Subsyndromal Depressive Symptoms After Symptomatic Recovery From Mania Are Associated With Delayed Functional Recovery

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Objective: This study examined whether the presence of subsyndromal depressive symptoms predicted functional recovery after an acute manic episode.

Method: Subjects with bipolar I disorder (according to the Structured Clinical Interview for *DSM-IV*) who, at the time of symptomatic recovery from an acute manic or hypomanic episode, had a concomitant functional recovery (n = 52) were compared on demographic variables and mood symptoms to those who had symptomatically recovered but not functionally recovered (n = 33). Demographic and mood variables were examined in the nonfunctionally recovered group to assess predictors of time to functional recovery. The primary functional outcome measure used was the Life Functioning Questionnaire, a 5-minute, gender-neutral self-report scale to measure role function in 4 domains: workplace, duties at home, leisure time with family, and leisure time with friends. Participants in the study were recruited from July 2000 through February 2005.

Results: Depressive symptoms, even at a subsyndromal level, were significantly associated with persisting functional impairment after symptomatic recovery from a manic episode ($P < .02$). Subsyndromal depressive symptoms also significantly predicted a slower time to functional recovery over the next 9 months ($P = .006$).

Conclusion: The presence of even mild subsyndromal depressive symptoms may interfere with functional recovery in patients with bipolar disorder after symptomatic recovery from a manic or hypomanic episode.

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Bipolar disorder affects approximately 1.8 million adults.[1] It is a recurrent illness marked by episodes of mood disturbance and recovery. Traditionally, studies have equated "recovery" with syndromal recovery (the resolution of affective syndromes), while largely ignoring functional recovery (patient functioning in various role domains in life). Functional recovery is defined as the restoration of normal role function in work, at home, or both. Work disability and social dysfunction are residual deficits that have been commonly reported after a mood episode resolves.[2–14] One follow-up study found that at 6 months after an admission for mania, 80% of patients with bipolar disorder were syndromally recovered, but only 43% were employed, and only 21% were working at their expected level of employment (functionally recovered).[10] Similarly, other studies following patients with bipolar disorder from 6 months up to 1.7 years after an index admission for mania have documented syndromal recovery but persistent functional disability in up to 60% of patients.[6–8,15–17]

The reasons for persistent impairment in role function after syndromal recovery from an affective episode remain elusive. Despite the prevalence and cost of work disability in both personal and societal terms, there is a paucity of information about the variables that contribute to these problems. It has been reported that the depressive pole of bipolar disorder is consistently associated with functional disability, whereas the hypomanic pole is not.[11,18–22] Patients considered to be syndromally recovered may have residual depressive symptoms below the threshold normally regarded as clinically significant. As functional impairment associated with depression in bipolar disorder can be seen even with relatively mild subsyndromal symptoms, it is possible that depressive symptoms may impair recovery of normal role function. In the current study, we examined the association of the presence of subsyndromal depressive symptoms—that is, those not significant enough to draw clinical attention—with functional impairment after recovery from a manic episode.

METHOD

Subjects

Participants in the study were recruited from consecutive admissions to the Resnick Neuropsychiatric Hospital at the University of California, Los Angeles; the West Los Angeles Veterans Affairs Medical Center inpatient and outpatient psychiatric units; and the Veterans Affairs Long Beach Healthcare System Outpatient Mood Disorders Clinic from July 2000 through February 2005. The study was approved by each local institutional review board. Additionally, referrals came from community outpatient clinics and private practice. Subjects gave written informed consent after the procedures were fully explained (prior to study enrollment).

Inclusion criteria for the study were (1) diagnosis of bipolar I disorder by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Axis I Disorders (SCID)[23]; (2) an episode of mania or hypomania within 3 months of study enrollment;

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(3) treatment for the index manic or hypomanic episode with a mood stabilizer or combination of mood stabilizers, such as, but not limited to, lithium, divalproex sodium, carbamazepine, or a second generation antipsychotic; and (4) history of having worked in the year prior to the index episode. "Work" was operationally defined to encompass a variety of full-time–equivalent "primary life roles," including work for pay, matriculated student status, and the homemaker role if the latter represents significant ongoing familial responsibility. Patients were excluded from the study if they had a significant alcohol or substance use disorder (abuse or dependence) within the past 3 months, rapid cycling within the year prior to enrollment or prior to index episode, or an organic mood disorder (eg, head trauma or cerebrovascular accident preceding first manic episode).

Individuals who met inclusion criteria were invited to participate in a longitudinal study to assess predictors of functional recovery. Subjects were initially followed at monthly visits in the first phase of the study to ensure symptomatic recovery.

Measures

Mood was assessed monthly using the SCID mood disorders module, Young Mania Rating Scale (YMRS),[24] and the 28-item version of the Hamilton Depression Rating Scale (HDRS-28),[25] which includes items that are more frequently observed in bipolar depression[26] in a 7-item extension.[27] Symptomatic recovery was defined as a YMRS score < 7 and no current mood disorder on the SCID over a 6-week period within the first 6 months after the acute manic or hypomanic episode. Subjects who did not achieve symptomatic recovery within 6 months of follow-up were not eligible for the second phase of the study. Subjects who achieved symptomatic recovery participated in the second study phase. Subjects underwent an initial baseline assessment that included HDRS, YMRS, and SCID mood module ratings. Additionally, social and occupational function was assessed using the Life Functioning Questionnaire (LFQ).[28] Subjects were also seen by a psychiatrist to assess medication compliance. Subjects were then assessed at monthly visits for up to 9 months using these scales.

