



# Lithium Suicide Prevention: A Brief Review and Reminder

## ABSTRACT

Suicide is a major public health problem throughout the world, occurring in over 800,000 people annually. Mood disorders are a common psychopathology and are a significant risk factor for suicidality. Lithium pharmacotherapy has been shown to reduce symptoms of suicidal behavior, especially in long-term patient interventions. Reasons for this remain unclear. Lithium treatment for individuals with affective disorders appears underutilized. Use of lithium is thought to reduce risk for suicidality, even if mood stabilization is not achieved and serum concentration is lower than the conventionally accepted therapeutic blood level ranges. In this article, the authors review the currently available literature on lithium's effect on suicidality and provide discussion on proposed mechanisms of action. This brief report serves as an important reminder to clinicians to include lithium pharmacotherapy in their armamentarium for treatment of affective disorders, especially when symptoms of suicidality are present.

**KEYWORDS:** lithium, suicide, suicide prevention, pharmacotherapy, risk of suicide, suicidal ideas

by SIMRAT KAUR SARAI, MD; HEMA MADHURI MEKALA, MD; and STEVEN LIPPMANN, MD

*Drs. Sarai and Mekala are research scholars and Dr. Lippmann is Emeritus Professor for the Department of Psychiatry and Behavioral Sciences at University of Louisville School of Medicine in Louisville, Kentucky.*

*Innov Clin Neurosci.* 2018;15(11–12):30–32

Suicide is a leading cause of death globally among all age groups.<sup>1</sup> More than 800,000 people die by suicide every year, which is about one person every 40 seconds.<sup>1</sup> For individuals aged 15 to 39 years, suicide is the most common cause of death.<sup>1</sup> The ratio of suicide attempts to death by suicide in youth is estimated to be approximately 25 to 1, compared with approximately 4 to 1 among elderly persons.<sup>1</sup>

About 32 percent of Americans will suffer from a mood disorder during their lifetime,<sup>2</sup> giving them a 30-fold greater risk of suicide compared with the general population.<sup>1</sup> Patients with bipolar disorder have a high risk for suicidal ideation, attempts, and completions. Approximately 25 to 50 percent of patients with bipolar disorder attempt suicide at least once, and their attempts are more frequently lethal than those by individuals with other psychiatric disorders; the ratio of attempts to completed suicides among patients with bipolar disorder is 3 to 1, compared with 30 to 1 among the general population.<sup>3</sup> Individuals with bipolar disorder use significantly more lethal methods of suicide than individuals with a bipolar I diagnosis.<sup>1</sup>

## SUICIDE PREVENTION

When compared with placebo treatment, lithium pharmacotherapy is associated with

fewer suicide attempts and fewer deaths from other causes.<sup>4</sup> Prescribing lithium to patients with bipolar disorder is associated with a lower rate of deliberate self-harm compared with those taking carbamazepine.<sup>5</sup> Lithium has been shown to reduce the risk of suicide and mortality in people with unipolar and bipolar depressive disorders.<sup>5</sup> Long-term lithium pharmacotherapy has been shown to diminish the suicide rate among patients who take it, regardless of sex or age.<sup>6</sup> Even refilling a lithium prescription once has been associated with a lower risk for suicide compared with those who never refill their prescription after filling it the first time; the risk for suicide decreases the more times a patient refills his or her lithium prescription.<sup>6</sup> Despite recommended guidelines for prescribing lithium to patients with affective disorders in acute and/or long-term therapy, the number of actual prescriptions provided is still under-represented.<sup>7</sup>

The anti-suicidal properties of lithium might be unrelated to the mood-stabilizing effects. There is a significant reduction in the number of suicide attempts among individuals who take lithium, even in those who do not respond well to lithium's mood symptom prophylaxis.<sup>8,9</sup> The anti-suicidal aspects of lithium appear to be as effective at low concentrations as at therapeutic levels.<sup>8</sup> Sustained low doses of lithium intake have been shown to decrease

**FUNDING:** No funding was provided.

**DISCLOSURES:** The authors have no conflicts of interest relevant to the content of this article.

**CORRESPONDENCE:** Steven Lippmann, MD; Email: [steven.lippmann@louisville.edu](mailto:steven.lippmann@louisville.edu)

suicidality.<sup>9</sup> Some researchers have even theorized that adding lithium to drinking water could potentially reduce the rate of suicide among the general population.<sup>8,9</sup> However, the actual concentration needed to induce anti-suicidal effects in people with affective disorders remains unclear.<sup>10</sup> Suicide prevention in patients taking lithium has been documented when the serum concentrations are within a therapeutic range of 0.5 to 1.0mmol/L.<sup>10</sup> The lowest efficacious lithium level in the long-term treatment of patients with bipolar disorder has been shown to be 0.4mmol/L, with optimal response achieved at concentrations between 0.6 and 0.75mmol/L.<sup>10</sup> Higher levels might benefit those with manic symptoms.<sup>10</sup>

