PsychoTropical Commentaries 2018:8;23-30

Endogenous Lithium & suicide: a critique

Gillman, P. K. PsychoTropical Research, Bucasia, Queensland, Australia

kg@matilda.net.au

Abstract

Papers by various research groups have suggested relationships between (inter alia) suicide, dementia, and aggressive behaviour with the levels of lithium in reticulated drinking-water supplies. The notion of adding Li to drinking water supplies has even been mooted and covered in the mass media. However, there are inconsistencies in relation to the amount of lithium in tap-water and its contribution to total dietary Li intake. There are no data confirming the crucial question of whether there are actually different blood levels of Li in subjects from different areas that have different Li tap-water levels, who are included in such associative epidemiological analysis. This paper clarifies some of these misunderstandings with relevant data from the scientific literature which has not been cited previously in this context. Such data clarify certain key points about Lithium intake, and the regulation of endogenous Lithium, which indicate clearly and unequivocally that such 'associative epidemiology' is methodologically unsound, conceptually flawed, incorrect, and naïvely over-interpreted.

Introduction

There are an increasing number of publications that can be described as 'associative epidemiology' trying to link Li in tap-water with various aspects of nervous system functioning, such as dementia, mood states and suicide, and aggressive behaviour.

I refer to these studies as 'associative epidemiology' because most of the scientific and logical observations and requirements that might indicate even a slight chance of an actual causal link are absent. The old trope of 'association is not causation' endures because each new generation of researchers repeat the same mistakes. This expanding area of investigation is an example of ignorance of basic science, of methodology, and misunderstanding of statistics and P-values (1). A Bayesian would want to think about the 'prior probability' and require rather better evidence. See:

https://www.healthknowledge.org.uk/e-learning/epidemiology/practitioners/causation-epidemiology-association-causation

I have previously discussed concepts related to establishing cause-and-effect relationships (Bradford Hill criteria), which are not well-observed in psychiatry (2). The above link contains a summary about this — my previous discussion (3, 4) was related to criticism of the weak cause-and-effect nexus between neuroleptic drugs and neuroleptic malignant syndrome (NMS).

The principles enumerated by Sir Austin Bradford Hill, that are often referred to as the Bradford Hill criteria, have sometimes been used a little simplistically and have been further refined more recently (5-7).

There are major misunderstandings in the published studies concerning regulation of trace Li in humans (endogenous intake), and the sources of ingested Li. This review discusses how these errors and misconceptions show that the studies thus far are of no validity or value.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Endogenous Lithium: trace levels and their regulation

The best replicated and latest data indicate that typical human 'endogenous' serum Li levels (i.e. background levels arising from obligate-ingestion from food and water) are around 0.0003 mmol/L and show low variation (~ 0.0001 -0.0005) in relation to dietary ingestion amounts. Current best estimates of dietary daily intake are 0.1-3 mg/day, of which ~30% is from 'water' (see below).

We were taught that naturally (i.e. in people not taking any form of Li treatment) there was no Li the body, and many doctors may still think that. It is, of course, a question of limits of detection/quantification (LODs/LOQs): usual laboratory methods are insufficiently sensitive to measure such low Li levels, and they are therefore not detected by medical laboratory tests.

The measurement of microgram levels of endogenous Li (and other trace metals) in biological tissues and fluids involves technical challenges and difficulties (8-10) and some older (<1996) reported measurements are probably best discounted.

The use of the measurement of fractional Li excretion in hypertension research, which involves measuring endogenous Se Li and 24 hr. Li excretion, has produced large samples of endogenous serum Li levels in humans (well in excess of 1,000 subjects). As a result, the group at the Studies Coordination Centre, Laboratory of Hypertension, Leuven, Belgium (11, 12), have concluded '*These observations suggest that serum lithium is tightly regulated (at ~0.0003 mmol/l), despite large variations in dietary intake*'. All subjects had 24 hr urine Li collected which had, in the Belgium sample an average of 5 μmol of Li, equating to a daily intake of ~0.3 mg of Li, and in a South African sample 1 μmol, equating to a daily intake of ~0.06 mg: yet the mean Se Li levels in these two groups were almost identical, and within a narrow range.

Cwynar et al. found almost identical results in 130 subjects in Poland (13).

Since Li intake can be inferred from the 24-hour urine samples these data also represent the largest body of values approximating typical dietary intake, and they suggest an intake of ~0.2 mg/day, which indicates that the French TDS estimate of 0.05 mg may be a slight under estimate.

Incidentally, out of 1278 subjects 36 were excluded because of a 'very high Li concentration in serum (>0.001 mmol/L)' which they considered indicated 'external contamination' (i.e. ingestion of 'supplements', e.g. Li-rich mineral water, see below).

