Psychological Medicine

cambridge.org/psm

Quality of life in bipolar disorder: towards a dynamic understanding

E. Morton[1], G. Murray[1], E. E. Michalak[2], R. W. Lam[2], S. Beaulieu[3], V. Sharma[4], P. Cervantes[5], S. V. Parikh[6] and L. N. Yatham[2]

[1]Faculty of Health, Arts and Design Swinburne University, Melbourne, Australia; [2]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada; [3]Bipolar Disorders Program, Department of Psychiatry, Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada; [4]Regional Mental Health Care London, London, ON, Canada; [5]Mood Disorders Program, Department of Psychiatry, McGill University Health Center (MUHC), Montreal, Canada and [6]Department of Psychiatry, Toronto Western Hospital, Toronto, ON, Canada

Original Article

Cite this article: Morton E, Murray G, Michalak EE, Lam RW, Beaulieu S, Sharma V, Cervantes P, Parikh SV, Yatham LN (2018). Quality of life in bipolar disorder: towards a dynamic understanding. *Psychological Medicine* **48**, 1111–1118. https://doi.org/10.1017/S0033291717002495

Received: 11 March 2017
Revised: 24 July 2017
Accepted: 3 August 2017
First published online: 18 September 2017

Key words:
Bipolar disorder; depression; functioning; mania; quality of life

Author for correspondence:
G. Murray, Ph.D., E-mail: gwm@swin.edu.au

Abstract

Background. Although quality of life (QoL) is receiving increasing attention in bipolar disorder (BD) research and practice, little is known about its naturalistic trajectory. The dual aims of this study were to prospectively investigate: (a) the trajectory of QoL under guideline-driven treatment and (b) the dynamic relationship between mood symptoms and QoL.
Methods. In total, 362 patients with BD receiving guideline-driven treatment were prospectively followed at 3-month intervals for up to 5 years. Mental (Mental Component Score – MCS) and physical (Physical Component Score – PCS) QoL were measured using the self-report SF-36. Clinician-rated symptom data were recorded for mania and depression. Multilevel modelling was used to analyse MCS and PCS over time, QoL trajectories predicted by time-lagged symptoms, and symptom trajectories predicted by time-lagged QoL.
Results. MCS exhibited a positive trajectory, while PCS worsened over time. Investigation of temporal relationships between QoL and symptoms suggested bidirectional effects: earlier depressive symptoms were negatively associated with mental QoL, and earlier manic symptoms were negatively associated with physical QoL. Importantly, earlier MCS and PCS were both negatively associated with downstream symptoms of mania and depression.
Conclusions. The present investigation illustrates real-world outcomes for QoL under guideline-driven BD treatment: improvements in mental QoL and decrements in physical QoL were observed. The data permitted investigation of dynamic interactions between QoL and symptoms, generating novel evidence for bidirectional effects and encouraging further research into this important interplay. Investigation of relevant time-varying covariates (e.g. medications) was beyond scope. Future research should investigate possible determinants of QoL and the interplay between symptoms and wellbeing/satisfaction-centric measures of QoL.

Bipolar disorder (BD) is a severe mental illness associated with a chronic course and recurring periods of mania and depression, ranked by the World Health Organization as the fifth leading cause of disease burden among mental disorders (Ferrari *et al.* 2016). Research attention in BD has broadened to include quality of life (QoL) as an important outcome of care alongside symptom management (Murray & Michalak, 2012; Morton *et al.* 2017), and indeed both patients with BD and clinicians have rated improvements in QoL as the most important outcome in the treatment of BD (Maczka *et al.* 2009). As a person-centred, recovery-oriented construct, QoL has powerful potential to represent consumer interests in research and clinical practice (Murray *et al.* 2017). Naturalistic, prospective investigations offer the opportunity to investigate trajectories of QoL under real-world treatment regimes and inform our understanding of its relationship to symptoms of BD.

While it is sometimes assumed that absence of mental illness equates to mental wellbeing, the two concepts share only a small portion of variance (Keyes, 2005). Consequently, constructs such as QoL have emerged as treatment goals in their own right in the care of mental illnesses generally (Basu, 2004) and in BD specifically (Murray & Michalak, 2012; Morton *et al.* 2017). QoL is prioritised by consumers and thus the personal recovery movement views QoL improvement as an outcome of equal importance to symptom remission (Murray *et al.* 2017). Popular interest in QoL is paralleled in the scientific BD literature, with publications referencing QoL increasing exponentially over recent years (Murray & Michalak, 2012). These studies show that QoL is impaired in individuals with BD relative to the general population, even during euthymic periods (Brissos *et al.* 2008; Gutiérrez-Rojas *et al.* 2008), suggesting that attention needs to be paid to improving this patient-valued outcome. We propose that a critical step towards this goal is to develop understanding of (a) the impact of current guideline-driven treatment on QoL in BD, and (b) the dynamic relationship between symptoms of BD and QoL: existing relevant literature is briefly reviewed before introducing the present study.

CAMBRIDGE UNIVERSITY PRESS

Attention to the impact of treatment regimens on QoL is needed to validate the assumption that current best practice improves QoL from the consumer perspective. Pharmacological interventions form the bedrock of current treatment guidelines, with psychosocial interventions and self-management strategies increasingly recognised and encouraged (Yatham *et al.* 2013), While QoL is increasingly used as a primary outcome variable to judge the *efficacy* of pharmacological and psychosocial interventions through randomised controlled trials (RCTs; Namjoshi *et al.* 2002, 2004, Shi *et al.* 2002, 2004, Endicott *et al.* 2007, 2008, Michalak *et al.* 2014), it is important to note that RCTs do not represent the reality of clinical practice in which polypharmacy, medication changes, and combined pharmacological and psychosocial strategies are common, and patient characteristics are heterogeneous (Post, 2009). The *effectiveness* of current best practice BD treatment at improving subjective QoL is unknown: naturalistic, longitudinal studies are therefore required to accurately gauge the impact of real world BD treatment strategies on QoL.

