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Baseline Disability and Poor Functioning in Bipolar Disorder Predict Worse Outcomes:
Results From the Bipolar CHOICE Study

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ABSTRACT

Objective: To examine the effects of treatment on functioning impairments and quality of life and assess baseline functioning and employment status as predictors of treatment response in symptomatic individuals from the Bipolar Clinical Health Outcomes Initiative in Comparative Effectiveness (Bipolar CHOICE) study.

Method: Bipolar CHOICE was an 11-site, 6-month randomized effectiveness study comparing lithium to quetiapine, each with adjunctive personalized treatments (APTs). We examined post hoc (1) the effects of treatment on functioning, (2) how changes in functioning differed between treatment responders and nonresponders, and (3) whether functioning and employment status mediated treatment response in 482 participants with *DSM-IV-TR* bipolar I or II disorder from September 2010 to September 2013.

Results: Treatment was associated with significant improvements in functioning and quality of life, regardless of treatment group (P values < .0001). Responders showed greater improvements in quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire P values < .05) and functioning (Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool P values < .05) than nonresponders. Unemployed or disabled participants at baseline had significantly greater illness severity at baseline than employed participants (P values < .05). Over the study duration, employed participants reported greater improvements in physical health and quality of life in leisure activities than both unemployed and disabled participants (P values < .05). Individuals who saw greater improvement in functioning and quality of life tended to show greater improvements in depressive and anxiety symptoms (P values ≤ .0001), as well as overall illness severity (P values < .001). Early (8 weeks) and very early (4 weeks) clinical changes in mood symptoms predicted changes in functioning and quality of life at 6 months (P values < .001).

Conclusions: Prior disability status was associated with a worse treatment response and prospective illness course. Results implicate functioning and employment status as important markers of illness severity and likelihood of recovery in bipolar disorder, suggesting that interventions that target functional impairment may improve outcomes.

Trial Registration: ClinicalTrials.gov identifier for the Bipolar CHOICE study: NCT01331304.

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Bipolar disorder is characterized by episodes of mood elevation and, most often, periods of depression.[1] Individuals with this disorder typically exhibit severe impairments compared to individuals without the disorder, including poorer overall functioning,[2–4] increased absenteeism at work,[5–8] decreased work productivity,[7] lower annual income,[7] high unemployment rates,[9–11] and lower overall quality of life.[5,12] Compared to those with major depressive disorder, individuals with bipolar disorder experience greater occupational disability.[13]

The traditional view of bipolar disorder posits that the illness is characterized by mood episodes of fixed periods and that full recovery could be achieved through the use of mood-stabilizing medications.[14] However, clinical and epidemiologic studies show that 30%–60% of individuals with bipolar disorder do not regain full social or occupational functioning after the onset of their illness,[15] and these individuals experience persisting work functioning problems even when in clinical remission.[16] Various determinants of functioning in patients with bipolar disorder have been investigated, such as depressive symptoms, early age at illness onset, longer and more frequent hospitalizations, comorbidity, lower socioeconomic status, and poorer premorbid functioning[17] (for a recent review, see Huxley and Baldessarini[18]). Of those, depressive symptoms appear to be the determinant most consistently related to lower overall psychosocial functioning.[17,19–24] For example, Altshuler et al[25] found that the presence and persistence of depressive symptoms, more so than manic ones, was most strongly correlated with functional impairment. Another study found that individuals were more likely to miss work due to their depressive symptoms rather than their

Clinical Points

- Disability recipients with bipolar disorder may be more difficult to treat, possibly because of a more severe illness symptomatology.
- Being disabled may serve as a proxy for a more severe form of psychiatric illness.
- Early response to treatment may serve as an indicator of future illness course.
- Improvements in functioning and quality of life were significantly associated with improvements in depressive symptoms, anxiety symptoms, and overall bipolar illness severity, but not manic or hypomanic symptoms.

manic symptoms.[26] Additionally, individuals with prolonged unemployment seem to experience a greater number of depressive episodes.[27] Other studies have found that occupational disability was associated with a greater number of lifetime manic episodes, as compared to patients without disability.[28,29]

In this study, we investigated the role of functional impairment, reduced quality of life, and employment in the Bipolar Clinical and Health Outcomes Initiative in Comparative Effectiveness (Bipolar CHOICE) study, a nationwide comparative effectiveness study of lithium and quetiapine, each with adjunctive personalized treatments (APTs [ie, evidence-based, guideline-informed treatment based on illness course, treatment history, and current symptomatology]), in patients with bipolar disorder. The Bipolar CHOICE primary outcome study[30] found that treatment with lithium and quetiapine with APT was associated with improvements in clinical symptoms across 6 months of treatment (eg, depression symptom severity, suicidal ideation), but there were no differences between lithium plus APT and quetiapine plus APT. In this post hoc analysis, we examined the effects of treatment on functioning and quality of life. We also explored the role of baseline characteristics (eg, functioning, quality of life, medications, and lifetime mood episodes) as predictors for treatment outcome. Given the association found in prior studies[24–26] between mood symptoms and functional impairment, we expected that poorer functioning was indicative of having a more severe psychiatric illness course, thus making it more difficult to treat. In line with this prediction, we had several hypotheses. First, in light of the primary outcome, we compared treatment responders and nonresponders and predicted that treatment would improve functioning and that treatment responders would show greater improvement in functioning as compared to nonresponders but that, overall, functioning would remain impaired. We also expected that variables possibly indicative of greater illness severity (ie, disability status, number of medications, and number of lifetime mood episodes at baseline) would predict the degree of improvement over the study duration. In other words, we hypothesized that individuals who are disability recipients use greater number of medications and reported a higher number of lifetime mood episodes would show less improvement in clinical outcomes, functioning, and quality of life. We also predicted that greater changes in clinical variables relating to symptom severity would correlate with greater improvements in functioning. Last, we explored whether early changes in clinical variables predicted changes in functioning. Prior studies[31,32] examining treatments for depression and obsessive-compulsive disorder showed that early response is strongly associated with final clinical outcomes. Therefore, we hypothesized that early (within 8 weeks) and very early (within 4 weeks) improvements in clinical variables relating to illness severity will predict greater improvements in functioning over the study duration.

METHOD

The Bipolar CHOICE study was an 11-site, 6-month randomized effectiveness study, which was conducted from September 2010 to September 2013, comparing lithium, a classic mood stabilizer, to quetiapine, a second-generation antipsychotic, each with APTs, in bipolar disorder. For a detailed description of the study design and primary outcome, see Nierenberg et al.[33] Briefly, following a baseline evaluation, patients were randomized to lithium plus APT or quetiapine plus APT with a single-blind design (only raters were blind to the treatment assignment) and were treated over the following 6 months. Visits occurred biweekly over the first 8 weeks and then monthly for the remaining 16 weeks. In addition to meeting with a study clinician at each visit, participants completed self-report questionnaires and assessments with blinded raters. Overall, participants improved across all measures of mood and functioning over the 6 months, regardless of treatment assignment. The lithium plus APT and quetiapine plus APT groups did not differ on either coprimary measure: treatment outcomes (change in illness severity and side effect burden as measured by the Clinical Global Impressions-Efficacy Index [CGI-EI]) or necessary clinical adjustments of psychiatric medications (NCAs).[33] The Bipolar CHOICE study was registered on ClinicalTrials.gov (identifier: NCT01331304).