In view of the size of the above sample discussion of other results (especially those using older assay methods), is superfluous. However, Miller found serum Li levels around 0.00016 mmol/L for normal subjects dwelling in the Denver metropolitan area. The mean 24-hr excretion rate was 0.005 mmol/day (14), identical to the value found by the Leuven group. Folkerd (15) found a mean 0.00027 +/- 0.02 mmol/l (n = 25, range 0.00013-0.00055 mmol/l).

In summary: at usual levels of dietary intake (~0.1-3 mg/day), which are now rather more reliably established, Se Li is tightly regulated between about 0.0001-0.0003 mmol/L. It is not proportional to intake in this range.

These data are informative concerning how illogical some research has been: Nunes et al. gave 0.3 mg/day to try to help dementia. Since this is in the normal dietary intake range, it seems a misconceived trial, since it is unlikely to have significantly altered pre-existing levels (16).

Shiotsuku's study (17) of subjects drinking large amounts of Li-rich mineral-water at a spa, although methodologically weak and lacking key data, seems to be the only study with Se Li estimations in subjects (n=43) ingesting Li in doses of around 20-50 mg/day — despite the poor description and methodology (one can hardly

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

believe this fellow is a real 'professor') the Se Li averaged 0.07 mmol/L, which is 100 times higher than usual endogenous levels.

> NB. An insight into the lax methodology in this study "*After drinking lithium mineral water, body weight was increased but not significantly (57.6±10.0 to 59.3±9.1 kg, p<0.08).*
>
> If you drink one liter of water you will be one kilo heavier — simple physics! Their analysis is irrational.

These data indicate that the tight regulation of Se Li levels at endogenous Li intakes of 0.1-3 mg/day breaks down once intake reaches around 5-20 mg/day, when it becomes proportional to the daily dose, as it is when Li is used therapeutically for BPD at doses of around 1,000 mg/day.

Tap-water: small proportion of daily intake

Therefore, the above data demonstrate that dietary Li intake below ~5 mg/day is tightly regulated and variations within this range will not much affect serum Li levels.

Furthermore, all the epidemiological research relates to average levels in the reticulated water supply (viz. tap-water). But that tap-water constitutes only a minor proportion of typical daily dietary Li intake. That is clear from data in the Second French TDS (18) which has produced a figure for daily Li intake of 0.05 mg/day, and water contributed only 35% of Li intake in adults, i.e. only 0.015 mg — not all of which is 'tap-water, a significant % is bottled water.

It is reasonable to deduce from those data that tap-water constitutes only about 10% of total daily Li intake in most people, and considerably less in many others (e.g. those people who drink mainly bottled water).

It should be noted that the consumption of bottled spring-water is a multi-billion-dollar industry throughout the 'western' world and bottled waters have five times higher average Li concentrations: viz. median level of bottled waters is 0.010 mg/L vs. 002 mg/L for tap-water. Sales figures suggest that about one thousand bottles of 'mineral' water are sold per person per year (USA: 30 billion bottles in 2008). In Europe the figure is around 50 L per person/year, Austrian data indicates around 90 L (19-24).

Source: http://efbw.eu/bwf.php?classement=07 (European Federation of Bottled Waters).

The extensive data that now exist on Li levels in reticulated water (which usually comes from surface water, rather than subterranean water) is reviewed elsewhere. It is notable that psychiatric publications in this area appear either not to be aware of these data, or not to have taken any notice of them (the seminal citations below do not appear in the 'Psych' literature). Levels in surface water are generally extremely low, usually a few thousandths of a mg/L (<0.002 mg/L) and often as low a few millionths of a mg/L (0.000,005 mg/L) (19-21, 25), but levels in bottled mineral water from springs and underground supplies can be quite high: this has been assessed at 884 different European sites which had a median level of 0.010 mg/L. Thus, a typical bottled mineral water is equivalent to 5 L of tap-water which indicates that even low levels of consumption would substantially alter the Li intake from 'water'. A large proportion of subjects live in areas where the concentration in tap water is only a few millionths of mg/L and do not ingest any significant amount of Li from tap-water, compared to typical daily total dietary intakes.

That makes it almost certain that a great majority of the subjects in these samples will have been ingesting more Li from bottled mineral/spring-water than from tap-water, undoubtedly enough to make a complete and utter nonsense of the 'epidemiological' data.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Two fatal flaws

In summary, there are two fatal flaws invalidating research concerning endogenous Li in tap-water and its effect on humans. First, at endogenous levels of intake serum Li is not proportional to intake, it is tightly regulated within a narrow range. Secondly, even if the ingested amount of Li made a difference, it would not be as a result of varying Li levels in the reticulated water supply, because that is a minor contributor to total dietary Li intake.

