ORIGINAL RESEARCH

Impact of Lithium on Suicidality in the Veteran Population

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Background: Lithium has known antisuicidal properties making it an important agent to study in veterans with psychiatric conditions, a population at high risk for suicide.

Methods: A single-site, retrospective chart review was conducted at a US Department of Veterans Affairs (VA) teaching hospital. Patients taking lithium for at least 6 months were identified using the VA Lithium Lab Monitoring Dashboard. The primary and secondary objectives were to evaluate the change in number of suicide attempts and suicidal ideation from 3 months prior to lithium initiation to 3 months after a 6-month duration of lithium.

Results: The review included 98 patients; 47 (47.9%) received concomitant psychotherapy, 50 (51.0%) were taking an antipsychotic, and 29 (29.6%) an additional mood stabilizer. During the 6-month intervention period, 75 (76.5%) patients had a lithium level drawn and 28 were in the therapeutic range. Of the 98 patients, hospitalization for suicide attempt decreased from 4.1% before lithium use to 0% after lithium use for 6 months (P = .045). Hospitalization for suicidal ideation also decreased from 13.3% before lithium use to 1.0% after lithium use for 6 months (P = .0004).

Conclusions: We observed a statistically significant reduction in hospitalization for suicide attempts and suicidal ideation in veterans prescribed lithium following nonfatal suicide behavior and suicidal ideation.

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Suicide is the tenth leading cause of death in the United States claiming nearly 48,000 individuals in 2019 and is the second leading cause of death among individuals aged 10 to 34 years.[1] From 1999 to 2019, the suicide rate increased by 33%.[1] In a retrospective study evaluating suicide risk in > 29,000 men, veterans had a greater risk for suicide in all age groups except for the oldest when compared with nonveterans.[2] Another study of > 800,000 veterans found that younger veterans were most at risk for suicide.[3] Veterans with completed suicides have a high incidence of affective disorders comorbid with substance use disorders, and therefore it is imperative to optimally treat these conditions to address suicidality.[4] Additionally, a retrospective case-control study of veterans who died by suicide matched to controls identified that the cases had significantly higher rates of mental health conditions and suicidal ideation. Given that the veteran population is at higher risk of suicide, research of treatments to address suicidal ideation in veterans is needed.[5]

Lithium and Antisuicidal Properties

Lithium is the oldest treatment for bipolar disorder and is a long-standing first-line option due to its well-established efficacy as a mood stabilizer.[6] Lithium's antisuicidal properties separate it from the other pharmacologic options for bipolar disorder. A possible explanation for lithium's unique antisuicidal properties is that these effects are mediated by its impact on aggression and impulsivity, which are both linked to an increased suicide risk.[7,8] A meta-analysis by Baldessarini and colleagues demonstrated that patients with mood disorders who were prescribed lithium had a 5 times lower risk of suicide and attempts than did those not treated with lithium.[9] Lithium's current place in therapy is in the treatment of bipolar disorder and major depressive disorder augmentation.[10-12] Smith and colleagues found that in a cohort study of 21,194 veterans diagnosed with mental health conditions and initiated on lithium or valproate, there were no significant differences in associations with suicide observed between these agents over 365 days; however, there was a significant increased risk of suicide among patients discontinuing or modifying lithium within the first 180 days of treatment.[13]

Currently, lithium is thought to be underutilized at the US Department of Veterans Affairs (VA) Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston, Texas, based on the number of prescriptions of lithium in the large population of veterans seen by mental health clinicians. MEDVAMC is a 538-bed academic teaching hospital serving approximately 130,000 veterans in southeast Texas. The Mental Health Care Line has

73 inpatient beds and an outpatient clinic serving > 12,000 patients annually. By retrospectively evaluating changes in suicidality in a sample of veterans prescribed lithium, we may be able to better understand the role that lithium plays in a population that has a higher suicide rate than does the general population. The primary objective of this study was to evaluate the change in number of suicide attempts from 3 months prior to lithium initiation to 3 months following a 6-month duration of lithium use. The secondary objective was to determine the change in suicidal ideation from the period prior to lithium use to the period following 6 months of lithium use.

