A review of the evidence supporting the use of lithium augmentation therapy for the reduction of suicidal behavior in patients with unipolar depression: Revisiting an overlooked benefit of an older medication

Elizabeth Jackson, PharmD[1]
Rene A. Endow-Eyer, PharmD, BCPP[2]

[1]PGY-1 Pharmacy Resident, Veterans Affairs San Diego Healthcare System
[2]Psychiatric Clinical Pharmacist Specialist, Veterans Affairs San Diego Healthcare System

ABSTRACT

Major depressive disorder is a serious, recurrent condition with significant impact on a person's quality of life and functioning, which carries a significant risk of premature death due to suicide. There is evidence that supports the effectiveness of lithium as an augmentation strategy for treatment-resistant depression, as well as for reducing suicidality in this population. This review introduces several theories regarding the proposed mechanism behind lithium's anti-suicidal effects and summarizes a selection of the pertinent literature supporting lithium's beneficial effects on suicidality.

KEYWORDS

major depressive disorder (MDD), depression, lithium, suicide

INTRODUCTION

Major depressive disorder (MDD) is associated with significant morbidity and mortality. It has been estimated that the lifetime risk of suicide in patients with major depression approaches 15%, and approximately 50-70% of people who commit suicide have a documented diagnosis of depression.[1] Further complicating the issue is that depression is often refractory to pharmacologic treatment; less than 50% of patients respond to the first antidepressant trial, and only 33% achieve remission.[2] Response and remission rates decrease even further with each successive medication trial.[3-4]

The mainstay of pharmacologic treatment for MDD is antidepressant medication, with selective serotonin reuptake inhibitors (SSRIs) being the most commonly prescribed antidepressant class.[5] While antidepressant agents have been shown to elicit both response and remission, there is no conclusive data that these medications affect suicidality.

The etiology of suicidal behavior is complex, thus it is recommended that a multifactorial approach must be taken in the management of suicidal patients.[6] Several risk factors for suicide, both modifiable and non-modifiable, are listed in Table 1.

Although lithium was first described in the literature for the treatment of "psychotic excitement" in 1949 by John Cade,[7] its mechanism of action is still not completely understood. Studies in the 1970's and 1980's yielded convincing evidence that lithium augmentation reduces suicidal behavior and improves outcomes in patients with unipolar depression.[8-11] While lithium is still considered a mainstay of treatment for bipolar disorder, it is not commonly used for unipolar depression, despite the fact that there is evidence that lithium is effective as an augmentation strategy in major depression.

LITHIUM AND SUICIDE PREVENTION

There are several theories regarding the mechanism by which lithium reduces suicidality. Lithium has been shown to reduce recurrence of major depressive episodes when used as augmentation therapy along with antidepressant medication.[8,10,12-20] However, studies have shown that lithium may have an anti-suicidal effect independent of its ability to reduce recurrence of depression.[21,22] In a study of 167 high risk patients with a history of suicide attempt, it was shown that patients who responded to lithium treatment had a pronounced reduction in suicide attempts (93.3%).[21] It was noted that > 80% of moderate responders and nearly 50% of poor responders had no further suicidal behavior after treatment with lithium. The results of this study suggest that lithium may still be able to reduce suicidality even if antidepressant response is not achieved with lithium augmentation therapy.

Another theory is that lithium decreases the risk of suicide by reducing aggression and impulsivity, a finding which has been shown in both human and animal studies.[22-29]

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Table 1: Risk factors for suicide[6]

Modifiable	Potentially modifiable	Non-modifiable
Mental health disorders		
Substance use disorder	Major depressive disorder	
	Bipolar disorder	
	Schizophrenia/schizoaffective	
	Anxiety disorders	
Social factors		
Relationship turbulence	Loss of health/autonomy	Loss of loved one
Family violence	Transitions in life	History of abuse
Poor social support	Anniversaries	
	Financial stressors	
	Legal issues	
	Barriers to accessing mental health care	
Medical conditions		
Diabetes	Worsening of chronic illness	History of traumatic brain injury
	Chronic pain	HIV
	Neurologic disorders	
	Cancer	
Pre-existing		
		Age (young or elderly)
		Gender (male)
		Race (Caucasian)
		Family history of suicide
		Family history of mental health disorder
		Same sex orientation
		Lower education level
Other		
	Impulsivity	History of suicide attempt

Additionally, lithium treatment may elicit a synergistic effect with antidepressants by enhancing serotonergic neurotransmission.[30] An added factor that may contribute to the decreased risk of suicide associated with lithium is the close follow-up associated with lithium treatment. It is conceivable that more frequent clinic visits and increased patient-provider interaction may reduce the risk of suicide and improve outcomes.[31]

Lithium's role in reducing suicidal behavior in depression is not a new consideration, as the first study addressing this concept was published in 1972.[32] Since then, a considerable amount of literature has been published in support of this theory. A study by Ahrens et al. demonstrated that during the first two years of lithium treatment, suicide mortality remained high among patients with major affective disorders (including bipolar disorder and major depressive disorder), yet among those who had been treated with ≥ 2 years of lithium maintenance, mortality from both suicide and cardiovascular causes approximated that of the general population.[33] This finding was further substantiated by the results of a meta-analysis by Baldessarini et al., where it was found that the risk for both suicide attempts and completions in patients with major affective disorders was initially 10 times that of the general population, but this risk fell below that of the general population with lithium maintenance treatment. The risk reduction was actually found to be higher in unipolar depression than bipolar depression (100% vs. 82%).[31]