Therefore, trying to correlate Li in tap-water with suicide, or any other state or condition, in different geographical areas with different water supplies is, *a priori*, irrational and without any scientific basis.

For those out there who still think that the refereeing system for scientific articles in journals is functioning adequately I suggest the example of the multiple papers that had been refereed (obviously inadequately) on this subject constitutes a solid refutation of that notion. Serotonin toxicity, my area of special expertise, proves this proposition even more decisively — the literature in this field has become a stream of utter nonsense; e.g. see here for the most egregious example to cross my desk for some time:

https://psychotropical.info/st-case-reports-update/

Publications about Lithium and Suicide

Here are yet more recent publications about Li and suicide to add to the steady trickle from the last two decades, which now seems to be turning into a flood (26-30). There are more, but since they are all a waste of time, money, and paper it is hardly worth bothering to search multiple databases for them.

All sorts of somewhat ill-considered suggestions have been aired, and picked-up by the media: e.g. McGrath et al recently stated: '… *the prospect that a relatively safe, simple, and cheap intervention (i.e. optimizing lithium concentrations in the drinking water) could lead to the primary prevention of dementia is a tantalizing prospect* (30), and others have made similarly ill-considered comments.

Lastly, the failure to measure serum levels of Li in a sample of subjects in the different areas who were exposed to different levels of Li in their tap-water, and to establish a reliable correlation between the two, is a quite extraordinary omission. One has to wonder where these researchers learnt their science and what they were thinking when they planned their projects (I will not even comment about the reviewers who approved the grants for these projects, some of which must have cost a great deal of money).

The irony is that they did not even need to do those measurements for themselves, because, as explained above, it has already been done for them, in more than 1000 subjects (11, 12) even though none of these researchers recognized that fact.

References

1. Greenland, S, Senn, SJ, Rothman, KJ, Carlin, JB, et al., Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur. J. Epidemiol., **2016**. 31(4): p. 337-50.

https://www.ncbi.nlm.nih.gov/pubmed/27209009

2. Phillips, CV and Goodman, KJ, The missed lessons of Sir Austin Bradford Hill. Epidemiol Perspect Innov, **2004**. 1(1): p. 3.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

https://www.ncbi.nlm.nih.gov/pubmed/15507128

3. Gillman, PK, Neuroleptic Malignant Syndrome: Mechanisms, Interactions and Causality. Mov. Disord., **2010**. 25(12): p. 1780-1790.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20623765

4. Gillman, PK, Neuroleptic malignant syndrome: half a century of uncertainty suggests a Chimera. Pharmacoepidemiol Drug Saf, **2010**. 19(8): p. 876-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20665596

5. Hernan, MA and Robins, JM, Estimating causal effects from epidemiological data. J. Epidemiol. Community Health, **2006**. 60(7): p. 578-86.

https://www.ncbi.nlm.nih.gov/pubmed/16790829

6. Muthen, B and Brown, HC, Estimating drug effects in the presence of placebo response: causal inference using growth mixture modeling. Stat. Med., **2009**. 28(27): p. 3363-85.

https://www.ncbi.nlm.nih.gov/pubmed/19731223

7. Maldonado, G and Greenland, S, Estimating causal effects. Int. J. Epidemiol., **2002**. 31(2): p. 422-9.

https://www.ncbi.nlm.nih.gov/pubmed/11980807

8. Subramanian, KS, Determination of metals in biofluids and tissues: sample preparation methods for atomic spectroscopic techniques. Spectrochimica Acta Part B: Atomic Spectroscopy, **1996**. 51(3): p. 291-319.

9. Lu, Y, Kippler, M, Harari, F, Grandér, M, et al., Alkali dilution of blood samples for high throughput ICP-MS analysis—comparison with acid digestion. Clin. Biochem., **2015**. 48(3): p. 140-147.

10. Clarke, WB, Guscott, R, Downing, RG, and Lindstrom, RM, Endogenous lithium and boron red cell-plasma ratios: normal subjects versus bipolar patients not on lithium therapy. Biol. Trace Elem. Res., **2004**. 97(2): p. 105-16.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14985621

11. Seidlerova, J, Staessen, JA, Maillard, M, Nawrot, T, et al., Association between arterial properties and renal sodium handling in a general population. Hypertension, **2006**. 48(4): p. 609-15.

https://www.ncbi.nlm.nih.gov/pubmed/16966578

12. Bochud, M, Staessen, JA, Woodiwiss, A, Norton, G, et al., Context dependency of serum and urinary lithium: implications for measurement of proximal sodium reabsorption. Hypertension, **2007**. 49(5): p. e34.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17389251

