



## Even very low but sustained lithium intake can prevent suicide in the general population?

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### SUMMARY

Although several meta-analyses have shown anti-suicidal properties of lithium in treating patients with mood disorders, these effects may be unrelated to the mood-stabilizing effects. Some epidemiological studies suggest 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. We hypothesize that even very low but sustained lithium intake can prevent suicide in the general population. If this is the case, increasing lithium levels of drinking water could potentially reduce the risk of suicide, and justify administering lithium to tap water.

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### Anti-suicidal effects of lithium and serum levels

Several meta-analyses have shown anti-suicidal effects of lithium [1–3] in patients with mood disorders. For example, Cipriani et al. [1] reviewed randomized controlled trials that primarily compared lithium with placebo in long-term prophylactic treatment for mood disorders, and showed that patients who received lithium were less likely to die by suicide (odds ratio = 0.26; 95% confidence interval = 0.09–0.77). In the reported studies [1–3] serum lithium was maintained at so-called therapeutic levels (e.g., 0.4–1.2 mmol/L) and although the studies were not primarily designed to detect anti-suicidal effects of lithium, the results can be regarded as important indirect evidence for anti-suicidal effects of lithium in patients with mood disorders.

Recently, Severus et al. [4] reviewed studies reporting on the long-term treatment of mood disorders in which patients were assigned to precisely specified target ranges of lithium level. They revealed that the minimum efficacious lithium level in the long-term treatment of bipolar disorder was 0.4 mmol/L with optimal response achieved at levels between 0.6 and 0.75 mmol/L, while higher levels may benefit patients with predominantly manic symptoms. As such, it appears that the mood-stabilizing effects of lithium at therapeutic levels are confirmed but what serum lithium levels are required for anti-suicidal effects? And are the levels comparable to those for mood-stabilizing effects?

Interestingly, Müller-Oelinghausen et al. [5] revealed that a significant reduction in suicide attempts occurred even in poor

responders to lithium prophylaxis for mood disorders. Therefore, it seems probable that the anti-suicidal effects of lithium may be unrelated to the mood-stabilizing effects. Moreover, the anti-suicidal effects of lithium may work at lower levels than so-called therapeutic levels and not only in patients with mood disorders but also in the general population.

### Lithium in drinking water and suicide rate

Schrauzer and Shrestha [6] investigated the association between lithium in drinking water and suicide rate in Texas. In their study, lithium levels in the drinking water of 27 Texas counties were significantly associated with reduced risk of suicide. Recently, Gonzalez et al. [7] performed a replication study in the same Texas counties, but they failed to reconfirm the association by using Pearson correlation coefficient. One of the reasons for the non-significant association may be that the difference in population of each county was large ranging from 46,011 (Val Verde) to 3,540,965 (Harris).

In our recent study [8], lithium levels in drinking water (tap water) of all the 18 municipalities of Oita prefecture, an average (economically, culturally, and politically) prefecture in Japan, was investigated in relation to its association with suicide rates in each municipality. Because of greater differences in population size across the 18 municipalities and in contrast to Gonzalez et al. study [7], weighted least squares regression analysis adjusted for the size of each population was used to investigate the association of lithium levels in drinking water in relation to suicide rate. As a result, lithium levels in drinking water of 18 municipalities of Oita ranged from 0.7 to 59 µg/L and the average of the standardized mortality

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ratio (SMR) of suicide rate in Oita for 2002–2006 was 105 (range 60–181), which corresponds well with the average SMR for Japan (100). The SMRs of suicide rate across the 18 municipalities were significantly and negatively associated with lithium levels in drinking water ( $\beta = -0.65$ ,  $p < 0.004$ ).

The results provided some evidence that even very low lithium levels induced by routine consumption of lithium from tap water may have anti-suicidal effects and that within these levels there is a dose–response relationship. However, it should also be noted that serum lithium levels of the residents were not measured. Moreover, as these findings were derived from a local prefecture and other factors such as psychosocial and economic factors were not taken into consideration, it is difficult to be conclusive. Nonetheless, the large size of  $\beta$  suggests that even very low lithium levels reduce suicide *both* in patients with mood disorders *and* in the general population because if the anti-suicidal effects was limited to patients with mood disorders alone, the size of  $\beta$  might have been considerably smaller.

The question arises as to why such low lithium levels show anti-suicidal effects? This is a very difficult question, but one possibility is that long-term exposure to lithium by routinely drinking water containing lithium may be a factor which mitigates low absolute levels.

### Hypothesis

We hypothesize that even very low but very long lithium levels can prevent suicide in the general population.

### Supposed mechanism(s) of anti-suicidal effects of lithium

Suicide is the most dangerous self-directed aggressive behavior. Siever [9] suggested that the processing of stimuli in relation to past emotional conditioning encoded in the amygdala and related limbic regions will trigger the “bottom–up drive” to an aggressive action, while the orbital frontal cortex and anterior cingulate gyrus will provide “top–down brakes” of the aggressive action. In studies of suicide, the orbital prefrontal cortex and anterior cingulate gyrus appear to play important roles in suppressing aggression via inhibitory projection to the amygdala [10]. Actually, positron emission tomography studies have shown reduced response in the prefrontal cortex and anterior cingulate gyrus after fenfluramine challenge to individuals who have attempted suicide [10].

Taking the fact into consideration that lithium has been reported to increase the volume of the prefrontal cortex and anterior cingulate gyrus [11], it seems likely that lithium may at least partially exert its anti-suicidal effect via reinforcing “top–down brakes” of aggressive action. Also, since lithium has been shown to increase the volume and function of the limbic system, such as the hippocampus [12], the anti-suicidal effects of lithium may consist of both reinforcing “top–down brakes” and decreasing “bottom–up drive” [13].

Although these explanations are plausible, it should be noted that such effects have been confirmed only in so-called therapeutic lithium levels, but not in the very low lithium levels.

### Testing the hypothesis

First, the findings of our study should be replicated in other areas and adjusted for confounding factors such as psychosocial and economical factors. Since we showed that yearly total sunshine could predict suicide rate [14], this factor should be taken into consideration. Second, serum lithium levels should be measured in residents to confirm the significantly positive association between lithium levels in their serum and in drinking water. Furthermore, it is necessary to confirm the significantly negative association between serum lithium levels and suicide rate.

Next, by using the above data, serum lithium levels for anti-suicidal effects should be identified. Finally, it is desirable to determine whether very low but very long lithium exposure can enhance neurotrophic factors, neuroprotective factors and/or neurogenesis and can really change the volume and function of the prefrontal cortex, anterior cingulate gyrus, amygdala and related limbic regions in the context of anti-suicidal effects of lithium.

If the hypothesis is proven then there is evidence to support the case that increasing lithium levels of drinking water can reduce the risk of suicide, which may justify administering an adequate dose of lithium to tap water. Such low levels of lithium are far below that required to produce lithium intoxication or other side effects and therefore potentially offer an easy, cheap and substantial strategy for world-wide suicide prevention.

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