The primary functional outcome measure used was the LFQ, a 5-minute, gender-neutral self-report scale to measure role function in 4 domains: workplace, duties at home, leisure time with family, and leisure time with friends.[28] In prior studies, the LFQ demonstrated both excellent test-retest reliability and high internal consistency and has been well validated against the Social Adjustment Scale–Self-Report[29] in comparable clusters.[28] An advantage of this functioning scale is that men are more likely to complete the "at home" items due to gender-neutral wording for domestic chores. Using a 4-point scale, a score of 1 on each item is indicative of no role impairment; a score of ≥ 2 on any item demonstrates some impairment in that domain. Scores on LFQ subsections A (leisure activities with friends), B (leisure activities with family), C (duties at home), and D (duties at work) were analyzed. For this report, we focused on the work subsection. A mean score of > 1.5 on all 4 items in that subsection was operationalized to demonstrate work-related impairment.

Subjects who met criteria for functional recovery (operationalized as a mean score of ≤ 1.5 on the LFQ at the baseline visit) were no longer followed. Subjects who were not functionally recovered at the time of symptomatic recovery were followed at monthly visits until they met functional recovery for 2 consecutive months or for a maximum of 9 months if they did not achieve functional recovery.

Of 209 subjects who consented to participate, 67 participated for 1 month or less and thus did not contribute functional data. Of these, 40 did not meet inclusion criteria, 18 dropped out soon after consenting to participate, 7 were noncompliant with study protocol or medication within the first month, 1 relapsed into depression, and 1 relapsed into alcohol use disorder. One hundred forty-two subjects had evaluable data, but, of these, only 89 (63%) met criteria for symptomatic recovery at the end of 6 months and comprise the participants in the current study.

Data Analysis

Two analyses were performed. First, a cross-sectional analysis was done at the visit in which subjects met criteria for symptomatic recovery (termed *baseline visit*) as defined above. Subjects who were functionally recovered at the time of symptomatic recovery ("baseline" visit) were compared to those who had not attained functional recovery at the time of symptomatic recovery. Next, a longitudinal analysis was performed; subjects who were not functionally recovered at the baseline visit were then followed for up to 9 months. Time to functional recovery was defined as the time from the baseline visit to the first visit in which the LFQ work total was ≤ 1.5.

Chi-square and *t* tests were used for the cross-sectional analyses. For the longitudinal analyses, the LFQ and HDRS scores were analyzed using proportional hazard and accelerated failure time survival regression (SAS PHREG, LIFEREG; SAS Institute Inc, Cary, North Carolina). In the proportional hazard analyses, the EXACT option was used for handling ties. In addition to using the total score of the HDRS-28 in the survival analysis, we looked at the separate contributions of the score of the first 21 items (HDRS-21) and the score of the 7 supplemental items (used to target features of bipolar depression) by including the 2 subtotals as separate covariates in a single proportional hazards model. We classified medications into 3 groups, anticonvulsants (valproate, carbamazepine), antipsychotics (olanzapine, risperidone), and lithium, and created 3 dichotomous dummy indicators (yes, no) for each at baseline (data were taken from the closest visit for 4 subjects who did not have medication data recorded at baseline). The impact of medication class on outcome and the relation of depressive symptoms to recovery were examined in 3 separate proportional hazard models that included the main effect of each of these indicators and its interaction with HDRS-28 score.

We stratified the HDRS-28 scores at baseline in 2 ways. First, we used a median split, cutting the scores into 2 groups with values of 0–11 versus 12 or more at visit 8.

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Second, although the numbers were small, we also divided the sample into thirds of n = 11 with HDRS-28 cutoff points of 0–6, 7–14, and 15 or above, which closely correspond to clinical ranges, with the aim of achieving as equal groups as possible in order to examine whether incremental steps in depression severity were associated with functional outcome. In both cases, we computed the Kaplan-Meier survival curves and tested the difference between strata defined by the dichotomous and trichotomous classifications.

RESULTS

Of the 89 subjects who were symptomatically recovered, 52 (58%) were functionally recovered at the time of symptomatic recovery. The remaining 37 subjects (42%) had not functionally recovered. Of these, 4 dropped out after the baseline visit and had no further follow-up. Thus, data from the 52 subjects who were functionally recovered at the time of symptomatic recovery were compared cross-sectionally to data from the 33 subjects who had not recovered functionally at the time of symptomatic recovery. Longitudinal analysis focused on these 33 subjects (37% of the sample).

