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Original Article

The relationship between clinical outcomes and quality of life in first-episode mania: a longitudinal analysis

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Objectives: Despite growing attention to the relationship between bipolar disorder (BD) and quality of life (QoL), there remains a lack of information about QoL in the early stages of BD, and about the course of QoL in people with BD over time. Here, we report on QoL and symptomatic outcomes over a 1.5-year period in a Canadian sample of first-episode mania patients.

Methods: Patients (n = 63) with DSM-IV-TR BD type I recovering from a recent episode of mania were recruited from a university-based hospital setting in Vancouver, BC, Canada and assessed at six monthly intervals for 18 months. In addition to symptomatic and cognitive assessments, two self-report QoL scales [the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the Medical Outcomes Study Short Form 36 (SF-36)] were administered.

Results: Baseline QoL scores were high, with mean Q-LES-Q scores at 70% of the maximum possible score; QoL continued to show a trend towards improvement over time. Multiple hierarchical regressions were used to explore predictors of QoL over time, finding that: (i) length of illness and severity of depressive symptoms at baseline predicted Q-LES-Q scores at both baseline and six months; (ii) the number of previous depressive episodes and severity of depression at baseline and 12 months all predicted QoL at 12 months; and (iii) only severity of depressive symptoms at 12 months predicted QoL at 18 months.

Conclusions: Our observation that QoL in patients who have recently experienced an episode of mania can be relatively preserved offers hope, both for healthcare providers and for those newly diagnosed. Further, that severity of depressive symptoms even in the early stages of the disease was the consistent predictor of QoL suggests that depressive symptoms need to be aggressively treated to improve QoL.

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The World Health Organization defines quality of life (QoL) as: '*an individual*'s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' (1). The QoL construct has been the recipient of substantial scientific attention in health outcomes research over the past two decades. We have witnessed a concomitant surge in bipolar disorder (BD) publications referencing QoL over the past 20 years (2). The bulk of this research has examined the relationship between clinical and illness-related factors and QoL. Several studies have investigated the relationship between depressive

symptoms and/or mood episodes and QoL. For example, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) described (negative) associations between severity of depression and subjectively assessed QoL (3). Others (4) have reported that QoL is more impaired in people with BD type II than in those with type I, further underscoring the potentially deleterious effect of depression upon perceived life quality. Findings regarding the impact of elevated mood states on QoL, however, are more mixed; some studies have reported that mania and hypomania are associated with impaired QoL (5, 6), whereas others report no association (3). Whether considering depressive or manic symptoms, however, existing research is consistent in suggesting that symptom severity is negatively correlated with QoL in people with BD (5).

Despite this surge of research interest, the BD/QoL research field remains relatively immature. Several significant gaps in the literature can be readily identified, not least of which concerns a lack of information about QoL in the early stages of BD and longitudinal data examining the course of QoL in BD over time. Although BD commonly manifests in adolescence and early adulthood (7), relatively little research has focused on first-episode mania (FEM) populations (in contrast to a robust body of work addressing first-episode schizophrenia (8, 9). In part, this may be a residual effect of the once widely held belief that, with adequate treatment, patients are likely to recover completely after an episode of mania. It was on this basis that manic–depressive psychosis was historically originally differentiated from the presumed progressive and deteriorating course of schizophrenia. However, more recent research has shown that complete functional recovery is not achieved by a substantial proportion of people with BD. Evidence suggests that, although the majority of first-episode patients with affective psychosis (most with BD) achieve symptomatic recovery by six months, less than a third achieve functional recovery by 12 and 24 months (10), a trend echoed in other research (11). Less is known about QoL in FEM; most QoL studies to date (12, 13) have been cross-sectional in design and conducted in multiple-episode populations, with the inevitable confounding of results by variables such as duration of illness, number of episodes, and treatment effects. In terms of theoretically advancing this field of research, the longitudinal study of FEM populations provides an excellent opportunity to explore outcomes on a prospective basis and to ascertain whether QoL impairments occur early in the course of BD, accrue over time, or are associated with treatment or other variables.

Here, we report on findings from the Systematic Treatment Optimization Program for Early Mania (STOP-EM), initiated in 2004 at the University of British Columbia (UBC) and Vancouver General Hospitals in Canada, designed to recruit FEM patients with BD type I with or without psychosis, hospitalized or not. The primary objective of the project was to gather information on clinical and functional course during the early phases of BD type I in a naturalistic setting. In the current study, we focused on evaluating QoL outcomes at baseline and at six, 12, and 18 months in the first 63 patients enrolled in the STOP-EM project, and on exploring the relationship between clinical and QoL outcomes. Our prediction, on the basis of the existing BD/QoL literature, was that depressive symptoms would also be a prominent predictor of QoL in this FEM sample.

