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Stressful life events predict delayed functional recovery following treatment for mania in bipolar disorder

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Abstract

Identifying predictors of functional recovery in bipolar disorder is critical to treatment efforts to help patients re-establish premorbid levels of role adjustment following an acute manic episode. The current study examined the role of stressful life events as potential obstacles to recovery of functioning in various roles. 65 patients with bipolar I disorder participated in a longitudinal study of functional recovery following clinical recovery from a manic episode. Stressful life events were assessed as predictors of concurrent vs. delayed recovery of role functioning in 4 domains (friends, family, home duties, work/school). Despite clinical recovery, a subset of patients experienced delayed functional recovery in various role domains. Moreover, delayed functional recovery was significantly associated with presence of one or more stressors in the prior 3 months, even after controlling for mood symptoms. Presence of a stressor predicted longer time to functional recovery in life domains, up to 112 days in work/school. Interventions that provide monitoring, support, and problem-solving may be needed to help prevent or mitigate the effects of stress on functional recovery.

Keywords

bipolar; mania; stress; functional recovery

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1. Introduction

Bipolar disorder is a disabling recurrent psychiatric illness that affects approximately 1% of the world's population (Goodwin and Jamison, 2007). Many individuals with bipolar disorder do not fully recover clinically between episodes, and continue to have residual symptomatology even if not in a diagnosable episode (Gitlin et al., 1995; Judd et al., 2002). Furthermore, studies have demonstrated that many clinically recovered individuals with bipolar disorder continue to have significant functional impairment (Keck et al., 1998; Hammen et al., 2000; Tohen et al., 2000, 2003; Altshuler et al., 2002a, 2006) with substantial numbers of people with bipolar disorders experiencing social and relational difficulties as well as significant problems in occupational roles. For example, studies that examined individuals after a hospitalization for mania have provided evidence that functional disability persists in up to 60% of patients, even when syndromal recovery had been attained (Harrow et al., 1990; Tohen et al., 1990, 2003; O'Connell et al., 1991; Keller et al., 1993; Goldberg et al., 1995; Cooke et al. 1996; Keck et al., 1998; MacQueen et al., 1997).

There has been considerable research aimed at understanding the clinical course of bipolar disorder, much of it based on naturalistic longitudinal and controlled treatment outcome studies of syndromal recovery and recurrence of depressive and manic episodes. Despite wide differences in research designs, baseline clinical features, and demographic characteristics, there is substantial agreement that outcomes defined as a "worse" course of bipolar disorder (longer time to recovery, time to recurrence, time ill) are predicted by more depressive episodes/symptoms, substance abuse, younger age of onset, and rapid cycling (Tohen et al., 1990, 2000, 2003; Nolen et al., 2004; Perlis et al., 2006, 2009).

Somewhat less research has explored the predictors of psychosocial functioning or the delay between clinical and functional recovery after episodes. Many of the same clinical variables that predict clinical course have also been shown to predict functional impairment (e.g., Goetz et al., 2007; Perlis et al., 2009). Many studies have noted in particular the negative impact of subclinical depressive symptoms on functioning (Gitlin et al., 1995; Altshuler et al., 2002a; Chengappa et al., 2005; Judd et al., 2005; Simon et al., 2007; Gyulai et al., 2008; Kauer-Sant'Anna et al., 2009). Recent studies have also suggested that certain indicators of neurocognitive impairment predict functional disability (Altshuler et al., 2007, 2008; Martino et al., 2009; Jaeger et al., 2009; Tabarés-Seisdedos et al., 2008; Dickerson et al., 2010).

Further study of predictors of functional recovery is warranted in order to improve treatment strategies, especially because poor functioning may itself predict further symptoms and episodes (e.g., Gitlin et al., 1995; Tohen et al., 2003; Nolen et al., 2004). In particular, little research has addressed the question of psychosocial factors that may contribute to functional disability despite clinical recovery.

The present study examines the role of stressful life events in the timing of functional recovery in bipolar disorder. There is evidence in unipolar depression that stressors predict both poorer clinical outcomes as well as greater social dysfunction over time (e.g., Cronkite et al., 1998). In the bipolar literature, several studies have examined the role of stressful life events and circumstances in bipolar episode recurrence (e.g., Cohen et al., 2004; Kim et al., 2007; Hammen and Gitlin, 1997; Swendsen et al., 1995; see Johnson and Roberts, 1995, for a review). Further, Johnson and Miller (1997) found that bipolar patients who experienced a recent major life event took more than 3 times longer to recover clinically from an episode than those who did not experience major events. However, limited research has prospectively addressed the role of life events in the course of functional recovery in bipolar disorder (e.g., Hammen et al., 2000). Conceptually, there is reason to believe that stressful

life events may influence functional recovery, as stressors can cause emotional and situational disruptions that could impede the ability to perform in crucial roles, perhaps especially when individuals are struggling to recover psychologically from the impact and consequences of their mood episodes.