A second assumption in need of further investigation relates to the impact of mood symptoms on QoL in BD. Data from cross-sectional studies generally suggest that depressive symptoms are associated with poorer QoL (Vojta *et al.* 2001; Yatham *et al.* 2004; Gazalle *et al.* 2006, 2007*a*; Hayhurst *et al.* 2006; Zhang *et al.* 2006; Simon *et al.* 2007). The cross-sectional influence of manic symptoms on QoL is less well understood, with some articles finding mania to be associated with poorer QoL, (Vojta *et al.* 2001; Simon *et al.* 2007; Gazalle *et al.* 2007*b*) and others finding no negative impact of mania (Hayhurst *et al.* 2006; Gazalle *et al.* 2007*a*). However, cross-sectional studies cannot illuminate directionality of effects. Limited investigation of the trajectory of QoL following first episode psychotic mania did not reveal an effect of symptoms at baseline with QoL at 18 months (Oldis *et al.* 2016): more sensitive analyses of time-varying relationships in the general BD population is needed to illuminate possible relationships. Additionally, although QoL change is typically assumed to be a downstream consequence of symptom changes in BD, it is not known whether changes in QoL may have reciprocal impacts on BD symptoms: potentially, improvements in wellbeing and functioning could moderate symptoms of the disorder (Murray & Michalak, 2012). Longitudinal studies are therefore required to inform understanding of the relationship between BD symptoms and QoL over time.

The present study

The present prospective observational study analysed data from the Health Outcome and Patient Evaluation-Bipolar Disorder (HOPE-BD) project, a multisite prospective naturalistic investigation of patients receiving guideline-driven treatment for BD in Canada. The primary aim of the HOPE-BD project was to prospectively examine treatment patterns, clinical outcomes, QoL, and resource utilisation of a Canadian BD sample receiving guideline-driven treatment.

As we have recently reviewed, it is important to recognise different emphases across existing measures of QoL in BD (Morton *et al.* 2017). Here, we chose the 36-item Short-Form Survey (SF-36; Ware *et al.* 1993) as a commonly used measure of QoL *qua* psychosocial and physical functioning. A further advantage of the SF-36 for the present purposes was its generation of two well-understood subscale scores (physical and mental functioning) for exploration.

The aim of the present analyses was to investigate: (i) the trajectory of QoL under guideline-driven treatment and (ii) the relationship between objective symptom measures and subjective QoL ratings over time. It was hypothesised that QoL would increase over time with guideline-driven treatment. Additionally, it was hypothesised that lower levels of depression would predict a positive change in QoL. Analyses of the impact of mania on trajectories of QoL and QoL as a predictor of change in symptom ratings were exploratory.

To the authors' knowledge, this is the first study to use multilevel modelling (MLM) to examine the naturalistic trajectory of QoL in a population receiving guideline-driven treatment. Additionally, it is the first study to report on the time-varying relationship between symptoms of BD and QoL.

Materials and method

Study design

Participants were recruited from 12 sites across Canada, including university and community hospitals and outpatient clinics, and prospectively followed every 3 months for a period of up to 5 years. Treating psychiatrists retained responsibility for delivering pharmacotherapies and other treatments according to Canadian Network for Mood & Anxiety Treatments (CANMAT) guidelines (1997). Patients or legally accepted delegates gave informed written consent for data to be collected. The study was approved by the University of British Columbia Research Ethics Board and the Ethics Boards at all sites that collected data.

Participants

Psychiatrists at participating sites referred eligible patients for participation. Inclusion criteria were: (i) diagnosed with BD-I, BD-II or BD not otherwise specified (NOS); diagnoses were confirmed at intake using the Mini-International Neuropsychiatric Interview (MINI; Sheehan *et al.* 1998), (ii) currently meeting or recently (within the past 3 months) met criteria for a (hypo) manic or depressive episode, or recently (within the past 3 months) changed treatment, (iii) under the care of a participating psychiatrist, (iv) aged 15 years or older, (v) competent and willing to provide informed consent (or consent given by a legally accepted delegate), and (vi) fluent in either English or French. Exclusion criteria for the study were: (i) diagnosed with either a (a) non-affective psychotic disorder, (b) substance-induced mood disorder, (c) mood disorder secondary to a medical condition, or (d) personality disorder with only subthreshold hypo/manic or depressive symptoms; (ii) unwilling or unable to participate in follow-up assessments (e.g. moving out of area); (iii) currently participating in a clinical treatment trial; or (iv) hospitalised longer than 6 months.

Measures

Symptoms

Both symptom measures were validated, widely used clinician-rated scales. Mania was assessed using the Young Mania Rating Scale (YMRS; Young *et al.* 1978), an 11-item scale with scores ranging from 0 to 60. Depression was measured on the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), a 10-item instrument with scores ranging from 0 to 60. All investigators were members of the

https://doi.org/10.1017/S0033291717002495 Published online by Cambridge University Press

Canadian Network for Mood and Anxiety Treatments, had received training on inter-rater reliability and had demonstrated excellent inter-rater reliability on previous clinical trials.