Methods

STOP-EM is a longitudinal study of clinical, functional, QoL, brain morphology, neurochemistry, and neurocognitive functioning in patients who have recently recovered from their first episode of DSM-IV-TR- (14) defined mania; full details of the program have been published elsewhere (15). Briefly, eligible patients were recruited from UBC and Vancouver General Hospitals and affiliated sites as well as through referrals from physicians and psychiatrists; were aged 14–35 years; and, although clinically stable, had experienced their first manic episode in the three months preceding enrollment. Patients could be enrolled with pure or mixed mania, with or without psychotic features, and with or without comorbidity, including substance use comorbidity; inclusion criteria were deliberately broad, to capture a wide range of clinical presentations. STOP-EM began enrolling patients in July 2004 and has been active continuously since this time.

At the baseline assessment, the individual's diagnoses of BD and first manic episode were confirmed using the Mini International Neuropsychiatric Interview (MINI) (16). Patients who enrolled in the program received open-label maintenance treatment [according to the Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical practice guidelines (15, 17)] from clinicians with expertise in the management of mood disorders. Patients were assessed as clinically indicated, and at a minimum of every six months. Sociodemographic variables were collected using a standardized protocol. Psychiatric and medical histories, and information about current and past medication use, were obtained

using all available sources of information, including patient interview, and, when available, collateral information from family members and health records. Symptomatology at each assessment point was evaluated using clinician-rated scales, including (but not limited to) the Young Mania Rating Scale (YMRS) (18) and the Hamilton Depression Rating Scale, 29-item version (HAM-D-29) (19). Cognitive assessment was conducted at baseline. The key cognitive measure utilized in the current study was the age-corrected T-score for learning trial 1–5 recall on the California Verbal Learning Test–II (20), as this measure of verbal learning has been shown to be reliably impaired in patients with both first manic-episode and established BD (21). QoL was assessed via two self-report scales, the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (22) and the Medical Outcomes Study Short Form 36 (SF-36) (23). The Q-LES-Q is a 93-item *generic* (non-disorder-specific) QoL scale assessing eight broad domains: physical health, mood, leisure time activities, social relationships, general activities, work (if applicable), household duties (if applicable), and school/coursework (if applicable). The relevant domains (i.e., excluding work or study domains when not applicable) of the Q-LES-Q can be averaged to produce a mean QoL score, expressed as a percentage, where higher values reflect better QoL. Alternatively, interpretation can focus on the scale's general activities domain, equivalent to the Q-LES-Q short-form. The scale is comprehensive, captures many domains of QoL, is widely used in studies of major depression, and has been validated for use in patients with BD (24). The SF-36, the most commonly used generic, non-disorder-specific health-related QoL or health status measure in BD research, has also been validated for this population (25). Both scales were administered on the same day as the clinician-administered symptom rating scales.

Ethics approval was received from the UBC Clinical Research Ethics Board, and written informed consent detailing the procedures and potential side effects was obtained from all participants prior to their participation.

Analytic approach

Analyses were conducted with SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA) (26). In order to maximize the available sample size and to avoid the possible introduction of bias because of missing data, the multiple imputation procedure was employed for longitudinal values, imputing five sets of values (27). Descriptive statistics examined distributions against the assumptions for each of the proposed analyses and we explored the presence of univariate and multivariate outliers in the sample. Outliers were omitted for statistical reasons, on the basis that the pattern of results observed in the participants' symptom and QoL scores showed abnormal and inconsistent patterns of trajectory (assumed to be the result of noise or unreliable reporting) as compared to the sample as a whole. Guided by knowledge of existing literature about candidate predictors of QoL in BD, we conducted a series of correlational analyses to assess the degree of association between sociodemographic and clinical characteristics with baseline Q-LES-Q and SF-36 sub-scales, mean and (for the SF-36) component summary scores. Socioeconomic variables explored included: age, gender, years of education, marital status, ethnicity, and employment status. Clinical variables warranting inclusion as potential correlates of QoL included: early versus late age of onset (≤18 years); mean duration of illness (length of time since first mood episode of either depression or mania); number of previous episodes (of depression or hypomania); comorbid anxiety; presence of psychosis; substance or alcohol abuse/dependence; current depressive symptomatology, as measured by the HAM-D; and current manic symptoms, as measured by the YMRS. We also explored the relationship between QoL and verbal learning. In cases in which we evaluated the association between two continuous variables, Pearson's r was computed. In those situations in which one of the variables was a dichotomous variable, Point Biserial r was evaluated.