Participants

A total of 482 adult participants enrolled in the study over 22 months. The institutional review board approved the study protocol at the respective sites, and participants provided written informed consent before starting any study-related procedure. Inclusion and exclusion criteria were limited in order to obtain a more diverse and generalizable sample. Eligible patients diagnosed with bipolar I or II disorder entered the study with at least mild symptoms of bipolar disorder (Clinical Global Impressions-Bipolar Version [CGI-BP][34] score ≥ 3). Potential participants were excluded from the study if they had any contraindication to lithium or quetiapine (eg, pregnancy, prior hypersensitivity, severe renal disease, lack of treatment response after an adequate trial), were currently in crisis such that hospitalization or more acute care was necessary, were currently taking lithium or quetiapine, or were unable to comply with study requirements. Participants were not excluded if they had

responded to lithium or quetiapine in the past, as long as they were willing to be randomized. The rationale and design of the Bipolar CHOICE study are detailed elsewhere.[33]

Assessments

Diagnosis and symptom severity. Lifetime and current diagnoses according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*),[1] including bipolar disorder and other psychiatric comorbidities, were established at the screening visit with the electronic Mini-International Neuropsychiatric Interview (eMINI-PLUS), an electronic extended version of a validated structured diagnostic interview.[35] Medical comorbidities were determined at study entry with a medical history, assessment of vital signs, and a fasting blood sample for routine chemistries. Clinical interviewers further obtained demographic information (eg, employment and disability status, household income, race), family psychiatric history, number of previous hospitalizations, and suicide attempts, age at illness onset, and illness duration. At every visit, blinded raters completed the CGI-BP to assess severity of mania, depression, and overall bipolar illness and the Bipolar Inventory of Symptoms Scale (BISS),[36,37] a structured interview that yields an overall score and multiple subscores, including mania and depression.

Functioning. Life functioning and quality of life were measured with the blinded rater-administered Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT)[21] and the self-reported Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[38] at study entry, midpoint, and end point. The LIFE-RIFT comprises an overall score and 4 subscales, work (ie, employment, household, student), relationships (ie, spouse, children, other relatives, friends), satisfaction, and recreation, to characterize the extent to which psychopathology has impacted current functioning. Higher LIFE-RIFT scores indicate greater functional impairment. The Q-LES-Q, which reflects subjective quality of life, also includes an overall score and 8 subscores: physical health, mood, leisure-time activities, social relationships, general activities, work, household duties, and school/coursework. Higher Q-LES-Q scores reflect increased quality of life.

Treatment response was defined by CGI-BP severity scores ≤ 2 for at least 8 weeks of the study. This definition is consistent with *DSM-IV* criteria for partial or full remission, and it has been used in several studies examining treatments in depression and bipolar disorder.[22,30,39,40]

Statistical Analyses

All statistical analyses were completed using Statistical Analysis Software (SAS; version 9.2, SAS Institute; Cary, North Carolina). The 2 treatment groups (lithium plus APT vs quetiapine plus APT) were pooled because the treatment groups did not differ on any clinical outcomes.[30] A mixed-effects regression was conducted to examine the main effect of treatment on functioning and how this effect differed between responders and nonresponders. These models account for baseline group differences in clinical variables, so no adjustments for other baseline variables were made. Responder status, consistent with the primary outcome article, was defined by CGI-BP scores ≤ 2 for at least 8 weeks of the study. We also compared demographic and clinical characteristics of responders versus nonresponders among those with poor baseline functioning using a stepwise multivariate logistic regression model similar to the model employed in the primary CHOICE article.[30] We considered various demographic and clinical variables as predictors of clinical improvement. Poor functioning at baseline was defined by LIFE-RIFT scores ≥ 15.

Next, participants were categorized by whether they were employed, unemployed, or a disability recipient. Participants were considered disability recipients for either psychiatric or other medical reasons. Note that participants endorsing "student," "retired," and "other" were excluded, as these groups were too small to be included in the analyses. Analyses of variance were conducted to examine whether these 3 groups differed on baseline clinical and demographic variables, mood and symptom severity, functioning, and medical/psychiatric comorbidities. Several clinical and demographic variables were included to show a clear picture of the characteristics of these 3 groups; therefore, due to the exploratory nature, adjustments for multiple comparisons were not conducted.

To explore employment, medications, and lifetime mood episodes as potential predictors of change in functioning, mixed-effects regression analyses that controlled for symptom severity at baseline (BISS total) were conducted on disabled, employed, and unemployed participants. Analyses assessed each group's change in functioning, differences between groups, and pairwise comparisons for significant variables.

To investigate the extent that overall changes in clinical variables (eg, BISS, CGI-BP, laboratory assessments, vital signs) correlate with changes in functioning, mixed-effects regression models were used to estimate the covariance (and correlation) between the patient-specific slopes of each outcome. We then calculated change scores and used linear regression models to explore the extent to which early changes (within 8 weeks) and very early changes (within 4 weeks) in clinical variables determine changes in functioning over 6 months.

RESULTS

Improvements in Functioning and Quality of Life

Pretreatment and 6-month functioning and quality of life scores are shown in Table 1.

Overall, we found that, across the study duration, participants improved on all measures of functioning, ie, LIFE-RIFT total, work, interpersonal relationships, satisfaction, and recreation, as well as Q-LES-Q physical health, subjective well-being, leisure time activities, social relationships, general activities, work, household duties, and school/courses (*P* values < .0001; Table 1).

Responders Versus Nonresponders

As compared to nonresponders, responders in the study saw greater improvements on the LIFE-RIFT total ($P = .01$), work ($P = .05$), and satisfaction ($P = .01$), as well as the Q-LES-Q physical health ($P = .01$), subjective well-being ($P < .0001$), social relationships ($P = .006$), general activities ($P = .007$), and household duties ($P = .01$; see Table 2 for summary of results). However, for treatment responders, functioning was not quite normalized in that LIFE-RIFT scores were still above what one would expect in healthy controls, suggesting there is a need for continued treatment.[21] Using previously established normal ranges for LIFE-RIFT and Q-LES-Q scores,[41,42] we examined the percentage of participants that fell within normal ranges in functioning and quality of life by the end of the study duration and found that the percentages ranged from 52% (in Q-LES-Q subjective feelings of well-being subscores) to 85% (LIFE-RIFT total scores). See Supplementary eTable 1 at PSYCHIATRIST.COM for a summary of these results.

Table 1. Main Effect of Treatment on Functioning

Scale	Baseline, Mean ± SD (n)	Change From Baseline to 6 Mo, Mean (95% CI)	*P* Value
LIFE-RIFT[a]			
Total	14.2 ± 3.4 (476)	−3.62 (−4.02 to −3.22)	< .0001
Work	3.6 ± 1.3 (476)	−1.03 (−1.18 to −0.89)	< .0001
Interpersonal relationships	3.7 ± 1.3 (481)	−0.64 (−0.79 to −0.49)	< .0001
Satisfaction	3.4 ± 1.0 (481)	−0.95 (−1.07 to −0.84)	< .0001
Recreation	3.5 ± 1.2 (481)	−1.01 (−1.16 to −0.87)	< .0001
Q-LES-Q[b]			
Physical health	41.6 ± 18.7 (479)	12.99 (11.00 to 14.97)	< .0001
Subjective well-being	45.6 ± 17.9 (478)	15.70 (13.76 to 17.65)	< .0001
Leisure time activities	46.0 ± 22.1 (478)	15.11 (12.67 to 17.54)	< .0001
Social relationships	44.7 ± 19.0 (475)	14.76 (12.54 to 16.97)	< .0001
General activities (Short Form total)	44.3 ± 17.8 (478)	15.42 (13.45 to 17.40)	< .0001
Work	52.1 ± 21.6 (239)	15.77 (12.71 to 18.82)	< .0001
Household duties	47.9 ± 22.0 (449)	15.00 (12.70 to 17.29)	< .0001
School/course	45.4 ± 22.9 (67)	18.33 (11.29 to 25.36)	< .0001

[a]Higher LIFE-RIFT scores reflect increased functional impairment (ie, higher is worse).
[b]Higher Q-LES-Q scores reflect increased quality of life (ie, higher is better).
Abbreviations: LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Participants With Poor Baseline Functioning: Responders Versus Nonresponders

Of those who had poor functioning at baseline (n = 234), 12% (n = 28) were responders. We found that bipolar type, depressive severity, and suicide risk were predictors of clinical improvement. Among the demographic factors, education was statistically significant in this subgroup of patients ($P < .05$). This finding suggests that, among those entering the study with poor functioning, patients who were less educated (no college vs at least some college) were much less likely to have symptomatic improvement over 6 months (1% vs 16%, $P = .03$). We also simplified the analysis using Fisher exact test to compare education (no college vs at least some college) and response status (responder vs nonresponders), which further supported this finding ($P = .0006$).