Quality of life

QoL was measured with the SF-36 (Ware *et al.* 1993), a 36-item self-report questionnaire. The SF-36 has eight subscales assessing: Physical Function, Role Limitations due to Physical Health, Bodily Pain, General Health, Vitality, Social Function, Role Limitations due to Emotional Problems, and Mental Health. Two component scores may be derived (Ware *et al.* 1994): one summarising physical QoL (Physical Component Score – PCS), and the other summarising mental QoL (Mental Component Score – MCS). The eight subscales and two component scores are scored 0–100, with higher scores representing better QoL. Scores were standardised according to Canadian norms (Hopman *et al.* 2000).

Assessment schedule

Confirmation of BD diagnosis via the MINI occurred at baseline. Symptom measures (YMRS and MADRS) and QoL (SF-36) were assessed at baseline and at follow-up assessments, which were conducted at 3-month intervals (within a 2-week window).

Trajectory analyses

MLM was used due to the hierarchical structure of the data (i.e. longitudinal observations are nested within individuals). This data structure, which would violate the assumption of independence of residuals required for linear regression models, is accounted for in MLM (Hox, 2010). In addition, MLM methods were chosen as they support estimation in situations where observations are missing. Data were analysed using the MIXED procedure of SPSS using full maximum likelihood estimation (IBM SPSS statistics for Windows, Version 22.0; 2013). Predictors where zero is a non-interpretable value (e.g. age) were centred around the sample mean. Given the exploratory nature of the study, the α level was set at 0.05.

Fixed and random effects were specified for the intercept and slope parameters in models unless otherwise stated. Random effects were removed in cases where models failed to converge due to lack of random variance (Heck *et al.* 2014). Residual terms at level 1 were specified as having an autoregressive covariance matrix: unobserved variance was assumed to differ between the time points, and it was assumed that correlation between occasions of measurement would decrease with greater duration between occasions of measurements (Heck *et al.* 2014). Level 2 residuals were specified as having a diagonal covariance matrix: it was assumed that the random effects for the intercepts and the slope did not correlate. The level 2 covariance structure was chosen as it permitted the estimation of intercept and slope variances. Models without random effects for slope must be estimated using a scaled identity covariance matrix.

MLM was employed as follows:

1. *Unconditional QoL growth models.* To examine the trajectories of QoL over time, growth models with linear and quadratic terms were fitted individually for MCS and PCS. Significant terms were retained for following analyses.

   Exploratory subscale analyses. Additional growth models were created to compare the trajectories of the SF-36 subscales [General Health, Role Limitations (Emotional), Social Functioning, Physical Functioning, Role Limitations (Physical), Pain, Vitality, and Mental Health].
2. *Level 2 predictors of QoL.* Age, sex, and BD diagnosis were entered as level 2 predictors in the growth models for PCS and MCS. Significant predictors were retained for following analyses.
3. *Models with time-lagged covariates.* Possible temporal relationships between symptoms and QoL were investigated as follows.
   a. Firstly, significant growth models for QoL were analysed controlling for earlier symptom covariates (MADRS and YMRS). That is, a model was created where QoL variables at the present visit (time) were predicted by symptom data from the previous visit (time – 3 months). The 3-month time lag was chosen due to the data structure.
   b. Secondly, to test the directionality of any relationship between QoL and symptoms of BD, models where symptom ratings (MADRS and YMRS) were predicted by earlier QoL (PCS and MCS) were calculated. Unconditional growth models for symptom measures and models evaluating level 2 predictors were created to permit identification of significant parameters to retain in models where lagged MCS and PCS acted as predictors. However, they are not the focus of the present analysis and are presented in online Supplementary Tables S1 and S2, respectively.

Results

Participant characteristics

A total of 362 participants aged 18–72 ($M = 42.75$, S.D. = 12.18) were recruited. The majority of participants ($n = 207$) were female, and approximately equal numbers were of Caucasian ($n = 158$) and non-Caucasian ($n = 164$) ethnicity. The majority of participants were recruited through teaching hospitals in (i) Vancouver, British Columbia ($n = 56$), (ii) London, Ontario ($n = 64$), and (iii) Montreal, Quebec ($n = 82$); and a private practice in Montreal ($n = 53$). Participants completed between one and 13 assessments ($M = 4.90$, S.D. = 3.30).

BD-I was the most common diagnosis ($n = 185$), followed by BD-II ($n = 120$) and BD-NOS ($n = 21$). Mood episodes at baseline were predominantly depressive ($n = 121$) with fewer manic ($n = 44$), hypomanic ($n = 20$), or mixed recorded ($n = 15$). At baseline, 106 (29%) were prescribed lithium, 84 (23%) sodium valproate, 14 (4%) carbamazepine, 36 (10%) risperidone, 40 (11%) olanzapine, 41 (11%) quetiapine, 41 (11%) lamotrigine, and 95 (26%) an antidepressant.

Mean MCS at baseline was lower than the Canadian norm (31.13 *v.* 51.7), as was PCS (48.16 *v.* 50.5; Hopman *et al.* 2000).

Trajectory analyses

1. Unconditional QoL growth models

The results of the unconditional growth models for MCS and PCS are displayed in Table 1. The linear slope parameter for MCS was positive and significant (*estimate* = 0.45, $p < 0.001$), with a significant negative quadratic (*estimate* = −0.006, $p < 0.05$) indicating the rate of growth slowed over time. The linear slope parameter for PCS was negative and significant (*estimate* = −0.14, $p < 0.05$), with a significant positive quadratic (*estimate* = 0.003, $p < 0.05$) indicating the decrement in PCS slowed over time. No random effect for slope was specified in the growth model for PCS.

https://doi.org/10.1017/S0033291717002495 Published online by Cambridge University Press

Table 1. Unconditional growth model results for MCS and PCS

	MCS	PCS
Intercept	33.09**	47.49**
Main effects		
Linear slope	0.45**	−0.14*
Quadratic slope	−0.006*	0.002*
Variance		
Within person	120.91	51.98**
Between-person (intercept)	0.14**	78.05**
Between-person (slope)	179.62**	*b*

Note: *$p < 0.05$, **$p < 0.001$, *b* parameter was not calculated.

