What Role Does (Should) Lithium Play in Suicide Treatment/Prevention?

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By Ute Lewitzka, MD [1] and Michael Bauer, MD, PhD [2]

An interesting pharmacological approach in terms of anti-suicidal strategies is the use of lithium for treatment of patients with affective disorders. Details here.

Suicide is a global phenomenon, and on September 4, 2014, the World Health Organization published the first report on suicide prevention. The report indicates that more than 800,000 people die by suicide every year—almost 1 person every 40 seconds. Although suicide occurs all over the world, approximately 75% of all suicides occur in low- and middle-income countries. It occurs in all age-groups; however, the highest rates are among persons 70 years and older. Suicide is the second leading cause of death in 15- to 29-year-olds. In most countries, suicide is more prevalent among men.

Working on suicide prevention strategies is of great importance and should include all facets of influence on suicidal behavior, such as pharmacological, psychological/psychotherapeutic, and sociological. Not only is there a need for more research on the neurobiological underpinnings in the evolution of psychiatric diseases (as one of the most important risk factors for suicide) and suicidality, but also more research on helpful therapeutic strategies is urgently needed.

An interesting pharmacological approach in terms of antisuicidal strategies is the use of lithium for treatment of patients with affective disorders. Lithium, one of the oldest substances used in modern psychiatry, has proved to have a suicide-preventing effect in the long-term treatment of affective disorders. There is evidence that lithium, independent of its mood-stabilizing effect, decreases suicides in patients with affective disorders. Most of the lithium studies were originally undertaken to investigate the drug’s mood-stabilizing effects. Findings about suicides or suicide attempts were secondary outcomes. Some of the evidence was drawn from meta-analyses (including large samples). Because lithium is only used in patients with affective disorders, no studies show an antisuicidal effect of lithium in patients with other psychiatric diseases, such as schizophrenia. Lithium was found to decrease aggressiveness in children with disruptive behavior. Other studies investigated lithium’s effect in patients with brain injuries who exhibited uncontrollable unstable behavior as well as in persons (eg, prisoners) with a high grade of impulsive behavior, such as certain types of personality disorders. It may be that lithium exerts an antisuicidal effect because it reduces aggression and impulsivity.

It is not clear what concentration of lithium is needed for the anti-suicidal effects in patients with affective disorders. Long-term studies show suicide-preventing effect in patients treated with lithium whose serum concentrations are within the normal range (approximately 0.5 to 1.0 mmol/L). On the other hand, a number of studies have shown that the concentration of lithium in drinking water might influence the suicide rate.

**Mechanism behind the suicide prevention effect of lithium**

Very early research postulated that the antisuicidal effect of lithium is mediated by its serotonergic influences. Lithium’s therapeutic effect has been related to its ability to enhance serotonin function and neurotransmission. Lithium has an influence on serotonin metabolism at the levels of release, turnover, synthesis, reuptake, and the sensitivity of different receptor subtypes. A study by Pandey and colleagues indicates an up-regulation of platelet serotonin 2A receptors in patients with bipolar disorder or schizoaffective disorder, with an increase in platelet serotonin 2A receptors in patients with suicidal behavior. Because other medications (eg, SSRIs) also influence the serotonergic system, this hypothesis seems to be only a contributing part of the mechanism behind the effects. Other researchers investigated the effect of lithium on prolactin release or on other transmitters, such as dopamine. Interestingly, clozapine (commonly used in treatment-refractory schizophrenia) has also shown a suicide-preventing effect. Another area of interest is the influence of lithium on glutamate and the γ-aminobutyric acid (GABA)ergic system. The effects of glutamate as well as of GABA were discussed in an article by Kalkman. A preclinical study showed that...
therapeutically relevant doses of lithium for 7 days led to a significant increase in the activity of glutamine synthetase and brain glutamine levels.\textsuperscript{13} The researchers concluded that the therapeutic effect against suicide is related to the increase in glutamine synthetase expression. Since the inhibition of glutamine synthetase might lead to a deficit in glutamine with consequent GABA and glutamate deficit, even simple food supplementation with glutamine might help reduce suicide. Up to now, no other studies investigated this hypothesis. Lithium also leads to an increase of GABA\textsubscript{B} receptors in the hippocampus.\textsuperscript{14}

More recently, the effects of lithium on second messenger pathways (eg, adenylate cyclase, inositol-metabolism) were studied. It is hypothesized that effects such as inhibitory action on adenylyl cyclase or the modification of inositol content play a role in the modulation of suicidal behavior.\textsuperscript{15} The effects of lithium on gene expression (eg, the modulation of glycogen synthase kinase 3) and the influence on transcription factors are also a focus of research. Recently, Can and colleagues\textsuperscript{16} published a comprehensive overview on several neurobiologically based actions of lithium.

