Measurement of lithium response in patients with bipolar disorder using the Retrospective Assessment of Response to Lithium Scale (Alda scale)

A narrative review

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ABSTRACT

Lithium is the first-line medication for the treatment of bipolar disorder (BD), but its exact biological mechanisms have not been identified. One of the major obstacles in lithium-related research is the difficulty in precisely and reliably measuring the response to lithium. The Alda scale was developed to retrospectively measure lithium response in a standardized way. However, several aspects should be considered in understanding previous studies that used the Alda scale. In this narrative review, we aim to review previous studies and present the limitations of prior findings. Additionally, we suggest future strategies for applying the Alda scale in measuring lithium response. Initial studies using the Alda scale mainly included patients who were on lithium monotherapy for a long-term period. However, lithium monotherapy is relatively rare in clinical practice. More importantly, in clinical practice, if patients do not respond well to lithium, clinicians do not prescribe it for a long-term period. Thus, a modified approach to include diverse patients is necessary to identify true poor responders. Most previous studies also mainly included European populations, and ancestrally diverse populations should be included in the research. Furthermore, applying the same scale to explore the effects of other medications would also enhance our understanding of the neurobiological mechanisms of psychiatric medications in BD. Applying electronic health record data in evaluating lithium response would soon facilitate large-scale studies. Future studies that include diverse clinical populations reflecting the clinical practice are necessary to advance precision psychiatry.

Keywords: Alda scale; Bipolar disorder; Lithium; Precision psychiatry

INTRODUCTION

Bipolar disorder (BD) is a mood disorder characterized by alternating recurrences of (hypo)mania and depression throughout a lifetime [1]. BD usually develops in early adulthood [2] and...
shows a chronic course [1]. According to the Global Burden of Disease Study 2019, the worldwide disease burden of BD is constantly increasing, and the mortality risks are high [3,4]. Recurrent mood episodes and subsyndromal mood symptoms significantly impact patients' function and quality of life after illness onset [1]. Untreated mood episodes in BD can lead to fatal outcomes such as suicide, homicide, and violence.

The primary treatment approach for BD is pharmacotherapy. Continuous lifetime pharmacotherapy after illness onset is just as important as acute-stage treatment to minimize the recurrence of episodes and maintain stability [5,6]. Effective maintenance treatment can also decrease the severity of mood symptoms in future episodes. Partially effective medication might not fully prevent recurrence but will decrease the frequency and/or severity of future episodes. Thus, evaluating the long-term treatment effects of medications is essential, and retrospective evaluation is inevitable.

Despite recent dramatic advancements in psychopharmacology, lithium remains the first-line mood stabilizer and the most effective treatment among the diverse medications used in BD [7,8]. Lithium demonstrates both acute treatment efficacy for depressive and manic episodes, as well as preventive efficacy against future mood episodes [5,6].

A favorable response to lithium indicates a generally favorable clinical outcome [9]. However, not everyone responds well to lithium. Only one-third of patients experience significant improvement after long-term lithium therapy [10], and it is still unclear who responds better to lithium among patients with BD.

Considering the unique position of lithium in the treatment of BD, it is important to understand its mechanisms. However, the precise therapeutic mechanisms of lithium are not yet fully understood. To understand its mechanisms, the first task is to establish a standardized and quantitative way to measure its therapeutic effects. The Retrospective Assessment of Response to Lithium Scale (Alda scale) was developed for this purpose by Martin Alda and colleagues [11,12]. It aims to quantitatively evaluate the therapeutic effects of lithium and has been applied in numerous international large-scale studies, showing excellent inter-rater reliability and validity.

Our research team has applied the Alda scale to patients with BD for the past decade. Throughout our experiences, however, we have realized that several aspects need to be considered when implementing and interpreting the Alda scale.

In this narrative review, we aim to share some of these aspects. We first summarize prior studies that utilized the Alda scale to evaluate lithium responses in patients with BD. We then present several limitations in previous studies and make suggestions on how to apply the scale to patients. We hope that this review will aid clinical researchers interested in understanding the factors associated with long-term treatment responses in BD.

THE ALDA SCALE

The Alda scale has two components: the A score and the B score. The A score quantifies changes in illness activity during lithium treatment on a scale of 0 (no change or deterioration) to 10 (no residual symptoms and full functional recovery). The B score accounts for potential confounding factors of treatment outcomes and is subdivided into five items: the number of episodes before lithium treatment (B1), frequency of episodes before lithium treatment (B2), duration of lithium treatment (B3), compliance during periods of stability (B4), and use of additional medication during periods of stability (B5). Each B item is rated on a scale of 0 to 2, and higher B scores suggest a reduced causal relationship between symptom improvement and the therapeutic effect of lithium. The overall Alda total score, indicating treatment response, is derived by subtracting the B score from the A score. Negative values are replaced with 0. Higher Alda total and Alda A scores suggest a more favorable treatment response [11].

The cut-off scores to define good responders were calculated using frequentist mixture analysis. In our study populations, the cut-off score was 5 for both the Alda total score and the Alda A score.

THE INTERNATIONAL CONSORTIUM ON LITHIUM GENETICS

Lithium response is considered to have a genetic basis. However, large samples are required to identify the genetic background. The International Consortium on Lithium Genetics (ConLigen) project aimed to identify the genetic determinants of response to lithium treatment in BD, as well as the genetic determinants of adverse events emerging during lithium treatment [13]. The Alda scale [11] was adapted as the primary measure to evaluate lithium response in this study.

