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The Effect of Personalized Guideline-Concordant Treatment on Quality of Life and Functional Impairment in Bipolar Disorder

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Ms. Greiter reports no competing interests.

Dr. Thase reports no conflicts of interest specifically pertaining to this project. During the past three years he has been an advisor/consultant to Alkermes, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck, MedAvante, Merck, Mylan, Neuronic, Otsuka, Pamlab, PharmaNeuroboost, Pfizer, Rexahn, Roche, Shire, Sunovion, Supernus, Takeda, and Teva, as well as the US Food and Drug Administration and the National Institute of Mental Health. During the same time frame, Dr. Thase has received honoraria for talks from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, and Pfizer and he has received research grants from Alkermes, AstraZeneca, Eli Lilly, Forest, GlaxoSmithKline, Otsuka, PharmaNeuroboost, and Roche, as well as the National Institute of Mental Health and the Agency for Healthcare Research and Quality.

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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 six 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 were 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 six 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.

Keywords

bipolar disorder; life functioning; quality of life; lithium

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^{1, 2}. Poor functioning is a predictor of relapse suggesting that it may be both a cause and a consequence of bipolar disorder³. Predictors of impaired functioning in individuals with bipolar disorder include poor premorbid functioning^{4, 5}, past or current substance abuse⁶, low socioeconomic status⁴, residual and subthreshold symptoms^{3, 6}, and male sex⁶.

Long-term treatment with a combination of psychotropic medications yields the best improvement in symptoms⁷. 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 performance⁸. Other studies have found that lithium monotherapy has not been successful at improving quality of life for those with bipolar disorder^{6, 7, 9}.

These mixed results may be due to variable definitions of functioning and quality of life assessments. Many quality 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-being¹⁰. 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 life¹⁰. Thus, the LIFE-Range of Impaired Functioning Tool (LIFE-RIFT)¹¹ and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)¹² 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.

Methods

Study Design

LiTMUS was a six-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 who 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 disorder¹⁴. 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 elsewhere¹⁴.

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 diagnoses¹⁵. 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)¹¹ and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)¹². 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)¹⁶, the Young Mania Rating Scale (YMRS)¹⁷, and the Beck Modified Scale of Suicidal Ideation (MSSI)¹⁸.

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 six 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.

Results

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

Over six 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 six 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 comorbid psychiatric diagnoses reported lower quality of life and life functioning at baseline (p -values < 0.05 , univariate data not shown). Patients who were more depressed at baseline experienced more improvement in quality of life and life functioning over the six month study period. In contrast, patients who were more manic at baseline experienced less improvement in quality of life over the study (p -values < 0.05 , univariate data not shown).

Variables included in our multivariate models for quality of life and functioning are presented in Table 2. Adjusting for all other covariates in the model, subjects who had more children, less income, higher depressive severity, and more comorbid psychiatric diagnoses reported worse functioning at baseline. Subjects who had a lower age of onset and who were less depressed experienced less improvement in functioning over the study. In regards to quality of life, patients who had less income, higher depressive severity, lower manic severity, and higher suicidality reported lower quality of life at baseline. Subjects who were less depressed and who were more manic experienced less improvement in quality of life over the study (see Table 2).

Discussion

Functioning and quality of life improved over the study duration regardless of treatment group. This suggests that OPT administered by expert clinicians may assist bipolar patients' ability to function more effectively; although the addition of low to moderate doses of lithium did not appear to confer any additional benefit. There was also not a significant association between lithium level and quality of life or life functioning. This may be due to the focus on using only low to moderate doses of lithium.

Our finding that having children is associated with lower life functioning individuals with bipolar disorder may be because their children have a higher incidence of psychiatric

disorders¹⁹. Thus, the responsibilities of parenting multiple children who might be psychiatrically compromised may be particularly complex for this population. These data also that bipolar parents may be a particularly vulnerable population for experiencing stress and impairment to functioning.

This study provides evidence that having a low income is associated with greater functional impairment and lower quality of life in bipolar disorder, similar to findings in the general population. Poor occupational adjustment (an indicator of low income) has been shown to be predictive of shorter time to relapse in bipolar disorder³, further suggesting that it is a likely contributor to lower quality of life and life functioning. This suggests that interventions (e.g., cognitive remediation)²⁰ aimed at getting bipolar individuals jobs or earning higher incomes may have an important impact on their quality of life.

It has been well documented that having a higher number of psychiatric co-morbidities is associated with lower functioning, such as comorbid substance use and anxiety^{21,22}. Substance abuse may lead to mixed states, rapid cycling, and an increased risk of suicide, hospitalization, and medication noncompliance²³, in addition to diminishing one's likelihood of seeking out clinical treatment²⁴. Anxiety comorbid conditions become more pronounced during manic and depressive episodes, and is associated with non-response to treatments²². These data also underscore our finding that higher depressive severity is associated with lower quality of life. Likewise, it is not surprising that suicidality was associated with lower quality of life, given that suicide attempts are linked to a number of genetic and experiential variables linked with poor functioning and quality of life (e.g., drug abuse²⁵, trauma²⁶, psychosocial stressors^{27,28}).