Another area of interest is the influence of lithium on structural changes in the brain. An imaging study by Yucel and colleagues\textsuperscript{17} demonstrated that bipolar patients who received lithium had an increase in volume of the hippocampus and the hippocampal head. Lithium can exert structural effects on the hippocampus even after a short time of exposure. All described actions of lithium are discussed as explanations for its therapeutic (mood-stabilizing) effect on affective disorders. There is no clear evidence that the same mechanisms are accountable for its suicide-preventing effect, especially since the origin and neurobiological underpinnings of suicidal behavior are not fully understood.

**Clinical implications**

Lithium has proved to be an effective augmentation strategy for the treatment of depressive episodes.\textsuperscript{18,19} However, despite the current evidence and corresponding recommended guidelines for the acute and maintenance therapy for affective disorders, the use of lithium is still underrepresented.\textsuperscript{20} Lithium therapy for patients with affective disorders should be especially considered in those who have a potential suicide risk, even if the mood-stabilizing effect is not sufficiently achieved. This consideration is justified by the observation of a certain independency of the suicide-preventing effect.\textsuperscript{21}

The physician should be especially cautious when termination of lithium therapy is planned because of an insufficient mood-stabilizing effect. In that case, the maintenance of lithium therapy could be debated only from the antisuicidal perspective; however, it is clear that this kind of use is off-label and therefore needs a documented explanation.

As stated in several guidelines, lithium therapy is indicated in patients with bipolar disorder and recurrent depressive disorder. Because of its antidepressive effect, it can also be used as augmentation strategy when an antidepressant alone is not sufficient. There are some indicators that are known to be predictors of a good lithium response (Table 1). It is well known that lithium is especially effective in patients with a typical course (eg, full remission between episodes, only mood-congruent psychotic symptoms, no psychiatric comorbidity). It is often less effective in bipolar patients with an atypical course (eg, residual symptoms between the episodes, mood-incongruent psychotic features, psychiatric comorbidity).

If properly used, lithium therapy is safe and effective. Historically, lithium was used in higher dosages, which led to serum peaks and therefore to potential kidney damage. This risk is lower when lithium is used under standardized conditions with the recommended monitoring. The comprehensive guide Lithium in Neuropsychiatry\textsuperscript{22} provides a broad outline of the many uses of lithium in neuropsychiatric disorders as well as indications for its use in internal medicine. It addresses various aspects of effective and safe use of lithium for clinical practice.

**Lithium for patients with affective disorders**

Once the patient has been assessed, an algorithm (Figure) can be used to determine whether there is a positive indication for lithium therapy. If there are no contraindications (Table 2), tailor the dosage carefully because there are a number of different lithium preparations available. Since lithium’s half-life is approximately 24 hours, once-a-day dosing is possible. However, from the clinical perspective, patients sometimes have fewer adverse effects when they take lithium twice a day. Dosing also depends on the type of lithium preparation (rapidly absorbed or slow release). The recommended serum concentration is between 0.6 and 0.8 mmol/L. Higher serum levels are more effective in preventing relapses, but they also increase the risk of adverse effects. After the first week of therapy, the serum lithium level should be measured 12±1 hours after the last dose has been taken to determine whether the dosage needs to be adjusted.\textsuperscript{22}
Monitoring serum lithium levels at least every 6 months is important so that any reduction in kidney function can be detected. A change in kidney function may occur even if the dosage has not been changed and the patient is adherent. Other factors that may be responsible for a change in kidney function include sodium imbalance and other medications. Sodium competes with lithium for glomerular excretion, and every patient who is starting a low-sodium diet needs to be monitored closely so that the lithium dosage can be adjusted if necessary.

