t is illegal to post this copyrighted PDF on any website. Lithium Antisuicidality: Is it All About Thymoleptic Actions?

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Despite the current expansion of the psychopharmacologic armamentarium for bipolar mood disorder (BMD) and shifting paradigms in clinical practice toward atypical antipsychotics as thymoleptics, lithium remains the only agent with double-blind evidence for efficacy in all 4 phases of BMD. Thus, lithium is the epitome of a "mood stabilizer" in the strictest sense.¹

Lithium is the only psychotropic agent that has been shown to prolong life by preventing completed suicide and decreasing cardiovascular mortality.² Lithium was also found to increase telomere length.³ However, it is globally underutilized.⁴

Lithium decreased risk of suicide in patients with BMD during long-term treatment in a meta-analysis by Baldessarini et al.⁵ This antisuicidality effect might extend to recurrent unipolar depression as well.⁶ An updated systematic review and meta-analysis⁷ of lithium in the prevention of suicide in mood disorders confirmed that in patients with unipolar depression, lithium was associated with a reduced risk of suicide and number of total deaths compared with placebo. Mechanisms of lithium antisuicidality are not yet fully elucidated (Table 1).

It seems that suicide-preventative action of lithium might be ascribed to its mood-stabilizing actions. It is conceivable that once mood is improved and euthymia prolonged, a reduction in suicide attempts can be expected.⁸

Interestingly, however, a modicum of evidence indicates that lithium might possess antisuicidal actions independent of thymoleptic properties. In a study of high-risk patients, Ahrens and Müller-Oerlinghausen⁹ reported that suicide attempts were reduced in all participants regardless of their improvement in terms of affective symptomatology.

Research¹⁰ has indicated that a reduction in impulsivity and aggressivity might be the key to lithium's antisuicidal actions. Impulsivity and aggressivity are tied to suicidality and are common traits in patients with BMD. Effects of lithium on these symptom domains have been extensively demonstrated in rodents.¹⁰ Other possible mechanisms include an increased glutamine synthetase expression.¹¹

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 Table 1. Proposed Antisuicidal Actions of Lithium

Thymoleptic actions and true prophylaxis Anti-impulsivity and antiaggressivity Increased glutamine synthetase expression Procognitive actions and improvement in decision-making performance Increased access to clinical care for mandatory monitoring

Reduced glutamate synthetase activity has been reported in cases of completed suicide in both depressed and nondepressed individuals.¹² Kalkman¹² demonstrated in animal models that lithium, a GSK-3 β inhibitor, increased the expression of glutamine synthetase and brain glutamine levels following 7 days of treatment.

Another proposed mechanism of lithium antisuicidality is through increased access to clinical care as a result of mandatory monitoring.¹³ Increased contact time with clinicians might enhance opportunities to probe suicidal ideation as well as identify red flags like dysphoria nervosa and agitation.

The role of lithium in improving decision-making capacity in patients with BMD is another likely contributory mechanism to antisuicidality. In a trial by Adida et al,¹⁴ a decision-making task was completed by euthymic outpatients with a diagnosis of BMD. Participants were split into 3 groups: those treated with lithium, those without lithium (on other pharmacotherapy), and matched healthy controls. Results showed that patients treated with lithium (P=.007) and healthy controls (P=.001) were significantly more likely to choose cards from the "safe decks" than patients who were not treated with lithium.¹⁴ Equally important is the finding that lithium discontinuation after long-term treatment increases risk of suicidal behavior by 20-fold unless it is slowly down titrated.¹⁵

What is missing is the optimal serum lithium level to obtain antisuicidal effects and the minimum duration of lithium treatment required to achieve a decrease in suicidality. A word of caution is in order with regard to the need to balance these antisuicidal actions against potential toxicity given the narrow therapeutic index that lithium is notorious for, whether it be secondary to excessive intake (accidental or suicidal overdose) or impaired excretion (with sodium and volume depletion enhancing lithium renal reabsorption).¹⁶ Adherence should also be factored in while adjusting serum levels that might be spuriously suboptimal with poor adherence.¹⁷

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