The duration of lithium pharmacotherapy needed for suicide prevention is important. Lithium is recommended as a long-term therapy for patients with depression and bipolar disorder; alternative medications should be considered for shorter interventions.<sup>2</sup> Even among in patients with only poor-to-moderate clinical response, researchers have observed a decrease in the number of suicide attempts when the patients take lithium compared with those individuals who have not yet been prescribed the drug.<sup>11</sup> Research supports the recommendation that lithium pharmacotherapy for treatment of affective disorders should be considered for anyone at high risk for suicide, even if mood-stabilization is not achieved.<sup>12</sup>

## SIDE EFFECTS

Lithium has been shown to induce increased thirst, nausea, diarrhea, polyuria, and/or tremor. Some of these side effects diminish or disappear following several weeks of treatment. Other potential long-term adverse effects are weight gain, edema, goiter, hypothyroidism, hyperparathyroidism with hypocalcemia, acne, psoriasis, and/or hair loss. Kidney dysfunction, significant nephrogenic diabetes insipidus, and possible renal failure are other potential adverse effects. Lithium intoxication is a serious complication that requires emergency medical care. Hemodialysis is indicated in cases of severe toxicity.

The benefits of lithium usually outweigh the adversities, especially with proper care and monitoring, and it is generally safe and

effective.<sup>1</sup> Even if a patient exhibits only partial response, the continuation of lithium therapy should be considered, especially among patients in which suicidal ideation is an active concern.<sup>1</sup>

## MECHANISMS OF ACTION

Lithium is a mood-stabilizing medication; therefore, patients who respond well are expected to experience fewer affective episodes, which logically would also decrease the risk for suicidal behavior. Diminished aggression and impulsivity have been observed among patients taking lithium, as well.<sup>13</sup>

Corticotrophin-releasing hormone alteration and noradrenergic and serotonergic system dysfunction have been implicated in suicidal thinking due to a lowered cerebral level of tryptophan and serotonin. Lithium, through its serotonin-agonistic properties, is believed to counteract this deficiency,<sup>10</sup> which might influence serotonin metabolism. Platelet serotonin 2<sub>A</sub> receptor up-regulation in people with psychiatric disorders is believed to alter suicidal behavior.<sup>14</sup> Lithium might also increase glutamate and γ-aminobutyric acid (GABA) ergic systems,<sup>15</sup> as well as augment GABA<sub>B</sub> receptors in the hippocampus.<sup>9</sup> Lithium is believed to enhance glutamine synthetase and brain glutamine levels, which might also diminish suicidal behaviors.<sup>14–16</sup> Animal research suggests that lithium might suppress impulsive behavior, thereby decreasing the risk for suicidal behavior in humans.<sup>1</sup> Inhibitory action on adenylyl cyclase and modification of inositol content also might modulate suicidal behavior.<sup>17</sup> The potential effects lithium has on gene expression at glycogen synthase kinase 3 and at transcription factors are currently being investigated.<sup>18</sup> Patients with bipolar disorder taking lithium evidence larger hippocampus volumes, even after short exposures.<sup>19</sup>

## CONCLUSION

Research supports the theory that long-term lithium pharmacotherapy has mitigating effects on suicidal behavior among patients with affective disorders. Whether this effect occurs early in treatment is not known.<sup>20</sup> The psychological effects precipitated by lithium exposure that tend to reduce suicidal behavior remain unclarified. It is important to learn more about the level of lithium required for it

to achieve anti-suicidal properties, as well as assess its anti-suicidal effects in patients with other psychiatric illnesses. The therapeutic efficacy of lithium and its effect on brain chemistry for people at high risk for suicide needs further study.<sup>1,11,21,22</sup>

For nearly 70 years, lithium has been recognized as an important method of treatment as a mood stabilizer for affective disorders. More recently, lithium has been increasingly recognized as a mitigator of suicidal behavior, even among those patients who do not respond to its mood-stabilizing effects.<sup>23–25</sup>

