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Cross-validation of clinical characteristics and treatment patterns associated with phenotypes for lithium response defined by the Alda scale

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ABSTRACT

Background: It is increasingly recognised that reliable and valid assessments of lithium response are needed in order to target more efficiently the use of this medication in bipolar disorders (BD) and to identify genotypes, endophenotypes and biomarkers of response.

Methods: In a large, multi-centre, clinically representative sample of 300 cases of BD, we assess external clinical validators of lithium response phenotypes as defined using three different recommended approaches to scoring the Alda lithium response scale. The scale comprises an A scale (rating lithium response) and a B scale (assessing confounders).

Results: Analysis of the two continuous scoring methods (A scale score minus the B scale score, or A scale score in those with a low B scale score) demonstrated that 21–23% of the explained variance in lithium response was accounted for by a positive family history of BD I and the early introduction of lithium. Categorical definitions of response suggest poor response is also associated with a positive history of alcohol and/or substance use comorbidities. High B scale scores were significantly associated with longer duration of illness prior to receiving lithium and the presence of psychotic symptoms.

Limitations: The original sample was not recruited specifically to study lithium response. The Alda scale is designed to assess response retrospectively.

Conclusions: This cross-validation study identifies different clinical phenotypes of lithium response when defined by continuous or categorical measures. Future clinical, genetic and biomarker studies should report both the findings and the method employed to assess lithium response according to the Alda scale.

1. Introduction

Bipolar disorder (BD) is a chronic disease characterized by a peak age of onset of 15–25 years, an 80% risk of episode recurrence (with a 50% risk of recurrence within one year of an index episode), a high prevalence of comorbid mental and physical disorders and significant inter-episode social and functional impairment (Goodwin and Jamison, 2007; Collins et al., 2011). The early age at onset (AAO) and persistent long-term morbidity explain why BD is ranked as one of the most burdensome public health problems globally, especially in

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young adulthood (Gore et al., 2011). Also, BD is associated with a significant increase in premature deaths from suicide and all-cause mortality, and it is estimated that the diagnosis is associated with an average lifespan reduction of about 10–15 years (Hayes et al., 2015). Empirical data from randomized controlled clinical trials and observational studies indicate that lithium prophylaxis can modify the course and outcome of BD (Geddes et al., 2004; Kessing et al., 2011; Muller-Oerlinghausen et al.,1994; Severus et al., 2014). However, concerns about the risk to benefit ratio have undoubtedly influenced the acceptability of lithium to some clinicians and patients, and this ambivalence has reduced the use of lithium as a first line treatment or delayed the introduction of long-term prophylaxis even in cases with a confirmed diagnosis of BD (Goodwin and Jamison, 2007; Muller-Oerlinghausen et al., 2012; Scott and Pope, 2002a; Scott and Pope, 2002b; Pope and Scott, 2003).

Confidence in prescribing lithium might be restored if biomarkers of lithium response were more clearly defined (Schulze et al., 2010). However, as there are no definitive biomarkers (genotypes or endophenotypes), clinicians primarily rely on recognizing a clinical phenotype of response (Schulze et al., 2010). A major challenge to identifying the latter is the need to find an acceptable measure lithium prophylactic efficacy that can be utilized across clinical and research settings. Three rating scales to assess lithium response are documented in the literature. The earliest scales to be published, the Illness Severity Index (ISI; Coppen et al., 1973) and the Affective Morbidity Index (AMI; Maj et al., 1985), used brief simple ratings of pre- to post-lithium change in episode frequency or morbidity to define clinical response. The most obvious difference between the scales is that the ISI score is adjusted for the age at which lithium use commenced. Whilst it is widely accepted that the scales have construct validity, there are no comprehensive reports on their performance or reliability and both scales have been superseded by the 'Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder' (also referred to as the Alda scale) (Grof et al., 2002).

The Alda scale provides a Total Score (TS) for lithium response that is derived from the scores on two sub-scales, namely the A scale (which assesses change in illness activity following the introduction of lithium) minus the B scale score (which includes factors that undermine the likelihood that any improvement is associated with lithium treatment) (Grof et al., 2002; Garnham et al., 2007). The inter-rater reliability of the Alda scale has recently been tested in a sample of more than 1300 lithium-treated cases whose response to prophylaxis was rated by 70 researchers at 29 different international sites who were all trained in the use of the scale (Manchia et al., 2013). The findings suggest a moderate level of inter-rater reliability for the TS, with kappas of .54–.66. However, the inter-rater reliability of the A scale score was increased to > .7 if the test sample was restricted to cases with B scale score was four or less (allowing the A scale score alone to be used to assess response in this selected population). Finally, the researchers indicated that whilst the TS could be used as a continuous measure of lithium response, it could also be used to define response categories: Full Response (FR), Partial Response (PR) and Non-Response (NR). At present, the cut-off between FR and PR is more consistent than the lower cut-off used to identify the NR group (Grof, 2010; Manchia et al., 2013).