METHODS

This was a single-site, retrospective chart review conducted between October 2017 and April 2018. Prior to data collection, the MEDVAMC Research and Development committee approved the study as quality assurance research. Patients with an active lithium prescription were identified using the VA Lithium Lab Monitoring Dashboard, which includes all patients on lithium, their lithium level, and other data such as upcoming appointments.

Inclusion criteria consisted of adults who were aged ≥ 18 years, had an active lithium prescription on the date of data extraction, and had an active lithium prescription for at least 6 months. Patients were excluded if they had < 3 months of data before and/or after lithium was used for 6 months, and if they were initiated on lithium outside MEDVAMC. Cumulatively, patients had to have at least 12 months of data: 3 months prior to lithium use, at least 6 months of lithium use, and 9 months after lithium initiation.

Suicide Attempt and Suicidal Ideation Identification

When determining the number of suicide attempts, we recorded 4 data points: Veterans Crisis Line notes documenting suicide attempts, hospital admissions for suicide attempts, suicide behavior reports within the indicated time frame, and mental health progress notes documenting suicide attempts. Suicidal ideation was measured in 4 ways. First, we looked at the percentage of outpatient mental health progress notes documenting suicidal ideation. Second, using the Patient Health Questionnaire-9 (PHQ-9) depression assessments, we looked at the percentage of patients that indicated several days, more than half the days, or nearly every day to the question, "Thoughts that you would be better off dead or of hurting yourself in some way."[14] Third, we recorded the percentage of suicide risk assessments that patients responded yes to both questions on current preoccupation with suicidal thoughts and serious intent and plan to commit suicide with access to guns, stashed pills, or other means. Finally, we noted the percentage of suicide risk assessments where the assessment of risk was moderate or high.

A retrospective electronic health record (EHR) review was performed and the following information was obtained: patient demographics, lithium refill history, concomitant psychotropic medications and psychotherapy, lithium levels, comorbidities at lithium initiation, presence of a high-risk suicide flag in the EHR, suicide risk assessments, suicide behavior reports, Veteran Crisis Line notes, PHQ-9 assessments, and hospital admission and mental health outpatient notes. The lithium therapeutic range of 0.6-1.2 mmol/L is indicated for bipolar disorder and not other indications where the dose is typically titrated to effect rather than level. Medication possession ratio (MPR) was also calculated

TABLE 1 Patient Demographic Data (N = 98)

Characteristics	Results
Sex, No. (%)	
Male	81 (82.7)
Female	17 (17.3)
Age, mean, y	50.5
Concomitant psychotherapy, No. (%)	47 (47.9)
Medications, No. (%)	
Single antipsychotic	50 (51.0)
Multiple antipsychotics	14 (14.3)
Lithium monotherapy	4 (4.1)
Concomitant mood stabilizer	29 (29.6)
Lamotrigine	14 (14.3)
Divaloprex	13 (13.3)
Carbamazepine	2 (2.0)
Lithium lab drawn during 6 months of use, No. (%)	75 (76.5)
Therapeutic lithium level (0.6-1.2 mmol/L), No. (%)	28 (37.3)
Medication possession ratio > 0.8, No. (%)	71 (72.4)

TABLE 2 Subcategory Analysis

Criteria	Prelithium, No. (%)	After 6 Mo Lithium, No. (%)
Outpatient mental health notes	656	484
Notes reporting suicidal ideation	107 (16.3)	21 (4.3)
Suicide risk assessments	68	15
Patient assessed as moderate high or risk	14 (20.6)	2 (13.3)
Patient reported current suicidal ideation or current suicide intent/plan	13 (19.1)	1 (6.7)
Patients with high risk flag for suicide	12 (12.2)	8 (8.2)

for lithium (sum of days' supply for all fills in period ÷ number of days in period). A high-risk suicide flag alerts clinicians and staff that a mental health professional considers the veteran at risk for suicide.[15] Statistical analysis was performed using the paired *t* test for means to assess proportional differences between variables for the primary and secondary outcomes. Descriptive statistics were used to describe the baseline characteristics.

