

A clinician's guide to psychosocial functioning and quality of life in bipolar disorder.

Erin E. Michalak, Department of Psychiatry, University of British Columbia, Vancouver, Canada and Greg Murray, Faculty of Life and Social Sciences, Swinburne University of Technology, Hawthorn, Australia

**Insert page numbers

Introduction

Assessing outcome in bipolar disorder: A shifting paradigm

A rationale for assessing psychosocial functioning and QoL in clinical practice

Psychosocial functioning in bipolar disorder: An overview

Focus on: Work and bipolar disorder

QoL in bipolar disorder: An overview

Focus on: How impaired is QoL in BD?

Focus on: Does QoL vary across mood state in BD?

Focus on: Can QoL be impacted by treatment interventions for BD?

Focus on: What does qualitative data tell us about QoL in BD?

Incorporating psychosocial functioning and QoL scales into clinical practice

Tables

References

Introduction

Bipolar disorder (BD) is a complex, chronic condition that can be characterized by a wide variety of symptoms and marked variability in outcome. An individual with BD can experience episodes of depression, hypomania or mania, and indeed, can experience a mixture of emotional states or cycle rapidly between them. Variability also occurs in terms of the frequency and length of episodes experienced by individuals with BD over their lifetime, the severity and type of symptoms encountered, and the degree of inter-episode recovery achieved. The presence of subsyndromal features between episodes, however, is the rule rather than the exception (for example, Post et al. 2003a). Also, it is now appreciated that depression is the predominant mood symptom in BD. For example, Judd and colleagues' seminal prospective studies (Judd et al. 2002; Judd et al. 2003) of the natural course of BD (for average timeframes of over a decade) showed that individuals with BD type I experienced symptoms of depression for approximately 31% of weeks, compared with 10% of weeks for hypo/manic symptoms (Judd et al. 2003). Individuals with BD type II experienced depression for a staggering 52% of weeks, in comparison just over 1% of weeks for hypo/manic symptoms. Similar findings have been reported for the Stanley Foundation Bipolar Network (SFBN) (for further details regarding SFBN methodology, see (Leverich et al. 2001; Post et al. 2001) cohort, where individuals with BD reported approximately threefold more depressive symptoms compared to hypomanic or manic over a twelve month period (Altshuler et al. 2006; Post et al. 2003b).

Assessing outcome in BD: A shifting paradigm

Outcome in BD has traditionally been determined by the assessment of externally assessed clinical information, such as rates of relapse, the number of times a person is hospitalised or degree of symptom reduction on clinician-rated assessment scales. More recently, however, there has been discussion about the need for additional forms of assessment to measure response to treatment in this population. For example, Keck (2004) has suggested that "*Functional outcomes are more meaningful measures of*

response to treatment for bipolar disorder than are scores on various psychiatric rating scales” (Keck, Jr. 2004) (p. 25).

Psychosocial functioning describes a person’s ability to perform the tasks of daily life and to engage in mutual relationships with other people in ways that are gratifying to the individual and others, and that meet the needs of the community in which the person lives. A complementary measurement paradigm that is attracting increasing interest in the bipolar disorders field concerns the assessment of quality of life (QoL). The World Health Organization has described QoL as an “*individuals’ 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*” (The WHOQOL Group 1995). This broad conceptualization of QoL has been distinguished by some from the concept of ‘health-related quality of life’ (HRQOL), which is said to refer specifically to those aspects of an individual’s life that are impacted by their health or ill health. From our point of view, it is difficult to imagine life domains that are unaffected by an individual’s state of physical or emotional wellbeing, so we choose to use the term QoL over HRQOL. Furthermore, although the terms functioning and QoL are sometimes used interchangeably in the literature, many researchers agree that functional status and QoL are not identical constructs (Coons et al. 2000). Psychosocial functioning tends to refer to the assessment of a small number of behavioural domains, and functioning is generally considered to be a contributing factor in QoL. Further, the majority of psychosocial functioning scales are objective, rather than subjective measures. In comparison, the assessment of QoL is usually (but not always) conducted subjectively, and QoL scales tend to assess wellbeing in a wider variety of domains than do functioning scales.

Having provided brief definitions of psychosocial functioning and QoL (as we construe the constructs), we will now turn to providing a rationale for incorporating such scales into clinical practice.

A rationale for assessing psychosocial functioning and QoL in clinical practice

A strong argument can be made for the importance of including functioning and/or QoL measures when assessing outcome in BD clinically. Our rationale is based on several key observations:

1. Individuals with BD may give higher priority to improvements in functioning or QoL than improvements in symptoms;
2. Symptoms and functioning are not as closely related as we might assume;
3. There is evidence that deficits in functioning/QoL can *precede* episode onset and *predict* subsequent episodes;
4. Treatment interventions with equivalent efficacy in symptom reduction can have differential effects in improving functioning/QoL.

With respect to Point 1, it seems (from our clinical experience at least) that peoples' goals for treatment tend to be orientated towards markers of functional recovery, or global life quality. For example, when we initiate a course of cognitive behavioural therapy (CBT) with an individual with BD, we will typically begin with a session examining the person's individual goals for the course of treatment. No client to date has responded to this goal-setting exercise by stating that they would like to see their mean depression score drop by 50%! Instead, people tend to say things like: 'I need to stay in work; otherwise this bout of depression will succeed in consuming me'. Or, 'I need to keep my marriage together', or 'I want to be able to have fun and enjoy my life like I used to'. These are the types of goals by which people with mood disorders judge the success of our pharmacological and psychosocial treatment interventions, and we need to routinely incorporate the assessment of such outcomes into clinical practice, in addition to continuing to assess symptomatic outcomes. It is reasonable to expect that the treatment alliance will also benefit when clinicians share this more holistic viewpoint.⁶

In our as yet unpublished 'Self-management strategies in bipolar disorder' study, we have been using qualitative methods to investigate definitions of wellness in 'high functioning' individuals with BD (level of functioning is determined on the basis of a comprehensive psychosocial functioning assessment scale, the Multidimensional Scale

for Independent Functioning or MSIF (Jaeger, Berns, & Czobor 2003). When asked to define what ‘functioning well’ means to them, participants in the study have tended to provide complex descriptions of good functioning that go beyond regulation of symptoms. For example, they describe their need to feel self-confident, maintain their ability to have fun, have healthy social relationships, enjoy life, meet their goals and maintain their creativity.