A one-way within-subjects repeated measure analysis of variance design using Bonferroni post-hoc adjustments to protect against an inflated risk of type I errors was used to examine longitudinal clinical and QoL outcomes, focusing on HAM-D, YMRS, Q-LES-Q, and SF-36 scale scores across four time points (baseline, six months, 12 months, and 18 months). For all analyses, statistical significance was set at $p < 0.05$ (or Bonferroni adjusted where multiple comparisons necessitated) and effect size was calculated as partial eta square. Polynomial contrasts were used to examine whether there was a linear, quadratic, or cubic trend effect across the different time points. Finally, predictors of Q-LES-Q (22) (focused on here as it represents QoL broadly, rather than *health-related* QoL, which is the specific focus of the SF-36) at baseline and at six, 12, and 18 months were investigated using hierarchical regressions, entering in the regression steps those predictors which were significantly associated in the previously identified correlations.

Results

Participants

Participant sociodemographic and clinical characteristics are presented in Table 1. Mean age for the sample was 22.8 years, with a range of 16–34 years; the gender ratio was close to parity, educational level high proportional to age, and 90% of the sample classified themselves as single. Nearly all participants presented with a first episode of mania (three with a mixed episode), and 65% of patients had one or more psychotic symptoms during the first manic/mixed episode. Mean duration of illness, defined as the time since the first lifetime mood episode of any type, was 3.0 years [standard deviation (SD) = 3.5]. The initial lifetime mood episode was depressive for 44% of the sample, hypomanic for 8%, and manic for all others. Thirty-four patients (54%) had a history of at least one depressive episode prior to the first manic episode and 11 (17%) had a history of a hypomanic episode. Three patients (5%) presented with current comorbid anxiety disorder at baseline (five with lifetime anxiety disorder) and 17 patients (27%) met DSM-IV criteria for comorbid substance or alcohol abuse/dependence (excluding nicotine). The participant sample was drawn from referrals from community-based psychiatrists in a wide catchment area in the Lower Mainland of British Columbia and did not represent a refractory sample, boding well for the generalizability of the sample to other Canadian FEM populations.

Outliers and missing data

Investigation of outliers identified three cases with single scores (extreme z-scores) and four with atypical combinations of scores or multivariate outliers (Mahalanobis distance, $p < 0.001$). After omission of these outlier cases ($n = 7$), a final sample size of $N = 63$ was included in the study. Missing data rates for QoL variables were calculated to be 23%, 33%, and 33% at the six-, 12-, and 18-month time points, respectively; careful evaluation of the patterns of missing data indicated that the multiple-imputation procedure was an optimal strategy to employ. We did not have detailed data on reasons for attrition in the sample, but geographic mobility was high in this young participant sample and is suspected to have accounted for many of these observed dropouts. Potential differences (e.g., severity of illness, level of psychosis, and QoL at baseline) between dropouts and non-dropouts were explored but no significant differences between groups were detected.

Table 1. Demographic and clinical characteristics

	First-episode mania patients (n = 63)
Age, years, mean (SD)	22.8 (4.3)
Sex, male, n (%)	30 (48)
Ethnicity, n (%)	
Caucasian	48 (76)
Asian	9 (14)
Other	6 (10)
Marital status, n (%)	
Single	57 (90)
Married	4 (6)
Divorced	2 (4)
Education, years, mean (SD)	13.9 (2.1)
Educational status	
Did not graduate high school	8 (13)
High school graduate	11 (17)
Enrolled in college/university	32 (51)
Completed college/university/ post-secondary education	12 (19)
Premorbid employment status, n (%)	
Student	35 (56)
Part time	3 (6)
Full time	19 (29)
Self-employed	2 (3)
Unemployed	4 (6)
Duration of illness, years, mean (SD)	3.0 (3.5)
Presence of psychosis in index manic episode, n (%)	41 (65)
Age at illness onset, years, mean (SD)	20.2 (5.1)
Age at mania onset, years, mean (SD)	22.7 (4.3)
Age at depression onset, years, mean (SD)	18.0 (4.9)
Initial lifetime mood episode, n (%)	
Mania	30 (48)
Hypomania	5 (8)
Depression	28 (44)
No. of previous depressive episodes, mean (SD)	1.1 (1.4)
Depressive episode before manic episode, n (%)	34 (54)
No. of previous hypomanic episodes, mean (SD)	0.4 (1.5)
Hypomanic episode before manic episode, n (%)	11 (17)
Comorbid anxiety disorder at baseline, n (%)	3 (5)
Comorbid substance or alcohol abuse/dependence, n (%)	17 (27)
Mood stabilizers, n (%)	
Lithium	26 (41)
Divalproex	32 (51)
Atypical antipsychotic agents, n (%)	51 (81)
Antidepressants, n (%)	4 (6)
Anxiolytics, n (%)	≤6 (9)
Medication dose, mean (SD)	
Lithium (mg)	975 (233)
Divalproex (mg)	1018 (357)

SD = standard deviation.