Exploratory subscale analyses

Growth models were created for each of the eight SF-36 subscales (see online Supplementary Table S3). Paralleling the trends seen in MCS (above), a significant positive linear effect and significant negative quadratic effect were found for the SF-36 subscales Role Limitations due to Emotional Problems (*linear estimate* = 1.01, $p < 0.001$; *quadratic estimate* = −0.01, $p < 0.05$)), Social Functioning (*linear estimate* = 0.68, $p < 0.001$; *quadratic estimate* = −0.008, $p < 0.05$) and Mental Health (*linear estimate* = 0.48, $p < 0.001$; *quadratic estimate* = −0.007, $p < 0.05$). A significant positive linear effect was found for the subscales General Health (*estimate* = 0.11, $p < 0.05$) and Vitality (*estimate* = 0.26, $p < 0.05$); no significant quadratic effects were observed for either of these subscales. No random effects for slope were retained in the models for Physical Functioning, Role Limitations due to Physical Problems, or Pain; in addition, no significant change over time was observed in these subscales.

2. Level 2 predictors of QoL

Age, sex, and BD diagnosis were entered as predictors for the growth models for MCS and PCS (Table 2). The only predictor to reach significance and be retained in future models of MCS was the main effect for sex (*estimate* = 3.54, $p < 0.05$): males had higher baseline mental QoL than females. There was a significant negative main effect of age on PCS (*estimate* = −0.20, $p < 0.001$): individuals older than the sample mean (42.75) had poorer baseline physical QoL. There was a positive main effect of sex on PCS (*estimate* = 4.57, $p < 0.05$): males had higher baseline physical QoL than females. Sex and age were retained as predictors in future PCS models. No significant interaction (slope) effects were observed for either MCS or PCS.

3. Models with time-lagged covariates

3.a Symptoms as time-lagged covariates. The growth models for MCS and PCS controlling for the effects of both MADRS and YMRS ratings from the previous visit (3 months) are displayed in Table 3. There was a significant negative main effect of earlier depression (MADRS) on MCS (*estimate* = −0.40, $p < 0.001$): lower depression ratings were associated with higher MCS ratings at the following visit. There was no significant main effect for earlier mania (YMRS) on MCS (*estimate* = −0.08, $p = 0.58$).

There was a significant negative main effect of earlier YMRS on PCS (*estimate* = −0.19, $p < 0.05$): higher YMRS ratings were associated with lower PCS at the following visit. There was no significant main effect for earlier MADRS ratings on PCS (*estimate* = −0.06, $p = 0.15$).

Table 2. Growth model results for MCS and PCS with level 2 predictors (mean-centred age, sex, and BD diagnosis)

	MCS	PCS
Intercept	27.29**	43.85**
Main effects		
Linear slope	0.61	−0.05
Quadratic slope	−0.005*	0.003*
BD-I	6.50	2.27
BD-II	2.13	1.09
BD-NOS	0^b	0^b
Age	0.13	−0.20**
Sex (male)	3.54*	4.57*
Interaction (slope) effects		
BD-I	−0.08	−0.06
BD-II	−0.20	−0.05
BD-NOS	0^b	0^b
Age	−0.002	−0.0002
Sex (male)	−0.15	−0.07
Variances		
Within person	123.48**	51.67**
Between-person (intercept)	80.20**	72.74**
Between-person (slope)	0.04*	*b*

Note: *$p < 0.05$, **$p < 0.001$, *b* parameter was not calculated, 0^b redundant parameter set to zero.

3.b QoL as time-lagged covariates. Unconditional growth models and investigation of level 2 predictors (age, sex, BD diagnosis) for MADRS and YMRS are displayed in online Supplementary Tables

Table 3. Growth models for MCS and PCS with effects of earlier (time – 3 months) MADRS and YMRS

	MCS	PCS
Intercept	37.26**	47.94**
Main effects		
Linear slope	0.36*	−0.17
Quadratic slope	−0.005	−0.003
Earlier MADRS	−0.40**	−0.06
Earlier YMRS	−0.08	−0.19*
Sex (male)	1.37	3.10*
Age	*b*	−0.19**
Variance		
Within individuals	129.73**	55.98**
Between-person (intercept)	65.30**	68.54**
Between-person (slope)	0.04*	*b*

Note: *$p < 0.05$, **$p < 0.001$, *b* parameter was not calculated.

https://doi.org/10.1017/S0033291717002495 Published online by Cambridge University Press

Table 4. Growth models for MADRS and YMRS with effects of earlier (time – 3 months) MCS and PCS

	MADRS	YMRS
Intercept	18.68**	4.59**
Main effects		
Linear slope	−0.08*	−0.02*
Earlier MCS	−0.16**	−0.03**
Earlier PCS	−0.07*	−0.03*
Sex (male)	−1.99*	*b*
Interaction (slope) effects		
Sex (male)	0.08	*b*
Variance		
Within individuals	36.22**	8.22**
Between-person (intercept)	10.68**	1.46**
Between-person (slope)	*b*	*b*

Note: *$p < 0.05$, **$p < 0.001$, *b* parameter was not calculated.

S1 and S2, respectively. Random effects for slope were not specified for MADRS and YMRS growth models. Of the level 2 predictors, only the main effect and interaction (slope) effect for sex were retained for future MADRS models. No level 2 predictors were retained for future PCS models.