In light of empirical gaps in the literature, the current study was based on a sample that had been treated for a manic episode to the point of clinical recovery. Functional recovery at the time of clinical (symptomatic) recovery was then assessed in several domains: work/school, home duties, activities with friends, and activities with family, along with recent stressful life events. The goal of the study was to evaluate the extent to which presence of one or more recent stressful life events was associated with whether patients had concurrent clinical and functional recovery or delayed functional recovery, controlling for the effects of residual symptoms of mania and depression. Analyses also examined time to functional recovery associated with recent stress exposure

2. Methods

2.1 Participants and procedures

Subjects were invited to participate in a two-phase study of which Phase II is the current study. In Phase I, participants were recruited after admission for treatment of a manic episode to the inpatient Resnick Neuropsychiatric Hospital at UCLA, West Los Angeles VA Medical Center inpatient psychiatric units, and the VA Long Beach Healthcare System Outpatient Mood Disorders Clinic. The study was approved by each local institutional review board. Additionally, referrals came from community outpatient clinics and private practice. Written informed consent was obtained from all subjects prior to study enrollment.

Participants were included in Phase I if they had a confirmed diagnosis of bipolar I disorder based on the Structured Clinical Interview for DSM-IV (SCID), an episode of mania or hypomania within 3 months of study enrollment, and were treated for the index manic or hypomanic episode with a mood stabilizer or combination of mood stabilizers such as lithium, divalproex sodium, carbamazepine or a second generation antipsychotic. Participants also had to have worked in the year prior to the index manic episode, with work defined broadly to include a variety of full-time equivalent "primary life roles," such as work for pay, matriculated student status, and the homemaker role if the latter represented significant ongoing familial responsibility. Patients were excluded from the study if they had significant alcohol or substance abuse or dependence within the past 3 months; rapid cycling within the year prior to enrollment or prior to the index episode; or an organic mood disorder. Two patients had current anxiety disorders, one had binge eating disorder.

Participants were followed for up to 6 months in Phase I and were assessed monthly using the SCID mood disorders module (Spitzer et al., 1996), Young Mania Rating Scale (YMRS; Young et al., 1978) and the 28-item version of the Hamilton Depression Rating Scale (Ham-D; Hamilton, 1967) which includes items specific to bipolar depression in the 7-item extension. Reliability and validity data on these measures have been widely reported in the literature. Treating psychiatrists rated medication compliance for each prescribed medication at each visit on a 5-point scale, and patients were continued in the study only if they maintained > 80% medication adherence at each study visit.

Clinical recovery was defined as a YMRS score < 7 and no current mood disorder on the SCID. Patients who did not achieve clinical recovery within 6 months of follow-up were no longer followed and were not eligible for the current phase (II) of the study (functional recovery). Subjects were invited to participate in the current study (Phase II) to evaluate

functional recovery during follow-ups if they had symptomatic recovery for a sustained period of 6 weeks during Phase I of the study.

At the point of clinical recovery, participants completed a Phase II baseline assessment that included assessment of functioning in multiple domains as well as stressful life events in the prior three months (described below). Those who were concurrently clinically and functionally recovered in all domains are included in the current analyses but were discontinued from further follow-up. Those who were clinically but not concurrently functionally recovered were followed monthly until they met functional recovery for 2 consecutive months, or for a maximum of 9 months if they did not achieve functional recovery. The monthly assessments included symptom and functioning ratings; stressful life events were assessed every three months.

The current study focuses on 65 participants who met the above criteria for clinical recovery and completed the baseline stress assessment. Of the 65 participants, 45% were male, and the mean age was 36.8 years ($SD = 11.3$ years, range = 18–63). Racially, 53% ($n = 34$) were Caucasian, 4.1% ($n = 8$) were African-American, 4.6% ($n = 9$) were Asian-American, 3.1% ($n = 6$) were Latino; 48% ($n = 31$) were single at the initial interview; 53% ($n = 35$) had at least a Bachelor's degree. The participants' average age at first diagnosis of affective disorder was 29.5 years ($SD = 11.9$ years) and average age at first affective symptoms was 19.6 years ($SD = 11.1$ years). Participants experienced a mean of 6.4 ($SD = 9.5$) prior depressive episodes and 9.7 ($SD = 22.9$) prior manic episodes.