Prospective symptom scores

Mood ratings across the four time points are presented in Table 2, illustrating that severity of depression symptoms, as measured by the HAM-D,

Table 2. Symptom ratings over time

Symptom scales	Baseline	6 months	12 months	18 months	Statistic, *F*	Eta effect size
HAM-D (29-item)	6.9 ± 8.9[a]	4.8 ± 5.1	3.7 ± 4.1	4.3 ± 4.8	4.24[d]	0.17
HAM-D (17-item)	5.2 ± 7.0[a]	3.4 ± 4.2	2.4 ± 3.3	2.9 ± 3.5	3.44[d]	0.15
YMRS	3.4 ± 5.4[b,c]	1.2 ± 2.9	1.7 ± 3.5	1.3 ± 3.5	3.32[d]	0.14

Values presented as mean ± standard deviation. HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.
[a]Baseline value significantly different from that at 12 months.
[b]Baseline value significantly different from that at 6 months.
[c]Baseline value significantly different from that at 18 months.
[d]All significant after Bonferroni adjustments for multiple comparisons; $p < 0.05$, two-tailed.

was in the sub-syndromal range across all time points and did not change significantly over time, with the exception of the baseline versus 12-months comparison. Severity of mania, as measured by the YMRS, decreased significantly over time. Specifically, baseline mania scores were observed to be significantly higher than at both the six- and 18-month assessment points, but only numerically lower at the 12-month assessment point. However, the observed changes in YMRS scores were small and the severity of manic symptoms was in the subthreshold range across all time points.

Prospective QoL scores

Table 3 shows that the mean Q-LES-Q scores at baseline were at 70% of maximum possible (MPS) score and the majority of the domain-level scores were also within the 65–70 percentile of MPS score. Quality of life scores showed a general trend towards improvement over time, with mean Q-LES-Q scores significantly higher at 12 and 18 months compared to baseline; mean scores at 18 months were at 79% of MPS [in comparison, age/sex controlled scores for the Q-LES-Q general activities domain, equivalent to the scale's short-form, have been reported to be 82% of MPS in people with no history of mental illness (28)]. Inspection of change over time in Q-LES-Q scores at a domain-level shows that QoL improved significantly over time in all domains. Health-related QoL at baseline, as measured by the SF-36, was not uniformly high; mean physical health component scores at baseline were 69% of MPS, whereas, mean mental health component scores were at 49%. At a domain level, the physical functioning and emotional well-being domains were 88% and 59% of MPS at baseline, compared to 92% and 56% in 25–34-year-olds from a Canadian general population sample (29). Examination of the SF-36 data at a component level shows that health-related QoL also improved over time. Specifically, the scale's physical health and mental health components were both significantly higher at six, 12, and 18 months compared to baseline. At an individual domain level, well-being in all domains, with the exception of physical functioning, pain, and general health, improved significantly over time.

Relationships between QoL, sociodemographic, and clinical variables over time

Table 4 depicts the correlations between mean Q-LES-Q score and sociodemographic and clinical variables at each time point. At baseline, a significant negative correlation was apparent between mean Q-LES-Q score and duration of illness ($r = -0.33$), as well as current alcohol abuse ($r = 0.32$). Duration of illness and Q-LES-Q scores were similarly correlated ($r = -0.33$) at six months, with poorer QoL in those with a longer duration of illness, but not at 12 or 18 months. Instead, number of previous depressive episodes was negatively correlated with QoL at 12 months ($r = -0.46$). At 18 months, current drug abuse was negatively correlated with Q-LES-Q score ($r = -0.31$) and there was a positive correlation between QoL and whether the individual held student-status ($r = 0.32$). Table 5 shows the correlations between mean Q-LES-Q and mania and depression ratings over time; not surprisingly, QoL showed moderate to large effect-size negative correlations with severity of depression, as measured on the HAM-D at each time point.

Predictors of Q-LES-Q at baseline and at six, 12, and 18 months were investigated using multiple hierarchical regressions, entering in the regression steps the predictors which were significantly associated with QoL in the above-described correlational analyses (i.e., HAM-D score, duration of illness, number of previous depressive episodes, current alcohol or drug abuse, years of education, student status). Duration of illness, current alcohol abuse, and severity of depressive symptoms, as measured by HAM-D score, accounted for 52% of the variance in mean baseline Q-LES-Q scores ($p < 0.0001$), with duration of illness and