Interestingly, depressive severity at baseline predicted more improvement in quality of life and life functioning over the six month study. These results were unexpected, as depressive symptoms in individuals with bipolar disorder have been shown to predict poorer outcomes and greater impairment²⁹. This finding, however, could simply be attributed to the fact that patients with more severe depression came into the study with worse quality of life and functioning. Thus, they had further to improve over the six month study in order to reach some average level of quality of life and functioning after 24 weeks of treatment (i.e. regression toward the mean). A similar argument could be made to explain the finding that more manic severity at baseline predicted less improvement in quality of life, as more severe mania was associated with higher quality of life at baseline (thus, less room to improve). Nevertheless, these data suggest that patients who were more depressed at study entry experienced a higher degree of 6-month improvement in quality of life and life functioning.

This study has a few potential limitations. First, LiTMUS was not powered to examine these two secondary outcomes, making this analysis exploratory. The associations between functioning, quality of life, and demographic and clinical variables warrant further investigation. Although we incorporated all available data from the LiTMUS cohort by employing mixed effects models, there is a possibility that data were missing *not* at random. Thus, our results are conditional on the assumption of the data missing at random.

This study demonstrated that optimized care, as defined by personalized, guideline-informed treatment, improves overall quality of life and life functioning in individuals with bipolar disorder; however, low to moderate doses of lithium did not further influence these outcomes. Given that specific clinical (i.e., symptoms, comorbidity, age of onset) and demographic (i.e., income, number of children) features predict life functioning and quality of life, further research is warranted on predictors of functioning and quality of life to enhance treatment and prevention strategies for bipolar disorder.

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Table 1

Baseline Demographic and Clinical Variables

	All randomized subjects (N=283) Mean (SD) or N (%)
Age	39.1 (12.3)
Age of onset	15.4 (7.6)
Number of children	1.4 (1.6)
Female	160 (57%)
Race	
White	213 (75%)
African American	48 (17%)
Asian	12 (4%)
Other/Missing	10 (4%)
Ethnicity	
Hispanic or Latino	39 (14%)
Not Hispanic or Latino	243 (86%)
Education	
< High school	19 (7%)
High school diploma/GED	58 (20%)
Some college	78 (28%)
Technical or associate's degree	27 (10%)
College diploma (bachelor's degree)	65 (23%)
Graduate or professional degree	36 (13%)
Employment Status	
Employed	115 (41%)
Unemployed	93 (33%)
Disability recipient	47 (17%)
Other	28 (10%)
Household income	
<25,000	137 (49%)
25K to 50K	57 (20%)
50K to 75K	36 (13%)
>75,000	52 (18%)
Bipolar Subtype I	216 (76%)
LIFE-RIFT	13.4 (3.6)
Q-LES-Q	46.2 (18.6)
CGI-BP severity	4.3 (0.9)
MADRS	22.5 (10.1)
YMRS	12.5 (8.2)
Suicidality (MSSI)	2.3 (4.0)
Number of comorbid psychiatric diagnoses	1.1 (1.1)

Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire, LIFE-RIFT: LIFE-Range of Impaired Functioning Tool, CGI-BP: Clinical Global Impressions Scale for use in bipolar illness, MADRS: Montgomery Asberg Depression Rating Scale, YMRS: Young Mania Rating Scale, MSSSI: Beck Modified Scale of Suicidal Ideation.

Table 2

Predictors of Life Functioning and Quality of Life at Baseline and Over Six Month Study.

Predictor Variable	LIFE-RIFT		Q-LES-Q	
	Baseline coefficient ¹ (p-value)	Slope coefficient ² (p-value)	Baseline coefficient ¹ (p-value)	Slope coefficient ² (p-value)
Number of children	0.26 (0.0077)	--	--	--
Household income ³	−0.22 (0.0942)	--	1.52 (0.0199)	--
Depression (MADRS)	0.20 (<0.0001)	−0.00578 (<0.0001)	−1.0498 (<0.0001)	0.02685 (<0.0001)
Mania (YMRS)	--	--	0.2106 (0.0354)	−0.02248 (0.0007)
Suicidality (MSSI)	--	--	−0.4811 (0.0236)	--
Number of psychiatric comorbidities	0.2592 (0.0739)	--	--	--
Age of onset	−0.02063 (0.3624)	−0.00270 (0.0675)	--	--

Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire, LIFE-RIFT: LIFE-Range of Impaired Functioning Tool, MADRS: Montgomery Asberg Depression Rating Scale, YMRS: Young Mania Rating Scale, MSSI: Beck Modified Scale of Suicidal Ideation.

Note: coefficients and p-values are based on multivariate linear mixed effects models.

¹ Baseline coefficient can be interpreted as the change in outcome (e.g. LIFE-RIFT) at baseline per one unit change in predictor (e.g. MADRS).

² Slope coefficient refers to the predictor-by-time interaction. The coefficient interpretation is the change in slope of the outcome (e.g. LIFE-RIFT) per one unit change in baseline predictor (e.g. MADRS).

³ For analysis, household income was coded as ordinal rank from 1 to 4, such that 1 corresponds with lowest income category (<25,000) and 4 corresponds with highest income category (>75,000).