Journal of Affective Disorders 178 (2015) 224–228

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

An exploratory study of responses to low-dose lithium in African Americans and Hispanics

Jodi Gonzalez Arnold [a,*], Stephanie Salcedo [b], Terrence A. Ketter [c], Joseph R. Calabrese [d], Dustin J. Rabideau [b], Andrew A. Nierenberg [b], Melissa Bazan [a], Andrew C. Leon [b], Edward S. Friedman [e], Dan Iosifescu [f], Louisa G. Sylvia [b], Michael Ostacher [c], Michael Thase [g], Noreen A. Reilly-Harrington [b], Charles L. Bowden [a]

[a] University of Texas Health Science Center San Antonio, USA
[b] Massachusetts General Hospital – Bipolar Clinic and Research Program, USA
[c] Stanford University School of Medicine, USA
[d] Case Western Reserve University, USA
[e] University of Pittsburgh School of Medicine, USA
[f] Mount Sinai School of Medicine, USA
[g] University of Pennsylvania School of Medicine, USA

ARTICLE INFO

Article history:
Received 25 July 2014
Accepted 19 February 2015
Available online 14 March 2015

Keywords:
Bipolar disorder
Hispanics
African Americans
Health disparities
Lithium
Treatment outcome

ABSTRACT

Objectives: Few prospective studies examine the impact of ethnicity or race on outcomes with lithium for bipolar disorder. This exploratory study examines differences in lithium response and treatment outcomes in Hispanics, African Americans, and non-Hispanic whites with bipolar disorder in the Lithium Treatment Moderate Dose Use Study (LiTMUS).

Methods: LiTMUS was a six-site randomized controlled trial of low-dose lithium added to optimized treatment (OPT; personalized, evidence-based pharmacotherapy) vs. OPT alone in outpatients with bipolar disorder. Of 283 participants, 47 African Americans, 39 Hispanics, and 175 non-Hispanic whites were examined. We predicted minority groups would have more negative medication attitudes and higher attrition rates, but better clinical outcomes.

Results: African Americans in the lithium group improved more on depression and life functioning compared to whites over the 6 month study. African Americans in the OPT only group had marginal improvement on depression symptoms. For Hispanics, satisfaction with life did not significantly improve in the OPT only group, in contrast to whites and African Americans who improved over time on all measures. Attitudes toward medications did not differ across ethnic/racial groups.

Conclusions: African Americans show some greater improvements with lithium than non-Hispanic whites, and Hispanics showed more consistent improvements in the lithium group. The impact of low-dose lithium should be studied in a larger sample as there may be particular benefit for African Americans and Hispanics. Given that the control group (regardless of ethnicity/race) had significant improvements, optimized treatment may be beneficial for any ethnic group.

1. Introduction

One aim of personalized medicine is to incorporate research on medication efficacy and tolerability differences by ethnicity/race (Murphy and McMahon, 2013). For bipolar disorder, there is limited information on whether medication responses are influenced by ethnic background. In studies assessing lithium red blood cell to plasma ratio in Caucasians and African Americans, African Americans had a higher lithium red blood cell to plasma ratio and also reported more side effects, suggesting African Americans may need lower doses to have better lithium tolerability (Strickland et al., 1995, 1993). Degenhardt et al. (2011) studied olanzapine to treat bipolar mania and found no differences in dosing or outcomes for African Americans compared to Caucasians; however, African Americans were more likely to discontinue treatment early and had some side effects at higher rates (Degenhardt et al., 2011). No studies have specifically investigated lithium red blood cell to plasma ratios or response to lithium in U.S. Hispanics. Studies of mania and depression suggest Hispanics may have better (Tamayo et al., 2007) or similar (Tamayo et al., in press) responses than whites (i.e. non-Hispanic) to

* Corresponding author.
E-mail address: arnoldjg@uthscsa.edu (J. Gonzalez Arnold).

http://dx.doi.org/10.1016/j.jad.2015.02.035
0165-0327/

antipsychotics. African Americans and Hispanics may have more negative attitudes toward taking psychiatric medication (Cooper et al., 2003; Nadeem et al., 2008) which may account for early study termination (Arnold et al., 2013; Sanchez-Lacay et al., 2001; Gonzalez et al., 2010; Stauffer et al., 2011).

The Lithium Treatment Moderate Dose Use Study (LiTMUS) examined the efficacy of adding low to moderate doses of lithium to personalized, guideline-based optimized pharmacological treatment. The LiTMUS main outcomes reported no differences on psychiatric or global symptom ratings when low-dose lithium was added to optimized treatment (Nierenberg et al., 2013). In this exploratory study, we examined whether African Americans or Hispanics had differential clinical outcomes to add-on lithium as compared to whites.

We predicted African Americans and Hispanics would discontinue add-on lithium (600 mg) sooner than whites and that their attitudes toward mood stabilizers would mediate this earlier discontinuation. We predicted that African Americans and Hispanics who remained in the lithium arm of the study would have greater improvement than whites on manic and depressive symptom severity, overall bipolar illness severity, life functioning, and quality of life.