Table 3. Change in Q-LES-Q and SF-36 scores over time

Domain	Baseline	6 months	12 months	18 months	Statistic, F	Eta effect sizes	Polynomial contrast
Q-LES-Q							
Physical health	67.7 ± 12.9[a,b]	70.8 ± 14.8[d]	74.8 ± 13.6	77.1 ± 11.6	11.70[f]	0.36	Linear, $F(1,62) = 29.92$ $p = 0.0001$, $\eta p^2 = 0.32$
Subjective feelings of well-being	66.5 ± 14.2[a,b]	70.7 ± 15.1[d,e]	77.7 ± 14.5	78.6 ± 15.3	13.74[f]	0.42	Linear, $F(1,62) = 39.90$ $p = 0.0001$, $\eta p^2 = 0.39$
Leisure time activities	72.2 ± 12.7[a,b]	74.5 ± 15.3[d]	78.5 ± 12.5	83.0 ± 12.6	10.23[f]	0.36	Linear, $F(1,62) = 28.09$ $p = 0.0001$, $\eta p^2 = 0.30$
Social relationships	73.3 ± 14.7[b]	75.8 ± 13.7	77.5 ± 14.6	80.3 ± 14.3	4.09[g]	0.18	Linear, $F(1,62) = 12.55$ $p = 0.002$, $\eta p^2 = 0.16$
General activities	67.9 ± 14.0[a,b]	73.9 ± 15.2	77.4 ± 12.7	77.7 ± 14.4	10.78[f]	0.37	Linear, $F(1,62) = 16.74$ $p = 0.0001$, $\eta p^2 = 0.21$ Quadratic, $F(1,62) = 5.91$ $p = 0.031$, $\eta p^2 = 0.08$
Mean Q-LES-Q score	69.6 ± 11.2[a,b]	73.2 ± 12.9[d]	77.2 ± 11.9	79.1 ± 12.1	12.06[f]	0.39	Linear, $F(1,62) = 36.21$ $p = 0.0001$, $\eta p^2 = 0.36$
SF-36							
Physical functioning	88.2 ± 14.0	92.9 ± 8.4	92.1 ± 9.2	91.0 ± 9.2	2.07	0.11	ns
Role limitations due to physical health	51.1 ± 42.4[a,b]	69.0 ± 35.4	77.2 ± 30.8	73.0 ± 33.4	6.29[f]	0.27	Linear, $F(1,62) = 10.63$ $p = 0.003$, $\eta p^2 = 0.14$ Quadratic, $F(1,62) = 8.88$ $p = 0.006$, $\eta p^2 = 0.12$
Role limitations due to emotional problems	42.8 ± 40.9	59.7 ± 42.4	63.1 ± 37.9	60.1 ± 43.3	3.80[g]	0.17	Quadratic, $F(1,62) = 7.59$ $p = 0.011$, $\eta p^2 = 0.10$ Linear, $F(1,62) = 5.61$ $p = 0.027$, $\eta p^2 = 0.08$
Energy/fatigue	44.6 ± 19.0[a,b]	52.3 ± 18.9	54.3 ± 19.0	57.1 ± 19.3	5.81[f]	0.24	Linear, $F(1,62) = 15.95$ $p = 0.001$, $\eta p^2 = 0.20$
Emotional well-being	58.9 ± 19.5[a,b,c]	66.9 ± 15.9	70.3 ± 16.9	70.3 ± 17.2	7.14[f]	0.28	Linear, $F(1,62) = 17.54$ $p = 0.0001$, $\eta p^2 = 0.21$ Quadratic, $F(1,62) = 6.57$ $p = 0.042$, $\eta p^2 = 0.09$
Social functioning	49.1 ± 29.3[a,b,c]	70.8 ± 23.9	75.3 ± 22.5	73.7 ± 24.5	13.62[f]	0.43	Linear, $F(1,62) = 29.84$ $p = 0.0001$, $\eta p^2 = 0.32$ Quadratic, $F(1,62) = 24.31$ $p = 0.0001$, $\eta p^2 = 0.27$
Pain	76.7 ± 24.1	80.5 ± 18.9	83.3 ± 18.5	81.6 ± 18.6	1.27	0.06	ns
General health	63.9 ± 18.8	69.4 ± 17.6	68.7 ± 18.0	65.5 ± 20.4	2.58	0.12	Quadratic, $F(1,62) = 6.50$ $p = 0.015$, $\eta p^2 = 0.09$
Physical health component summary score	69.3 ± 19.2[a,c]	77.6 ± 15.3	80.1 ± 15.2	77.5 ± 16.2	11.70[f]	0.26	Quadratic, $F(1,62) = 12.94$ $p = 0.001$, $\eta p^2 = 0.17$ Linear, $F(1,62) = 6.22$ $p = 0.02$, $\eta p^2 = 0.09$
Mental health component summary score	48.9 ± 22.2[a,b,c]	62.4 ± 21.0	65.6 ± 19.9	65.2 ± 22.1	13.74[f]	0.35	Linear, $F(1,62) = 21.23$ $p = 0.0001$, $\eta p^2 = 0.25$ Quadratic, $F(1,62) = 17.31$ $p = 0.0001$, $\eta p^2 = 0.21$

Values presented as mean ± standard deviation. ns = not significant; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; SF-36 = Medical Outcomes Study Short Form 36.
[a]Baseline value significantly different from that at 12 months.
[b]Baseline value significantly different from that at 18 months.
[c]Baseline value significantly different from that at 6 months.
[d]6-month value significantly different from that at 18 months.
[e]6-month value significantly different from that at 12 months.
[f]$p < 0.005$, [g]$p < 0.05$ two-tailed; all significant after Bonferroni adjustments for multiple comparisons.