2.2 Phase II measures

2.2.1 Assessment of role functioning—The Life Functioning Questionnaire (LFQ; Altshuler, Mintz, and Leight, 2002b) is a 14-item, gender-neutral, self-report questionnaire designed to assess role functioning in multiple domains over the preceding month. The four domains assessed included leisure time with friends, leisure time with family, duties at home, and duties in the workplace/school. The items are scored on a 4-point Likert scale ranging from one (no problems) to 4 (severe problems). The LFQ has demonstrated strong psychometric properties; the intraclass correlation coefficient for reliability was $.70$ on all four domains and Cronbach's alpha was $.84$ on all four domains (Altshuler et al., 2002b). It has been well validated against comparable clusters in the Social Adjustment Scale-Self Report (Altshuler et al., 2002; Weissman and Bothwell, 1976). The LFQ was administered at each monthly study visit. Functional recovery in a domain was operationally defined as a mean score of <1.5 across items in that domain.

2.2.2 Acute stress—The UCLA Life Stress Interview (Hammen et al., 1987) evaluated occurrence of stressful life events (i.e., acute stressors) in the past three months. Interview methods are considered superior to self-report checklists in completeness and accuracy, careful timing of event occurrence, and objective scoring unbiased by respondents' mood state (Hammen, 2005). It is modeled after the contextual threat methods of Brown and Harris (1978) and has been used extensively by Hammen and colleagues (e.g., Hammen, 1991; Hammen et al., 1989). Information on the context of each event was obtained by the interviewer, and later presented to an independent rating team that was blind to the participant's symptoms and subjective response to the event. The interview was administered when participants at the Phase II baseline visit (when they first met clinical recovery status), and at subsequent 3-month intervals. In two studies with bipolar patients, interrater reliabilities for severity ratings were 0.77 (Ellicott et al., 1990) and 0.90 (Cohen et al., 2003).

Stressful life events were scored as presence/absence of at least one significant life event in the 3 months prior to functional recovery (or a random 3-month period if no functional

recovery occurred in Phase I). This approach was taken because 75% of all participants reported no life major events in the 3-month window, and the majority who experienced events had only one event.

2.3 Statistical methods

Descriptive statistics examined proportions of each category of functional outcome (concurrent, delayed, no recovery) by domain content. One-way anovas with planned contrasts compared concurrent vs. delayed functional recovery groups and delayed versus nonrecovered groups, on HAM-D and YMRS scores prior to each content domain functional recovery assessment. Logistic regression analyses were used to test the contribution of recent stressors to functional outcome status (concurrent with clinical recovery vs. delayed), controlling for HAM-D and YMRS residual scores in the month before functional recovery. Four separate regressions were conducted, one for each role domain. Kaplan-Meier survival analyses were conducted to evaluate the time to achieve functional recovery in each of the four domains, as a function of presence/absence of recent stressors.

3. Results

Table 1 shows the distribution of timing of functional recovery in relation to clinical recovery. A majority of patients achieved clinical and functional recovery at the same time (57%–69% across role domains). Overall, functional recovery status was attained by 54% of patients in all four domains ($n = 35$), and all but three participants reached functional recovery status in at least one of the four domains. Specific recovery rates were 83% ($n = 54$) in the friends domain; 77% ($n = 50$) in the family domain; 82% ($n = 53$) in home duties; and 77% ($n = 50$) in the work/school domain. The rates of functional recovery did not differ significantly across domains.

3.1 Functional recovery concurrent with symptomatic recovery vs. delayed functional recovery

A key hypothesis was whether stress contributed to delayed functional recovery following clinical recovery. Logistic analyses compared the concurrent and delayed functional recovery groups on presence of at least one stressful life event in the prior 3 months, controlling for residual subsyndromal depressive and manic symptoms in the month prior to functional recovery. Delayed recovery of work/school functioning was significantly associated with presence of one or more stressors in the prior 3 months, β (S.E.) = 2.07 (0.73), Wald = 7.98, OR = 7.93 (1.89 – 33.3), $P = 0.005$. Similarly in the friendship domain and family domain, presence of a stressor significantly predicted delayed functional recovery, (friendship: β (S.E.) = 2.08 (0.87), Wald = 5.76, OR = 7.99 (1.46 – 43.65), $P = 0.02$, family: β (S.E.) = 2.34 (0.96), Wald = 5.98, OR = 10.37 (1.59 – 67.7), $P = 0.01$.) There was no significant association between delayed recovery and stress occurrence in the home duties domain, OR = 2.84 (0.57 – 14.09). Descriptive information on YMRS and HAM-D scores are presented in Table 2. Symptoms were generally not significant predictors of concurrent versus delayed recovery, except that home duties functioning was related to higher HAM-D scores among those in the delayed recovery group, an unexpected finding requiring further study.