So far, diverse researchers from over 41 countries have joined ConLiGen. The most recent study from this project included 2,039 patients [14]. They found that lithium response was associated with a diminished burden of mania, depression, substance and alcohol abuse, psychosis, and suicidal
ideation in patients with bipolar I disorder. Among genomic markers, a stronger lithium response was associated with a lower polygenic load for diabetes and hypertension in bipolar I disorder.

**THINGS TO CONSIDER WHEN USING THE ALDA SCALE**

The Alda total score
One issue with the Alda scale lies in the method of calculating the total score. The Alda total score is generated by subtracting the B score from the A score. Any negative score is recorded as 0. However, each B subscale (B1–B5), each reflecting different confounding factors, is regarded as having an identical contribution to affecting treatment response when using this method. Additionally, scores of ‘1’ and ‘2’ in the B subscale are not proportional to be regarded as continuous measures. Scott et al. [12] also suggested using the B scale as a multidimensional index instead of treating it as a single measure.

In our recent studies, we used the Alda A score instead of the Alda total score as the primary measure of lithium response. We regarded each individual B item as a separate covariate and then applied a machine-learning approach to adjust the effects of each confounding factor.

Patients under polypharmacy
To avoid potential confounding effects of other medications, initial reports using the Alda scale mainly included those who were on lithium monotherapy. However, this causes biased samples. If someone is a poor lithium responder, they are less likely to be on monotherapy. Clinicians will try augmentation therapy with other medications. Furthermore, combination therapy is the most recommended and widely applied strategy in bipolar treatment these days. The most recent treatment guidelines all recommend combination therapy for a faster response [6]. Reflecting this guideline, real-world clinical data showed that those on lithium monotherapy are less than 20%. Our recent study showed less than 10% of study participants were on monotherapy [15]. Our study participants were recruited from the bipolar specialty clinic of three major tertiary medical centers, where most patients generally have more severe symptoms. Patients with more severe symptoms are generally treated with polypharmacy. Thus, we included all patients regardless of what medications were co-prescribed. We believe that patients under polypharmacy should be included in all future studies that aim to explore lithium response.

Duration of lithium use
Initial recommendations for assessing lithium responses suggest including individuals who have been on lithium treatment for at least 2 years. However, considering that lithium is a medication with substantial side effects [16], clinicians will change the medication if they conclude that lithium is not effective. In our study, poor responders had shorter durations of lithium use compared to good responders [15]. So, including only patients who have used lithium for more than two years may create a bias by selecting only those who responded well to lithium. Considering that medications without acute efficacy generally do not have long-term efficacy either, those who were on lithium for a relatively short-term period should also be included as study participants. Reasons for short-term use can be explored afterward to identify true poor responders.

Lack of ancestral diversity
Most previous studies were mainly conducted within European ancestry populations, and only a few studies included Asian populations. Data from different ancestry populations showed decreased predictability due to different linkage disequilibrium structures. Recently, diverse studies have aimed to collect data from diverse populations, and these studies will broaden our understanding of the neurobiological mechanisms of BD.

Application of Alda scale to other medications
Although lithium is the first-line medication for BD, other medications also have efficacy in both the acute and maintenance phases. Valproate [17] and lamotrigine [18] have been shown to have preventative effects as well as effectiveness during acute episodes. In a meta-analysis of randomized controlled trials, a significantly lower risk of new episodes was observed with several atypical antipsychotics, including aripiprazole, asenapine, olanzapine, quetiapine, and risperidone long-acting [19]. Thus, the Alda scale can also be applied to other BD medications besides lithium. Our research team previously applied the Alda scale to valproate [15]. However, only limited studies have applied the Alda scale to other medications in BD, and none have applied it to antipsychotics. Further studies with other treatment agents are necessary.

Utilization of electronic health record
Although ConLiGen rigorously tried to collect data to explore
lithium response, the number of participants included in the study is still somewhat unsatisfactory. If we are able to utilize electronic health records (EHR) to measure lithium response, sample sizes will increase dramatically. Up until now, the application of EHR in measuring lithium responses has never been tried. Direct application of the Alda scale will be impossible, but a modified application might be possible. Comparisons of the number of hospitalizations or emergency room visits can be used as a proxy for lithium responses. Considering medication complexity can represent more severe illness, the amount of co-prescribed medications can also be used as a proxy for lithium responses. Using EHR data, the duration of lithium use, co-prescribed medications, and laboratory test-based side effects can be examined as well.

A study using Finnish registry data showed that lithium was the only drug that could decrease rates of psychiatric and somatic admission [20]. Likewise, we will be able to identify lithium responders using EHR. Further studies that combine EHR and genomic data are necessary.

CONCLUSION

Lithium is one of the most important treatment agents for BD. To start precision psychiatry, we need to understand the neurobiological mechanisms of lithium. To achieve this, we must be able to distinguish groups of patients with similar traits and responses to lithium. Therefore, a scale that accurately assesses responses to lithium is necessary. The Alda scale is a breakthrough for the precise and standardized evaluation of long-term lithium response. However, to apply the Alda scale properly, the aforementioned factors should be considered. We need to include patients who are on polypharmacy, have used lithium for a short period of time, and have ancestral diversity. In addition, diverse clinical factors, from symptoms of mood episodes to potential underlying traits, should be included. Future studies with larger samples from diverse ancestries will help researchers understand the biological mechanisms of lithium responses. Additionally, the long-term effects of other medications can also be examined using the Alda scale. This will eventually lead to precision psychiatry and the further development of newer treatment agents for BD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.