HAM-D score making a significant unique contribution (part $r = 0.22$ and part $r = 0.59$, respectively) but current alcohol abuse not being significant.

HAM-D scores at baseline and at six months, and duration of illness accounted for 38% of the variance in mean Q-LES-Q scores at six months ($p < 0.0001$); after controlling for duration of

Table 4. Correlations between quality of life, sociodemographic, and clinical characteristics over time (N = 63)

	Age (years)	Female	Caucasian	Marital status (single)	Student (yes)	Education (years)	Mean duration of illness	No. of previous depressive episodes	Drug abuse (yes)	Alcohol abuse (yes)	Verbal learning
Mean Q-LES-Q											
Baseline	−0.15	−0.04	−0.03	−0.05	0.20	−0.08	−0.33[a]	−0.18	−0.12	−0.32[a]	−0.04
6 months	−0.08	0.11	−0.13	−0.16	0.13	0.01	−0.33[a]	−0.22	−0.24	−0.21	−0.02
12 months	−0.17	0.12	−0.07	0.003	0.26	0.03	−0.28	−0.46[b]	−0.17	−0.14	−0.16
18 months	−0.04	0.08	−0.10	−0.04	0.32[a]	−0.001	−0.13	−0.26	−0.31[a]	−0.10	−0.16

For ease of reporting, only Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scores are provided in Tables 4 and 5. The pattern of results observed for the Medical Outcomes Study Short Form 36 (SF-36) was similar across time points; full SF-36 data are available on request. Further, these correlational analyses are considered to be exploratory in nature and the results subsidiary to the results of the regression analyses performed.
[a]$p < 0.05$.
[b]$p < 0.005$ two-tailed.

Table 5. Correlations between QoL and symptom ratings over time (N = 63)

	Hamilton Depression Rating Scale				Young Mania Rating Scale			
	Baseline	6 months	12 months	18 months	Baseline	6 months	12 months	18 months
Mean Q-LES-Q								
Baseline	−0.57[a]	−0.19	0.001	−0.15	−0.22	−0.10	0.13	0.10
6 months	−0.37[a]	−0.52[a]	−0.16	−0.17	−0.27[b]	−0.24	0.15	0.05
12 months	−0.35[a]	−0.24	−0.32[b]	−0.30	−0.12	−0.14	−0.06	−0.05
18 months	−0.26	−0.18	−0.26	−0.36[c]	−0.06	−0.10	−0.003	−0.08

QoL = quality of life; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.
[a]$p < 0.005$ two-tailed Spearman's correlation.
[b]$p < 0.05$ two-tailed Spearman's correlation.
[c]$p < 0.01$ two-tailed Spearman's correlation.

illness, HAM-D score at baseline accounted for further additional variance (R^2 change = 0.10, $p < 0.03$). Severity of depression at baseline and severity of depressive symptoms at six months accounted for further additional variance (for its part, the variance explained by depressive symptoms at six months after controlling for length of illness and depression symptoms at baseline was R^2 change = 0.20, $p < 0.002$). Number of previous depressive episodes (part $r = 0.22$), and HAM-D scores at baseline (part $r = 0.30$) and at 12 months (part $r = 0.36$) all made a significant contribution to mean Q-LES-Q scores at 12 months, but HAM-D score at six months did not. Finally, only HAM-D score at 12 months made a significant contribution to the prediction of Q-LES-Q scores at 18 months (part $r = 0.24$).

In order to explore the influence of more severe symptoms on QoL, we dichotomized the sample into those with a baseline HAM-D score of <7 ($n = 47$) versus >7 ($n = 16$). Examining Q-LES-Q scores, we found a significant time effect [$F(3,183) = 16.03$, $p = 0.0001$] as well as a main effect of group, indicating that participants who were in remission had significantly higher Q-LES-Q scores, $F(1,61) = 14.34$, eta square = 0.21. There were no significant interaction effects between time and depression levels. An equivalent analysis was not conducted for the YMRS scores as only four participants had a score above the commonly accepted cut-off point of 12 on this scale.