Table 2 also indicates that those who never attained functional recovery during follow-up despite achievement of clinical remission had significantly higher HAM-D and YMRS scores than the concurrent recovered group at the interviews closest to the functional assessments. However, the never-recovered were similar to the delayed functional recovery group in symptomatology, and where there were significant differences, the non-recovered group indicated higher symptom levels. On stress, the participants who failed to achieve

functional recovery were similar to (not significantly different from) the delayed functional recovery on three of the domains, and had significantly higher stress levels ($P < 0.01$) prior to assessment of one domain (family relations).

3.2 Time to functional recovery

In order to further probe the effect of recent stressful life events on functional recovery, survival analyses were conducted to predict time to functional recovery associated with presence/absence of stressors in the three months prior to functional recovery (cases with no functional recovery were censored). In the work/school domain, participants who did not experience a stressful life event had a mean time to recovery of 11.4 days ($SD = 7.4$ days), whereas participants who did experience a stressful life event had a mean time to functional recovery of 111.7 days ($SD = 37.3$ days), log-rank = 12.99, $P < 0.001$. In the friend domain, participants who did not experience a stressful life event had a mean time to recovery of 3.8 days ($SD = 2.1$ days), whereas participants who did experience a stressful life event had a mean time to recovery of 58.4 days ($SD = 28.0$ days), log-rank = 11.56, $P < 0.001$.

Similarly, in the family domain, participants who did not experience a stressful life event had a mean time to recovery of 0.8 days ($SD = 0.8$ days), whereas participants who did experience a stressful life event had a mean time to recovery of 25.9 days ($SD = 11.6$ days), log-rank = 10.58, $P < 0.001$. In the home duties domain, participants who did not experience a stressful life event had a mean time to recovery of 16.2 days ($SD = 9.4$ days), and participants who did experience a stressful life event had a mean time to recovery of 37.3 days ($SD = 20.8$ days) log-rank = 0.35, *ns*.

In view of the significant role of stressor occurrence in predicting time to functional recovery, analyses compared the stress and no stress groups on clinical and demographic factors to see if any differences suggested possibly confounding sources of functional outcome. The stress and no-stress groups did not differ on age or gender, although participants who experienced at least one event had significantly more years of education than those without an event, $t(59) = 2.95$, $P < 0.01$. The two groups did not differ on marital status, employment state, age of first mood symptoms or diagnosis, or number of manic or depressive episodes.

4. Discussion

The present study was designed to examine whether the occurrence of recent stressful life events was associated with delayed functional recovery after symptomatic recovery in a sample treated for a manic episode, and predict time to recovery for groups differing in stress occurrence. It is always hoped and intended that successful treatment will mean clinical recovery accompanied by return to adequate functioning in key roles, but it has become evident that there may be gaps between clinical, and work and social outcomes. The majority of patients in the present study did in fact show concurrent clinical and role functioning recovery, but some showed a notable delay between clinical and functional recovery, and a small number had persisting impairment in role domains throughout the follow-up despite recovery from a manic episode.

As hypothesized, those who had delayed functional recovery were significantly more likely than those with concurrent functional recovery to have experienced at least one recent stressful life event. The relationship between stress and delayed recovery was apparent in the friend, family, and work/school domains (but not in home duties). Stress occurrence predicted delay in functional recovery even after controlling for the effects of residual depressive and manic symptoms. Further, survival analyses indicated that the presence of at least one stressful life event was associated with a statistically significant delay in functional

recovery after clinical recovery, ranging from 26 days (family functioning), to 58 days (friendship functioning), and 112 days (work/school functioning). The occurrence of stressors in the 3 months prior to functional recovery was not predicted by medication compliance, clinical history, or demographic factors, although factors that contribute to stress exposure are an important topic for future study (Hammen, 2005).

