; Sugawara, Yasui-furukori, Ishii, Iwata, & Terao, 2013), Greece (Giotakos, Nisianakis, Tsouvelas, & Giakalou, 2013), Italy (Pompili et al., 2015), and Austria (Helbich, Leitner, & Kapusta, 2012; Vita, De Peri, & Sacchetti, 2015) have all shown a negative correlation between increasing lithium levels and suicide mortality. One dissenting study completed in the East of England (Kabacs, Memon, Obinwa, Stochl, & Perez, 2011) showed no such correlation. Of note, for the studies that did find a correlation, the measured lithium levels were much lower than what is considered therapeutic for the treatment of bipolar and major depressive disorder. Based on a total daily intake of 2 l of water (Kapsuta & Konig, 2015), the highest measured lithium concentration from these studies (219 ppb in Texas) would result in just 0.438 mg (0.063 mEq) per day, as opposed to the typical therapeu-

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Figure 1. Alabama state map showing selected counties where water samples were collected for this study. (United States Geological Survey 2004).

tic dose of 169–338 mg or 24.5–49.0 mEq of elemental lithium per day (Lexi-Drugs, 2016). However, even among those studies that demonstrated a negative correlation between lithium concentration and suicide rate, the results were not always consistent. The Italian study (Pompili et al., 2015) only found significant results for the 1980s and only for women. Several studies in Japan have found varying results in respect to sex. A study in 2009 (Ohgami et al., 2009) found significance only for males with marginal significance for females. Then in 2013 (Sugawara et al., 2013), another study found significance only for women. The 2015 (Ishii et al., 2015) study showed overall significance in the crude statistical model but after adjustment for confounders found significance only for men. A final study in 2016 (Shiotsuki et al., 2016) again provided significance only for males.

Suicide continues to be a growing problem in the United States. According to the Centers for Disease Control (CDC), the national suicide rate per 100,000 people increased from 11.1 in 2004 to 13.4 in 2014 (CDC, 2015). The state of Alabama is no exception to this trend with a rate increase of 11.9 to 14.7 over the same 10-year period. Hence, further research into potential mitigating factors to suicide risk is needed.

Table 1. Average percent of male and female population by county during 1999–2013

County	Male (% CV)	Female (% CV)
Bullock	53.68 (2.2)	46.32 (5.1)
Coosa	50.01 (4.3)	49.99 (3.0)
Cleburne	49.78 (2.2)	50.22 (2.3)
Cherokee	49.44 (3.7)	50.56 (3.0)
Madison	48.94 (8.3)	51.06 (8.0)
Lawrence	48.91(1.3)	51.09 (0.8)
Tuscaloosa	48.34 (7.6)	51.66 (7.1)
Hale	48.11 (6.1)	51.89 (3.8)
Conecuh	48.11 (2.1)	51.89 (3.6)
Mobile	47.91 (1.8)	52.09 (1.7)
Montgomery	47.51 (1.4)	52.49 (1.3)
Jefferson	47.26 (0.3)	52.74 (0.5)
Lowndes	47.14 (7.8)	52.86 (7.9)
Marengo	46.98 (3.3)	53.02 (3.5)
Sumter	45.49 (3.9)	54.51 (3.2)

Note. %CV = percent coefficient of variation.

Additionally, limited information is available about lithium levels in drinking water across the United States. The United States Geological Survey (USGS) collects water samples to determine the concentration of trace elements in the water supply (Ayotte et al., 2011). While these data provide a general overview of lithium levels across the United States, they do not provide the detailed information required for local-level research analysis. Additional lithium data at a more local level (e.g., counties, cities) are necessary to evaluate its potential association with incidence of suicide.

The purpose of this study was to determine whether lithium levels in the drinking water of selected Alabama counties correlate with their suicide rate; additionally, confounders including gender and poverty were evaluated.

Method

County Selection

In order to provide as much variety in demographic characteristics as possible, while ensuring a broad range of rates, 15 of Alabama's 67 counties were chosen based on their suicide rate, population, and geographic location. The five counties with the highest suicide rates, five with the lowest suicide rates, and five with the highest populations were chosen. Figure 1 is a map of the selected counties within the state of Alabama. The suicide rate was based on 15-year averages using data from the Alabama Department of Public Health (ADPH) and the CDC (ADPH, 2016; CDC, 2015). This rate spanned 1999–2013 and was calculated per 100,000 people. Gender demographics for each county sampled were collected and are shown in Table 1.

Sample Collection

Five water samples were collected from each county, for a total of 75 samples. Samples were collected during May 2016 in uniform plastic containers from public spaces in multiple cities and townships in each county. Specific locations included various restaurants, private residences on city or county water systems, and water fountains located in public shops, malls, college campuses, and convenience stores. Samples were stored in a cooler during transport and a refrigerator while awaiting analysis to prevent potential microbial growth.