With respect to Point 2, it is important to be aware that the relationship between symptoms and functioning/QoL is not always clear-cut; some individuals with BD appear to function well despite relatively severe symptoms, whilst others who could be deemed dysfunctional present with few symptoms. A relatively large body of evidence suggests that marked functional deficits often remain after symptomatic recovery in BD. For example, one study of first-episode patients (Tohen et al. 2000) reported that 98% of the sample achieved syndromal recovery within two years, compared to only 38% achieving functional recovery (defined as the proportion of patients who regained occupational and living situations equivalent to those they held prior to their episode), suggesting that the speed with which a person restores their functioning after an episode is influenced by more than disease state alone. Further, inter-episode functioning also frequently remain compromised in the condition (MacQueen, Young, & Joffe 2001). Available research indicates that 25-35% of individuals with BD continue to experience partial impairment in their work and social functioning; a similar proportion will exhibit extreme functional problems (Dion et al. 1988; Goldberg, Harrow, & Grossman 1995; Harrow et al. 1990; Tohen, Wateraux, & Tsuang 1990).

With respect to Point 3, there is now growing evidence that deficits in functioning/QoL can occur prior to the onset of a full episode. Research in the schizophrenia field, for example, has shown that individuals who are considered to be at risk for a first episode of psychosis (the sample were deemed to be in a ‘putative early prodromal state’) exhibited poorer QoL than healthy controls, and lower affective QoL than the first-episode patient comparison sample, suggesting that subjective QoL can be compromised prior to the

onset of first positive schizophrenia symptoms (Bechdolf et al. 2005). From a clinical standpoint, then, there is some early evidence that diminishing functioning or QoL could be a harbinger of hard times to come in some individuals who are at risk for developing a mental illness. A recent study in the BD literature has indicated that impaired psychosocial functioning can predict subsequent depressive, but not manic, symptoms in individuals with BD (Weinstock & Miller 2008).

With respect to Point 4, there is now evidence that pharmacological treatments with equivalent efficacy in relation to symptom relief can have quite different impacts on psychosocial functioning or QoL. For example, Shi and colleagues randomised 453 patients with acute mania to olanzapine or haloperidol (Shi et al., 2002). Although remission rates in the two intervention groups were similar at 6 and 12 weeks, olanzapine was associated with greater improvement in health functioning at both time points and greater impact on work functioning at 12 weeks. Omitting the measurement of functioning or QoL may, therefore result in the omission of important clinical data.

Having provided a rationale for incorporating the assessment of functioning and/or QoL into clinical practice, we will now move on to review some of the literature on psychosocial functioning in BD, focusing upon one area that may be particularly amenable to clinical intervention, the domain of work. If the reader is interested in exploring the scientific literature pertaining to other domains of functioning (for example, social or marital life), a review chapter can be found in Johnson and Leahy's book: Psychological treatment of bipolar disorder (Hammen & Cohen 2004).

Focus on: Work and bipolar disorder

Although the symptoms of BD have been recognised for centuries, attention has only fairly recently been directed towards improving our understanding of the impact of the condition upon psychosocial functioning. One important but often overlooked (or poorly captured) area of functioning is an individual's ability to work. At a basic level, this can be interpreted simply as a person's ability to obtain and maintain paid employment. At a

more complex level, it can refer to an individual's ability to engage in work, paid or unpaid, that they perceive to be meaningful, personally satisfying and in keeping with their educational achievements, expectations, skills or vocational aspirations. Although there is a far larger body of research addressing the relationship between employment and schizophrenia, several quantitative studies have now been conducted in bipolar populations, and have generally indicated that BD can have a profoundly negative impact upon occupational functioning.

In a review published in 2004, Dean and colleagues identified 14 quantitative studies that had assessed work impairment in patients with BD (Dean, Gerner, & Gerner 2004). The studies were quite heterogeneous, alternatively assessing degree of work impairment by rates of long-term unemployment, occupational functioning, absenteeism due to emotional or physical problems and reduced work performance. For example, several studies indicated that rates of employment are low in people with BD in comparison to those observed in the general population, and those observed in patients with other affective disorders. In one study that prospectively followed individuals (N=67) for 6 months following hospitalization for an episode of mania, 43% were employed during this time, with only 21% working at their expected level of employment, although 80% of the sample were considered to be symptom free or mildly symptomatic (Dion et al. 1988). Another prospective study reported that only 42% of a sample of 73 patients with BD were in continuous employment over a 1.7 year observation period (Harrow et al. 1990). When examining degree of work impairment by type of BD, research has indicated that BD type II is associated with similar levels of impairment as BD type I (Ruggero et al. 2007). The same study reported that one third of people with BD type II had missed over a year of work in the last five years due to the illness (although there was more absenteeism from work in individuals with BD type I, this difference appeared to be accounted for by more frequent episodes of hospitalization).

Several variables have been shown to be predictive of poor work functioning in patients with BD, including demographic or clinical characteristics and lack of social support. For example, Dickerson and colleagues (2004) examined variables associated with employment status in individuals (N=117) diagnosed with BD type I and II, including demographic variables, cognitive functioning, symptom severity and course of illness (Dickerson et al. 2004). Multivariate analysis indicated that current employment status was significantly associated with level of cognitive functioning, severity of symptoms, history of psychiatric hospitalization and level of maternal education. In other research, substance misuse and personality trait scores have been shown to be associated with degree of impairment in work functioning (Loftus & Jaeger 2006), although not at a multivariate level. Another interesting study of individuals (N=52) with BD type I found that the presence of a strong, supportive relationship was actually a stronger predictor of work functioning than clinical status (recent or current symptoms or number of previous hospitalizations) (Hammen, Gitlin, & Altshuler 2000). Similar results have been reported in other studies; level of current psychiatric symptoms does not reliably predict occupational functioning (Dion et al. 1988; Kuznir et al. 1996). Instead, for some people, there appears to be a marked time-lag between recovery from a mood episode and return to the workforce, if indeed that return occurs at all.

In order to better understand the effects of BD upon employment, it is important to take into consideration the ways in which these effects are experienced, and a small number of qualitative studies have now addressed this issue. In a notable study, Tse and Yeats (2002) assessed the factors related to successful employment in a relatively large sample (N=67) of people with BD in New Zealand (Tse & Yeats 2002). Two main factors were found to determine readiness to re/join the workforce: 1) recovery from their acute episode of BD and ii) goodness of fit between the individual, their job, the support available to them and wider contextual components. Specifically, having a sense of determination, good professional qualifications, a good work record, faith in God and good illness management skills were important individual factors in determining whether vocational integration was successful or not. Work factors related to the meaning and

value the person derived from their occupation, and the nature and structure of the job (for example, whether there was a balance between routine and flexibility). Perceived support consisted of either support within the workplace (from managers, colleagues or in terms of entitlement to leave) or wider social support (friends and family, professional or community support groups). Finally, wider contextual components included factors such as lack of perceived stigma towards people with psychiatric illness and appropriate governmental policies and legislation. Importantly, Tse and Yeats note that: *“being employed should not be viewed as the end of the rehabilitation process in itself. Achieving an employment status can potentially act as a catalyst to prompt the person concerned to further advance his/her career pursuits and recovery from BD”*.