MCS and PCS were added as time-lagged covariates to growth models for symptom measures (MADRS and YMRS; see Table 4). There was a significant negative main effect of earlier MCS on both MADRS (*estimate* = −0.16, $p < 0.001$) and YMRS (*estimate* = −0.03, $p < 0.001$): higher levels of MCS were associated with lower symptom ratings at the following visit. Similarly, there was a significant negative main effect of earlier PCS on both MADRS (*estimate* = −0.07, $p < 0.05$) and YMRS (*estimate* = −0.03, $p < 0.05$): higher levels of PCS were associated with lower symptom ratings at the following visit.

Discussion

The HOPE-BD study naturalistically followed 362 patients with BD receiving guideline-driven treatment over a period of up to 5 years. Here, we analysed both symptoms and QoL at 3-month intervals. Mental QoL (measured on the MCS) was found to increase over time, and the rate of improvement in mental QoL slowed over time. Physical QoL (PCS) was found to worsen over time, with a gradually slowing rate of decrement. Novel analyses of the dynamic relationship between symptoms of BD and mental QoL found: (a) reduction in depressive symptoms was associated with later improvements in mental QoL, (b) reduction in manic symptoms was associated with later improvements in physical QoL, and (c) improvements in both physical and mental QoL were associated with subsequent reduction in symptoms of BD.

MLM analyses led to the hopeful finding that, with guideline driven treatment, mental QoL improves over time among people with BD, albeit with a gradual reduction in rate of improvement. Improvement in the subscales Social Functioning, Role Limitations due to Emotional Problems, and Mental Health paralleled the MCS growth curve. Positive impacts on role and social functioning as a consequence of guideline-driven treatment may be expected given the known negative impact of manic and particularly depressive symptoms on social and occupational functioning in BD (Rosa *et al.* 2010). If replicated, these novel findings have significant implications for prognostic discussions with patients.

In contrast to mental QoL, PCS ratings in this population were observed to decrease over time in a non-linear fashion. In addition, PCS ratings were poor in this BD population as compared with Canadian norms. The finding that physical QoL is poor in individuals with BD is not unexpected: individuals with BD not only suffer from higher rates of physical health comorbidities than the general population (Kilbourne *et al.* 2004; Krishnan, 2005), but may also face added burden from adverse physical effects of psychotropic medication on their QoL (Yen *et al.* 2008). However, the finding that physical QoL worsened in this sample demands further attention to methods to improve physical health and functioning in BD (for a review of the emerging evidence for lifestyle interventions for physical health in BD, see Bauer *et al.* 2016). Lack of significant change on the role limitations due to Physical Problems, Physical Functioning, Vitality, and Pain subscales, along with positive change in the General Health and Vitality subscales may seem counterintuitive given the growth curve results observed for PCS (above). However, this is due to the nature of the MCS/PCS scoring algorithms: these are norm-based scores, such that MCS and PCS here reflect the QoL of this population relative to Canadian averages (Hopman *et al.* 2000). Additionally, summary scores are produced from positively and negatively weighted physical and mental subscales in order to remove shared variance (Ware *et al.* 1994).

The study's novel investigation of dynamic relationships between symptoms of BD and mental QoL supported common assumptions, but also identified new associations warranting further study. Improvements in mental QoL were found to be predicted by improvements in the preceding visit's depression ratings, while depression did not significantly impact subsequent physical QoL ratings. This is consistent with (but permits stronger causal inference than) the numerous cross-sectional analyses suggesting a negative influence of depressed mood on QoL (Vojta *et al.* 2001; Yatham *et al.* 2004; Hayhurst *et al.* 2006; Simon *et al.* 2007; Gazalle *et al.* 2007*a*). The present study contributes to ongoing clarification of the role of mania in QoL in BD: earlier mania did not impact on mental QoL at the following visit; however, improvements in physical QoL were predicted by improvements in the preceding visit's mania ratings. It may be expected that higher levels of mania would be associated with subsequent decrements in physical QoL, given the intense physical effects of this highly dysregulated state and the side effect profile of antimanic medications required to address it (de Hert *et al.* 2011); further research is required to elucidate mechanisms through which mania may impact QoL.

Most strikingly, modelling analyses also found that improvements in mental and physical QoL were associated with subsequent benefits for the symptoms of BD: improvements in both mental and physical QoL were associated with later reduction in mania and depression. To our knowledge, this is the first empirical study supporting the longstanding humanistic assumption that improvements in subjective QoL may predict clinical improvements in BD (Murray & Michalak, 2012). QoL may play a uniquely predictive role in *mental* health (IsHak *et al.* 2011): improved subjective perception of life circumstances and positive impacts in valued life areas such as leisure and social

https://doi.org/10.1017/S0033291717002495 Published online by Cambridge University Press

relationships would intuitively be expected to stabilise mood. In fact, evidence-based and emerging treatments for BD such as cognitive behaviour therapy, interpersonal and social rhythm therapy, and mindfulness training target aspects of QoL such as perceptions of self, others and the future, engagement in positive activities, and management of stressful life circumstances (Frank *et al.* 2000; Lam *et al.* 2010; Murray *et al.* 2017). The impact of subjective QoL on later symptoms may also relate to changes to objective circumstances (e.g. functioning): scores on functioning measures and employment status have been shown to predict treatment response (Deckersbach *et al.* 2016). Finally, the potential role of physical QoL as a predictor of future manic symptoms suggests attention to the developing field of interventions for physical health in BD (Bauer *et al.* 2016): for example, exercise has been associated with improved sleep quality in BD (Nusslock *et al.* 2007), which would be expected to have downstream impacts on manic symptoms (Frank *et al.* 2000). The *subjective* nature of the QoL assessment used in this study directs particular attention to interventions which target evaluations of physical health [e.g. yoga, mindfulness, relaxation training (Bernstein *et al.* 2016)]. Investigation of possible mechanisms through which QoL may impact later symptoms will illuminate this relationship further and identify additional therapeutic targets.