Sample Analysis

Lithium concentration was measured using a Shimadzu ICPE-9000 (Columbia, MD) inductively coupled plasma emission spectrophotometer (ICPE). The limit of detection for lithium was established at 0.1 ppb. Calibration standards (1, 2, 5, 10, 50, and 100 ppb) were prepared by sequential dilution of a commercially available lithium standard (High Purity Standards, Charleston, SC, expiration date: 6/2017) using deionized water. The calibration curve was found to be linear over this range with a corresponding correlation coefficient of $> .9999$. In order to prepare the samples for analysis, 70% nitric acid was added to obtain a final concentration of 2% (v/v) nitric acid. Each sample was measured in triplicate using the most predominate emission wavelength (670.784 nm). During analysis, a standard check assay (50 ppb) was undertaken every 20 samples and recalibration performed if the average of the triplicate measurements deviated by more than 10%.

Data Analysis

The average of the five water samples from each county was used to represent the lithium level for that county. The lithium level was then plotted against the 15-year average suicide rate and a nonlinear line of best fit was applied. Spearman's rank correlation and bivariate scatter plots were used to determine significance ($\alpha = 0.05$, 95% confidence interval, two-tailed test) using GraphPad Prism version 6.07 (La Jolla, CA). Several potential confounding factors were also considered: age, gender, and the percent of each county's population below established poverty rate (Gliatto & Rai, 1999). Suicide data delineated by age and gender were collected from ADPH (2016). Gender and poverty data were obtained from the United States Census Bureau (2016). Suicide rates were age standardized using the 2000 US standard million population (National Cancer Institute, 2016) and then analyzed using the same statistical methods previously mentioned. Male and female suicide rates were calculated and subsequently compared with lithium levels using nonlinear regression and Spearman's rank correlation with a two-tailed confidence interval of 95%. The percent of the population below poverty level for each county was compared with suicide rate for each county using nonlinear regression and Spearman's rank test.

Results

Averaged lithium levels (five samples per county), range, standard deviation, and 15-year average population normalized (per 100,000) suicide rates are listed in Table 2. The average lithium levels measured in the collected water samples varied by greater than a 300-fold change across the selected counties. As shown in Figure 2, there is an inverse relationship between measured lithium concentration and suicide rate. Spearman's rank correlation showed a statistically significant association between measured lithium concentration and suicide rate ($r = -.6286$, $p = .0141$). For gender-based association, the male-only suicide rate versus lithium concentration remained significant ($r = -.625$, $p = .0148$). However, female only suicide rate versus lithium concentration was not significant ($r = -.4393$, $p = .1032$). After age-standardization, as shown in Figure 3, the data remained significant with Spearman's test ($r = -.625$, $p = .0148$). The level of poverty was significantly associated with suicide rate, $r = -.5821$ and $p = .0252$ (Figure 4).

Discussion

Our study found a statistically significant inverse association between measured lithium levels and suicide rater across the 15 Alabama counties tested. These results are in agreement with many previous studies conducted in

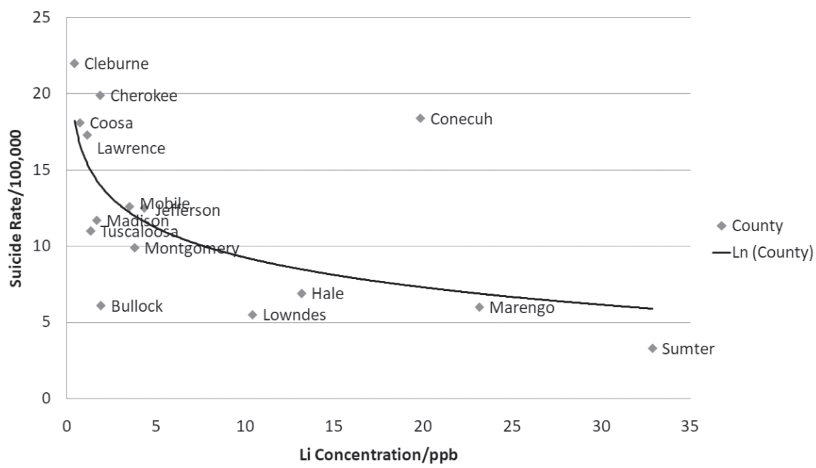

Figure 2. Plot showing the association between lithium in drinking water and incidence of suicide.

