

# Naturally Occurring Low-Dose Lithium in Drinking Water

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Recently, a series of ecological studies<sup>1–7</sup> on antisuicidal properties of naturally occurring lithium contents in drinking water have sparked interest among researchers. In this issue, Ishii and colleagues<sup>8</sup> present further argument for the hypothesis that even low lithium doses—or rather, doses of lithium at a supplemental level—might have their place in suicide prevention.

With limitations, there is some evidence from randomized controlled trials (RCTs) supporting lithium in therapeutic doses as a suicide preventative in individuals with unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia, or rapid cycling. Although based on secondary analyses of spontaneous reports of suicidal behavior and completed suicide rather than systematic assessment of suicidality during RCTs, recent meta-analyses by Cipriani et al<sup>9,10</sup> and Baldessarini et al<sup>11</sup> suggest that the risk reduction of suicide might be as high as 60%–80%. These RCTs included measures of plasma lithium levels between 0.6–1.1 mmol/L, which corresponds to recommended doses of 600–1,200 mg/d lithium carbonate by mouth.<sup>9,10</sup> However, the estimates of risk reduction by lithium have been criticized as too optimistic, and the first prospective RCTs of lithium versus valproate in bipolar disorder showed no difference in suicide events or attempts between both compounds,<sup>12</sup> which share a common mode of action on glycogen synthase kinase-3β (GSK-3β), brain-derived neurotrophic factor (BDNF), and other neurobiological markers.<sup>13</sup>

Besides the general question about lithium's antisuicidal properties, the important point with ecological studies like the one presented by Ishii and colleagues<sup>8</sup> is that natural lithium contents of tap water range up to 1 mg or more of dissolved lithium per liter per day (1 L of water with 1 mg/L lithium per day corresponds to 6.9 mg lithium carbonate per day), depending on the geographic origin of the drinking water.<sup>2,14</sup> Under the assumption that individuals drink not more than 2 L water per day (corresponding to a daily dose of 13.8 mg lithium carbonate by mouth), such an intake would result in a daily dose of approximately 1% of a therapeutic lithium dose.

However, Ishii and colleagues<sup>8</sup> report even much lower doses of up to 130 µg/L lithium drinking water, but they are in the range found in previous ecological studies from Japan, eg, 59 µg/L in Oita<sup>1</sup> or even only 12.0 µg/L in Aomori prefecture.<sup>6</sup> From a clinical perspective, preventing suicides

in individual patients with such low dosages of lithium seems implausible.

However, before rejecting the plausibility of the results, we should bear in mind that ecological studies are not designed to address individual cases or to inform about causality. They serve to generate hypotheses, which in turn should be modeled and evaluated in further appropriate study designs. Prospective low-dose lithium RCTs would be necessary, but the power of such studies would be limited by the fact that suicides are rare events,<sup>15,16</sup> and the attempt to conduct a trial even with standard doses of lithium has recently failed.<sup>17</sup> It is also likely that effects of lithium on suicide in low-dose trials would be lower than those in established standard-dose trials, thus further limiting the power of such prospective studies. Therefore, prospective standard- and low-dose lithium trials for suicidal ideation or suicide attempts still remain a challenge.

A more promising way for future low-dose lithium trials would be the focus on neuroprotective effects in other psychiatric and neurologic disorders<sup>18</sup> that are better biologically understood than suicidality. For example, clinical evidence of low-dose lithium is growing for Alzheimer's dementia. Similar to bipolar patients on continuous standard doses of lithium who, when compared to patients without lithium were found to be less likely develop Alzheimer's disease,<sup>19</sup> patients with Alzheimer's disease were shown to have their cognitive impairment stabilized with even low doses of lithium (300 µg/d by mouth) over 15 months.<sup>20</sup>

Although the effects of low-dose lithium supplementation are still not fairly understood, a rationale might exist for individual supplementation with lithium for persons from lithium-depleted regions. A minimum daily requirement of 1,000 µg of dissolved lithium per day for healthy adults has been postulated by Schrauzer,<sup>14</sup> a dosage similar or equal to environmental lithium levels ingested daily in some geographic areas.<sup>1–6</sup> In fact, some natural mineral waters contain even much higher levels of lithium and are consumed unsupervised every day.<sup>14</sup> But with accumulating evidence for possible long-lasting neurobiological effects of low-dose lithium, regular lithium supplementation is recommended to take place only under a monitoring by a physician. Further research on the effects of low-dose lithium is necessary and will shed light on its complex therapeutic effects.

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