As with any other medication, lithium can cause adverse effects. The most frequent acute effects are hand tremor, increased thirst, nausea, diarrhea, and abdominal distress. Usually most of these effects disappear after several weeks or lose intensity. A number of other adverse effects can occur in the long term, including changes on ECGs, weight gain, edema, euthyroid goiter, hypothyroidism, hyperparathyroidism with hypocalcemia, acne, psoriasis, and hair loss.

There are several possible strategies to cope with adverse effects, such as dose reduction and change in dosing intervals. Most important is the ongoing and comprehensive education of the patient and his or her family as well as the sensitivity to listen to patient concerns.

A serious complication of treatment is lithium intoxication. We distinguish between an acute overdose (eg, caused by intake as a suicidal act) and chronic toxicity (eg, caused by fluid loss or drug interaction). Signs of acute or chronic intoxication are tremor, anxiety, ataxia, nystagmus, choreoathetosis, and lethargy; and at higher levels, agitation, confusion, nausea, vomiting, diarrhea, and signs of cerebellar dysfunction.

Severe toxicity can lead to seizures, coma, and tachyarrhythmia. Patients with any of these signs need immediate medical attention; usually they are admitted to an ICU. Hemodialysis may be needed for acute or chronic lithium intoxication. As the intracellular lithium exits cells and reenters the bloodstream, a repeated hemodialysis might be necessary. In any case, continued measurement of lithium level (every 2 to 4 hours) is mandatory until therapeutic values are achieved.

CASE VIGNETTE
A 60-year-old man with bipolar II disorder has had 3 manic episodes in the past 2 years. Many pharmacological strategies have been initiated, including lithium and atypical neuroleptics. Over the long term, he became alcoholdependent. Multiple therapies were tried, and several abstinence periods lasted more than a year. Over the years, he has suffered a heart attack and a tumor of his adrenal gland that required several surgeries. He never married, has no children, and was unemployed (he now receives a pension as an invalid).

Despite the multiple risk factors, he never considered suicide. It is highly speculative whether this is the effect of lithium therapy.

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Summary
Lithium is a fascinating drug. Its ability to reduce suicidal risk distinguishes it from other medications used in affective disorders. Despite this unique effect, it still is a medication that needs careful assessment and monitoring, and patient adherence is essential. A trustworthy relationship between the physician, the patient, and the patient’s family is important. Lithium might be a treatment option for patients with affective disorders, especially those at risk for suicide.

<table>
<thead>
<tr>
<th>TABLE 1: Predictors of a good lithium response</th>
<th>TABLE 2: Predictors and absolute contraindications for lithium treatment</th>
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</thead>
<tbody>
<tr>
<td>Positive family history for bipolar disorder</td>
<td>Medical condition with increased risk for lithium-induced toxicity</td>
</tr>
<tr>
<td>Previous response with lithium</td>
<td>Acute alcoholism</td>
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<tr>
<td>Maximal response with lithium</td>
<td>Depression</td>
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<tr>
<td>Full remission between episodes</td>
<td>Psychosis</td>
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<td>Good adherence</td>
<td>History of prolonged extrapyramidal side effects</td>
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|                                              | Small cell carcinoma 

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TABLE 2: Relative and absolute contraindications for lithium treatment

Figure. Algorithm for lithium therapy in bipolar disorder

Disclosures:
Dr Lewitzka is Senior Physician and Head of the suicide research group and Dr Bauer is Professor and Chair in the department of psychiatry and psychotherapy at Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. Dr Lewitzka has received speakers honoraria from Lilly and Lundbeck and has accepted reimbursements of travel expenses to congresses from Lundbeck and AstraZeneca. Dr Bauer has received grant/research support from The Stanley Medical Research Institute, NARSAD, Deutsche Forschungsgemeinschaft, European Commission (FP7), American Foundation for Suicide Prevention, and Bundesministerium für Bildung und Forschung (BMBF). He is has been a consultant for Alkermes, AstraZeneca, Bristol-Myers Squibb, Ferrer Internacional, Janssen, Lilly, Lundbeck, Otsuka, Servier, and Takeda, and he has received speakers honoraria from AstraZeneca, Bristol-Myers Squibb, Ferrer Internacional, Glaxo-SmithKline, Lilly, Lundbeck, Otsuka, and Pfizer.

References:


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