Discussion

The present study evaluated QoL outcomes early in the course of BD and explored the relationship between clinical outcomes and QoL over an 18-month time frame in patients in a naturalistic treatment setting following their first episode of mania. One of our most striking findings was that perceived QoL was high in this sample of newly diagnosed patients; baseline mean (total) Q-LES-Q scores were at 70% of MPS, rising to 79% of MPS at 18 months. Other studies using the Q-LES-Q have reported on mean scores for the general activities domain of the Q-LES-Q (synonymous with its short form, minus the two global items on

medication and global life satisfaction). For example, in the foundational Q-LES-Q validation paper (22), mean scores for the general activities domain were 83% of MPS in a general population sample (N = 67). Elsewhere, scores on the same domain in samples with no or minimal history of mental illness have been reported to be 82% and 84%, respectively (28). Schechter et al. (28) provide a scoring convention whereby respondents who fall within 10% of the mean of the community sample reported in the study of Endicott et al. (22) are considered to be within the normal range. In our sample, general activities domain scores were 68% at baseline, rising to 74%, 77%, and 78% at each of the six-month assessment points. Thus, the sample demonstrated QoL scores approaching the normal range at baseline, and within the normal range at subsequent assessment points. Another way of conceptualizing these findings is to examine studies that have administered the Q-LES-Q in other BD populations. An informal review of available studies that have reported on mean or *General Activities* Q-LES-Q scores reveals that perceived QoL is typically poorer in samples of patients with a longer duration of illness or more established diagnoses (3, 12, 30–32).

How should we understand the relatively high QoL observed in this population of FEM patients? One explanation is that QoL in people newly diagnosed with BD after an index episode of mania is not injuriously negatively impacted; people in the early stages of the disorder may retain the resiliency to bounce back to premorbid QoL levels. One design consideration is that the STOP-EM program enrolled patients following treatment of their first manic episode; we do not have information on their QoL at the time of their acute mania or, indeed, their premorbid levels of well-being and life satisfaction. Participants may have experienced a decrease in their QoL that was rapidly ameliorated by guideline-driven pharmacotherapy (15). Alternatively, the sample's QoL may not have been profoundly impacted by their episode of mania, although this hypothesis is not supported by first-episode studies in the schizophrenia field. We remain unclear as to what might be underpinning this observation. Perhaps, early on in the course of their illness, people still retain hope, and this is maintained as they observe that initial treatments may be effective. However, as the illness course progresses and more episodes are experienced, this hope wanes, the reality of the struggle with their chronic condition sets in, and perceived QoL decreases. Or, perhaps, chronic treatment with medication diminishes QoL over time. As we note below, the STOP-EM project was not optimally designed to yield insights into the powerful candidate psychosocial predictors of QoL. We know from other research, for example, that subjective experiences and understandings of diagnosis of severe mental illness can have ramifications for outcomes and QoL [e.g., (33, 34)]. Regardless, the sample experienced significant, albeit modest (about 10% of MPS score), improvements in mean Q-LES-Q scores over the subsequent 18-month assessment period. The physical health and mental health component summary scales of the SF-36 were also significantly higher at six, 12, and 18 months compared to baseline.

We predicted that depressive symptoms would be a prominent predictor of QoL in this FEM sample; indeed, Q-LES-Q scores showed moderate to large effect-size negative correlations with depression severity at each assessment point. Multivariate analyses indicated that both illness duration and depression severity significantly contributed to baseline Q-LES-Q scores. The severity of depressive symptoms at baseline and at six-months significantly contributed to Q-LES-Q scores at six months, and the number of previous depressive episodes and severity of depressive symptoms (at baseline and 12 months) made a significant contribution to mean Q-LES-Q scores at 12 months. Finally, depressive symptoms at 12 months significantly predicted Q-LES-Q scores at 18 months. In keeping with findings from other research (13), it is striking to note that even subsyndromal depressive symptoms (mean 29-item HAM-D ranged between 4 and 7 – in the subsyndromal range – at the various assessment points) can have a marked impact on QoL. Our observation that duration of illness and number of previous episodes of depression were also predictive of QoL (less markedly) is also in keeping with current literature (12, 13).

We did not observe relationships between a range of other putative predictors of QoL, including verbal learning. Prior studies in non-FEM samples are inconsistent with regard to the role of memory functioning in predicting QoL, as significant associations between memory functioning and QoL have been observed in some (35) but not other (36, 37) studies. Mixed findings have also been reported when other cognitive domains such as attention or executive function have been investigated (35–37), and in some instances correlations with QoL have only emerged on global, rather than individual, cognitive domain measures (38). These mixed findings underscore the likely complexity of the association between cognition and QoL and the need for further research. Regardless, based on our study and existing data,

it may be that the association between cognitive impairment (e.g., verbal learning) and diminished QoL develops or exacerbates as the illness progresses, in concert with a worsening in QoL. Our failure to find a relationship between cognition and QoL in our FEM sample may also be attributed to the fact that QoL was only mildly diminished to relatively intact at this early point in the illness.