Through the use of large-scale, longitudinal data, the present study is able to illustrate for the first time the common-sense prediction that QoL improvements are associated with downstream impacts on both depressive and manic BD symptoms (Malhi *et al.* 2015). If this finding proves robust in future research, it will encourage renewed therapeutic effort on interventions for BD specifically targeting consumers' QoL goals (Leitan *et al.* 2015; Murray *et al.* 2017). A focus on QoL as a treatment outcome is consistent with calls to attend to broader psychological, physical, and functional outcomes in mental health (Slade, 2010). The novel analyses of the present study add weight to this call by suggesting that interventions directly targeting QoL have the potential for downstream benefits for the symptoms of BD. Future research could specifically test mechanisms by which subjective QoL may have impacts on mood symptoms, including the impacts of cognitive strategies (as in cognitive therapy, mindfulness) and behavioural interventions (such as lifestyle changes and interpersonal and social rhythm therapy).

Limitations

A number of limitations should be noted. While the long-term prospective design has marked advantages over cross-sectional methods, temporal precedence alone is insufficient to establish causality. Additionally, the naturalistic design precludes specific statements about the variety of treatments received by participants beyond the broad criterion of 'guideline-driven treatment'. A comprehensive investigation of all relevant time-varying covariates (e.g. medication use, psychosocial treatments) is beyond the current scope. This study represents an initial attempt to track QoL and symptoms across time, and generates hypotheses for future investigation. Future studies should account for other possible determinants of QoL, (e.g. treatment changes, life events, disease progression, etc.). The present study was not designed to evaluate the relative predictive power of QoL compared with other determinants of symptoms in BD (e.g. physical health, unemployment, etc.), and indeed there is no agreed upon method to calculate effect sizes as they are commonly understood in other statistical analyses (Roberts & Monaco, 2006; Peugh, 2010). However, the exploratory findings here suggest that QoL is an important predictor, which should be taken into account in future studies which evaluate multiple competing variables. The use of the SF-36 to measure QoL situates the present study within a body of work characterising QoL as related to functioning (Morton *et al.* 2017) – results may not generalise to measures associated with conceptualisations of QoL as wellbeing or satisfaction.

Missing data were a limitation of the present dataset. As with any long-term, prospective, multisite study, data were lost due to participant dropout, erratic attendance, or site-related issues in data collection. The issue of missing data does raise some questions that the present analysis is unable to clarify, for example, mechanisms explaining the interaction between age and physical QoL. An advantage of the analysis used is that MLM supports estimation in situations where observations are missing (Heck *et al.* 2014). As number of completed assessments correlated only weakly with MCS ($r_s = 0.19$), PCS ($r_s = -0.04$), and symptom ratings (MADRS: $r_s = -0.12$; YMRS: $r_s = -0.08$), we inferred that missing data from participant dropout were unlikely to systematically bias findings.

Conclusion

Within its limitations, the present study demonstrates for the first time that individuals receiving consensus treatment for BD show linear improvements in their mental QoL. Investigation of temporal relationships between QoL and symptoms of BD suggested bidirectional effects, and generates novel hypotheses for future research. Guideline-driven treatment was found to positively impact symptoms and subsequent QoL. Evidence for positive impacts of QoL on downstream symptoms encourages further research into optimising QoL in BD.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717002495.

Acknowledgements. The HOPE-BD study was funded by Astrazeneca with an unrestricted grant to Dr Lakshmi Yatham.

Declaration of Interest. Ms Emma Morton reports no financial relationships with commercial interests. Professor Greg Murray reports no financial relationships with commercial interests. Dr Erin Michalak reports no financial relationships with commercial interests. Dr Raymond Lam has received speaker honoraria from AstraZeneca, Canadian Network for Mood and Anxiety Treatments, Canadian Psychiatric Association, Lundbeck, Lundbeck Institute, and Otsuka; is on the consultant/advisory board at Allergan, Asia-Pacific Economic Cooperation, Bristol Myers Squibb, Canadian Depression Research and Intervention Network, Canadian Network for Mood and Anxiety Treatments, Janssen, Lundbeck, Medscape, Pfizer, and Takeda; has received research funds from Brain Canada, Bristol Myers Squibb, Canadian Institutes of Health Research, Canadian Depression Research and Intervention Network, Canadian Network for Mood and Anxiety Treatments, Janssen, Lundbeck, Movember Foundation, Pfizer, St. Jude Medical, University Health Network Foundation, and Vancouver Coastal Health Research Institute; has the following patent: Lam Employment Absence and Productivity Scale (LEAPS); and has book royalties through Cambridge University Press, Informa Press, Oxford University Press. Dr Serge Beaulieu is on the speaker bureau at Astra Zeneca, Eli Lilly, Otsuka, Sunovion, Bristol Myers Squibb (BMS), Lundbeck, and Pfizer; is on the consultant/advisory board at Astra Zeneca, Forest Laboratories, Merck, Pfizer, Bristol Myers Squibb (BMS), Lundbeck, Otsuka, and Sunovion; has received peer-reviewed research funding from CIHR, RSMQ, FRSQ, NARSAD, Stanley Foundation, and Pfizer Research Award; has received research support

from Astra Zeneca, Lundbeck, Sunovion, Bristol Myers Squibb (BMS), and Otsuka. Dr Verinder Sharma has received grant support from, participated on scientific advisory boards for, or served on the speakers' bureaus of Kinect, Stanley Medical Research Institute, Assurex, Genome Canada and Sunovian Pharmaceuticals. Dr Pablo Cervantes reports no financial relationships with commercial interests. Dr Sagar Parikh has received a research grant from Assurex, has consulted for Bristol Myers Squibb, Takeda, and Sunovion, and has shares in Mensante. He has received non-commercial research funding from CIHR, Ontario Brain Institute, UHN Foundation, Flinn Foundation, and University of Michigan. Dr Lakshmi Yatham has been on speaker/advisory boards for, or has received research grants from: Alkermes, Allergan, AstraZeneca, Bristol Myers Squibb, CIHR, CANMAT, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen, Teva, the Michael Smith Foundation for Health Research, Pfizer, Servier and the Stanley Foundation.