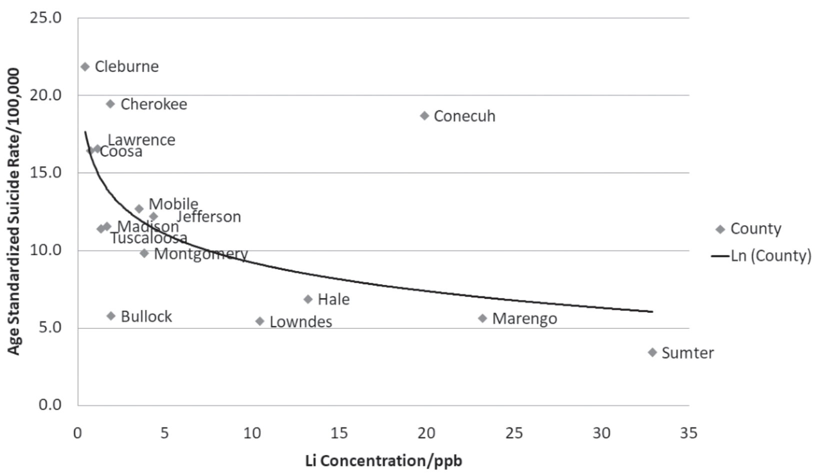

Figure 3. Plot showing association between age-standardized rate of suicide with lithium in drinking water.

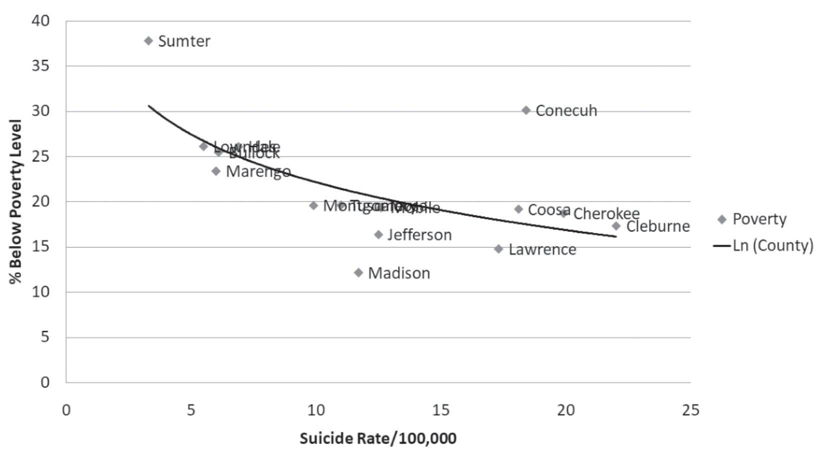

Figure 4. Plot showing percent of population by county versus suicide rate.

various countries. A report by Blüml and colleagues (Blüml et al., 2013) found a negative association with suicide rates in Texas when comparing 3,126 lithium measurements across 226 counties using linear and Poisson regression models being adjusted for socioeconomic factors. Measured lithium levels in this study had a much larger range (2.8–219 ppb) than in our study. In Japan, a study by Ohgami and colleagues (2009) showed an inverse association ($\beta = -.65$, $p < .004$) between lithium in tap water and suicide rates for males in the general population in 18 municipalities of Oita prefecture between 2002 and 2006. The association was only marginally significant for females ($\beta = -.46$, $.05 < p < .06$). In this study a weighted least squares regression analysis adjusted for the size of each population was used owing to differences in the population of the municipalities. Others (Shiotsuki et al.,

Table 2. Measured lithium values (ppb) and 15-year average suicide rate[a]

County	Average (range)	*SD*	Suicide rate/ 100,000 (*SD*)
Cleburne	0.4 (0.1–1.1)	0.4	22.0 (8.9)
Cherokee	1.9 (0.3–6.9)	2.8	19.9 (9.9)
Conecuh	19.8 (4.8–40.7)	13.0	18.4 (11.2)
Coosa	0.7 (0.1–1.4)	0.6	18.1 (8.7)
Lawrence	1.1 (0.7–1.6)	0.3	17.3 (8.4)
Mobile	3.5 (0.5–7.1)	2.4	12.6 (2.5)
Jefferson	4.3 (3.6–6.9)	1.4	12.5 (1.7)
Madison	1.7 (0.8–3.3)	0.9	11.7 (2.8)
Tuscaloosa	1.3 (0.6–4.0)	1.5	11.0 (1.7)
Montgomery	3.8 (0.5–11.5)	4.5	9.9 (1.7)
Hale	13.2 (7–20.6)	6.3	6.9 (8.4)
Bullock	1.9 (1.6–2.0)	0.2	6.1 (6.7)
Marengo	23.2 (2.6–59.9)	21.9	6.0 (5.6)
Lowndes	10.4 (1.7–22.6)	11.0	5.5 (4.9)
Sumter	32.9 (14–60.6)	22.6	3.3 (6.6)

Note. [a]Average and range (low to high levels within a county) of measured Li levels (ppb) in drinking water samples by county (n = 5 per county). Suicide rates are over 15-year period (1999–2013) and population normalized. *SD* is the standard deviation of each reported parameter.