RESULTS

A total of 214 patients with an active prescription for lithium were identified on the Lithium Lab Monitoring Dashboard on October 31, 2017. After exclusion criteria were applied, 98 patients were included in the study (Figure 1). The 2 most common reasons for exclusion were due to patients not being on lithium for at least 6 months and being initiated on lithium at an outside facility. One patient was enrolled in a lithium research study (the medication ordered was lithium/placebo) and another patient refused all psychotropic medications according to the progress notes.

Most of the 98 patients (82.7%) were male with average age 50.5 years (Table 1). Almost half the patients (n = 47) were concomitantly participating in psychotherapy, and 50 (51.0%) patients received at least 1 antipsychotic medication. Twenty-nine patients had an active prescription for an additional mood stabilizer, and only 4 (4.1%) patients received lithium as monotherapy. Only 75 (76.5%) patients had a lithium level drawn during the 6 months of therapy, with 28 (37.3%) patients having a therapeutic lithium level (0.6 - 1.2 mmol/L). Seventy-one patients (72.4%) were adherent to lithium therapy with a MPR > 0.8.[16] Participants had 13 different psychiatric diagnoses at the time of lithium initiation; the most common were bipolar spectrum disorder (n = 38; 38.8%), depressive disorder (n = 27; 27.6%), and posttraumatic stress disorder (PTSD) (n = 26; 26.5%). Of note, 5 patients had a diagnosis of only PTSD without a concomitant mood disorder.

For the primary outcome, hospitalization for a suspected suicide attempt decreased from 4 (4.1%) before lithium use with a mean (SD) 0.04 (0.20) attempts per person to none within 3 months after lithium use for 6 months ($t(97) = 2.03$, $P = .045$) (Figure 2). The secondary outcome of hospitalization for suicidal ideations also decreased from 13 (13.3%) before lithium use with a mean (SD) 0.1 (0.3) ideations per person to 1 (1.0%) within 3 months after lithium use for 6 months with a mean (SD) 0.01 (0.1) ideations per person ($t(97) = 3.68$, $P = .0004$). Veteran Crisis Line calls also decreased from 4 (4.1%) with a mean (SD) 0.04 (0.2) calls per person to 1 (1.0%) within 3 months after 6 months of lithium with a mean (SD) 0.01 (0.1) calls per person ($t(97) = 1.75$, $P = .08$). The comparison of metrics from 3 months before lithium initiation and within 3 months after use saw decreases in all categories (Table 2). Outpatient notes documenting suicidal ideation decreased, as did the number of patients with a high-risk suicide flag.

DISCUSSION

The results of this study suggest lithium may have a role in reducing suicidality in a veteran population. There was a statistically significant reduction in hospitalizations for suicide attempt and suicidal ideation after at least 6 months of lithium use. These results are comparable with a previously published study that observed significant decreases in suicidal behavior and/or hospitalization risks among veterans taking lithium compared with those not taking lithium.[17] Our study was similar in respect to the reduced hospitalizations among a veteran population; however, the previous study did not report a difference in suicide attempts and lithium use. This could be related to the longer follow-up time in the previous study (3 years) vs our study (9 months).

Our study identified a significant reduction in Veteran Crisis Line calls after at least

