

Format for ANSWERING REVIEWERS



January 7, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: Is lithium potentially a trace element?

Author: Takeshi Terao

Name of Journal: *World Journal of Psychiatry*

ESPS Manuscript NO: 15355

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Replies to Reviewer 489383

1) The author focus on the lithium in the drinking water. What about lithium in the common food products? Which products are reach of lithium? Are there differences between lithium levels in the food between cuisines? Are there any correlations between lithium in the food and mental health?

We added the following sentences in **Introduction**.

“Lithium is taken up by all plants, although it appears not to be required for their growth and development. At high levels in the soil, lithium is toxic to all plants, causing a chlorosis-like condition. Uptake and sensitivity to lithium are species dependent. Consequently, grains and vegetables have 0.5-3.4 mg/kg of lithium, dairy products have 0.5 mg/kg of lithium and meat has 0.012 mg/kg (Schrauzer , 2002). Although there has been a study showing effects of nutritional lithium supplementation on mood (Schrauzer and de Vroey, 1994), no study could directly investigate the association between lithium in the food and mental health.”

2) The primary indication of lithium as a CNS drug is bipolar disorder, particularly, the manic episodes. It would be therefore important to address the correlation between lithium as a trace element and mania.

We added the following sentences in **Trace Lithium Effect on Mania and Psychosis**.

“To our knowledge, there has been no reports on effects of lithium as a trace element on mania. This is probably because in a routine psychiatric setting we prescribe about 600-1,000 mg per day of lithium to our patients for producing approximately 0.4 – 1.0 mEq/L of therapeutic lithium levels for mania, which is much larger than the lithium levels of drinking water. Therefore, it seems likely that apart from anti-manic effects of lithium, anti-aggressive effects of lithium could potentially prevent suicide in those who take lithium contained drinking water for a long time (Terao, 2008 & 2009).”

3) Are there any correlations between lithium consumption and schizophrenia and other psychotic illnesses?

We added the following sentences in **Trace Lithium Effect on Mania and Psychosis**.

“Nonetheless, there has been a study showing that the incidence of patient’s first admissions and prevalence of readmission as well as the diagnosis of psychosis, neurosis, and personality disorder to state mental hospitals from each Texas counties was inversely proportional to the lithium content of their residential drinking water (Dawson et al, 1970).”

4) Potential mechanisms of action of lithium as a CNS drugs should be reminded.

We added the following sentences in **Trace Lithium Effect on Suicide**.

“Taking the fact into consideration that lithium has been reported to increase the volume of the prefrontal cortex and anterior cingulate gyrus (Monkul et al, 2007) it seems likely that lithium may at least partially exert its antisuicidal effect via reinforcing “top-down brakes” of aggressive action. Since lithium has been shown to increase the volume and function of the limbic system, such as the hippocampus (Yucel et al, 2007), antisuicidal effects of lithium may consist of both reinforcing “top-down brakes” and decreasing “bottom-up drive.” Therefore, lithium may have superior antisuicidal effects relative to other mood stabilizers (Terao, 2008).”

5) In addition to its beneficial effects on the CNS, aversive and side effects lithium should be reminded.

We added the following sentences in **Conclusion**.

“Moreover, although it seems probable that such low levels of lithium in drinking water are far below the levels required to produce aversive and side effects, it is also important to assess side-effects of lithium in drinking water on thyroid function, pregnant women, the unborn, and other potent impairment.”

Replies to Reviewer 2445250

1. The definition of trace element used here is the direct citation from the Bowen's Trace Elements in Biochemistry (1966) and therefore the reference is needed.

Thank you very much and I added the reference.

2. When referring to the important effects of lithium on health, its experimental anti-cancer effects should be mentioned (Huili Li et al., 2014). Likewise, an increased cancer risk in patients with bipolar affective disorder (BarChana et al., 2008) also can be associated with long-term lithium treatment.

We added the following sentences in **Trace Lithium Effect on Cancer**.

“Although experimental anti-cancer effects of lithium have been shown (Huili Li et al., 2014), the range of lithium levels used in the study was 10 mM to 60 mM, which is clearly in the toxic level. Therefore, toxic effects of lithium might have brought about apoptosis in colon cancer cell line. Actually, enhanced but not reduced cancer risk was shown in bipolar disorder patients who were probably receiving long-term lithium treatment (BarChana et al, 2008). At the moment, anti-cancer effects of lithium is yet to be determined.”

3. SIRs should read as Standardized Incidence Ratios.

I wrote SMRs but not SIRs. However, I spell SMR out as Standardized Mortality Ratio.

4. English errors should be corrected (e.g., "...how levels are required..." should read "...what levels are required...").

Thank you very much and I corrected them.

Replies to Reviewer 2445209

Dear author, the content of your Editorial is interesting, but the language should be revised by a native speaker.
The reviewer

I asked a native speaker to correct the manuscript.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Psychiatry*.

Sincerely yours,

A rectangular box containing a handwritten signature in black ink. The signature consists of two stylized, cursive-like characters that appear to be 'T' and 'T'.

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