Ethical Standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

References

Basu D (2004) Quality-of-Life issues in mental health care: past, present, and future. *German Journal of Psychiatry* **7**, 35–43.

Bauer IE, Gálvez JF, Hamilton JE, Balanzá-Martínez V, Zunta-Soares GB, Soares JC *et al.* (2016) Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. *Journal of Psychiatric Research* **74**, 1–7.

Bernstein EE, Rabideau DJ, Gigler ME, Nierenberg AA, Deckersbach T and Sylvia LG (2016) Patient perceptions of physical health and bipolar symptoms: the intersection of mental and physical health. *Journal of Affective Disorders* **189**, 203–206.

Brissos S, Dias VV, Carita AI and Martinez-Arán A (2008) Quality of life in bipolar type I disorder and schizophrenia in remission: clinical and neurocognitive correlates. *Psychiatry Research* **160**, 55–62.

Canadian Network for Mood and Anxiety Treatments (CANMAT) (1997) The treatment of bipolar disorder: review of the literature, guidelines, and options. *Canadian Journal of Psychiatry* **42**, 67–100.

Deckersbach T, Nierenberg AA, McInnis MG, Salcedo S, Bernstein EE, Kemp DE *et al.* (2016) Baseline disability and poor functioning in bipolar disorder predict worse outcomes: results from the bipolar CHOICE study. *Journal of Clinical Psychiatry* **77**, 100–108.

de Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I *et al.* (2011) Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry* **10**, 52–77.

Endicott J, Paulsson B, Gustafsson U, Schiöler H and Hassan M (2008) Quetiapine monotherapy in the treatment of depressive episodes of bipolar I and II disorder: improvements in quality of life and quality of sleep. *Journal of Affective Disorders* **111**, 306–319.

Endicott J, Rajagopalan K, Minkwitz M and Macfadden W (2007) A randomized, double-blind, placebo-controlled study of quetiapine in the treatment of bipolar I and II depression: improvements in quality of life. *International Clinical Psychopharmacology* **22**, 29–37.

Ferrari AJ, Stockings E, Khoo JP, Erskine HE, Degenhardt L, Vos T *et al.* (2016) The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. *Bipolar Disorders* **18**, 440–450.

Frank E, Swartz HA and Kupfer DJ (2000) Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. *Biological Psychiatry* **48**, 593–604.

Gazalle FK, Andreazza AC, Hallal PC, Kauer-Sant'Anna M, Ceresér KM, Soares JC *et al.* (2006) Bipolar depression: the importance of being on remission. *Revista Brasileira de Psiquiatria* **28**, 93–96.

Gazalle FK, Frey BN, Hallal PC, Andreazza AC, Cunha ÂBM, Santin A *et al.* (2007*a*). Mismatch between self-reported quality of life and functional assessment in acute mania: a matter of unawareness of illness? *Journal of Affective Disorders* **103**, 247–252.

Gazalle FK, Hallal PC, Andreazza AC, Frey BN, Kauer-Sant'Anna M, Weyne F *et al.* (2007*b*). Manic symptoms and quality of life in bipolar disorder. *Psychiatry Research* **153**, 33–38.

Gutiérrez-Rojas L, Gurpegui M, Ayuso-Mateos JL, Gutiérrez-Ariza JA, Ruiz-Veguilla M and Jurado D (2008) Quality of life in bipolar disorder patients: a comparison with a general population sample. *Bipolar Disorders* **10**, 625–634.

Hayhurst H, Palmer S, Abbott R, Johnson T and Scott J (2006) Measuring health-related quality of life in bipolar disorder: relationship of the EuroQol (EQ-5D) to condition-specific measures. *Quality of Life Research* **15**, 1271–1280.

Heck RH, Thomas SL and Tabata LN (2014) *Multilevel and Longitudinal Modeling with IBM SPSS*. New York: Routledge.

Hopman WM, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S, Berger C *et al.* (2000) Canadian normative data for the SF-36 health survey. *CMAJ: Canadian Medical Association Journal* **163**, 265–271.

Hox JJ (2010) *Multilevel Analysis: Techniques and Applications*, 2nd edn. New York: Routledge.

IsHak WW, Greenberg JM, Balayan K, Kapitanski N, Jeffrey J, Fathy H *et al.* (2011) Quality of life: the ultimate outcome measure of interventions in major depressive disorder. *Harvard Review of Psychiatry* **19**, 229–239.

Keyes CL (2005) Mental illness and/or mental health? Investigating axioms of the complete state model of health. *Journal of Consulting and Clinical Psychology* **73**, 539–548.

Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I *et al.* (2004) Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disorders* **6**, 368–373.

Krishnan KR (2005) Psychiatric and medical comorbidities of bipolar disorder. *Psychosomatic Medicine* **67**, 1–8.

Lam DH, Jones SH and Hayward P (2010) *Cognitive Therapy for Bipolar Disorder: A Therapist's Guide to Concepts, Methods and Practice*. Chichester, West Sussex: John Wiley & Sons.