Employment

Clinical and demographic features by employment/disability status are shown in Supplementary eTable 2. Within the Bipolar CHOICE cohort, 175 participants (36.3%) were employed, 170 (35.5%) were unemployed, and 74 (15.4%) were disability recipients.

The 3 groups differed in various baseline demographic and clinical variables (see Supplementary eTable 2). For example, disability recipients tended to be older than unemployed and employed participants. Employed participants were significantly more likely to be married and to have completed at least some college (*P* values < .05). Compared to disability recipients, employed participants also reported an earlier age at mania onset, as well an earlier age at onset of their first mood episode. Unemployed or disabled participants had significantly greater illness severity, as measured by BISS total scores, at baseline than employed participants (*P* values < .05). Unemployed participants reported the highest depression severity pretreatment, as measured by the BISS and CGI-BP depression subscores, and disability recipients reported the highest BISS mania subscores (see Supplementary eTable 1 for pairwise comparisons). Disability recipients reported a greater number of previous hospitalizations, medical and anxiety comorbidities, and higher prevalence of hyperlipidemia and hypertension, and they were more likely to be diagnosed with a manic episode, posttraumatic stress disorder, and agoraphobia (see Supplementary eTable 2 for additional pairwise comparisons). Disability recipients were less likely to meet criteria for lifetime substance abuse. In addition, employed participants reported more life satisfaction than unemployed participants (lower LIFE-RIFT satisfaction subscore). The 3 groups did not differ significantly on most of the Q-LES-Q subscales at baseline, with the exception that disabled participants endorsed more impairment than their employed and unemployed counterparts on the Q-LES-Q household duties subscale. Consistent with the main outcomes from the entire sample,[30] participants in this subset of employed, unemployed, and disabled participants did not differ by treatment group in terms of recovery or NCAs (*P* values > .05).

Treatment Effects on Functioning

Although all 3 groups improved on all LIFE-RIFT and Q-LES-Q subscores (*P* values < .05), there were significant group differences between employment status groups on the Q-LES-Q physical health, subjective well-being, and leisure-time activities scales. Over the 6 months of treatment, employed participants reported greater improvements in physical health than both unemployed ($P = .02$) and disabled participants ($P = .006$). Similarly, employed participants reported greater improvements in quality-of-life leisure activities than both unemployed ($P = .01$) and disabled participants ($P = .01$). Furthermore, disabled participants

Table 2. Effect of Treatment on Functioning by Responder Status[a]

Scale	Baseline		Change From Baseline				Difference in 6-Mo Change (Responder – Nonresponder), Mean (95% CI)	*P* Value
	Nonresponder, Mean ± SD (N)	Responder, Mean ± SD (N)	Nonresponder, Mean (95% CI)	*P* Value	Responder, Mean (95% CI)	*P* Value		
LIFE-RIFT								
Total	14.7 ± 3.4 (373)	12.7 ± 3.0 (103)	−3.29 (−3.76 to −2.83)	<.0001	−4.47 (−5.28 to −3.66)	<.0001	−1.17 (−2.10 to −0.25)	.0128
Work	3.7 ± 1.3 (373)	3.1 ± 1.1 (103)	−0.90 (−1.06 to −0.73)	<.0001	−1.24 (−1.53 to −0.94)	<.0001	−0.34 (−0.68 to −0.01)	.0462
Interpersonal relationships	3.9 ± 1.3 (378)	3.3 ± 1.3 (103)	−0.53 (−0.71 to −0.36)	<.0001	−0.84 (−1.14 to −0.53)	<.0001	−0.30 (−0.65 to 0.05)	.0898
Satisfaction	3.5 ± 1.0 (378)	3.1 ± 0.9 (103)	−0.88 (−1.02 to −0.75)	<.0001	−1.22 (−1.46 to −0.99)	<.0001	−0.34 (−0.61 to −0.07)	.0135
Recreation	3.6 ± 1.2 (378)	3.2 ± 1.2 (103)	−0.96 (−1.13 to −0.79)	<.0001	−1.16 (−1.46 to −0.86)	<.0001	−0.20 (−0.54 to 0.14)	.2467
Q-LES-Q								
Physical health	39.2 ± 18.0 (376)	50.4 ± 18.7 (103)	11.45 (9.13 to 13.76)	<.0001	17.43 (13.45 to 21.40)	<.0001	5.98 (1.43 to 10.53)	.0101
Subjective well-being	43.6 ± 17.9 (375)	52.8 ± 15.8 (103)	13.38 (11.15 to 15.62)	<.0001	22.42 (18.58 to 26.26)	<.0001	9.04 (4.64 to 13.43)	<.0001
Leisure time activities	44.1 ± 21.9 (375)	53.2 ± 21.4 (103)	13.48 (10.62 to 16.35)	<.0001	17.13 (12.22 to 22.05)	<.0001	3.65 (−1.98 to 9.28)	.2030
Social relationships	42.9 ± 18.7 (372)	51.3 ± 18.8 (103)	12.68 (10.10 to 15.27)	<.0001	19.78 (15.37 to 24.19)	<.0001	7.10 (2.05 to 12.15)	.0060
General activities	42.0 ± 17.5 (375)	52.8 ± 16.2 (103)	13.61 (11.33 to 15.89)	<.0001	19.78 (15.87 to 23.68)	<.0001	6.17 (1.70 to 10.64)	.0070
Work	49.8 ± 21.9 (179)	59.0 ± 19.2 (60)	15.70 (11.85 to 19.54)	<.0001	15.26 (9.42 to 21.10)	<.0001	−0.43 (−7.24 to 6.37)	.8998
Household duties	46.3 ± 22.7 (350)	53.3 ± 18.3 (99)	13.35 (10.65 to 16.05)	<.0001	19.89 (15.34 to 24.44)	<.0001	6.54 (1.31 to 11.77)	.0144
School/course	42.6 ± 22.6 (53)	55.9 ± 21.8 (14)	17.83 (9.25 to 26.42)	.0001	18.73 (1.99 to 35.47)	.0302	0.90 (−17.72 to 19.52)	.9205

[a]Responder is defined as Clinical Global Impressions-Bipolar version severity score ≤ 2 for at least 8 weeks.
Abbreviations: LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Table 3. Estimated 6-Month Difference Between Employment Groups[a]

Scale	Group Difference, *P* Value	Employed – Unemployed		Employed – Disabled		Unemployed – Disabled	
		Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value
LIFE-RIFT							
Total	.4592	−0.48 (−1.50 to 0.54)	.3543	−0.79 (−2.15 to 0.57)	.2552	−0.31 (−1.64 to 1.03)	.6492
Work	.6703	−0.15 (−0.50 to 0.20)	.4007	−0.15 (−0.62 to 0.32)	.5360	0.00 (−0.46 to 0.46)	.9916
Interpersonal relationships	.5314	−0.16 (−0.54 to 0.21)	.3836	−0.25 (−0.75 to 0.24)	.3132	−0.09 (−0.57 to 0.39)	.7166
Satisfaction	.7672	−0.02 (−0.31 to 0.26)	.8673	−0.14 (−0.51 to 0.24)	.4757	−0.11 (−0.48 to 0.25)	.5447
Recreation	.7805	−0.09 (−0.45 to 0.27)	.6121	−0.16 (−0.63 to 0.32)	.5131	−0.07 (−0.53 to 0.40)	.7799
Q-LES-Q							
Physical health	.0099	5.50 (0.82 to 10.18)	.0215	8.80 (2.60 to 15.00)	.0055	3.30 (−2.69 to 9.30)	.2793
Subjective well-being	.0367	2.34 (−2.51 to 7.18)	.3429	8.44 (2.00 to 14.88)	.0103	6.10 (−0.12 to 12.33)	.0545
Leisure time activities	.0106	7.70 (1.74 to 13.67)	.0116	10.34 (2.46 to 18.23)	.0103	2.64 (−4.99 to 10.27)	.4961
Social relationships	.2166	2.47 (−2.93 to 7.87)	.3693	6.34 (−0.82 to 13.50)	.0823	3.87 (−3.05 to 10.80)	.2719
General activities	.2912	1.57 (−3.30 to 6.43)	.5264	5.15 (−1.29 to 11.60)	.1166	3.59 (−2.65 to 9.82)	.2588
Work	.9363	−0.38 (−9.09 to 8.33)	.9314	2.21 (−10.98 to 15.39)	.7406	2.59 (−11.87 to 17.05)	.7237
Household duties	.6289	1.46 (−4.05 to 6.97)	.6018	3.51 (−3.75 to 10.77)	.3418	2.05 (−5.07 to 9.17)	.5710
School/course	.3465	−14.81 (−39.37 to 9.74)	.2111	−14.25 (−39.97 to 11.47)	.2482	0.56 (−27.14 to 28.27)	.9652