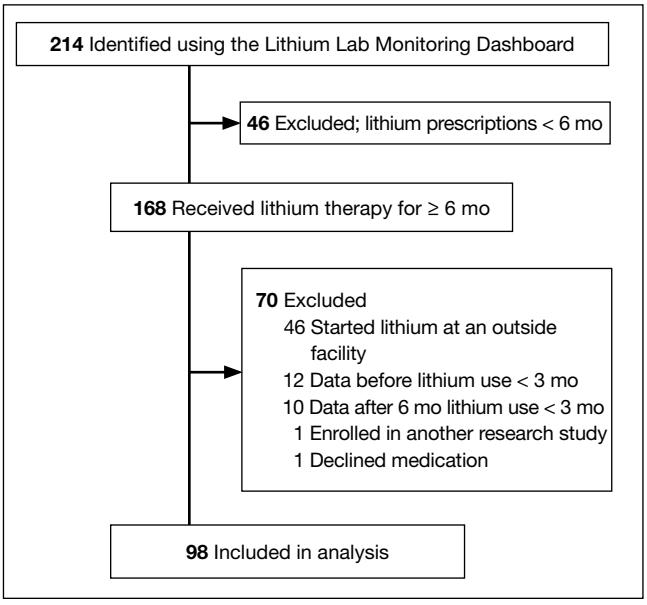
6 months of lithium use. While a reduction in suicidal ideations could be implicated in the decrease in crisis line calls, there may be a confounding variable. It is possible that after lithium initiation, veterans had more frequent contact with health care practitioners due to laboratory test monitoring and follow-up visits and thus had concerns/crises addressed during these interactions ultimately leading to a decreased utilization of the crisis line. Interestingly, there was a reduction in mental health outpatient notes from the prelithium period to the 3-month period that followed 6 months of lithium therapy. However, our study did not report on the number of mental health outpatient notes or visits during the 6-month lithium duration. Additionally, time of year/season could have an impact on suicidality, but this relationship was not evaluated in this study.

The presence of high-risk suicide flags also decreased from the prelithium period to the period 3 months following 6 months of lithium use. High-risk flags are reviewed by the suicide prevention coordinators and mental health professionals every 90 days; therefore, the patients with flags had multiple opportunities for review and thus renewal or discontinuation during the study period. A similar rationale can be applied to the high-risk flag as with the Veteran Crisis Line reduction, although this change could also be representative of a decrease in suicidality. Our study is different from other lithium studies because it included patients with a multitude of psychiatric diagnoses rather than just mood disorders. Five of the patients had a diagnosis of only PTSD and no documented mood disorder at the time of lithium initiation. Additional research is needed on the impact of lithium on suicidality in veterans with PTSD and psychiatric conditions other than mood disorders.

Underutilization of Lithium

Despite widespread knowledge of lithium's antisuicidal effects, it is underutilized as a mood stabilizer in the US.[18] There are various modifiable barriers that impact the prescribing as well as use of lithium. Clinicians may not be fully aware of lithium's antisuicidal properties and may also have a low level of confidence in patients' likelihood of adherence to laboratory monitoring.[18,19] Due to the narrow therapeutic index of lithium, the consequences of nonadherence to monitoring can be dangerous, which may deter mental health professionals from prescribing this antisuicidal agent. At MEDVAMC, only 72.4% of patients with a lithium prescription had a lithium level drawn within a 6-month period. This could be attributed to patient nonadherence (eg, the test was ordered but the patient did not go) or clinician nonadherence (eg, test was not ordered).