In our own more recent qualitative study, we reported on the relationship between BD and work in participants in a variety of employment situations, ranging between those with no employment history through to those in highly skilled professional positions (Michalak et al. 2007b). Five main themes emerged from the data: lack of continuity in work history, loss, illness management strategies in the workplace, stigma and disclosure in the workplace, and interpersonal problems at work. Potential barriers for people with BD in the workplace and possible solutions for clinicians are provided in Table 1.

Having provided an overview of some of the research that has examined psychosocial functioning in BD, and having taken an in-depth look at one aspect of functioning (the work domain), we will now turn to examine research into QoL in BD.

QoL in bipolar disorder: An overview

The following section is intended to provide a succinct overview of some of the existing research into QoL in BD. For more a more theoretical analysis of the body of literature around QoL in BD see (Michalak et al. 2007a). Issues pertaining specifically to the relationship between bipolar depression and QoL are reviewed comprehensively in (Michalak et al. 2008).

Five systematic reviews of research into QoL in BD have been published to date – three aimed to be comprehensive (Dean, Gerner, & Gerner 2004; Michalak, Yatham, & Lam 2005; Namjoshi & Buesching 2001) and two focused specifically upon clinical trial data (Revicki et al. 2005; Michalak & Murray 2008). In the first of the reviews, Namjoshi and colleagues (2001) identified 10 studies assessing QoL published prior to 1999. Building on this work, Dean and colleagues (2004), described studies published prior to November 2002 that had assessed QoL, work-impairment or healthcare costs and utilization in patients with BD. This review applied a broad definition of QoL, including studies utilising scales that assessed single domains of functioning such as the Global Assessment of Functioning (GAF) (Endicott et al. 1976) scale. Using these criteria, the authors identified 65 studies, allowing them to conclude that: (i) the QoL of patients with BD is similar to that of patients with unipolar depression and equal or lower than that observed in patients with chronic medical conditions and, (ii) treatment interventions for BD have been shown to have a beneficial impact on life quality. In the most recent of the (comprehensive) reviews, we identified 28 studies when using relatively tight inclusion criteria (Michalak, Yatham, & Lam 2005). The studies were quite heterogeneous; several undertook to assess QoL during different phases of the disorder, for example, cross-sectional research that compared perceived QoL in euthymic, manic or depressed patients with BD. Other studies compared QoL in BD samples and other populations, (both psychiatric and medical groups). Finally, we identified a small number of studies that had used a QoL instrument to assess outcome in trials of treatment inventions for the condition. At the time of the review, the studies were also of variable scientific quality. Methodological shortcomings included small sample sizes, cross-sectional designs, unusual diagnostic methods or poorly differentiated diagnostic groups, use of poorly validated QoL instruments and lack of control for clinical variables.

Two reviews have assessed data from clinical trials that have incorporated QoL assessment scales. In the first, Revicki and colleagues (2005) focused on pre-2003 trials, finding just three studies that had included QoL outcome assessments. More recently, we conducted a review of studies published up to June 2006, identifying 10 clinical trials, 8

studies of pharmacological treatment interventions and 2 of psychosocial interventions (Michalak & Murray 2008). On the basis of this review, we concluded that:

- QoL outcome measures appear to provide additional important information over that provided by symptomatic measures;
- There is some evidence that QoL in BD improves relatively slowly after treatment;
- Emerging research into adjunctive psychosocial treatments suggests that even relatively brief interventions may have effects on QoL;
- Existing literature on QoL in BD is relatively immature. In particular, there is no current consensus about which QoL instruments are most appropriate for use as outcome measures (at the time of the review there was no disorder-specific measure to assess QoL in BD).

The following section will briefly review the literature on QoL in BD that may be of particular interest to the clinician, addressing four specific questions:

- 1) How impaired is QoL in BD?
- 2) Does QoL vary across mood state in BD?
- 3) Can QoL be impacted by treatment interventions for BD?
- 4) What does qualitative data tell us about QoL in BD?

Focus on: How impaired is QoL in bipolar disorder?

Several studies have attempted to ascertain the degree of impairment in QoL experienced by individuals with BD.

Unsurprisingly, QoL in bipolar populations appears to fall far below that observed in general population samples, at least in the realms of emotional or psychosocial well-being. For example, one study using the Medical Outcomes Study SF-36 (Ware et al. 1993), the most widely used QoL measure in this population to date, compared scores

between individuals with BD (N = 44) with previously reported norms for a general population sample (Arnold et al. 2000). The SF-36 contains 8 subscales that assess physical functioning, social functioning, role limitations (physical), role limitations (emotional), pain, mental health, general health, and vitality. The results of the study indicated that QoL was significantly compromised in people with BD in all SF-36 domains except physical functioning. .

In other research, Yatham and colleagues (Yatham et al. 2004) have compared QoL in individuals with BD type I (N=920) who were either currently depressed, or had experienced a recent episode of depression with general population norms. Scores were significantly lower across all scale domains in the bipolar group compared with norms reported for the US general population, with markedly lower scores in the mental health, vitality, social functioning and role emotional domains. Yatham and colleagues went on to compare these scores with those derived from seven large studies of QoL in patients with unipolar depression. Scores on four domains (general health, social functioning, role-physical and role-emotional) were lower than those observed in unipolar depression. In contrast, the unipolar samples tended to exhibit higher scores in the bodily pain domain.

Several studies have compared QoL in BD with QoL in other psychiatric populations. For example, the NEMESIS study compared SF-36 scores in 136 adults with BD with that observed in a variety of other psychiatric disorders (ten Have et al. 2002). Participants with BD showed significantly more impairment in most SF-36 domains compared with other participants. For example, in the domain of mental health, participants with BD type I experienced significantly lower scores than people with other mood, anxiety or substance use disorders. Other research (Chand et al. 2004; Atkinson, Zibin, & Chuang 1997; Goldberg & Harrow 2005) has compared QoL in patients with schizophrenia with that observed in patients with BD, but has to date generated mixed results (see Michalak et al. 2007a for a detailed review of this body of research).

Clinical take home message: Studies using a range of measures have generally confirmed that QoL is, in a range of domains and to a marked extent, lower amongst patients with BD than in the normal population. Beyond this commonsense finding, there is some evidence that QoL is poorer in BD than in other mood and anxiety disorders.