A reliable scale to measure treatment response is critical to current and future research in BD. The Alda scale is an important tool that has been applied in many studies such as research into genetic markers of lithium response (e.g. Chen et al., 2014; Hou et al., 2016). However, there are still relatively few studies of the clinical characteristics of individuals demonstrating different levels of lithium response on Alda Scale, and the majority of the available publications that examine such clinical cross-validation originate from Grof and his collaborators (Duffy et al., 2003; Grof et al., 2002; Garnham et al., 2007; Passmore et al., 2003; Pfennig et al., 2010). Most of the studies used the TS as a continuous measure of response or used TS-defined response categories (FR, PR, NR). Using these approaches, Grof et al. (2002) noted that FR to lithium was significantly greater in those probands with a first-degree relative with BD who had demonstrated a good response to lithium. Pfenning et al. (2010) identified that psychotic features predicted poorer lithium response, whilst Passmore et al. (2003) reported that lithium and lamotrigine responders differed on a number of individual and familial characteristics (e.g. lithium responders had an episodic course and family history of BD; lamotrigine responders had more rapid cycling and family history of schizo-affective disorders). Our own study identified that family history of BD I predicted FR in a proband, but a lifetime history of mixed episodes or of an alcohol use disorder (AUD) predicted PR or NR (Sportiche et al., 2016).

Of all the clinical studies undertaken with the Alda Scale, only Garnham et al. (2007) examined what combinations of characteristics best predict lithium response. The study included 120 BD cases and identified three factors that independently contributed to the prediction of FR: an episodic pattern of illness, a lifetime diagnosis of BD II, and an earlier age at onset of BD (AAO). The finding on earlier AAO is not found consistently in other studies, but it is noteworthy as it lends some support to the idea of using an age-adjustment in the assessment of lithium response, as proposed by the originators of the ISI scale (Coppen et al., 1973). Garnham et al.'s (2007) study also examined several other issues related to the magnitude of response to different mood stabilizers, including an analysis of response levels according to the order of prescription of prophylaxis (i.e. whether receiving lithium as a first or second line treatment was associated with good or poor response, etc.). Several aspects were examined but, to briefly summarize the findings that are relevant to this paper, the TS was higher for lithium than for anticonvulsant mood stabilizers, and the response to lithium was higher when it was used as the first line treatment.

In summary, there are several approaches to measuring response to lithium using the Alda scale described in the literature, including the recent recommendation to use of the continuous score on the A scale in those with a low B scale score. Publications on clinical factors and treatment patterns associated with different magnitudes of lithium response vary in the factors selected for study and the analytic strategies employed (analysis of individual factors or combinations of factors). Furthermore, there are no studies that examine any clinical factors associated with the new definition of lithium response (A score in cases with a low B score) and no information regarding the clinical features of cases with a high or low B scale score. This is relevant as it is now proposed that a high B scale score can be used to exclude cases from studies (because the high B score may render the assessment of lithium response unreliable); however, we do not know if cases with a high B scale score share any specific clinical characteristics. Overall, there appear to be several key gaps in our knowledge about the clinical characteristics of lithium responders defined according to different criteria on the Alda scale. As such, we examine lithium response when measured (a) as a continuous variable using the TS on the Alda scale; (b) as a continuous variable using the A scale score alone in a selected sample of cases (with a B scale score = < 4); and (c) using response categories defined according to the cut-off scores on the TS (i.e. FR, PR, NR). The specific aims of this study are to examine.

(i) the clinical characteristics associated with different definitions of the lithium response phenotype;
(ii) the explained variance in lithium response associated with the use of continuous or categorical measures of response using the Alda scale; and
(iii) to determine if any clinical factors best differentiate between groups defined by a high (B > 5) or low (B≤4) B scale score.

2. Methods

An Institutional Review Board gave ethical approval for a programme of research on BD, and all participants gave written informed