[a]Analyses adjusted for baseline Bipolar Inventory of Symptoms Scale total.
Abbreviations: LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

reported greater losses in subjective well-being than both employed ($P = .01$) and unemployed participants ($P = .05$ at a trend level). See Table 3 for a summary of results.

Medications and Lifetime Mood Episodes as Predictors of Functioning and Quality of Life

A greater number of baseline psychiatric medications were associated with decreased improvement in Q-LES-Q social relationships subscore. That is, for every 1 additional psychiatric medication at baseline, the Q-LES-Q social relationship subscore decreases by 2.2 points at 6 months (95% CI, −4.01 to −0.46; $P = .01$). In addition, a greater number of lifetime mood episodes was associated with increased improvement in Q-LES-Q household chores subscores. For every additional lifetime episode, the Q-LES-Q household chore subscore increases by 2.32 (95% CI, 0.01 to 4.62; $P = .049$).

Clinical Changes Associated With Improvements in Functioning and Quality of Life

Improvement in overall LIFE-RIFT and Q-LES-Q scores was associated with improved BISS depression, BISS anxiety, BISS total, CGI-BP depression, and CGI-BP overall severity scores across the study period. As such, patients who saw more improvement in functioning and quality of life tended also to see more improvement in depressive symptoms, anxious symptoms, and overall illness burden. Of these significant associations, trends in anxiety and depressive

Table 4. Association Between Changes in Clinical Variables and Functioning Over Study Duration

Variables		Estimated Covariance of Slopes		
Functioning	Clinical	Covariance of Slopes (95% CI)	Correlation Coefficient	*P* Value
LIFE-RIFT total	BISS			
	Depression	0.75 (0.39 to 1.11)	0.74	.0001
	Mania	−0.15 (−0.39 to 0.09)	−0.26	.2303
	Anxiety	0.77 (0.42 to 1.13)	0.99	<.0001
	Total	1.48 (0.63 to 2.34)	0.68	.0007
	CGI-BP			
	Depression	0.12 (0.06 to 0.18)	0.76	.0001
	Mania	−0.00 (−0.05 to 0.05)	−0.01	.956
	Overall	0.11 (0.05 to 0.16)	0.87	.0001
	HDL	−0.10 (−1.05 to 0.85)	−0.18	.8292
	LDL	1.40 (−0.90 to 3.70)	1.00	.234
	Total cholesterol	1.68 (−0.93 to 4.30)	0.89	.2066
	Weight	0.42 (−0.25 to 1.08)	0.32	.2196
	Body mass index	0.05 (−0.05 to 0.16)	0.25	.3241
Q-LES-Q general	BISS			
	Depression	−5.30 (−7.11 to −3.48)	−0.84	<.0001
	Mania	−0.30 (−1.47 to 0.87)	−0.06	.6197
	Anxiety	−4.29 (−6.04 to −2.55)	−0.65	<.0001
	Total	−11.78 (−16.07 to −7.48)	−0.75	<.0001
	CGI-BP			
	Depression	−0.75 (−1.04 to −0.45)	−0.69	<.0001
	Mania	−0.12 (−0.37 to 0.13)	−0.12	.334
	Overall	−0.64 (−0.91 to −0.38)	−0.70	<.0001
	HDL	4.05 (−0.40 to 8.51)	0.66	.0745
	LDL	6.79 (−3.70 to 17.28)	0.70	.2047
	Total cholesterol	12.99 (0.98 to 25.00)	0.68	.034
	Weight	−0.56 (−3.88 to 2.76)	−0.04	.7398
	Body mass index	−0.15 (−0.67 to 0.38)	−0.07	.5875

Abbreviations: BISS = Bipolar Inventory of Symptoms Scale, CGI-BP = Clinical Global Impressions-Bipolar Version scale, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

symptoms correlated most strongly with trends in quality of life and functioning. Additionally, Q-LES-Q general scores were associated with higher total cholesterol across the 6 months of treatment (Table 4).

Early Clinical Change and Change in Functioning and Quality of Life

Early (8 weeks) and very early (4 weeks) clinical changes in BISS scores (depression, anxiety, and total) and CGI-BP scores (depression, mania, overall) predicted changes in functioning on the LIFE-RIFT at 6 months (Table 5). Early and very early clinical changes in BISS scores (depression, mania, and total) and CGI-BP scores (depression, mania, overall) predicted changes in quality of life on the Q-LES-Q at 6 months.

DISCUSSION

We aimed to investigate the role that disability status and treatment play in functioning for symptomatic individuals with bipolar disorder. Overall, treatment with either lithium or quetiapine plus APT led to statistically and clinically significant improvements in clinical severity, functioning, and quality of life, even though the treatment groups did not differ. Employment and disability status predicted changes in functioning over the study duration such that employed participants reported better physical health and quality of life in leisure activities at the end of the study compared to unemployed and disabled participants. Not surprisingly, at baseline, we found that disability recipients and unemployed participants experienced greater illness severity than employed participants. These findings were consistent with previous research[43,44] showing that being employed correlates with less cognitive impairment, better treatment response, and better functioning in the bipolar population. Beyond clinical status, research[29] has shown that occupational disability among individuals with bipolar disorder is also associated with factors such as older age, less education, and not being in a stable relationship, consistent with our findings. However, one unexpected finding was that unemployed and employed participants had an earlier mania onset than disability recipients. Because this was counterintuitive to our predictions, we do not have an explanation for why disabled participants had a later mania onset.

Finally, in the sample as a whole, improvements in functioning and quality of life were significantly associated with improvements in depressive symptoms, anxiety symptoms, and overall bipolar illness severity, but not manic or hypomanic symptoms. An explanation for the latter finding could be that hypomanic and subthreshold manic symptoms tend to have a lesser, if any, effect on functioning[45]; alternatively, since half of the present sample spent less than 20% of the past year in an elevated mood state, there may not have been a large enough sample for us to detect an association between manic symptoms and functioning. Our findings are consistent with prior research[17,23] demonstrating that improvements in functioning were significantly associated with improvements in mood and other symptoms of bipolar disorder.