Focus on: Does QoL vary across mood state in BD?

The course of BD can include a range of abnormal mood states, including the co-occurrence of extremes of mania and depression. It is reasonable to expect that QoL would be negatively affected by the depressive episodes of BD, and as noted above, the relatively large study of Yatham and colleagues (2004) did find remarkably low QoL amongst individuals with BD who were either depressed or had experienced a recent episode of depression. Other recent research has indicated that QoL may be more impaired in individuals with BD II than in those with BD I, further underscoring the deleterious effect of depression in BD upon life quality (Maina et al. 2007).

The complex issue of QoL across clinical states in BD has recently been addressed more comprehensively in a cross-sectional study of the first 2000 participants enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder, or STEP-BD (Zhang et al. 2006). STEP-BD, a large multicentre prospective, naturalistic study that features several embedded randomized-controlled trials measured QoL via the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al. 1993) and the SF-36 (Ware et al. 1993). In addition, the study assessed a comprehensive battery of possible confounders, including demographic and socioeconomic factors, family history, psychiatric comorbidity, clinical characteristics, personality, social support, negative life events and attributional style. The primary finding from the analysis was that depressive symptoms were strongly associated with poorer emotional QoL, even after relevant confounding variables were controlled for. Conversely, apparent “supranormal” QoL reported in patients with hypomania or mania (compared to that of euthymic patients) disappeared after statistical control. Related to this are results from an earlier study which found negative QoL impacts of “elevated” mood states. Vojta and colleagues

administered a short form of the SF-36 to individuals with BD who were in a manic/hypomanic episode (N=16), depressive episode (N=26), mixed episode (N=14) or who were euthymic (N=30), finding that individuals with mania/hypomania showed significantly lower QoL scores than those who were euthymic, and depressed or mixed episodes were associated with significantly poorer QoL again (Vojta et al. 2001).

Clinical take home message: Although manic or hypomanic symptoms distinguish BD from unipolar depression in the current classification, much of the morbidity and mortality in BD appears to be a consequence of the depressive phase of the disorder. QoL in individuals with BD is most impaired during episodes of depression, but also appears to be lowered in manic and possibly even hypomanic states

Focus on: Can QoL be impacted by treatment interventions for BD?

In a review of the literature (Michalak, Yatham, & Lam 2005) we identified 10 treatment outcome studies that had incorporated a QoL outcome measure: 8 clinical trials that examined pharmacological interventions for BD and 2 studies that assessed non-pharmacological interventions. The following section will review key findings from these studies.

Namjoshi and colleagues have conducted a series of studies examining the efficacy of olanzapine as a treatment for BD. In the first of these, Namjoshi and colleagues (Namjoshi et al. 2002) evaluated the impact of acute (3-week) treatment with olanzapine or placebo and long-term (49-week open label) treatment of BD type I (manic/mixed). During the acute-phase treatment period, treatment-related improvements in QoL were only apparent for the physical functioning domain of the SF-36. Improvement in other aspects of QoL (specifically, pain, vitality, general health and social functioning) occurred during the open label treatment period, indicating that olanzapine may have a relatively rapid effect in terms of improving physical functioning in patients with acute mania, but other QoL domains may be slower to respond to treatment. Shi and colleagues compared the treatment effects of olanzapine and haloperidol in individuals

with acute mania (N=453) (Shi et al. 2002; Tohen et al. 2003). During acute treatment, significantly greater improvement in five of the SF-36 domains was apparent in the olanzapine group. Superiority of olanzapine over haloperidol persisted over the study's 6-week continuation phase, during which time improvements in work and household functioning also became apparent. Other research has examined the effects of adding olanzapine to lithium or valproate in patients with BD (N=224) (Namjoshi et al. 2004). Combination therapy was associated with better outcome in several QoL domains compared to lithium or valproate monotherapy. The SF-36 and a broader QoL scale were used in a study comparing the benefits of olanzapine alone versus an olanzapine-fluoxetine combination or placebo (Shi et al. 2004). Compared with placebo, patients who received olanzapine showed greater improvement at 8 weeks in SF-36 mental health summary scores, and three domain scores. The combination group fared significantly better in terms of QoL improvement than the olanzapine-alone group.

The Q-LES-Q has been administered at baseline (hospital discharge), 6 and 12 weeks in a comparison of divalproex sodium and olanzapine in the treatment of acute mania (Revicki et al. 2003). No significant treatment effects were detected in Q-LES-Q scores in the study, although only 52 (43%) of the 120 patients randomized to either divalproex or olanzapine completed the QoL instrument. The authors reported an association between weight gain and poorer change scores in the physical, leisure, and general activities domains of the Q-LES-Q at 6 weeks (but not at 12 weeks). Negative correlations were reported between increased weight (at 6 weeks) and overall life satisfaction, physical health, mood, general activities and satisfaction with medication on the Q-LES-Q. More recent research has also reported an association between increased weight and lower QoL (as measured by the SF-36 and a weight-related QoL scale) in patients with BD (Kolotkin et al. 2008).

Finally, QoL data have now been published from the BOLDER study (Calabrese et al. 2005; Endicott et al. 2007). BOLDER was a large, 8-week, multicenter, double-blind, randomized, fixed-dose, placebo-controlled monotherapy study of quetiapine (600 or 300 mg/day) versus placebo in outpatients with DSM-IV bipolar I or bipolar II disorder, with

or without rapid cycling, in a major depressive episode. The study administered the 16-item short form of the Q-LES-Q (Q-LES-Q SF) at baseline, weeks 4 and 8 to assess QoL, finding 12 and 11 point increase in Q-LES-Q SF scores at last assessment in the high and low dose groups respectively, compared to a 7-point change in the placebo group (i.e. significantly greater improvement in QoL in both groups after 8 weeks of treatment compared to placebo). The 12-point change in Q-LES-Q SF score observed in the BOLDER study is in keeping with outcome data from other depression studies (Kocsis et al. 1997; Miller et al. 1998), indicating that QoL in patients with BD is amenable to relatively rapid change, even when study inclusion criteria are broadened to include greater diagnostic heterogeneity, such as rapid cycling and BD type II patients. In a more recent publication, (Endicott et al. 2007), the minimal clinically important difference (MCID) for the Q-LES-Q SF was calculated; for a moderate effect size (0.5) a minimum score of 7 points on the Q-LES-Q would be required. For a large effect size (0.8) a score of 10 would be necessary. Both quetiapine groups showed effect sizes in the moderate range (0.4-0.5) indicating that the intervention had a clinically meaningful impact upon QoL, as well as a statistically significant impact. MCID determined by a 1-point decrease on the Clinical Global Impression-Severity scale (CGI-S) (Guy 1976) was 15 points on the Q-LES-Q, or a decrease of 12 points to be assessed as 'minimally improved' on the same scale.