The study adds to the increasing emphasis on the importance of understanding the nature and predictors of functional recovery (e.g., Altshuler et al., 2006; Goldberg et al., 1995; MacQueen et al., 1997; Tohen et al., 2000). Previous studies have found that subsyndromal symptoms contribute to impaired functional recovery (e.g., Altshuler et al., 2002a; Chengappa et al., 2005; Judd et al., 2005). The current study builds on the literature implicating the occurrence of stressful life events in the course of unipolar depression, and in the growing body of research on stress in bipolar disorder—particularly bipolar depression (reviewed in Johnson and Roberts, 1995). The limited existing research has suggested that stress may delay clinical improvement (Johnson and Miller, 1997), but it appears to have an even greater disruptive effect on role functioning than clinical outcomes for some individuals, especially in friendship and work/school domains.

The mechanisms that account for the disruptive effects of stress on functional recovery in relation to clinical recovery need further study. It could be speculated that stress affects a variety of neuroendocrine, neurocognitive, affective, attitudinal, and behavioral processes that undermine adaptive coping and problem-solving necessary to sustain effective performance of role requirements. The content of stressful life events may of course differ from person to person, but common events such as having problems with family members, changing jobs or work conditions, and or problems in relation to a loved one, can all cause a variety of emotional and behavioral disruptions. Such disruptions may not only affect functioning in the same domain but may also create a cascade of challenges and adjustments in other domains as well. For example, loss or change of employment not only affects functioning in that domain but may also lead to changes in schedules, finances, and personal confidence that can have an impact on adjustment in relations with friends and family. It may also be speculated that stressful events and their impact may further challenge the supportive relationships that help individuals function adequately in the face of adversity, especially given that those supports may have already been strained by the experience of a patient's manic episode. Moreover, different domains of functioning may differ in their susceptibility to and tolerance for emotional and behavioral consequences of stressful events. In a previous study we reported on predictors of work functioning (Hammen et al., 2000), but functioning in close relationships may have different antecedents.

The current study's finding that stressful life events disrupt the process of returning to premorbid functioning has important implications for treatment. The results suggest that patients may benefit from therapies which focus on helping them cope more effectively with and even prevent negative life events. There is ample evidence of the benefits, in terms of symptom reduction, delay of recurrence, as well as better interpersonal functioning, of combining pharmacotherapy with psychotherapies focused on psychoeducation, interpersonal, family, and cognitive-behavioral interventions (reviewed in Miklowitz & Johnson, 2009).

It must also be noted that stressors and mood symptoms likely each affect the occurrence of each other in a bidirectional process (Hammen, 1991). Thus, adjunctive psychosocial interventions may be beneficial in helping not only to alleviate the negative impact of stressors but also attempt to anticipate and mitigate the ways in which individuals' symptoms, characteristics, and circumstances may contribute to the occurrence of acute events.

The results should be considered in light of several limitations. The samples of those with delayed or nonrecovery of premorbid functioning in key roles were relatively small. Many individuals who did not attain concurrent clinical and functional recovery dropped out and were not followed for the entire follow-up period, which would have permitted more extensive observation of the effects of stress. Nevertheless, all participants had at least a baseline stress evaluation covering a comparable 3 months prior to their current status. Reasons for nonrecovery of functioning despite clinical remission at baseline remains an issue for further study, as those participants' symptomatology and stress levels were generally not different from those who had delayed recovery of functioning. Why some individuals did functionally recover after a delay while others did not may be due to additional personal and situational characteristics not examined in the present study, but are of considerable clinical interest. All of the functional outcome assessments were based on self-reported data. The instrument employed has been shown to be valid and reliable, but future studies with objective, independent ratings would be useful. As noted earlier, the mechanisms by which the occurrence of recent stressors may have contributed to delays in achieving adequate functioning in various roles remain to be investigated.

Our study had several advantages: it was longitudinal and included both outpatients and inpatients with a recent manic episode. It explored 4 different domains of functioning that are important in most people's lives, employing a psychometrically established measure of role impairments. Also, the assessment of stressful life events used a well-established interview to obtain full details of the nature and timing of the events, not dependent on subjective interpretations by the participants.

In conclusion, the return of patients who have recently experienced a manic episode to premorbid functioning in multiple roles is an important goal of treatment. The experience of stressful life events may create delays in attaining adequate functional outcomes even after symptomatic recovery. Thus, even after patients recover symptomatically from mania, clinicians should consider how they can be vigilant and helpful in dealing with the disruptions caused by stressful events, thus promoting patients' rapid return to adequate levels of functioning in important roles.