The present findings further illustrate that multiple factors affect and are affected by functional outcomes in bipolar disorder, implicating functioning as a critical variable in the conceptualization and treatment of this illness. Among individuals with poor baseline functioning, in particular, we found that bipolar diagnosis type, depressive symptom severity, and suicide risk significantly predicted clinical improvement, which is consistent with the model in the primary outcome article.[30] In contrast, we also found that education was a significant predictor among this subgroup, meaning that individuals with poor functioning and lower levels of education were less likely to show symptom improvements. There is a need for more effective treatments for patients with low functioning, evidenced by the fact that those participants with greater functional impairments at baseline saw less treatment response as well as the least improvement in functioning, physical health, quality of life in leisure activities, and subjective well-being. One promising

Table 5. Improvement in Functioning per 1-Unit Increase in Early and Very Early Clinical Variables

Functioning (week 24)	Clinical	Early Clinical Change (week 0–8) Mean ± SD (n)	Early Clinical Change (week 0–8) Increase in Functioning per 1-Unit Increase in Early Clinical Variable, Mean (95% CI)	Early Clinical Change (week 0–8) *P* Value	Very Early Clinical Change (week 0–4) Mean ± SD (n)	Very Early Clinical Change (week 0–4) Increase in Functioning per 1-Unit Increase in Very Early Clinical Variable, Mean (95% CI)	Very Early Clinical Change (week 0–4) *P* Value
LIFE-RIFT total: mean = 10.4, SD = 3.7	BISS						
	Depression	−8.1 ± 8.2 (399)	0.10 (0.06 to 0.15)	< .0001	−6.6 ± 8.0 (417)	0.05 (0.00 to 0.10)	.0357
	Mania	−4.5 ± 6.5 (399)	0.07 (0.00 to 0.13)	.0457	−3.6 ± 6.1 (417)	0.06 (−0.01 to 0.13)	.1049
	Anxiety	−7.2 ± 8.8 (399)	0.09 (0.05 to 0.14)	< .0001	−5.4 ± 8.4 (417)	0.06 (0.02 to 0.11)	.0097
	Total	−26.2 ± 20.5 (399)	0.05 (0.03 to 0.07)	< .0001	−20.8 ± 19.0 (417)	0.04 (0.02 to 0.06)	.0009
	CGI-BP						
	Depression	−1.3 ± 1.4 (399)	0.71 (0.43 to 1.00)	< .0001	−1.1 ± 1.4 (417)	0.46 (0.17 to 0.75)	.0021
	Mania	−0.9 ± 1.3 (399)	0.36 (0.06 to 0.67)	.0200	−0.6 ± 1.2 (417)	0.55 (0.22 to 0.88)	.0010
	Overall	−1.4 ± 1.3 (399)	1.03 (0.74 to 1.33)	< .0001	−1.1 ± 1.2 (417)	0.83 (0.50 to 1.16)	< .0001
	Weight	1.8 ± 7.6 (388)	−0.01 (−0.06 to 0.04)	.6937	1.4 ± 6.1 (407)	0.00 (−0.07 to 0.07)	.9788
	Body mass index	0.3 ± 1.2 (388)	−0.06 (−0.39 to 0.27)	.7170	0.2 ± 1.0 (407)	−0.02 (−0.45 to 0.41)	.9190
Q-LES-Q general: mean = 60.8, SD = 19.6	BISS						
	Depression	−8.1 ± 8.2 (399)	−0.48 (−0.73 to −0.23)	.0001	−6.6 ± 8.0 (417)	−0.25 (−0.51 to 0.00)	.0543
	Mania	−4.5 ± 6.5 (399)	−0.39 (−0.72 to −0.06)	.0205	−3.6 ± 6.1 (417)	−0.35 (−0.71 to 0.00)	.0522
	Anxiety	−7.2 ± 8.8 (399)	−0.34 (−0.57 to −0.11)	.0046	−5.4 ± 8.4 (417)	−0.14 (−0.38 to 0.11)	.2851
	Total	−26.2 ± 20.5 (399)	−0.25 (−0.35 to −0.15)	< .0001	−20.8 ± 19.0 (417)	−0.17 (−0.28 to −0.06)	.0031
	CGI-BP						
	Depression	−1.3 ± 1.4 (399)	−3.34 (−4.80 to −1.88)	< .0001	−1.1 ± 1.4 (417)	−2.03 (−3.54 to −0.52)	.0087
	Mania	−0.9 ± 1.3 (399)	−2.26 (−3.80 to −0.72)	.0041	−0.6 ± 1.2 (417)	−3.51 (−5.19 to −1.82)	< .0001
	Overall	−1.4 ± 1.3 (399)	−4.80 (−6.36 to −3.24)	< .0001	−1.1 ± 1.2 (417)	−3.82 (−5.55 to −2.09)	< .0001
	Weight	1.8 ± 7.6 (388)	0.04 (−0.23 to 0.31)	.7717	1.4 ± 6.1 (407)	−0.06 (−0.41 to 0.29)	.7337
	Body mass index	0.3 ± 1.2 (388)	0.19 (−1.51 to 1.89)	.8238	0.2 ± 1.0 (407)	−0.32 (−2.54 to 1.90)	.7761

Abbreviations: BISS = Bipolar Inventory of Symptoms Scale, CGI-BP = Clinical Global Impressions-Bipolar Version scale, LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

intervention is the use of adjunctive psychotherapy in this population, given that adjunctive psychotherapy has been found to lead to significant improvements in functioning and symptom severity over 2-year periods.[46] Furthermore, these findings suggest that poorer functioning may be indicative of having a more severe illness course, which then leads to greater difficulties in being able to treat. Another possibility is that individuals that have a greater psychiatric illness severity end up with greater functional disabilities. Although the direction of this relationship cannot be determined, if individuals are disabled at the start of treatment, our findings indicate that they may be more difficult to treat.

Our findings should be considered in the context of some methodological limitations. First, our employment and disability groups were determined by the participants' reported employment status at baseline, and we did not assess whether disability recipients were eligible based on psychiatric or medical conditions. It is unknown whether participants that reported being unemployed could be eligible to be a disability recipient, and this may partially explain why we found some similarities in demographics and clinical characteristics between these 2 groups. Additionally, employment status was not reassessed at time points later in the study. Second, personality disorders were not included in diagnostic interviews; Grande et al[29] found that having a personality disorder significantly predicted being a disability recipient. Additionally, assessments did not include a measure of cognitive impairment, which has been shown to be a strong predictor of functioning and employment status in bipolar disorder.[43,44] Furthermore, data were collected in the context of a clinical trial, limiting the generalizability of these results. For example, the percentage of unemployed participants and disability recipients appears higher in this sample than in naturalistic observational studies.[43] Because participants had to be able to come in for regular study visits, our sample may have excluded more disabled individuals that were more functionally impaired. There is also a possibility that our sample includes overrepresentation of participants with low socioeconomic status or without health insurance. Finally, because our study did not include a placebo group, we cannot infer causality and rule out the possibility that participants' improvement could be due to the spontaneous course of the disease. However, it is important to note that, regardless of treatment group (lithium or quetiapine), both groups seemed to improve significantly.

Overall, results showed that pharmacologic treatment for bipolar disorder can improve functioning and quality of life. Functional impairments were associated with clinical symptoms and treatment response, which suggests that disability and functioning impairments may serve as a proxy for greater psychiatric illness severity. Therefore, further research is warranted to examine whether targeting functional impairment in treatment would improve outcomes.