Although pharmacology forms the bedrock of treatment for BD, there is a clear need for other treatment modalities that augment the effects of medication in this complex condition. Over the last two decades, we have seen an upsurge of interest in examining the role of psychological interventions as an adjunct to the pharmacological treatment of BD, with most of this research examining the efficacy of psychotherapy as a treatment intervention. Several multi-modal psychotherapeutic interventions for BD have been developed, such as Family Focused Treatment (FFT) (Miklowitz et al. 1988; Miklowitz & Goldstein 1997), Interpersonal and Social Rhythm Therapy (Frank, Swartz, & Kupfer 2000) and CBT (Otto, Reilly-Harrington, & Sachs 2003). Surprisingly few (Patelis-Siotis et al. 2001; Dogan & Sabanciogullari 2003; Michalak et al. 2005) studies of psychosocial treatment interventions for BD, however, have used QoL measures to assess

outcome. This may be an important oversight, because it may be in functional/QoL outcomes that psychosocial interventions make their strongest contribution.

Clinical take home message: Research using QoL as an outcome measure has indicated that QoL measures provide additional important information over that provided by symptom measures. Although based on a small number of studies, there is some evidence that QoL improves relatively slowly after treatment (perhaps paralleling functional recovery).

Focus on: What does qualitative data tell us about QoL in BD?

As part of development of a disorder-specific scale to assess QoL in BD, we conducted a series of qualitative interviews to identify the ways in which BD impacts upon QoL (Michalak et al. 2006). We sought the views of a representative sample of people diagnosed with both BD I and BD II. Clinical characteristics of the sample ranged widely between individuals who had been clinically stable for several years through to inpatients who were recovering from a severe episode of depression or mania. The results of the study provided some interesting initial data concerning the impact of BD upon QoL. The majority of participants described how the condition had had a profoundly negative effect upon their life quality, often having serious and enduring effects on their ability to find meaningful work, become educated, maintain their independence, have healthy social and intimate relationships and have a coherent sense of self. Having said this, we also interviewed a number of people who were functioning exceptionally well despite their diagnosis; a minority of people even espoused the view that their condition had opened up new doors of opportunity for them, for example, in terms of positively changing their career paths or social networks. On the whole, however, even these individuals described having undergone several years of hardship and adjustment before getting 'back on track'.

Respondents described a wide variety of factors that influenced their QoL, including but not limited to: side effects of medications, occupation, education, physical functioning,

environment, healthcare factors, leisure activities, routine and sexuality. Some of the factors raised (for example, independence, identity, stigma and disclosure, and spirituality) are not frequently examined in relation to QoL, yet they appear to have a significant impact upon peoples' ability to live their lives to the full in the context of BD. We are continuing to develop the QoL.BD in close consultation with individuals with BD in the hope of maximizing the validity of the resulting scale.

Clinical take home message: Qualitative research has indicated that QoL in BD is impacted by a wide range of influences over and above the degree of symptoms experienced. It is important to invite patients to consider these factors when developing treatment plans or assessing the impact of treatment interventions.

Incorporating psychosocial functioning and QoL scales into clinical practice

Chapter **x** of this volume makes specific recommendations for psychosocial functioning and QoL scales that are appropriate for use in routine clinical practice, in particular, recommending the use of the Q-LES-Q SF (note that the short form of the Q-LES-Q has the same content as the General Activities section of the regular Q-LES-Q) to assess QoL and the MICRECC version of the GAF (Niv et al. 2007) or the FAST (Rosa et al. 2007) to assess functioning in individuals with BD. There are currently no consensus guidelines for the clinical measurement of outcomes for psychosocial functioning or QoL in BD. Drawing on our own clinical experience, research and related literature, however, we are able to make provisional recommendations for monitoring psychosocial functioning or QoL in clinical practice (Table 2).

Concluding remarks

There has been a recent upsurge of interest in defining and measuring psychosocial functioning and QoL in BD. Although research is at an early stage, there is no doubt that symptom measures alone constitute a limited assessment of BD outcomes, and more valid understandings (scientifically and clinically) are achieved with the addition of QoL

measures. Existing research has revealed, for example, the marked negative impact of BD on QoL, a disjunction between symptom level and functional outcome in BD, and the apparent primacy of depressive symptoms over hypo/manic in BD QoL outcomes. The emerging body of research clearly suggests that it is both feasible and important to assess functioning and QoL in patients with this complex psychiatric condition. For the practicing clinician, routinely adding a QoL measure to outcome monitoring will enrich understanding of patient progress, with consequent benefits for tailoring treatment regimens and for the therapeutic alliance.

Table 2. Provisional recommendations for monitoring psychosocial functioning/QoL in BD in clinical practice

- Only use assessment scales that have demonstrated validity in this population
- In the absence of a disorder-specific scale for QoL in BD, it is appropriate to use QoL scales developed for individuals with unipolar depression or other psychiatric conditions. The Q-LES-Q is the most extensively used scale of this type; it can be recommended for use in patients with BD; it is available for clinical use in long and short forms (see Chapter x for reprint of the short form) and shows sound psychometric properties, including responsiveness.
- When assessing functioning/QoL, also assess symptoms of depression and hypomania or mania using valid, clinically appropriate assessment scales
- While you might expect an individual's symptoms of depression or hypomania to respond to treatment over a relatively short period of time, changes in some functioning/QoL domains (e.g., social or occupational wellbeing) take longer to occur. Therefore assess functioning/QoL over longer periods of time than you would traditionally assess symptomatic outcome
- Best practice suggests annual monitoring of functioning/QoL in individuals whose condition is stable to observe the interaction between developmental stages and the illness itself

Table 1. Improving functioning in the workplace: Tips for the clinician

Issue

Individual believes s/he has little perceived control over moods in the workplace.

Possible role for clinician

Assist the individual in developing a strategy for recognising and acting upon prodromes in the workplace

Issue

The individual is ambivalent about/non-adherent with medications for BD due to a sense of loss for periods of increased productivity at work during highs.

Possible role for clinician

Conduct cost-benefit analysis with individual. For example, encourage them to consider: i) Is the increased productivity worthwhile if the episode escalates into a full mania? ii) Are there potential physiological/psychosocial consequences of experiencing repeated mood episodes? iii) Is the increased productivity always associated with good quality, appropriate work? iv) Is the individual's creativity/productivity definitely hampered by mood stabilizing medications?