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References

- Altshuler LL, Gitlin MJ, Mintz J, Leight KL, Frye MA. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. *Journal of Clinical Psychiatry* 2002a; 63:807–811. [PubMed: 12363122]
- Altshuler LL, Mintz J, Leight K. The Life Functioning Questionnaire (LFQ): A brief, gender-neutral scale assessing functional outcome. *Psychiatry Research* 2002b;112:161–182. [PubMed: 12429362]
- Altshuler LL, Post RM, Black DO, Keck PE Jr, Nolen WA, Frye MA, Suppes T, Grunze H, Kupka RW, Leverich GS, McElroy SL, Walden J, Mintz J. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: Results of a large, multisite study. *Journal of Clinical Psychiatry* 2006;67:1551–1560. [PubMed: 17107246]
- Altshuler LL, Tekell J, Biswas K, Kilbourne AM, Evans D, Tang D, Bauer MS. Executive function and employment status in patients with bipolar disorder. *Psychiatry Research* 2007;58:1441–1447.
- Altshuler LL, Bearden C, Green MF, van Gorp W, Mintz J. A relationship between neurocognitive impairment and functional impairment: a pilot study. *Psychiatry Research* 2008;157:289–293. [PubMed: 17868903]

- Brown, G.; Harris, T. *Social Origins of Depression: A Study of Psychiatric Disorder in Women*. Free Press; New York: 1978.
- Chengappa KN, Hennen J, Baldessarini RJ, Kupfer DJ, Yatham LN, Gershon S, Baker RW, Tohen M. Recovery and functional outcomes following olanzapine treatment for bipolar mania. *Bipolar Disorders* 2005;7:68–76. [PubMed: 15654934]
- Cohen AN, Hammen C, Henry RM, Daley SE. Effects of stress and social support on recurrence in bipolar disorder. *Journal of Affective Disorders* 2004;82:143–143. [PubMed: 15465589]
- Cooke RG, Robb JC, Young LT, Joffe RT. Well-being and functioning in patients with bipolar disorder assessed using the MOS 20-ITEM short form (SF-20). *Journal of Affective Disorders* 1996;39:93–93. [PubMed: 8827417]
- Cronkite RC, Moos RH, Twohey J, Cohen C, Swindle R Jr. Life circumstances and personal resources as predictors of the ten-year course of depression. *American Journal of Community Psychology* 1998;26:255–280.
- Dickerson F, Origoni A, Stallings C, Khushalani S, Dickinson D, Medoff D. Occupational status and social adjustment six months after hospitalization early in the course of bipolar disorder: A prospective study. *Bipolar Disorders* 2010;12:10–20.
- Ellicott A, Hammen C, Gitlin M, Brown G, Jamison K. Life events and the course of bipolar disorder. *American Journal of Psychiatry* 1990;147:1194–1198. [PubMed: 1974746]
- Gitlin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. *American Journal of Psychiatry* 1995;152:1635–1640. [PubMed: 7485627]
- Goetz I, Tohen M, Reed C, Lorenzo M, Vieta E. EMBLEM Advisory Board. Functional impairment in patients with mania: Baseline results of the EMBLEM study. *Bipolar Disorders* 2007;9:45–52. [PubMed: 17391349]
- Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: a longitudinal follow-up study. *American Journal of Psychiatry* 1995;152:379–384. [PubMed: 7864263]
- Goodwin, FK.; Jamison, KR. *Manic-depressive illness: Bipolar disorders and recurrent depression*. 2. Oxford University Press; New York: 2007.
- Gyulai L, Bauer MS, Marangell LB, Dennehy EB, Thase ME, Otto MW, Zhang H, Wisniewski SR, Miklowitz DJ, Rapaport MH, Baldassano CF, Sachs GS. Correlates of functioning in bipolar disorder. *Psychopharmacology Bulletin* 2008;41:51–64. [PubMed: 19015629]
- Hamilton M. Development of a rating scale for a primary depressive illness. *British Journal of Social and Clinical Psychology* 1967;6:278–296. [PubMed: 6080235]
- Hammen C. Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology* 1991;100:555–561. [PubMed: 1757669]
- Hammen C. Stress and depression. *Annual Review of Clinical Psychology* 2005;1:293–319.
- Hammen C, Adrian C, Gordon D, Burge D, Jaenicke C, Hiroto D. Children of depressed mothers: Maternal strain and symptom predictors of dysfunction. *Journal of Abnormal Psychology* 1987;96:190–198. [PubMed: 3680756]
- Hammen C, Ellicott A, Gitlin M, Jamison K. Sociotropy/autonomy and vulnerability to specific life events in patients with unipolar depression and bipolar disorders. *Journal of Abnormal Psychology* 1989;98:154–160. [PubMed: 2708658]
- Hammen C, Gitlin M. Stress reactivity in bipolar patients and its relation to prior history of disorder. *American Journal of Psychiatry* 1997;154:856–856. [PubMed: 9167516]
- Hammen C, Gitlin M, Altshuler L. Predictors of work adjustment in bipolar I patients: A naturalistic longitudinal follow-up. *Journal of Consulting and Clinical Psychology* 2000;68:220–225. [PubMed: 10780121]
- Harrow M, Goldberg JF, Grossman LS, Meltzer HY. Outcome in manic disorders. A naturalistic follow-up study. *Archives of General Psychiatry* 1990;47:665–671. [PubMed: 2113802]
- Jaeger J, Berns S, Loftus S, Gonzalez C, Czobor P. Neurocognitive test performance predicts functional recovery from acute exacerbation leading to hospitalization in bipolar disorder. *Bipolar Disorders* 2009;9:93–102. [PubMed: 17391353]
- Johnson S, Miller I. Negative life events and time to recovery from episodes of bipolar disorder. *Journal of Abnormal Psychology* 1997;106:449–457. [PubMed: 9241946]