Leitan ND, Michalak EE, Berk L, Berk M and Murray G (2015) Optimizing delivery of recovery-oriented online self-management strategies for bipolar disorder: a review. *Bipolar Disorders* **17**, 115–127.

Maczka G, Siwek M, Skalski M and Dudek D (2009) Patients' and doctors' attitudes towards bipolar disorder – do we share our beliefs? *Psychiatria Polsk* **43**, 301–312.

Malhi G, Bassett D, Boyce P, Bryant R, Fitzgerald P, Fritz K *et al.* (2015) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian & New Zealand Journal of Psychiatry* **49**, 1087–1206.

Michalak EE, Guiraud-Diawara A and Sapin C (2014) Asenapine treatment and health-related quality of life in patients experiencing bipolar i disorder with mixed episodes: post-hoc analyses of pivotal trials. *Current Medical Research and Opinion* **30**, 711–718.

Montgomery SA and Asberg M (1979) A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Morton E, Michalak EE and Murray G (2017) What does quality of life refer to in bipolar disorders research? A systematic review of the construct's definition, usage and measurement. *Journal of Affective Disorders* **212**, 128–137.

Murray G, Leitan ND, Thomas N, Michalak EE, Johnson SL, Jones S *et al.* (2017) Towards recovery-oriented psychosocial interventions for bipolar disorder: quality of life outcomes, stage-sensitive treatments, and mindfulness mechanisms. *Clinical Psychology Review* **52**, 148–163.

Murray G and Michalak EE (2012) The quality of life construct in bipolar disorder research and practice: past, present, and possible futures. *Bipolar Disorders* **14**, 793–796.

Namjoshi MA, Rajamannar G, Jacobs T, Sanger TM, Risser R, Tohen MF *et al.* (2002) Economic, clinical, and quality-of-life outcomes associated with olanzapine treatment in mania: results from a randomized controlled trial. *Journal of Affective Disorders* **69**, 109–118.

Namjoshi MA, Risser R, Shi L, Tohen M and Breier A (2004) Quality of life assessment in patients with bipolar disorder treated with olanzapine added to lithium or valproic acid. *Journal of Affective Disorders* **81**, 223–229.

Nusslock R, Abramson LY, Harmon-Jones E, Alloy LB and Hogan ME (2007) A goal-striving life event and the onset of hypomanic and depressive

episodes and symptoms: perspective from the behavioral approach system (BAS) dysregulation theory. *Journal of Abnormal Psychology* **116**, 105–115.

Oldis M, Murray G, Macneil CA, Hasty MK, Daglas R, Berk M *et al.* (2016) Trajectory and predictors of quality of life in first episode psychotic mania. *Journal of Affective Disorders* **195**, 148–155.

Peugh JL (2010) A practical guide to multilevel modeling. *Journal of School Psychology* **48**, 85–112.

Post RM (2009) Myth of evidence-based medicine for bipolar disorder. *Expert Reviews of Neurotherapeutics* **9**, 1271–1273.

Roberts JK and Monaco JP (2006) Effect size measures for the two-level linear multilevel model. *Paper Presented at the Annual Conference of the American Educational Research Association [AERA]*, San Francisco, CA.

Rosa AR, Reinares M, Michalak EE, Bonnin CM, Sole B, Franco C *et al.* (2010) Functional impairment and disability across mood states in bipolar disorder. *Value in Health* **13**, 984–988.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E *et al.* (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* **59**, 22–33.

Shi L, Namjoshi MA, Swindle R, Yu X, Risser R, Baker RW *et al.* (2004) Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial. *Clinical Therapeutics* **26**, 125–134.

Shi L, Namjoshi MA, Zhang F, Gandhi G, Edgell ET, Tohen M *et al.* (2002) Olanzapine *versus* haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. *International Clinical Psychopharmacology* **17**, 227–237.

Simon GE, Bauer MS, Ludman EJ, Operskalski BH and Unutzer J (2007) Mood symptoms, functional impairment, and disability in people with bipolar disorder: specific effects of mania and depression. *Journal of Clinical Psychiatry* **68**, 1237–1245.

Slade M (2010) Mental illness and well-being: the central importance of positive psychology and recovery approaches. *BMC Health Services Research* **10**, 26.

Vojta C, Kinosian B, Glick H, Altshuler L and Bauer MS (2001) Self-reported quality of life across mood states in bipolar disorder. *Comprehensive Psychiatry* **42**, 190–195.

Ware JE, Kosinski M and Keller SD (1994) *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: The Health Institute, New England Medical Centre.

Ware JE, Snow KK, Kosinski M and Gandek B (1993) *SF-36 Health Survey: Manual and Interpretation Guide*. Boston, MA: The Health Institute, New England Medical Centre.

Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M *et al.* (2013) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disorders* **15**, 1–44.

Yatham LN, Lecrubier Y, Fieve RR, Davis KH, Harris SD and Krishnan AA (2004) Quality of life in patients with bipolar I depression: data from 920 patients. *Bipolar Disorders* **6**, 379–385.

Yen CF, Cheng CP, Huang CF, Yen JY, Ko CH and Chen CS (2008) Quality of life and its association with insight, adverse effects of medication and use of atypical antipsychotics in patients with bipolar disorder and schizophrenia in remission. *Bipolar Disorders* **10**, 617–624.

Young RC, Biggs JT, Ziegler VE and Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry* **133**, 429–435.

Zhang H, Wisniewski SR, Bauer MS, Sachs GS and Thase ME (2006) Comparisons of perceived quality of life across clinical states in bipolar disorder: data from the first 2000 Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) participants. *Comprehensive Psychiatry* **47**, 161–168.