Issue

BD may impact upon individual's ability to engage in what they view as meaningful work

Possible role for clinician

Work with individual to take a creative approach towards identifying rewarding and meaningful forms of employment (for example, volunteer work, self-employment, competitive employment, sheltered work, transitional work or casual work (Tryssenaar 1998).

Issue

Individual feels hopeless about their career future.

Possible role for clinician

Encourage client to remember their long-term work goals; while initial work placements may appear demeaning or unrewarding, these may be impermanent phases that will be replaced by more satisfying and positive employment opportunities as their stamina, strengths and capabilities improve over time.

Issue

Individual is overwhelmed by the negative impacts of their BD upon their employment.

Possible role for clinician

Ask individual to consider whether there are any positive impacts of BD upon their work life. For example, has having BD opened up new avenues of employment? Does having the condition give them greater empathy for colleagues struggling with mental health problems? Do they consider themselves more resilient than they were before their diagnosis?

Issue

Individual is struggling with symptoms of BD in the workplace.

Possible role for clinician

Explore possible management strategies to impede cascade into increasing severity of episode. For example, is it likely to be beneficial if the individual reduces their workload, changes their work activities, enlists the help of trusted co-workers or seeks further support from their healthcare/social support system?

Issue

Individual is concerned about stigma in the workplace.

Possible role for clinician

Explore potential coping strategies, for example, waiting for a period of time before disclosing diagnosis in a new job, garnering support from a trusted co-worker.

References

- Altshuler, L. L., Post, R. M., Black, D. O., Keck, P. E., Jr., Nolen, W. A., Frye, M. A., Suppes, T., Grunze, H., Kupka, R. W., Leverich, G. S., McElroy, S. L., Walden, J., & Mintz, J. 2006, "Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study", *J.Clin.Psychiatry*, vol. 67, no. 10, pp. 1551-1560.
- Arnold, L. M., Witzeman, K. A., Swank, M. L., McElroy, S. L., & Keck, P. E., Jr. 2000, "Health-related quality of life using the SF-36 in patients with bipolar disorder compared with patients with chronic back pain and the general population", *J.Affect.Disord.*, vol. 57, no. 1-3, pp. 235-239.
- Atkinson, M., Zibin, S., & Chuang, H. 1997, "Characterizing quality of life among patients with chronic mental illness: a critical examination of the self-report methodology", *Am.J.Psychiatry*, vol. 154, no. 1, pp. 99-105.
- Bechdolf, A., Pukrop, R., Kohn, D., Tschinkel, S., Veith, V., Schultze-Lutter, F., Ruhrmann, S., Geyer, C., Pohlmann, B., & Klosterkötter, J. 2005, "Subjective quality of life in subjects at risk for a first episode of psychosis: a comparison with first episode schizophrenia patients and healthy controls", *Schizophr.Res.*, vol. 79, no. 1, pp. 137-143.
- Calabrese, J. R., Keck, P. E., Jr., Macfadden, W., Minkwitz, M., Ketter, T. A., Weisler, R. H., Cutler, A. J., McCoy, R., Wilson, E., & Mullen, J. 2005, "A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression", *Am.J.Psychiatry*, vol. 162, no. 7, pp. 1351-1360.
- Chand, P. K., Mattoo, S. K., & Sharan, P. 2004, "Quality of life and its correlates in patients with bipolar disorder stabilized on lithium prophylaxis", *Psychiatry Clin.Neurosci.*, vol. 58, no. 3, pp. 311-318.
- Coons, S. J., Rao, S., Keininger, D. L., & Hays, R. D. 2000, "A comparative review of generic quality-of-life instruments", *Pharmacoeconomics.*, vol. 17, no. 1, pp. 13-35.
- Dean, B. B., Gerner, D., & Gerner, R. H. 2004, "A systematic review evaluating health-related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder", *Curr.Med.Res.Opin.*, vol. 20, no. 2, pp. 139-154.

Dickerson, F. B., Boronow, J. J., Stallings, C. R., Origoni, A. E., Cole, S., & Yolken, R. H. 2004, "Association between cognitive functioning and employment status of persons with bipolar disorder", *Psychiatr.Serv.*, vol. 55, no. 1, pp. 54-58.

Dion, G. L., Tohen, M., Anthony, W. A., & Waternaux, C. S. 1988, "Symptoms and functioning of patients with bipolar disorder six months after hospitalization", *Hosp.Community Psychiatry*, vol. 39, no. 6, pp. 652-657.

Dogan, S. & Sabanciogullari, S. 2003, "The effects of patient education in lithium therapy on quality of life and compliance", *Arch.Psychiatr.Nurs.*, vol. 17, no. 6, pp. 270-275.

Endicott, J., Nee, J., Harrison, W., & Blumenthal, R. 1993, "Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure", *Psychopharmacol.Bull.*, vol. 29, no. 2, pp. 321-326.

Endicott, J., Rajagopalan, K., Minkwitz, M., & 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", *Int.Clin.Psychopharmacol.*, vol. 22, no. 1, pp. 29-37.

Endicott, J., Spitzer, R. L., Fleiss, J. L., & Cohen, J. 1976, "The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance", *Archives of General Psychiatry*, vol. 33, no. 6, pp. 766-771.

Frank, E., Swartz, H. A., & Kupfer, D. J. 2000, "Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder", *Biol.Psychiatry*, vol. 48, no. 6, pp. 593-604.

Goldberg, J. F. & Harrow, M. 2005, "Subjective life satisfaction and objective functional outcome in bipolar and unipolar mood disorders: a longitudinal analysis", *J.Affect.Disord.*, vol. 89, no. 1-3, pp. 79-89.

Goldberg, J. F., Harrow, M., & Grossman, L. S. 1995, "Course and outcome in bipolar affective disorder: a longitudinal follow-up study", *Am.J.Psychiatry*, vol. 152, no. 3, pp. 379-384.

Guy, W. 1976, *ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338*. US Department of Health, Education and Welfare, Rockville, MD.

Hammen, C. & Cohen, A. N. 2004, "Psychosocial functioning," in *Psychological treatment of bipolar disorder*, S. L. Johnson & R. L. Leahy, eds., The Guilford Press, New York, pp. 17-34.

Hammen, C., Gitlin, M., & Altshuler, L. 2000, "Predictors of work adjustment in bipolar I patients: a naturalistic longitudinal follow-up", *J.Consult Clin.Psychol.*, vol. 68, no. 2, pp. 220-225.

Harrow, M., Goldberg, J. F., Grossman, L. S., & Meltzer, H. Y. 1990, "Outcome in manic disorders. A naturalistic follow-up study", *Arch.Gen.Psychiatry*, vol. 47, no. 7, pp. 665-671.