- Johnson SL, Roberts JR. Life events and bipolar disorder: implications from biological theories. *Psychological Bulletin* 1995;117:434–449. [PubMed: 7777648]
- Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser JD, Keller MB. Psychosocial disability in the course of bipolar I and II disorders: A prospective, comparative, longitudinal study. *Archives of General Psychiatry* 2005;62:1322–1330. [PubMed: 16330720]
- Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Archives of General Psychiatry* 2002;59:530–537. [PubMed: 12044195]
- Kauer-Sant'Anna M, Bond DJ, Lam RW, Yatham LN. Functional outcomes in first-episode patients with bipolar disorder: A prospective study from the Systematic Treatment Optimization Program for Early Mania project. *Comprehensive Psychiatry* 2009;50:1–8. [PubMed: 19059506]
- Keck P, McElroy S, Strakowski S, West S, Sax K, Hawkins J, Bournce M, Haggard P. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episodes. *American Journal of Psychiatry* 1998;155:646–652. [PubMed: 9585716]
- Keller MB, Lavori PW, Coryell W, Endicott J, Mueller TI. Bipolar I: A five-year prospective follow-up. *Journal of Nervous and Mental Disease* 1993;181:238–245. [PubMed: 8097229]
- Kim EY, Miklowitz DJ, Biuckians A, Mullen K. Life stress and the course of early-onset bipolar disorder. *Journal of Affective Disorders* 2007;99:37–44. [PubMed: 17084905]
- MacQueen GM, Young LT, Robb JC, Cooke RG, Joffe RT. Levels of functioning and well-being in recovered psychotic versus nonpsychotic mania. *Journal of Affective Disorders* 1997;46:69–69. [PubMed: 9387088]
- Martino DJ, Marengo E, Igoa A, Scápola M, Ais ED, Perinot L, Strejilevich SA. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: A prospective 1 year follow-up study. *Journal of Affective Disorders* 2009;116:37–42. [PubMed: 19033081]
- Miklowitz DJ, Johnson SL. Social and familial factors in the course of bipolar disorder: Basic processes and relevant interventions. *Clinical Psychology: Science and Practice* 2009;16:281–296. [PubMed: 19684882]
- Nolen WA, Luckenbaugh DA, Altshuler LL, Suppes T, McElroy SL, Frye MA, Kupka RW, Keck PE Jr, Leverich GS, Post RM. Correlates of 1-year prospective outcome in bipolar disorder: Results from the Stanley Foundation Bipolar Network. *American Journal of Psychiatry* 2004;161:1447–1454. [PubMed: 15285972]
- O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE. Outcome of bipolar disorder on long-term treatment with lithium. *British Journal of Psychiatry* 1991;159:123–129. [PubMed: 1888958]
- Perlis RH, Dennehy EB, Miklowitz DJ, DeBello MP, Ostacher M, Calabrese JR, Ametrano RM, Wisniewski SR, Bowden CL, Thase ME, Nierenberg AA, Sachs G. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: Results from the STEP-BD study. *Bipolar Disorders* 2009;11:391–400. [PubMed: 19500092]
- Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, Ketter TA, Miklowitz DJ, Otto MW, Gyulai L, Reilly-Harrington NA, Nierenberg AA, Sachs GS, Thase ME. Predictors of recurrence in bipolar disorder: Primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *American Journal of Psychiatry* 2006;163:217–224. [PubMed: 16449474]
- Simon GE, Bauer MS, Ludman EJ, Operskalski BH, Unutzer J. Mood symptoms, functional impairment, and disability in people with bipolar disorder: Specific effects of mania and depression. *Journal of Clinical Psychiatry* 2007;68:1237–1245. [PubMed: 17854249]
- Spitzer, RL.; Williams, JB.; Gibbon, M.; First, MB. Structured Clinical Interview for DSM-IV. Biometrics Research Department, NYC Psychiatric Institute; New York: 1996.
- Swendsen J, Hammen C, Heller T, Gitlin M. Correlates of stress reactivity in patients with bipolar disorder. *American Journal of Psychiatry* 1995;152:795–795. [PubMed: 7726323]
- Tabarés-Seisdedos R, Balanzá-Martínez V, Sánchez-Moreno J, Martínez-Aran A, Salazar-Fraile J, Selva-Vera G, Rubio C, Mata I, Gómez-Beneyto M, Vieta E. Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *Journal of Affective Disorders* 2008;109:286–299. [PubMed: 18289698]