## REFERENCES

- Lewitzka U, Severus E, Bauer R, et al. The suicide prevention effect of lithium: more than 20 years of evidence—a narrative review. *Int J Bipolar Disord.* 2015;3(1):1–6.
- Pederson T. Lithium still tops in reducing suicide risk in depression, bipolar disorder. PsychCentral site. Last updated: 8 Aug 2018. <https://psychcentral.com/news/2013/06/29/lithium-still-tops-in-reducing-suicide-risk-in-depression-bipolar-disorder/56637.html>. Accessed December 8, 2017.
- Torem MS. Beyond lithium: using psychotherapy to reduce suicide risk in bipolar disorder: novel approach teaches patients to “disown” suicidal thoughts, internalize future. *Curr Psychiatry.* 2011;10(10):39.
- Kopman J. Lithium remains extremely effective in preventing suicide, study finds. Everyday Health site. 27 Jun 2013. <https://www.everydayhealth.com/depression/lithium-remains-extremely-effective-in-preventing-suicide-study-finds-5218.aspx>. Accessed December 8, 2017.
- Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ.* 2013;346:36–46.
- Kessing LV, Søndergård L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. *Arch Gen Psychiatry.* 2005;62(8):860–866.
- Pfennig A, Bauer M. S3 guidelines on bipolar disorders are contemporary and important instruments for clinical practice [in German]. *Nervenarzt.* 2013; 84:874–875.
- Terao T, Goto S, Inagaki M, Okamoto Y. Even very low but sustained lithium intake can prevent suicide in the general population? *Med Hypotheses.* 2009; 73(5):811–812.

9. Lewitzka U, Bauer M. What role does (should) lithium play in suicide treatment/prevention? *Psychiatric Times*. 2014;31(12):10–13.
10. Steiner J, Bogerts B, Sarnyai Z, et al. Bridging the gap between the immune and glutamate hypotheses of schizophrenia and major depression: potential role of glial NMDA receptor modulators and impaired blood–brain barrier integrity. *World J Biol Psychiatry*. 2012;13(7):482–492.
11. Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. *J Clin Psychiatry*. 1999;60:77–84.
12. Ahrens B, Müller-Oerlinghausen B. Does lithium exert an independent antisuicidal effect? *Pharmacopsychiatry*. 2001;34(04):132–136.
13. Comai S, Tau M, Pavlovic Z, Gobbi G. The psychopharmacology of aggressive behavior: a translational approach, part 2—clinical studies using atypical antipsychotics, anticonvulsants, and lithium. *J Clin Psychopharmacol*. 2012;32(2):237–260.
14. Kalkman HO. Circumstantial evidence for a role of glutamine-synthetase in suicide. *Med Hypotheses*. 2011;76:905–907.
15. Marcus SR, Nadiger HA, Chandrakala MV, et al. Acute and short-term effects of lithium on glutamate metabolism in rat brain. *Biochemical Pharmacol*. 1986;35(3):365–369.
16. Motohashi N. GABA receptor alterations after chronic lithium administration: comparison with carbamazepine and sodium valproate. *Prog Neuropsychopharmacol Biol Psychiatry*. 1992;16:571–579.
17. Kovacsics CE, Gottesman II, Gould TD. Lithium's antisuicidal efficacy: elucidation of neurobiological targets using endophenotype strategies. *Annu Rev Pharmacol Toxicol*. 2009;49:175–198.
18. Can A, Schulze TG, Gould TD. Molecular actions and clinical pharmacogenetics of lithium therapy. *Pharmacol Biochem Behav*. 2014;123:3–16.
19. Yucel K, Taylor VH, McKinnon MC, et al. Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology*. 2008;33(2):361.
20. Lewitzka U, Jabs B, Fülle M, et al. Does lithium reduce acute suicidal ideation and behavior? a protocol for a randomized, placebo-controlled multicenter trial of lithium plus treatment as usual (TAU) in patients with suicidal major depressive episode. *Bio Med Central Psychiatry*. 2015;15(1):117.
21. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2007;68:935–940.
22. Bschor T, Lewitzka U, Pfennig A, Bauer M. Twenty-five years of lithium augmentation [German]. *Nervenarzt*. 2007;78:1237–1247.
23. Schou M. Fifty years of treatments for bipolar disorder: a celebration of John Cade's discovery. *Aust N Z J Psychiatry*. 1999;33:51–122.
24. Khan A, Khan SR, Hobus J, et al. Differential pattern of response in mood symptoms and suicide risk measures in severely ill depressed patients assigned to citalopram with placebo or citalopram combined with lithium: role of lithium levels. *J Psychiatr Res*. 2011;45(11):1489–1496.
25. Tondo L, Baldessarini RJ. Antisuicidal effects in mood disorders: are they unique to lithium? *Pharmacopsychiatry*. 2018; doi: 10.1055/a-0596-7853. **ICNS**