2. Methods

2.1. Procedure

LiTMUS was a six-site randomized 6-month clinical trial conducted from April 2008 to March 2010. LiTMUS examined the efficacy of adding low to moderate doses of lithium (averaging 600 mg) to optimized treatment (OPT; personalized, guideline-based pharmacological treatment) as indicated by the Texas Implementation of Medical Algorithm (Suppes et al., 2005). Participants were randomized to lithium plus OPT vs. OPT without lithium. Participants attended biweekly the first two months and then monthly for four months. In the lithium plus OPT group, lithium dosages were 600 mg/day for the first two months, and individual clinical adjustments were permitted thereafter. The full study details, design, and rationale have been described elsewhere (Nierenberg et al., 2009). This study was approved by the Institutional Review Boards at each participating institution, in accordance with the Helsinki Declaration of 1975. Subjects provided verbal and written informed consent prior to participation.

2.2. Participants

Two hundred eighty three adult participants were randomized. Participants met DSM-IV criteria for bipolar disorder, were currently symptomatic as indicated by a Clinical Global Impression of Severity for Bipolar Disorder (CGI-BP-S) score ≥ 3, and had not taken lithium for at least 30 days. Primary exclusion criteria were (1) contraindication to lithium; (2) requiring acute inpatient hospitalization; (3) requiring current detoxification from opiates, barbiturates, or alcohol; (4) history of lithium intolerance; (5) renal impairment; (6) thyroid stimulating hormone $>$ 20% over the upper normal limit; or (7) unwilling to comply with study requirements and procedures.

Ethnicity/Race: Participants were asked to report their ethnicity (Hispanic/Latino, not Hispanic/Latino, or unknown). Separately, they reported their race and could indicate any of the following that applied: White, African American/black, Asian/Asian American, Native American/American Indian, or Native Hawaiian/Pacific Islander. Those reporting any Hispanic/Latino background were classified as Hispanic regardless of race. Subjects were not asked country of Hispanic/Latino origin. Those noting white and not Hispanic were classified as white, and African American/black and not Hispanic were classified as African American. Due to small sample sizes, subjects reporting other or multiple ethnic/racial groups were not included in this analysis. The six sites contributed to the ethnic/race sample as follows: Massachusetts General Hospital – 14% of African Americans and 7% of Hispanics; Case Western Reserve – 28% of African Americans and no Hispanics; Stanford University School of Medicine – 4% of African Americans and 21% of Hispanics; University of Pennsylvania – 28% of African Americans and no Hispanics; University of Pittsburgh Medical Center – 19% of African Americans and 10% of Hispanics; University of Texas Health Science Center San Antonio – 9% of African Americans and 62% of Hispanics.

2.3. Measures

At the baseline visit, participants' demographics (e.g., age, gender, number of children, education, employment status, marital status, birthplace, and income) were collected. To determine current and lifetime DSM-IV diagnoses, participants were interviewed using the clinician-rated Extended Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and the SCID DSM-IV Substance Use Disorder Module.

Participants also reported their attitudes towards mood stabilizers, bipolar disorder, medication side effects and stigma using the Attitudes toward Mood Stabilizer Medication Questionnaire (AMSQ), a modified version of the of the Lithium Attitudes Questionnaire (Harvey, 1991). Higher scores indicate more negative attitudes towards mood stabilizers.

Mood symptoms, functioning and side effects were assessed at every study visit. Blinded clinician raters assessed manic symptoms using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and depressive symptoms using the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979); higher scores on these scales indicate greater symptom severity. The Clinical Global Impression of Severity for Bipolar Disorder (CGI-BP-S) was used to assess overall bipolar symptom severity (Spearing et al., 1997).

At baseline, as well as weeks 12 and 24, participants rated their overall functioning and life satisfaction using the LIFE-Range of Impaired Functioning Tool (LIFE-RIFT) (Leon et al., 2000) and quality of life was assessed using the Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) (Endicott et al., 1993). Lower scores indicate better functioning on the LIFE-RIFT and higher scores indicate better quality of life on the QLES-Q-SF.

2.4. Statistical methods

We provide descriptive statistics of ethnicity/race by treatment group in the entire LiTMUS cohort ($N=283$). For the remainder of our analysis, we considered only those subjects who self-identified as African American/Black ($N=47$), Hispanic ($N=39$), and white (non-Hispanic) ($N=175$) as defined above.

First, we compared African Americans and Hispanics to whites on various baseline demographic and clinical variables using two-sample *t*-tests for continuous variables and chi-square tests for categorical variables. Mixed-effects regression models were used to see whether there were improved outcomes over time between African Americans and Hispanics compared to whites. We considered whether ethnic/racial group improved on each outcome within each treatment group and whether there was a differential effect of ethnicity/race between treatment groups. Due to the non-linear nature of response in LiTMUS, log(time) was used in the mixed effects models.

We produced Kaplan–Meier plots and log-rank tests to determine whether African Americans and Hispanics were more likely to have shorter time to lithium discontinuation compared to whites. We defined discontinuation as either discontinuation of lithium (prior to 6 months) or loss to follow-up. Patients who completed on protocol