13. Cwynar, M, Gasowski, J, Gluszewska, A, Krolczyk, J, et al., Blood pressure, arterial stiffness and endogenous lithium clearance in relation to AGTR1 A1166C and AGTR2 G1675A gene polymorphisms. J Renin Angiotensin Aldosterone Syst, **2016**. 17(2): p. 1470320316655669.

https://www.ncbi.nlm.nih.gov/pubmed/27339867

14. Miller, NL, Durr, JA, and Alfrey, AC, Measurement of endogenous lithium levels in serum and urine by electrothermal atomic absorption spectrometry: a method with potential clinical applications. Anal. Biochem., **1989**. 182(2): p. 245-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2610339

15. Folkerd, E, Singer, DR, Cappuccio, FP, Markandu, ND, et al., Clearance of endogenous lithium in humans: altered dietary salt intake and comparison with exogenous lithium clearance. Am. J. Physiol., **1995**. 268(4 Pt 2): p. F718-22.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7733329

16. Nunes, MA, Viel, TA, and Buck, HS, Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimers disease. Curr Alzheimer Res, **2012**.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22746245

17. Shiotsuki, I, Terao, T, Ogami, H, Ishii, N, et al., Drinking spring water and lithium absorption: a preliminary study. German Journal of Psychiatry, **2008**. 11: p. 103-106.

18. Kalonji, E, Sirot, V, Noel, L, Guerin, T, et al., Nutritional Risk Assessment of Eleven Minerals and Trace Elements: Prevalence of Inadequate and Excessive Intakes from the Second French Total Diet Study. European Journal of Nutrition & Food Safety, **2015**. 5(4): p. 281-296.

19. Krachler, M and Shotyk, W, Trace and ultratrace metals in bottled waters: Survey of sources worldwide and comparison with refillable metal bottles. Sci. Total Environ., **2009**. 407: p. 1089-1096.

20. Demetriades, A, Reimann, C, and Birke, M, European Ground Water Geochemistry Using Bottled Water as a Sampling Medium in Clean Soil and Safe Water. 2012, Springer Netherlands: Dordrecht. p. 115-139.

21. Reimann, C and M, B, Geochemistry of European bottled water. 268 pp. Available online at:

http://www.schweizerbart.de/publications/detail/artno/001201002. 2010, Stuttgart: Borntraeger Science Publishers.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

22. Levei, E, Hoaghia, M, and Savastru, R, Quality assessment of Romanian bottled mineral water and tap water. Environmental monitoring and assessment, **2016**. 188(9): p. 521.

23. González-Weller, D, Rubio, C, Gutiérrez, ÁJ, González, GL, et al., Dietary intake of barium, bismuth, chromium, lithium, and strontium in a Spanish population (Canary Islands, Spain). Food Chem. Toxicol., **2013**. 62: p. 856-868.

24. Harari, F, Åkesson, A, Casimiro, E, Lu, Y, et al., Exposure to lithium through drinking water and calcium homeostasis during pregnancy: a longitudinal study. Environ. Res., **2016**. 147: p. 1-7.

25. Salminen, R, Batista, M, Bidovec, M, Demetriades, A, et al., Geochemical atlas of Europe. Part 1 – Background information, methodology and maps. Geological Survey of Finland, Espoo, Finland, **2005**: p. http://www.gtk.fi /.

26. Shimodera, S, Koike, S, Ando, S, Yamasaki, S, et al., Lithium levels in tap water and psychotic experiences in a general population of adolescents. Schizophr. Res., **2018**.

https://www.ncbi.nlm.nih.gov/pubmed/29895414

27. Parker, WF, Gorges, RJ, Gao, YN, Zhang, Y, et al., Association Between Groundwater Lithium and the Diagnosis of Bipolar Disorder and Dementia in the United States. JAMA Psychiatry, **2018**.

https://www.ncbi.nlm.nih.gov/pubmed/29799907

28. Ishii, N and Terao, T, Trace lithium and mental health. J Neural Transm (Vienna), **2018**. 125(2): p. 223-227.

https://www.ncbi.nlm.nih.gov/pubmed/29234900

29. Brown, EE, Gerretsen, P, Pollock, B, and Graff-Guerrero, A, Psychiatric benefits of lithium in water supplies may be due to protection from the neurotoxicity of lead exposure. Med. Hypotheses, **2018**. 115: p. 94-102.

https://www.ncbi.nlm.nih.gov/pubmed/29685207

30. McGrath, JJ and Berk, M, Could Lithium in Drinking Water Reduce the Incidence of Dementia? JAMA Psychiatry, **2017**. 74(10): p. 983-984.

https://www.ncbi.nlm.nih.gov/pubmed/28832875

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au