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consultation fees, and/or royalties from Medacorp, Massachusetts General Hospital (MGH) Psychiatry Academy, BrainCells, Clintara, Systems Research and Applications Corporation, Boston University, Tufts University, Catalan Agency for Health Technology Assessment and Research, National Association of Social Workers Massachusetts, Massachusetts Medical Society, and Oxford University Press. **Dr Nierenberg** is a consultant for Abbott Laboratories, AstraZeneca, Basilea, BrainCells, Brandeis University, Bristol-Myers Squibb, Cephalon, Corcept, Eli Lilly, Forest, Genaissance, GlaxoSmithKline, Innapharma, Janssen, Jazz, Lundbeck, Merck, Novartis, Pamlab, PGx Health, Pfizer, Ridge Diagnostics, Roche, Sepracor, Schering-Plough, Shire, Somerset, Sunovion, Takeda, Targacept, and Teva; is a stakeholder in Appliance Computing (MindSite), Brain Cells, and InfoMed (potential share of income); receives research support from Agency for Healthcare Research and Quality (AHRQ), Bristol-Myers Squibb, Cederroth, Cyberonics, Elan, Forest, GlaxoSmithKline, Janssen, LichtwerPharma, Eli Lilly, Mylan (formerly Dey Pharmaceuticals), NARSAD, NIMH, Pamlab, Pfizer, Shire, Stanley Foundation, and Wyeth-Ayerst; has received honoraria from MGH Psychiatry Academy in the past 3 years (prior to 3 years ago, honoraria from Bristol-Myers Squibb, Cyberonics, Forest, GlaxoSmithKline, Eli Lilly, Shire, and Wyeth-Ayerst); receives other income from legal case reviews for CRICO, MBL Publishing (for past services as editor-in-chief of *CNS Spectrums*), Slack Inc (for services as associate editor of *Psychiatric Annals*), and being a member of the editorial board, *Mind Mood Memory*, Belvior Publications; has copyright joint ownership with MGH for Structured Clinical Interview for Montgomery-Asberg Depression Rating Scale and Clinical Positive Affect Scale; and has received additional honoraria from American Drug Utilization Review Society (ADURS), American Society for Clinical Psychopharmacology, Zucker Hillside Hospital, Forest, Janssen, Biomedical Development, Boston Center for the Arts, University of Pisa, University of Wisconsin at Madison, University Texas Southwest at Dallas, Health New England, Harold Grinspoon Charitable Foundation, Eli Lilly, AstraZeneca, Brandeis University, International Society for Bipolar Disorder, 2nd East Asian Bipolar Forum, Mid-Atlantic Permanente Research Institute, and Up-to-Date. **Dr McInnis** has received grants for research support from NIMH, Heinz C Prechter Research Fund, and the Michigan Institute for Clinical Health Research; and has received consulting income from the Qatar National Research Foundation and Merck. **Dr Kemp** has served on the speakers/advisory boards for AstraZeneca, Sunovion, Takeda, and Lundbeck; is a consultant to Bristol-Myers Squibb, Teva, Corcept, and Janssen; and has received grant/research support from NARSAD, Cleveland Foundation, and the Depressive and Bipolar Alternative Treatment Foundation. His spouse is a minor stockholder of Sanofi and Abbott. **Dr Shelton** has been a consultant to Bristol-Myers Squibb, Cerecor, Cyberonics, Eli Lilly, Forest, Janssen, Medtronic, Naurex, Pamlab, Pfizer, Ridge Diagnostics, and Takeda; has received grant support from Assures Health, Bristol-Myers Squibb, Eli Lilly, Elan, Euthymics Bioscience, Forest, Janssen, Jazz, Naurex, Novartis, Otsuka, Pamlab, Pfizer, Repligen, Ridge Diagnostics, St. Jude Medical, and Takeda. **Dr McElroy** is a consultant to or member of the scientific advisory boards of Alkermes, Bracket, F. Hoffman-La Roche, Corcept, Naurex, MedAvante, Shire, Sunovion, and Teva; is a principal or co-investigator on studies sponsored by AHRQ, Alkermes, AstraZeneca, Cephalon, Eli Lilly, Forest, Marriott Foundation, NIMH, Orexigen Therapeutics, Shire, Takeda, and Transcept; and is an inventor on US patent no. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and along with the patient's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson, which has exclusive rights under the patent. **Dr Sylvia** was a shareholder in Concordant Rater Systems; has served as a consultant to United Biosource Corporation, Clintara, Bracket, and Clinical Trials Network; has received grant/research support from NIMH, Patient-Centered Outcomes Research Institute, and American Foundation for Suicide Prevention; has received honoraria from MGH Psychiatry Academy; and receives royalties from New Harbinger. **Dr Kocsis** has received research grants and contracts from AHRQ, NIMH, National Institute on Drug Abuse, Burroughs Wellcome Trust, Pritzker Consortium, Elan, Takeda, Forest, AstraZeneca, and Roche; is on the speaker's bureau at Pfizer and Merck; and is on the advisory board at Corcept. **Dr Friedman** received grant support from NIMH, AHRQ, Novartis, St. Jude Medical, Medtronic, Repligen, AstraZeneca, Roche, and Takeda; receives royalties from Springer; and has been a consultant to Pamlab. **Dr Singh** has been a speaker for Bristol-Myers Squibb, Merck, and Sunovion and has received research support from Novartis and AstraZeneca. **Dr Tohen** was an employee of Lilly (1997–2008) and has received honoraria from or consulted for Abbott, AstraZeneca, Alkermes, Bristol-Myers Squibb, GlaxoSmithKline, Lilly, Johnson & Johnson, Otsuka, Merck, Sunovion, Forest, Roche, Elan, Lundbeck, Teva, Pamlab, Wyeth, and Wiley Publishing; his spouse was a full time employee at Lilly (1998–2013). **Dr Bowden** is a research collaborator with Elan and a consultant to Teva. 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Norton & Company; and has equity holdings in MedAvante. His spouse is employed at Peloton Advantage, which conducts business with Pfizer. **Dr Reilly-Harrington** receives royalties from Oxford University Press, the American Psychological Association, and New Harbinger; serves as a consultant to United Biosource, Clintara; and was a shareholder in Concordant Rater Systems. **Dr Kinrys** has received research support from Astra-Zeneca, Bristol-Myers Squibb, Cephalon, Elan, Eli Lilly, Forest, GlaxoSmithkline, Sanofi/Synthelabo, Sepracor, Pfizer, UCB Pharma, and Wyeth-Ayerst; has been an advisor or consultant to AstraZeneca, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pfizer, Sepracor, UCB Pharma, and Wyeth-Ayerst; and has been a speaker for AstraZeneca, Forest, GlaxoSmithKline, Sepracor, and Wyeth-Ayerst. **Dr Kamali** has received research support from Janssen. **Dr Bobo**, **Mss Salcedo** and **Bernstein**, and **Mr Rabideau** report no competing interests.

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Supplementary Material

Article Title: Baseline Disability and Poor Functioning in Bipolar Disorder Predict Worse Outcomes: Results From the Bipolar CHOICE Study

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List of Supplementary Material for the article

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Supplemental eTable 1. Percentage of patients who fall within normal[1] range of quality of life/ functioning by time period.

Scale (Normal Range)	Baseline % (n/N)	Six Months % (n/N)
LIFE-RIFT: Total	50.8% (242/476)	84.6% (296/350)
Q-LES-Q subjective feelings of well-being	14.9% (71/478)	52.2% (188/360)
Q-LES-Q general activities	18.6% (89/478)	56.4% (203/360)
Q-LES-Q household duties	54.1% (243/449)	81.3% (278/342)
Q-LES-Q leisure time activities	38.7% (185/478)	68.4% (247/361)
Q-LES-Q physical health	23.6% (113/479)	55.1% (199/361)
Q-LES-Q school/course	49.3% (33/67)	83.9% (52/62)
Q-LES-Q social relationships	32.0% (152/475)	65.6% (236/360)
Q-LES-Q work	36.4% (87/239)	73.6% (156/212)

Note: For Q-LES-Q, normal ranges were based on table 5 in Schechter, Endicott, and Nee.[1] To get the lower bound of normal, we took the mean minus 2SDs. Thus, we considered anything above the lower bound to be within the range of normal. For the LIFE-RIFT total score, normal range was based on model-based mean / SD in Leon et al.[2] for patients in "recovery" (as opposed to in "episode"). To get the upper bound of normal, we took the mean plus 2SDs. Thus, anything below the upper bound was considered normal.

[1]Normal ranges (mean ± 2 SD) of each measure:

LIFE-RIFT: Total	3.76 to 14.40	(i.e. normal if <15)
Q-LES-Q subjective feelings of well-being	63.10 to 106.3	(i.e. normal if >63.10)
Q-LES-Q general activities	59.20 to 104.4	(i.e. normal if >59.20)
Q-LES-Q household duties	44.10 to 111.3	(i.e. normal if >44.10)
Q-LES-Q leisure time activities	52.50 to 106.5	(i.e. normal if >52.50)
Q-LES-Q physical health	53.30 to 107.3	(i.e. normal if >53.30)
Q-LES-Q school/course	44.60 to 111.0	(i.e. normal if >44.60)
Q-LES-Q social relationships	52.00 to 103.2	(i.e. normal if >52.00)
Q-LES-Q work	58.00 to 107.6	(i.e. normal if >58.00)

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Supplemental eTable 2. Baseline clinical and demographic features by employment/disability status.