A recent review by Cipriani et al., including 48 randomized controlled trials, showed that lithium was more effective than placebo in decreasing the number of suicides and deaths from any cause in patients with mood disorders, and specifically in individuals with unipolar depression (odds ratios: 0.36 and 0.13, respectively).[34] Guzzetta et al. found that the overall risk of suicide and suicide attempts was 88.5% lower with lithium versus without lithium augmentation in patients with major depressive disorder.[35] The International Group for the Study of Lithium-treated Patients (IGSLi), covering > 5,000 patient-years, also showed that adequate long-term lithium treatment significantly decreased excess mortality of patients with affective disorders down to the level of the general population.[36]

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SIDE EFFECTS AND ADVERSE DRUG REACTIONS

While the evidence appears to support the efficacy of lithium augmentation in the reduction of suicidal behavior in patients with depression, there are also factors that must be taken into consideration when making the decision to prescribe lithium. Potential adverse effects associated with lithium include hypothyroidism, tremor, acne, weight gain, gastrointestinal disturbances, cognitive impairment, electrocardiographic changes, and rarely nephrotoxicity.[37] However, it has been shown that many adverse effects may be avoided by maintaining lower, yet therapeutic, serum levels.[38] Furthermore, there is concern that lithium may be associated with Ebstein's anomaly, a congenital cardiovascular malformation, therefore clinicians may prefer to avoid this medication in women of child-bearing potential.[39] There are also several important drug interactions that must be considered when prescribing lithium. Most nonsteroidal anti-inflammatory drugs (NSAIDs) and several classes of antihypertensives, including angiotensin converting enzyme inhibitors (ACEIs) and thiazide diuretics, should be avoided as concomitant use may increase the risk of lithium toxicity.[40,41] Additionally, rare case reports of serotonin syndrome following combination of lithium with other serotonergic agents, have been reported.[42-44] Finally, serum lithium levels must be monitored when initiating therapy, changing lithium dose, and periodically during maintenance treatment, which raises pharmacoeconomic and adherence concerns.[45]

DOSING AND SERUM LEVELS

A question that may arise when considering the use of lithium as augmentation for unipolar depression is that of dosing. There are no specific recommendations for the dosing of lithium as an adjunctive therapy in unipolar depression. In a study assessing the benefit of lithium added to a tricyclic antidepressant, serum concentrations ranged from 0.4-1.2 mEq/L; however, marked improvement in symptoms was observed at lithium concentrations of 0.4-0.5 mEq/L.[46] A study by Bauer et al. suggested that lithium exerts a significant effect at a dose of 600-800 mg/day and recommends target concentrations of 0.6-0.8 mEq/L.[16] Coppen et al reported that a lithium trough level of 0.5-0.7 mEq/L was the most effective blood concentration. These levels were well-tolerated with only minor side effects.[47] Lepkifker et al reported a significant reduction in suicidal behavior with average lithium trough concentration of 0.4-0.8 mEq/L.[20] Thus the current evidence suggests that the target lithium trough levels for depression should be similar to those for lithium maintenance therapy in bipolar disorder. The "ideal" serum lithium level for maintenance therapy in bipolar disorder is debated, but recent reviews and experts tend to agree that a serum concentration of 0.5-0.8mEq/L should be targeted to maximize efficacy while minimizing side effects.[45,48]

TREATMENT GUIDELINES

Despite substantial evidence, there was no existing U.S. published guideline that specifically recommended the use of lithium for prevention of suicide as an augmentation agent in unipolar depression until recently. Although lithium had been added to the recommendations in the 2010 American Psychiatric Association (APA) Guideline for Major Depressive Disorder, and mentioned in the APA guideline for suicide prevention, prescribing rates of lithium for augmentation of depression have remained surprisingly low.[49] A study of 244,859 Veterans Affairs patients with a diagnosis of MDD and an antidepressant prescription reported that while 22% of patients received an augmenting agent, only 0.5% of patients received lithium.[50]

The newly published 2013 Veterans Affairs – Department of Defense (VA-DoD) guideline for the Assessment and Management of Patients at Risk for Suicide recommends that "lithium augmentation should be considered for patients diagnosed with unipolar depressive disorder who have had a partial response to an antidepressant and for those with recurrent episodes who are at high risk for suicidal behavior, provided they do not have a contraindication to lithium use and the potential benefits outweigh the risks."[6] These new recommendations may increase awareness of the efficacy of lithium in decreasing suicidality in unipolar depression.

CONCLUSION

Major depressive disorder is associated with a significant risk of premature death due to suicide. There is substantial evidence supporting lithium's specific anti-suicidal effect in both bipolar disorder and major depression. Despite such evidence, prescribing rates of lithium continue to decrease, likely due to concerns regarding side effects, monitoring, and lithium toxicity. Yet, suicide rates are increasing across all geographical locations in the United States.[51] A study by Goodwin, et al highlights a haunting trend; in a population sample of over 20,000 outpatients with bipolar disorder followed over seven years it was shown that patients experienced a 2.7 times increased risk of suicide death while treated with divalproex compared to being treated with lithium.[52] Additionally, it was noted that prescribing rates of lithium decreased dramatically over the time course of the study.

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This was associated with a statistically insignificant, yet notable, increase in suicide rates over time. Hopefully, with increased awareness of the anti-suicidal effect of lithium, prescribers will be more inclined to use this medication to prevent suicide in patients with major affective disorders.

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