- Tohen M, Strakowski S, Zarate C, Hennen J, Stoll A, Suppes T, Faedda G, Cohen B, Gebre-Medhin P, Baldessarini R. The McLean-Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. *Biological Psychiatry* 2000;48:467–476. [PubMed: 11018220]
- Tohen M, Waternaux CM, Tsuang MT, Hunt AT. Four-year follow-up of twenty-four first-episode manic patients. *Journal of Affective Disorders* 1990;19:79–86. [PubMed: 2142702]
- Tohen M, Zarate C, Hennen J, Khalsa H, Strakowski S, Gebre-Medhin P, Salvatore P, Baldessarini R. The McLean-Harvard first-episode mania study: prediction of recovery and first recurrence. *American Journal of Psychiatry* 2003;160:2099–2170. [PubMed: 14638578]
- Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. *Archives of General Psychiatry* 1976;33:1111–1115. [PubMed: 962494]
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry* 1978;133:429–435. [PubMed: 728692]

Table 1

Number (%) and timing of functional recovery in patients treated for manic episodes

Domain of Functioning	Concurrent with Clinical Recovery	Delayed after Clinical Recovery	No Functional Recovery
Friends	45 (0.69)	9 (0.14)	11 (0.17)
Family	43 (0.66)	7 (0.11)	15 (0.23)
Home Duties	42 (0.65)	11 (0.17)	12 (0.18)
Work/School	37 (0.57)	13 (0.20)	15 (0.23)

Table 2

Means (S.D.) of subclinical symptoms (HAM-D and YMRS) prior to concurrent, delayed functional recovery or non-recovery, by domain

Domain of Functioning	Concurrent with Clinical Recovery	Delayed after Clinical Recovery	Not Functionally Recovered
<i>HAM-D28 Score</i>			
Friends	6.93 (7.06)	10.11 (4.11)	11.00 (8.43)
Family	6.72 (6.53) [^]	11.57 (6.68)	12.40 (9.48) [^]
Home Duties	5.48 (4.71) ^{+^}	12.09 (6.06) ⁺	11.42 (9.41) [^]
Work/School	5.67 (4.96) [^]	7.23 (7.49) [*]	14.33 (9.08) ^{^*}
<i>YMRS Mania Score</i>			
Friends	1.51 (1.47) [^]	2.33 (2.12)	3.73 (3.82) [^]
Family	1.58 (1.85) [^]	1.86 (1.77)	3.27 (3.19) [^]
Home Duties	1.39 (1.52) [^]	1.45 (1.29) [*]	3.79 (3.63) ^{^*}
Work/School	1.55 (1.68) [^]	1.46 (1.27) [*]	3.20 (3.53) ^{^*}

⁺Planned comparison between Concurrent and Delayed: significant difference $P < 0.01$

[^]Planned comparison between Concurrent and Not Functionally Recovered: significant difference $P < 0.01$

^{*}Planned comparison between Delayed and Not Functionally Recovered: significant difference $P < 0.01$