	Group				
Variable	**Employed [0]**	**Unemployed [1]**	**Disability Recipient [2]**	**p-val**	**Significant Pairwise Differences**
	***M* ± *SD* (N)**	***M* ± *SD* (N)**	***M* ± *SD* (N)**		
Age of depression onset	16.1 ± 7.5 (174)	17.0 ± 8.6 (170)	17.6 ± 8.7 (74)	0.351	
Age of mania onset	18.6 ± 8.6 (175)	20.3 ± 10.2 (168)	22.0 ± 10.6 (72)	0.028	0 - 2
Age of first episode	14.8 ± 7.1 (175)	16.3 ± 8.5 (170)	17.4 ± 8.7 (74)	0.043	0 - 2
BISS total	52.9 ± 16.5 (175)	58.4 ± 19.5 (170)	60.7 ± 20.4 (74)	0.002	0 - 1, 0 - 2
BISS depression	16.7 ± 7.3 (175)	18.8 ± 7.1 (170)	17.5 ± 8.1 (74)	0.028	0 - 1
BISS mania	8.4 ± 5.7 (175)	9.0 ± 6.3 (170)	10.9 ± 6.7 (74)	0.015	0 - 2, 1 - 2
BISS anxiety	14.7 ± 7.8 (175)	17.0 ± 8.5 (170)	17.0 ± 9.0 (74)	0.025	0 - 1, 0 - 2
CGI overall	4.3 ± 0.8 (175)	4.6 ± 0.9 (170)	4.5 ± 0.9 (74)	0.003	0 - 1
CGI depression	4.1 ± 1.1 (175)	4.5 ± 1.1 (170)	4.2 ± 1.3 (74)	0.004	0 - 1, 1 - 2
CGI mania	2.9 ± 1.2 (175)	3.0 ± 1.3 (170)	3.2 ± 1.3 (74)	0.196	
LIFE-RIFT: total	13.9 ± 3.1 (175)	14.6 ± 3.5 (166)	14.4 ± 3.8 (72)	0.123	
LIFE-RIFT: satisfaction	3.3 ± 0.9 (175)	3.6 ± 0.9 (170)	3.4 ± 1.1 (73)	0.011	0 - 1
LIFE-RIFT: recreation	3.5 ± 1.2 (175)	3.6 ± 1.1 (170)	3.5 ± 1.4 (73)	0.750	
LIFE-RIFT: work	3.4 ± 1.2 (175)	3.6 ± 1.5 (166)	3.6 ± 1.4 (72)	0.429	
LIFE-RIFT: interpersonal relationships	3.7 ± 1.2 (175)	3.8 ± 1.2 (170)	3.8 ± 1.4 (73)	0.409	
Q-LES-Q physical health	40.4 ± 18.1 (174)	41.7 ± 18.7 (169)	39.9 ± 19.2 (74)	0.721	
Q-LES-Q subjective feelings of well-being	46.0 ± 15.5 (174)	42.9 ± 18.2 (169)	48.3 ± 20.9 (73)	0.064	
Q-LES-Q work	51.2 ± 20.8 (159)	47.5 ± 25.1 (31)	58.3 ± 21.9 (17)	0.254	

	Group				
Variable	**Employed [0]**	**Unemployed [1]**	**Disability Recipient [2]**	**p-val**	**Significant Pairwise Differences**
Q-LES-Q household duties	46.6 ± 19.8 (169)	47.8 ± 22.5 (152)	54.3 ± 26.1 (71)	0.044	0 - 2, 1 - 2
Q-LES-Q school/course	51.9 ± 25.7 (18)	50.6 ± 17.8 (12)	51.7 ± 24.6 (9)	0.988	
Q-LES-Q leisure time activities	44.2 ± 21.2 (174)	46.8 ± 22.8 (168)	46.9 ± 23.6 (74)	0.507	
Q-LES-Q social relationships	45.3 ± 17.6 (174)	43.0 ± 18.3 (166)	43.8 ± 22.3 (73)	0.521	
Q-LES-Q general activities (SFtotal)	45.8 ± 16.5 (174)	42.3 ± 17.9 (168)	43.8 ± 20.8 (74)	0.199	
Q-LES-Q satisfaction with medications	83.3 ± 41.8 (174)	88.2 ± 39.6 (167)	79.9 ± 37.4 (72)	0.289	
Q-LES-Q overall	42.5 ± 23.8 (173)	38.9 ± 23.3 (166)	42.9 ± 28.2 (74)	0.309	
Years in the USA	36.6 ± 12.8 (175)	39.3 ± 11.7 (170)	43.5 ± 10.5 (74)	0.000	0 - 1, 0 - 2, 1 - 2
Body Mass Index (BMI)	28.8 ± 6.9 (175)	30.7 ± 7.6 (167)	32.3 ± 8.2 (74)	0.002	0 - 1, 0 - 2
Weight	184.7 ± 47.2 (175)	194.4 ± 49.5 (167)	198.5 ± 49.0 (74)	0.063	
Height	67.1 ± 3.9 (175)	66.8 ± 3.9 (168)	65.9 ± 4.1 (74)	0.096	
Framingham risk score	2.8 ± 4.6 (162)	3.7 ± 5.2 (144)	4.5 ± 6.3 (64)	0.058	
# Psychiatric meds (baseline)	1.0 ± 1.1 (175)	1.1 ± 1.4 (170)	1.3 ± 1.5 (74)	0.247	
# Previous hospitalizations	0.8 ± 2.0 (174)	1.7 ± 3.4 (170)	3.7 ± 7.7 (74)	0.000	0 - 1, 0 - 2, 1 - 2
# Medical comorbidities[1]	1.1 ± 1.1 (175)	1.3 ± 1.3 (170)	1.8 ± 1.5 (74)	0.001	0 - 2, 1 - 2
# Anxiety comorbidities[2]	1.0 ± 1.1 (175)	1.4 ± 1.5 (170)	1.7 ± 1.5 (74)	0.001	0 - 1, 0 - 2
Age	38.3 ± 11.6 (175)	40.0 ± 11.3 (170)	44.3 ± 10.4 (74)	0.001	0 - 2, 1 - 2
	% (n/N)	**% (n/N)**	**% (n/N)**		

	Group				
Variable	**Employed [0]**	**Unemployed [1]**	**Disability Recipient [2]**	**p-val**	**Significant Pairwise Differences**
Female	56.0% (98/175)	57.6% (98/170)	63.5% (47/74)	0.545	
Hispanic	13.1% (23/175)	8.8% (15/170)	13.5% (10/74)	0.38	
Married	42.3% (74/175)	26.5% (45/170)	24.3% (18/74)	0.002	0 - 1, 0 - 2
Some college	82.9% (145/175)	65.9% (112/170)	64.9% (48/74)	0.001	0 - 1, 0 - 2
Income > $50,000	47.7% (83/174)	14.9% (25/168)	6.8% (5/74)	0	0 - 1, 0 - 2, 1 - 2
Childhood abuse	52.3% (91/174)	56.5% (96/170)	64.9% (48/74)	0.191	
Emotional	38.3% (67/175)	43.5% (74/170)	47.3% (35/74)	0.368	
Physical	22.3% (39/175)	30.0% (51/170)	37.8% (28/74)	0.037	0 - 2
Sexual	28.0% (49/175)	28.2% (48/170)	45.9% (34/74)	0.012	0 – 2, 1 – 2
Other	3.4% (6/175)	1.2% (2/170)	2.7% (2/74)	0.415	
Depression family history	67.6% (117/173)	66.9% (111/166)	71.2% (52/73)	0.795	
Bipolar disorder family history	55.0% (94/171)	47.0% (77/164)	58.3% (42/72)	0.182	
Suicide family history	11.5% (20/174)	10.2% (17/166)	12.5% (9/72)	0.865	
Alcohol family history	59.0% (102/173)	52.4% (87/166)	56.2% (41/73)	0.478	
Drug family history	41.0% (71/173)	39.8% (66/166)	38.4% (28/73)	0.921	
Psychosis family history	12.1% (21/174)	16.9% (28/166)	21.9% (16/73)	0.139	
Hypertension	12.6% (22/174)	21.8% (37/170)	35.1% (26/74)	0	0 - 1, 0 - 2, 1 - 2

