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Brief report

The effect of personalized guideline-concordant treatment on quality of life and functional impairment in bipolar disorder

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ABSTRACT

Objectives: The aims of this study were to evaluate correlates and predictors of life functioning and quality of life in bipolar disorder during a comparative effectiveness trial of moderate doses of lithium.
Methods: In the Lithium treatment moderate-dose use study (LiTMUS), 283 symptomatic outpatients with bipolar disorder type I or II were randomized to receive lithium plus "optimal personalized treatment (OPT)", or OPT alone. Participants were assessed using structured diagnostic interviews, clinician-rated blinded assessments, and questionnaires. We employ linear mixed effects models to test the effect of treatment overall and adjunct lithium specifically on quality of life or functioning. Similar models are used to examine the association of baseline demographics and clinical features with quality of life and life functioning.
Results: Quality of life and impaired functioning at baseline were associated with lower income, higher depressive severity, and more psychiatric comorbid conditions. Over 6 months, patients in both treatment groups improved in quality of life and life functioning (p-Values < 0.0001); without a statistically significant difference between the two treatment groups (p-Values > 0.05). Within the lithium group, improvement in quality of life and functioning was not associated with concurrent lithium levels at week 12 or week 24 (p-Values > 0.05). Lower baseline depressive severity and younger age of onset predicted less improvement in functioning over 6 months.
Conclusions: Optimized care for bipolar disorder improves overall quality of life and life functioning, with no additional benefit from adjunct moderate doses of lithium. Illness burden and psychosocial stressors were associated with worse quality of life and lower functioning in individuals with bipolar disorder.

1. Introduction

Individuals with bipolar disorder experience impaired functioning (ability to effectively manage occupational or interpersonal domains) and quality of life (self-reporting one's sense of well-being and satisfaction), even during periods of sustained remission of symptoms (Robb et al., 1997; Sierra et al., 2005). Poor functioning is a predictor of relapse suggesting that it may be both a cause and a consequence of bipolar disorder (Gitlin et al., 1995). Predictors of impaired functioning in individuals with bipolar disorder include poor premorbid functioning (Zarate et al., 2000; Carlson et al., 2012), past or current substance abuse (Tohen et al., 1990), low socioeconomic status (Zarate et al., 2000), residual and subthreshold symptoms (Gitlin et al., 1995; Tohen et al., 1990), and male sex (Tohen et al., 1990).

Long-term treatment with a combination of psychotropic medications yields the best improvement in symptoms (Baethge

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et al., 2005). Monotherapy with lithium has had mixed results in improving psychosocial functioning and quality of life. A naturalistic study of bipolar I patients followed for 2 years after a mean of 4.5 years after hospitalization found that, those treated with lithium monotherapy had fewer relapses, as well as better adjustment and work performance (Goldberg et al., 1996). Other studies have found that lithium monotherapy has not been successful at improving quality of life for those with bipolar disorder (Tohen et al., 1990; Baethge et al., 2005; Bocchetta et al., 1997).

These mixed results may be due to variable definitions of functioning and quality of life assessments. Many qualities of life measures focus on course of illness and physical symptoms, yet do not reflect patients' perspective of their ability to function and overall well-being (Carr et al., 2003). This is noteworthy as most researchers and clinicians agree that it is important to take subjective indicators into account when obtaining a global measure of functioning and quality of life (Carr et al., 2003). Thus, the LIFE-Range of Impaired Functioning Tool (LIFE-RIFT) (Leon et al., 2000) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al., 1993) were chosen for LiTMUS because they emphasize the respondent's view of their quality of life.

The first aim of this study was to examine quality of life and life functioning outcomes at baseline and after 6 months of treatment for participants in the Lithium Treatment-Moderate dose Use Study (LiTMUS). To the best of our knowledge, this is the first study to examine the effectiveness of low to moderate dose lithium on quality of life. Second, we examined whether certain demographic and clinical characteristics at baseline predicted improvement of quality of life and life functioning over 6 months.