Jaeger, J., Berns, S. M., & Czobor, P. 2003, "The multidimensional scale of independent functioning: a new instrument for measuring functional disability in psychiatric populations", *Schizophr.Bull.*, vol. 29, no. 1, pp. 153-168.

Judd, L. L., Akiskal, H. S., Schettler, P. J., Coryell, W., Endicott, J., Maser, J. D., Solomon, D. A., Leon, A. C., & Keller, M. B. 2003, "A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder", *Arch.Gen.Psychiatry*, vol. 60, no. 3, pp. 261-269.

Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Maser, J., Solomon, D. A., Leon, A. C., Rice, J. A., & Keller, M. B. 2002, "The long-term natural history of the weekly symptomatic status of bipolar I disorder", *Arch.Gen.Psychiatry*, vol. 59, no. 6, pp. 530-537.

Keck, P. E., Jr. 2004, "Defining and improving response to treatment in patients with bipolar disorder", *J.Clin.Psychiatry*, vol. 65 Suppl 15, pp. 25-29.

Kocsis, J. H., Zisook, S., Davidson, J., Shelton, R., Yonkers, K., Hellerstein, D. J., Rosenbaum, J., & Halbreich, U. 1997, "Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: psychosocial outcomes", *Am.J.Psychiatry*, vol. 154, no. 3, pp. 390-395.

Kolotkin, R. L., Corey-Lisle, P. K., Crosby, R. D., Swanson, J. M., Tuomari, A. V., L'italien, G. J., & Mitchell, J. E. 2008, "Impact of obesity on health-related quality of life in schizophrenia and bipolar disorder", *Obesity.(Silver.Spring)*, vol. 16, no. 4, pp. 749-754.

Kusznir, A., Scott, E., Cooke, R. G., & Young, L. T. 1996, "Functional consequences of bipolar affective disorder: An occupational therapy perspective.", *Canadian Journal of Occupational Therapy* no. 63, pp. 313-322.

Leverich, G. S., Nolen, W. A., Rush, A. J., McElroy, S. L., Keck, P. E., Denicoff, K. D., Suppes, T., Altshuler, L. L., Kupka, R., Kramlinger, K. G., & Post, R. M. 2001, "The Stanley Foundation Bipolar Treatment Outcome Network. I. Longitudinal methodology", *J.Affect.Disord.*, vol. 67, no. 1-3, pp. 33-44.

Loftus, S. T. & Jaeger, J. 2006, "Psychosocial outcome in bipolar I patients with a personality disorder", *J.Nerv.Ment.Dis.*, vol. 194, no. 12, pp. 967-970.

MacQueen, G. M., Young, L. T., & Joffe, R. T. 2001, "A review of psychosocial outcome in patients with bipolar disorder", *Acta Psychiatr.Scand.*, vol. 103, no. 3, pp. 163-170.

Maina, G., Albert, U., Bellodi, L., Colombo, C., Faravelli, C., Monteleone, P., Bogetto, F., Cassano, G. B., & Maj, M. 2007, "Health-related quality of life in euthymic bipolar disorder patients: differences between bipolar I and II subtypes", *J.Clin.Psychiatry*, vol. 68, no. 2, pp. 207-212.

Michalak, E. E., Murray, G., Young, A., & Lam, R. W. 2007a, "Quality of life impairment in bipolar disorder.," in *Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders. New Perspectives on Research and Treatment.*, M. Ritsner & A. G. Awad, eds., Springer, Dordrechht, The Netherlands., pp. 253-274.

Michalak, E. E., Murray, G., Young, A. H., & Lam, R. W. 2008, "Burden of bipolar depression : impact of disorder and medications on quality of life", *CNS.Drugs*, vol. 22, no. 5, pp. 389-406.

Michalak, E. E. & Murray, G. W. 2008, "Using quality of life as an outcome measure in patients with bipolar disorder", *Aspects of Affect*, vol. 2, no. 2.

Michalak, E. E., Yatham, L. N., Kolesar, S., & Lam, R. W. 2006, "Bipolar disorder and quality of life: a patient-centered perspective", *Qual.Life Res.*, vol. 15, no. 1, pp. 25-37.

Michalak, E. E., Yatham, L. N., & Lam, R. W. 2005, "Quality of life in bipolar disorder: A review of the literature.", *Health and Quality of Life Outcomes.*, vol. 3, no. 72.

Michalak, E. E., Yatham, L. N., Maxwell, V., Hale, S., & Lam, R. W. 2007b, "The impact of bipolar disorder upon work functioning: a qualitative analysis", *Bipolar.Disord.*, vol. 9, no. 1-2, pp. 126-143.

Michalak, E. E., Yatham, L. N., Wan, D. D., & Lam, R. W. 2005, "Perceived quality of life in patients with bipolar disorder. Does group psychoeducation have an impact?", *Can.J.Psychiatry*, vol. 50, no. 2, pp. 95-100.

Miklowitz, D. J. & Goldstein, M. J. 1997, *Bipolar Disorder: A Family-focused treatment approach* Guilford Press, New York.

Miklowitz, D. J., Goldstein, M. J., Nuechterlein, K. H., Snyder, K. S., & Mintz, J. 1988, "Family factors and the course of bipolar affective disorder", *Arch.Gen.Psychiatry*, vol. 45, no. 3, pp. 225-231.

Miller, I. W., Keitner, G. I., Schatzberg, A. F., Klein, D. N., Thase, M. E., Rush, A. J., Markowitz, J. C., Schlager, D. S., Kornstein, S. G., Davis, S. M., Harrison, W. M., & Keller, M. B. 1998, "The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine", *J.Clin.Psychiatry*, vol. 59, no. 11, pp. 608-619.

Namjoshi, M. A. & Buesching, D. P. 2001, "A review of the health-related quality of life literature in bipolar disorder", *Qual.Life Res.*, vol. 10, no. 2, pp. 105-115.

Namjoshi, M. A., Rajamannar, G., Jacobs, T., Sanger, T. M., Risser, R., Tohen, M. F., Breier, A., & Keck, P. E. 2002, "Economic, clinical, and quality-of-life outcomes associated with olanzapine treatment in mania. Results from a randomized controlled", *J.Affect.Disord.*, vol. 69, no. 1-3, pp. 109-118.

Namjoshi, M. A., Risser, R., Shi, L., Tohen, M., & Breier, A. 2004, "Quality of life assessment in patients with bipolar disorder treated with olanzapine added to lithium or valproic acid", *J.Affect.Disord.*, vol. 81, no. 3, pp. 223-229.