2016) have reported this same finding with males after adjusting for meteorological factors (e.g., annual mean temperature, sunshine, rainfall, and snowfall) using the same statistical analysis. The measured lithium range in this study (0.1–43 ppb) was more comparable to levels in our study. In contrast to these results, another study (Pompili et al., 2015) reported a partially supported negative association for women only ($r = -.125$, $p = .07$) using an unweighted linear correlation employing 157 samples from 2009–2010 over 145 Italian communities. Contrary to these studies, a study by Kabacs and coleagues (2011) in England found no correlation using Pearson's correlation coefficient (r) and bivariate scatter plots for both genders ($r = -.03$, $p = .838$). Further analysis by gender also showed no significant correlation ($r = -.054$, $p = .715$ for males; $r = .042$, $p = .777$ for females). The highest lithium level in the English study was just 21 ppb (a single occurrence), with most measurements being much lower (91.4% of subdivisions were less than 10 ppb). Additionally, sampling was limited to the East of England region only, which is made up of six counties further divided into 47 subdivisions. Furthermore, only a single sample from each subdivision was taken and subsequently analyzed for lithium. It is also possible that there is a concentration threshold for effective suicide prevention that was not met in the English study. Conversely, the logarithmic relationship shown in the current study suggests even small increases in lithium concentration can have an effect. Therefore, there are likely other, stronger factors, affecting the outcome of the England study. Some of these potential factors include the confounders tested in this study. Of the tested confounders, only gender and poverty were found to be statistically significant in our study. The rate of female suicide averaged about one fifth that of the male rate across counties. It is possible that suicide rate alone is not adequate to compare the effect of lithium between genders. Suicide attempts might also need to be included in the evaluation owing to the different methods typically used by men and women. According to the study "The gender paradox in suicidal behavior and its impact on the suicidal process" (Schrijvers et al., 2012), women are more likely to attempt suicide using methods with lower case fatality rates than those used by men, that is, overdose rather than firearms. Another possibility is that lithium affects men and women differently, with a stronger preventative effect in men. Including the studies in 2009, 2015, and 2016 in Japan (Ishii et al., 2015; Ohgami et al., 2009; Shiotsuki et al., 2016), this is the fourth study to find a stronger correlation of lithium in suicide prevention in men than in women. However, it should be noted that at therapeutic levels of lithium there is no difference in effect due to gender (Viguera, Tondo, & Baldessarini, 2000).

Standardizing suicide rates for age had no effect on the statistical significance or relationship between lithium concentrations and suicide rates. These results suggest that the age distribution of suicides does not vary significantly between the Alabama counties tested. The association between poverty and suicide rates was statistically significant and notably, the direction of the association was the opposite of what might be expected. That is, with increasing poverty came decreased suicide rates. While this result was not expected it could be due to the magnitude of the percentage of the population below poverty level based on the total population of each county. Thus, a smaller percentage of more populated counties would be at or below the poverty rate as compared with less populated counties that would have a higher percentage. Additional research would be necessary to determine other contributing factors that may account for this observation.

Limitations

This study had several limitations. The first concerns geographic disparities in lithium concentration across individual counties. That is, water sources are not necessarily uniform within a county. Water utility companies may use many sources in their water supply between, and even within, plants. In addition, several different plants or companies can exist in one county. This variety can lead to a skewed average value for lithium concentration and poor representation of true levels for some areas. Another sampling limitation includes the lack of samples from other sources of lithium. Many rural areas use wells rather than the public water supply, and bottled water, soda, and food sources can also vary in their lithium content. Additionally, lithium concentration may vary seasonally or yearly. This potential difference would not be accounted for by the one sample collection time used for this study. The year in which samples were collected (2016) is also different from the years in which suicide data were collected (1999–2013). If lithium levels differ from year to year, these comparisons may be invalid.

Conclusion

This study found an inverse association between lithium concentrations in drinking water and suicide rates for 15 Alabama counties. Two confounding factors of gender and poverty level were found to be significant. While the rate of male-only suicide was found to be significant, the rate of female-only suicide was not. Future research in which biological levels of lithium are sampled in addition to water levels would be useful in elucidating the relationship between these variables. Furthermore, clinical trials or long-term city-to-city comparative ecological studies are also needed to help exclude confounding factors. Broader ecological studies could easily be completed if more water utility companies begin to measure lithium levels as part of normal safety checks. The summation and careful evaluation of these data are needed before trace levels of lithium can be considered for use in assuaging the increasing rates of suicide in the United States.

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Conflict of Interest: None

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