2. Methods

2.1. Study design

LiTMUS was a 6-month, six-site, parallel-group, randomized effectiveness trial of adjunctive low to moderate doses of lithium therapy in outpatients with bipolar I or II disorder that were at least mildly symptomatic at study entry. OPT was openly administered, guideline-informed, empirically supported, and personalized pharmacologic treatment based on current symptoms, prior treatment history, and course of disorder. The only requirements for OPT were that participants were prescribed at least one mood stabilizer and followed guidelines for treating bipolar disorder (Nierenberg et al., 2009). Participants were either randomized to receive open lithium plus OPT or OPT without lithium. Clinicians and participants knew the treatment assignments, while raters who measured the primary outcomes were blinded. This study was approved at each study sites' Internal Review Board. The full study details of LiTMUS have been described elsewhere (Nierenberg et al., 2009).

2.2. Measures

All participants were assessed using structured diagnostic interviews, clinician-rated assessments, and self-reported questionnaires. Diagnoses were confirmed using the Extended Mini-International Neuropsychiatric Interview, a validated, structured, clinician-administered diagnostic interview, to determine current and lifetime Diagnostic and Statistical Manual-Version IV diagnoses (Sheehan et al., 1998). The Structured Clinical Interview for DSM-IV Substance Use Disorder Module was used to assess substance use disorders because it provides more detail regarding substance use course specifiers than the MINI.

This analysis examined the two secondary outcomes of LiTMUS: the LIFE-Range of Impaired Functioning Tool (LIFE-RIFT) (Leon et al., 2000) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al., 1993). The LIFE-RIFT is a brief, clinician-administered measure of the degree of functional impairment across several domains: interpersonal, work, and recreation, and satisfaction. The Q-LES-Q is a self-report measure assessing the degree of enjoyment and satisfaction experienced across multiple domains (i.e., physical health, feelings, work, household duties, school, leisure, social, and overall). Other assessments used in this analysis the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the Young Mania Rating Scale (YMRS) (Young et al., 1978), and the Beck Modified Scale of Suicidal Ideation (MSSI) (Beck et al., 1979).

2.3. Statistical analyses

We conducted mixed effects linear regression to determine if there was a treatment effect on quality of life (i.e., Q-LES-Q) or life functioning (i.e., LIFE-RIFT). In the model, we included main effects of treatment group, time, and a treatment by time interaction. A random intercept and slope mixed model was fit to account for within-patient correlation. We also ran simple regressions to examine whether concurrent lithium levels correlated with quality of life or life functioning at weeks 12 and 24.

Similar mixed effects models were used to test the association of baseline demographics and clinical features with quality of life and life functioning both at baseline and over the 6 month study. Predictors included age, education, ethnicity, number of children, household income, marital status, gender, depressive (MADRS) and manic severity (YMRS), suicidality (MSSI), number of psychiatric comorbidities, family history of mood disorder, age of onset, and rapid cycling. After obtaining univariate results, we fit multivariate mixed effects models for each outcome to determine which predictors remained significant adjusting for other variables in the model. In addition to time, any variables with univariate p-Values < 0.1 were entered into the multivariate model. If a variable by time interaction met this criteria (univariate $p < 0.1$), then we automatically included the non-interactive (i.e. baseline) effect of this variable. Terms were removed sequentially from the model if $p > 0.1$. Due to the exploratory nature of this paper, no adjustment for multiple hypothesis testing was made.

3. Results

Table 1 summarizes the baseline demographic and clinical variables of all randomized subjects in LiTMUS.

Over 6 months, patients in both treatment groups improved in quality of life and life functioning (p-Values < 0.0001). The estimated (model-based) 6-month increase in quality of life (Q-LES-Q) was 9.4 for OPT group and 10.7 for Li+OPT group. The estimated 6-month decrease in functional impairment (LIFE-RIFT) was 2.3 for OPT and 2.4 for Li+OPT. Improvement in quality of life or life functioning over the course of 6 months was not statistically different between the two treatment groups (p-Values > 0.05).

Within the Li+OPT group, lithium levels over time were 0.44 mEq/L at week 12 ($N=90$; median=0.40, SD=0.29, range=0.00–1.60), and 0.47 mEq/L at week 24 ($N=83$; median=0.40, SD=0.34, range=0.00–1.80). Quality of life and functioning were not associated with concurrent lithium levels at week 12 or week 24 (p-Values > 0.05).

In exploring the univariate associations of each possible predictor with quality of life and functioning at baseline, we found similar results between the two outcomes. Subjects who had less income, who were more depressed, more suicidal and had more