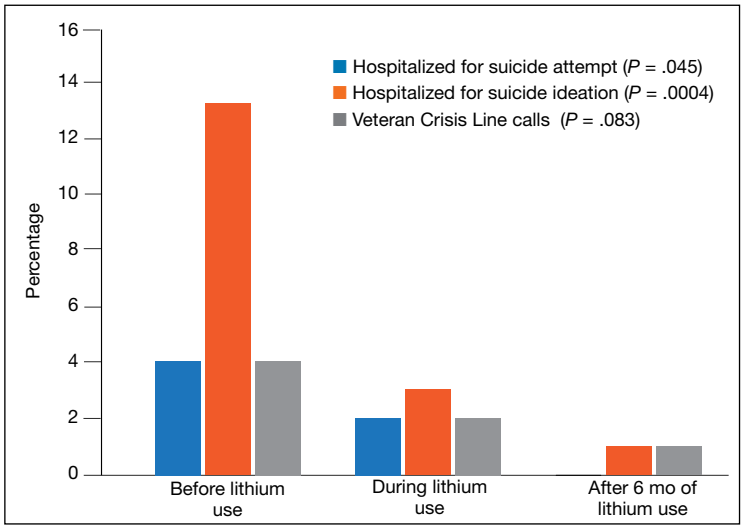
FIGURE 1 Patient Selection



With increased clinician education as well as clinics dedicated to lithium management that allow for closer follow-up, facilities may see an increased level of comfort with lithium use. Lithium management clinics that provide close follow-up may also help address patient-related concerns about adverse effects and allow for close monitoring. To facilitate lithium monitoring at MEDVAMC, mental health practitioners and pharmacists developed a lithium test monitoring menu that serves as a "one-stop shop" for lithium baseline and ongoing test results.

In the future, we may study the impact of this test monitoring menu on lithium prescribing. One may also consider whether lithium levels need to be monitored at different frequencies (eg, less frequently for depression than bipolar disorder) depending on the diagnoses. A better understanding of the necessity for therapeutic monitoring may potentially reduce barriers

FIGURE 2 Primary and Secondary Outcomes



to prescribing for patients who do not have indications that have a recommended therapeutic range (eg, bipolar disorder).

Lithium Adherence

A primary patient-related concern for low lithium utilization is poor adherence. In this sample, 71 patients (72.4%) were considered fully adherent. This was higher than the rate of 54.1% reported by Sajatovic and colleagues in a study evaluating adherence to lithium and other anticonvulsants in veterans with bipolar disorder.[20] Patients' beliefs about medications and overall health as well as knowledge of the illness and treatment may impact adherence.[21] The literature indicates that strategies such as cognitive behavioral therapy (CBT) and didactic lectures positively impact patients' attitudes about lithium, which ultimately influences adherence.[21-23] Involving a family member or significant other in psychotherapy may also improve lithium adherence.[21] Specifically in the VA, to address knowledge deficits and improve overall adherence, the Lithium Lab Monitoring Dashboard could be used to identify and invite new lithium starts to educational groups about lithium. These groups could also serve as lithium management clinics.

Limitations

There were several limitations to this study. This was a single-site, retrospective chart review with a small sample size. We studied a cross-section of veterans with only active prescriptions, which limited the sample size. The results should be interpreted cautiously because < 40% of patients who had a level drawn were in the therapeutic range. Patients whose lithium levels were outside of the therapeutic range may have not been fully adherent to the medication. Further analysis based on reason for lithium prescription (eg, bipolar disorder vs depression vs aggression/impulsivity in PTSD) may be helpful in better understanding the results.

Additionally, while we collected data on concomitant mood stabilizers and antipsychotics, we did not collect data on concurrent antidepressant therapy and only 4% of patients were on lithium monotherapy. Data regarding veterans undergoing concurrent CBT during their lithium trial were not assessed in this study and could be considered a confounding factor for future studies. We included any Veteran Crisis Line call in our results regardless of the reason for the call, which could have led to overreporting of this suicidality marker.

Given its small sample size, this study should be considered as hypothesis-generating. Further studies are needed to address lithium's antisuicidal effects in specific diagnoses (eg, PTSD, anxiety, schizoaffective disorder) to better understand its place in therapy. Studies evaluating the relationship between dosing and suicidality may help provide insight into whether the antisuicidal effect of lithium is dose-dependent and whether a specific dose range rather than a therapeutic level should be targeted for antisuicidal purposes.

CONCLUSIONS

People treated for an affective disorder have a 30-times greater risk of suicide than do those in the general population; however, as lithium can reduce the risk of suicide and self-harm, it should continue to have an important role in clinical practice.[24] At MEDVAMC, we observed a statistically significant reduction in hospitalization for suicide attempts and suicidal ideation in veterans prescribed lithium following nonfatal suicide behavior and suicidal ideation. Prospective randomized placebo-controlled studies are needed to better understand lithium's antisuicidal effects.

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Ethics and consent
Prior to data collection, the Michael E. DeBakey VA Medical Center (MEDVAMC) Research and Development Program approved the study as quality assurance.

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