To date, no studies containing information on longitudinal QoL outcomes in FEM patients have been published. Conus et al. (39) have provided longitudinal (six- and 12-month) data on 87 first-episode patients with psychotic mania, finding that functional recovery at 12 months was predicted by functional recovery at six months, (younger) age, family history of affective disorder, and substance misuse. However, that study used the observer-rated Quality of Life Scale (QLS) (40), which is more aptly described as a measure of psychosocial functioning than QoL; QoL and functioning are not synonymous constructs (41). A key observation in the Conus et al. study relates to the apparent discrepancy between functional and symptomatic outcomes – while 90% of their FEM sample patients achieved syndromal recovery at 12 months, 40% had not recovered symptomatically and over 60% had not recovered functionally. Other research in FEM patient samples has pointed to similarly poor functional outcomes (11, 42, 43).

The relationship between functional and symptomatic outcomes was examined in the STOP-EM program (44) up to the six-month assessment point using a psychosocial functioning scale known as the Multidimensional Scale of Independent Functioning which has been validated for BD populations (45, 46). Functional outcomes for the STOP-EM sample were somewhat more favorable than those cited in other studies; for example, the proportion of patients with at least moderate impairment in functioning decreased from 62% at baseline to 26% at six months. As was the case with QoL, depressive symptoms played a driving role: remission of depressive symptoms at six-months was associated with better functioning and predicted functional status at six months.

Limitations and strengths

Our research is not without limitations. First, there are considerations relating to the symptomatic outcomes on which we focused. In the current study, we explored baseline six-, 12-, and 18-month mood symptom ratings. We did not interrogate the data as to whether patients relapsed into episodes of mania, depression, mixed mania, and/or mixed depression, and we are not reporting on the burden of subthreshold depression symptoms over time (as measured, for example, by a daily mood chart), known to be a powerful predictor of QoL in this population (13). Second, ideally, we would have been able to administer a QoL assessment upon referral to the STOP-EM program; our *baseline-assessment* point, in fact, represents the point at which patients had recently recovered from their first episode of mania. There is continuing debate about the reliability and validity of assessing subjective well-being during mania (5, 41); it would be useful, however, for us to have had information on perceived QoL upon referral to the program. Third, our capacity to speak to psychosocial predictors of QoL outcomes in this dataset is limited. The strengths in the design of STOP-EM include the longitudinal assessment of clinical factors that are candidate predictors of outcomes in BD. The program did not assess the range of psychosocial factors that have been associated with clinical outcomes in BD [e.g., social support, life events, personality, reward sensitivity (47, 48)] and might be hypothesized to also be predictive of QoL outcomes. Fourth, there are considerations relating to our approach to the assessment of QoL in the STOP-EM project. At the time of study design, the Q-LES-Q was considered to be the best available scale for assessing generic QoL in patients with BD (12). However, disorder-specific QoL scales are likely to be more sensitive than their more generic counterparts to a change in clinical state (49, 50), having the potential to capture information that could otherwise be missed (51). For example, the newly developed Quality of Life in Bipolar Disorder Scale (QoL.BD) (24), has shown improved sensitivity to changes in clinical state compared to the Q-LES-Q in this population (24). Of particular relevance here is the fact that FEM patients were included in the patient-centered development of the QoL.BD, potentially increasing the likelihood that areas of interest to this population are represented in the scale. For example, the QoL.BD contains a domain assessing sense of self/identity, shown in other research to be of importance to this population (52, 53), and perhaps of particular pertinence to people newly diagnosed with a chronic severe mental illness. Finally, our sample size is modest.

Our study also has several strengths. Although STOP-EM is a naturalistic study and, as such, does not readily allow for the assessment of the impact of different treatments on QoL, the results from the study are likely quite generalizable to real-world clinical settings, with the caveat that the sample showed higher-than-average high premorbid edu-

cation levels. This research has noteworthy treatment implications. First and foremost, our findings offer a message of hope, both for clinicians and for people newly diagnosed with BD. The relatively intact QoL we observed in this sample of FEM patients implies that the QoL deficits commonly observed in multiple-episode patients (12) may be the result of disease progression, increasing illness severity or burden, or prolonged treatment effects. This provides us with a point of leverage, and credence to the argument that early identification of BD, combined with systematic and thorough treatment, can potentially stay the course of this condition, which often erodes and undermines QoL (54). Second, to a limited degree, our results underscore other research indicating that substance misuse in BD does not bode well for QoL and functional outcomes (39) and there is a need for clinical vigilance for substance misuse issues and targeted treatment interventions. Third, our results add to a formidable body of research demonstrating that we must drive home the message that aggressive treatment of residual symptoms of depression is essential to attain optimal outcomes.

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