Niv, N., Cohen, A. N., Sullivan, G., & Young, A. S. 2007, "The MIRECC version of the Global Assessment of Functioning scale: reliability and validity", *Psychiatr.Serv.*, vol. 58, no. 4, pp. 529-535.

Otto, M. W., Reilly-Harrington, N., & Sachs, G. S. 2003, "Psychoeducational and cognitive-behavioral strategies in the management of bipolar disorder", *J.Affect.Disord.*, vol. 73, no. 1-2, pp. 171-181.

Patelis-Siotis, I., Young, L. T., Robb, J. C., Marriott, M., Bieling, P. J., Cox, L. C., & Joffe, R. T. 2001, "Group cognitive behavioral therapy for bipolar disorder: a feasibility and effectiveness study", *J.Affect.Disord.*, vol. 65, no. 2, pp. 145-153.

Post, R. M., Denicoff, K. D., Leverich, G. S., Altshuler, L. L., Frye, M. A., Suppes, T. M., Rush, A. J., Keck, P. E., Jr., McElroy, S. L., Luckenbaugh, D. A., Pollio, C., Kupka, R., & Nolen, W. A. 2003a, "Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method", *J.Clin.Psychiatry*, vol. 64, no. 6, pp. 680-690.

Post, R. M., Leverich, G. S., Altshuler, L. L., Frye, M. A., Suppes, T. M., Keck, P. E., Jr., McElroy, S. L., Kupka, R., Nolen, W. A., Grunze, H., & Walden, J. 2003b, "An overview of recent findings of the Stanley Foundation Bipolar Network (Part I)", *Bipolar.Disord.*, vol. 5, no. 5, pp. 310-319.

Post, R. M., Nolen, W. A., Kupka, R. W., Denicoff, K. D., Leverich, G. S., Keck, P. E., Jr., McElroy, S. L., Rush, A. J., Suppes, T., Altshuler, L. L., Frye, M. A., Grunze, H., & Walden, J. 2001, "The Stanley Foundation Bipolar Network. I. Rationale and methods", *Br.J.Psychiatry Suppl*, vol. 41, p. s169-s176.

Revicki, D. A., Matza, L. S., Flood, E., & Lloyd, A. 2005, "Bipolar disorder and health-related quality of life: review of burden of disease and clinical trials", *Pharmacoeconomics.*, vol. 23, no. 6, pp. 583-594.

Revicki, D. A., Paramore, L. C., Sommerville, K. W., Swann, A. C., & Zajecka, J. M. 2003, "Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: health-related quality of life and medical cost outcomes", *Journal of Clinical Psychiatry*, vol. 64, no. 3, pp. 288-294.

Rosa, A. R., Sanchez-Moreno, J., Martinez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van, R. W., yuso-Mateos, J. L., Kapczinski, F., & Vieta, E. 2007, "Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder", *Clin.Pract.Epidemol.Ment.Health*, vol. 3, p. 5.

Ruggero, C. J., Chelminski, I., Young, D., & Zimmerman, M. 2007, "Psychosocial impairment associated with bipolar II disorder", *J.Affect.Disord.*, vol. 104, no. 1-3, pp. 53-60.

Shi, L., Namjoshi, M. A., Swindle, R., Yu, X., Risser, R., Baker, R. W., & Tohen, M. 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", *Clin.Ther.*, vol. 26, no. 1, pp. 125-134.

Shi, L., Namjoshi, M. A., Zhang, F., Gandhi, G., Edgell, E. T., Tohen, M., Breier, A., & Haro, J. M. 2002, "Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status", *Int.Clin.Psychopharmacol.*, vol. 17, no. 5, pp. 227-237.

ten Have, M., Vollebergh, W., Bijl, R., & Nolen, W. A. 2002, "Bipolar disorder in the general population in The Netherlands (prevalence, consequences and care utilisation): results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS)", *J.Affect.Disord.*, vol. 68, no. 2-3, pp. 203-213.

The WHOQOL Group 1995, "The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization.", *Soc.Sci.Med.*, vol. 41, no. 10, pp. 1403-1409.

Tohen, M., Goldberg, J. F., Gonzalez-Pinto Arrillaga, A. M., Azorin, J. M., Vieta, E., Hardy-Bayle, M. C., Lawson, W. B., Emsley, R. A., Zhang, F., Baker, R. W., Risser, R. C., Namjoshi, M. A., Evans, A. R., & Breier, A. 2003, "A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania", *Arch.Gen.Psychiatry*, vol. 60, no. 12, pp. 1218-1226.

Tohen, M., Hennen, J., Zarate, C. M., Jr., Baldessarini, R. J., Strakowski, S. M., Stoll, A. L., Faedda, G. L., Suppes, T., Gebre-Medhin, P., & Cohen, B. M. 2000, "Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features", *Am.J.Psychiatry*, vol. 157, no. 2, pp. 220-228.

Tohen, M., Waternaux, C. M., & Tsuang, M. T. 1990, "Outcome in Mania. A 4-year prospective follow-up of 75 patients utilizing survival analysis", *Arch.Gen.Psychiatry*, vol. 47, no. 12, pp. 1106-1111.

Tryssenaar, J. 1998, "Vocational exploration and employment and psychosocial disabilities," in *Psychosocial Occupational Therapy: A Holistic Approach.*, Singular Publishing Group., San Diego, CA., pp. 351-373.

Tse, S. & Yeats, M. 2002, "What helps people with bipolar affective disorder succeed in employment: a grounded theory approach", *Work*, vol. 19, no. 1, pp. 47-62.

Vojta, C., Kinosian, B., Glick, H., Altshuler, L., & Bauer, M. S. 2001, "Self-reported quality of life across mood states in bipolar disorder", *Compr.Psychiatry*, vol. 42, no. 3, pp. 190-195.

Ware, J. E., Snow, K. K., Kosinski, M., & Gandek, B. SF-36 Health Survey: Manual and interpretation guide. 1993. Boston, MA, The Health Institute.

Weinstock, L. M. & Miller, I. W. 2008, "Functional impairment as a predictor of short-term symptom course in bipolar I disorder", *Bipolar.Disord.*, vol. 10, no. 3, pp. 437-442.

Yatham, L. N., Lecrubier, Y., Fieve, R. R., Davis, K. H., Harris, S. D., & Krishnan, A. A. 2004, "Quality of life in patients with bipolar I depression: data from 920 patients", *Bipolar Disord.*, vol. 6, no. 5, pp. 379-385.

Zhang, H., Wisniewski, S. R., Bauer, M. S., Sachs, G. S., & Thase, M. E. 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", *Compr.Psychiatry*, vol. 47, no. 3, pp. 161-168.