	Group				
Variable	**Employed [0]**	**Unemployed [1]**	**Disability Recipient [2]**	**p-val**	**Significant Pairwise Differences**
Hyperlipidemia	20.0% (35/175)	19.4% (33/170)	33.8% (25/74)	0.033	0 – 2, 1 – 2
Kidney disease	4.0% (7/175)	2.4% (4/170)	2.7% (2/74)	0.667	
Seizures	2.9% (5/175)	6.5% (11/170)	9.5% (7/74)	0.104	
Hepatitis	2.9% (5/174)	3.5% (6/170)	9.5% (7/74)	0.069	
Thyroid disease	6.3% (11/175)	4.1% (7/170)	4.1% (3/74)	0.604	
Head trauma with loss of consciousness	16.0% (28/175)	17.1% (29/170)	16.2% (12/74)	0.963	
Asthma	14.3% (25/175)	21.2% (36/170)	29.7% (22/74)	0.019	0 - 2
Migraines	30.3% (53/175)	24.7% (42/170)	27.4% (20/73)	0.511	
Cancer	4.0% (7/175)	4.1% (7/170)	6.8% (5/74)	0.605	
Suicidality (lifetime)	65.7% (115/175)	60.6% (103/170)	62.2% (46/74)	0.607	
Suicidality (past 12 months)	25.1% (44/175)	23.5% (40/170)	14.9% (11/74)	0.204	
Major depressive episode (current)	68.6% (120/175)	79.4% (135/170)	77.0% (57/74)	0.061	
Major depressive episode (lifetime)	95.4% (167/175)	96.5% (164/170)	98.6% (73/74)	0.491	
Manic episode (current)	12.0% (21/175)	14.7% (25/170)	28.4% (21/74)	0.006	0 – 2, 1 – 2
Manic episode (lifetime)	61.1% (107/175)	67.1% (114/170)	85.1% (63/74)	0.002	0 – 2, 1 – 2
Hypomanic episode (current)	14.9% (26/175)	12.4% (21/170)	2.7% (2/74)	0.048	0 – 2, 1 – 2
Hypomanic episode (lifetime)	40.6% (71/175)	31.8% (54/170)	14.9% (11/74)	0.001	0 - 1, 0 - 2, 1 - 2
Panic disorder (current)	16.0% (28/175)	30.0% (51/170)	25.7% (19/74)	0.009	0 - 1, 0 - 2, 1 - 2
Panic disorder (lifetime)	30.9% (54/175)	40.6% (69/170)	39.2% (29/74)	0.146	

	Group				
Variable	Employed [0]	Unemployed [1]	Disability Recipient [2]	p-val	Significant Pairwise Differences
Agoraphobia (current)	27.4% (48/175)	37.1% (63/170)	59.5% (44/74)	0	0 - 1, 0 - 2, 1 - 2
Social phobia (current)	17.7% (31/175)	30.0% (51/170)	29.7% (22/74)	0.018	0 - 1, 0 - 2
OCD (current)	11.5% (20/174)	8.8% (15/170)	13.5% (10/74)	0.514	
PTSD (current)	9.1% (16/175)	11.8% (20/170)	23.0% (17/74)	0.013	0 – 2, 1 – 2
Alcohol dependence (12 months)	9.1% (16/175)	8.2% (14/170)	2.7% (2/74)	0.24	
Alcohol abuse (12 months)	17.7% (31/175)	15.3% (26/170)	5.4% (4/74)	0.055	
Alcohol abuse (lifetime)	55.4% (97/175)	50.0% (85/170)	47.3% (35/74)	0.419	
Alcohol dependence (lifetime)	36.6% (64/175)	32.4% (55/170)	40.5% (30/74)	0.441	
Substance dependence (12 months)	14.3% (25/175)	16.5% (28/170)	6.8% (5/74)	0.143	
Substance dependence (lifetime)	51.4% (90/175)	48.8% (83/170)	58.1% (43/74)	0.412	
Substance abuse (12 months)	13.1% (23/175)	10.0% (17/170)	8.1% (6/74)	0.447	
Substance abuse (lifetime)	30.3% (53/175)	28.2% (48/170)	14.9% (11/74)	0.042	0 – 2, 1 – 2
Substance use disorder (12 months)	25.1% (44/175)	23.5% (40/170)	14.9% (11/74)	0.204	
Substance use disorder (lifetime)	65.7% (115/175)	60.6% (103/170)	62.2% (46/74)	0.607	
Psychosis (life)	1.7% (3/175)	3.0% (5/169)	1.4% (1/74)	0.645	
Psychosis (current)	1.1% (2/175)	1.2% (2/169)	1.4% (1/74)	0.99	
Bulimia (current)	5.1% (9/175)	1.8% (3/168)	1.4% (1/74)	0.157	
Generalized Anxiety Disorder (current)	22.9% (40/175)	22.5% (38/169)	21.6% (16/74)	0.977	

	Group				
Variable	**Employed [0]**	**Unemployed [1]**	**Disability Recipient [2]**	**p-val**	**Significant Pairwise Differences**
ADHD (combined)	28.9% (50/173)	22.0% (37/168)	20.5% (15/73)	0.229	
ADHD (inattentiveness)	9.2% (16/173)	6.5% (11/168)	4.1% (3/73)	0.342	
ADHD (hyperactivity/ impulsivity)	1.2% (2/173)	2.4% (4/168)	2.7% (2/73)	0.627	
Psychotropics	54.3% (95/175)	45.3% (77/170)	58.1% (43/74)	0.109	
Benzodiazepines	15.4% (27/175)	14.1% (24/170)	24.3% (18/74)	0.132	
Antidepressants	25.1% (44/175)	25.9% (44/170)	24.3% (18/74)	0.966	
Antipsychotics	9.1% (16/175)	15.9% (27/170)	16.2% (12/74)	0.129	
Anticonvulsants/Other	24.6% (43/175)	24.7% (42/170)	32.4% (24/74)	0.385	
Stimulants	4.6% (8/175)	2.9% (5/170)	5.4% (4/74)	0.611	
Anxiolytics/Sedatives/Hypnotics	18.9% (33/175)	17.6% (30/170)	28.4% (21/74)	0.142	
Mood stabilizers	21.1% (37/175)	21.2% (36/170)	25.7% (19/74)	0.697	
6+ manic episodes in the past year	21.8% (38/174)	22.8% (38/167)	31.1% (23/74)	0.272	
6+ depressive episodes in the past year	20.8% (36/173)	22.0% (37/168)	28.4% (21/74)	0.418	
> 60% time spent manic in the past year	9.7% (17/175)	8.3% (14/169)	8.2% (6/73)	0.876	
> 60% time spent depressed in the past year	32.6% (57/175)	41.2% (70/170)	40.5% (30/74)	0.215	

Note: If overall p-value from ANOVA < 0.05, pairwise comparisons were made and those listed are <0.05.

[1] # Medical comorbidities include hypertension, hyperlipidemia, kidney disease, seizures, hepatitis, thyroid, head trauma, asthma, migraines, cancer.

[2] # Anxiety comorbidities include panic, agoraphobia, social phobia, GAD, OCD, PTSD