The demographic and course of illness data on subjects in the current study are shown in Table 1, stratified by functional recovery status. There were no significant demographic or illness history differences between groups. However, those who remained functionally impaired at the time of symptomatic recovery had significantly more depressive symptoms than those who were functionally recovered at the time of symptomatic recovery (HDRS-28 $t = 4.43$, $P < .0001$; HDRS-21 $t = 3.82$, $P = .0004$).

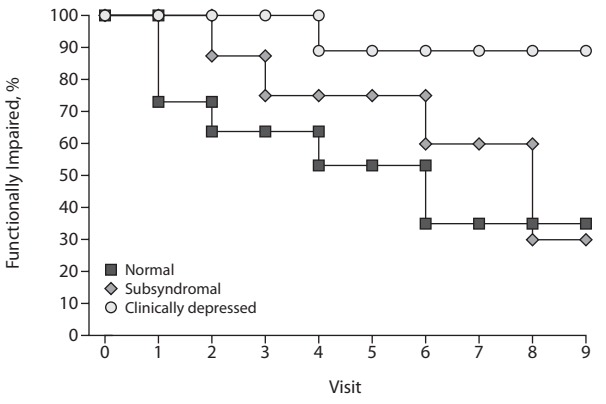
Data analyzed using either proportional hazard or accelerated failure time survival regression analyses yielded similar results, and only the proportional hazard regression results are reported. The proportional hazard yielded a significant association with the HDRS-28 scores ($\chi^2_1 = 5.25$, $P = .022$). The longitudinal data were skewed and thus were log transformed to normalize for the primary analysis. The log transformation–normalized HDRS-28 data yielded a $\chi^2_1 = 7.62$, $P = .006$. That is, baseline depressive symptoms predicted time to longitudinal functional recovery. The analysis, using survival curves based on stratifying at an HDRS cutoff point of less than 12 at the baseline visit, was significant (Wilcoxon $\chi^2_1 = 5.43$, $P = .02$). The analysis using 3 subgroups, displayed in Figure 1, was also significant, and the curves were ordered as expected on the basis of severity (Wilcoxon $\chi^2_2 = 6.240$, $P = .044$; treating the grouping variable as a linear covariate yielded essentially the same Wilcoxon $\chi^2_1 = 6.25$, $P = .012$). In a supplemental proportional hazards analysis that included the HDRS-21 mean score and mean score of the supplemental 7 items specific to bipolar depression as separate subscores, only the mean of the extra 7 items specific to bipolar depression was a significant predictor (7-item extension $\chi^2_1 = 4.86$, $P = .027$; original 21 HDRS items $\chi^2_1 = 0.16$, $P = .686$). Thus, the predictive power of the 28-item HDRS came from the 7 items specific to bipolar depression. For exploratory purposes, each of the 7 added items was analyzed in separate proportional hazard regression models. None of the items were predictive alone (P ranges = .1–.44),

Table 1. Demographic and Clinical Variables at Baseline (N = 89)

Variable	Not Functionally Recovered at Baseline (n = 37)[a]	Functionally Recovered at Baseline (n = 52)[a]	Statistic	*df*	*P*
Sex, female	18 (49)	25 (48)	$\chi^2 = 0.00$	1	.96
Age, y	38.0 ± 11.6[b]	35.1 ± 11.6[b]	$t = 1.19$	87	.24
Education, y	15.3 ± 1.9[b]	15.3 ± 2.4[b]	$t = 0.09$	78	.92
Age diagnosed, y	30.8 ± 11.8[b]	28.9 ± 12.0[b]	$t = 0.70$	80	.48
Age first mood symptoms, y	19.0 ± 9.9[b]	19.8 ± 10.1[b]	$t = -0.34$	75	.73
No. of prior manic episodes	5 (0–134, + 0)[c]	3 (1–104, + 2)[c]	$\chi^2 = 1.20$	1	.27
No. of prior depressive episodes	5 (0–50, + 7)[c]	4 (0–40, + 6)[c]	$\chi^2 = 1.42$	1	.23
Ethnicity			$\chi^2 = 6.06$	4	.19
White	20 (54)	26 (50)			
African American	2 (5)	7 (13)			
Asian or Pacific Islander	8 (22)	4 (8)			
Latino	2 (5)	7 (13)			
Other	5 (14)	8 (15)			
Marital status			$\chi^2 = 0.68$	2	.71
Single	20 (54)	28 (54)			
Married	7 (19)	13 (25)			
Divorced	10 (27)	11 (21)			
HDRS-21 score[d]	7.31 ± 5.5[b]	3.5 ± 3.1[b]	$t = 3.82$	52.5	.0004
HDRS-28 score[d]	11.5 ± 7.9[b]	5.1 ± 4.5[b]	$t = 4.43$	52.6	< .0001

[a]All data presented as n (%) unless otherwise noted. [b]Data reported as mean ± SD. [c]Numbers reported are median and range, with numbers of participants responding "too many to count" given after the plus sign (+). The statistic is the nonparametric Kruskal-Wallis χ^2 test. [d]HDRS score at start of 9-month follow-up (week 8). Statistic is the *t* test for unequal variances.
Abbreviation: HDRS = Hamilton Depression Rating Scale (21-item version and 28-item version).

Figure 1. Percent Remaining Impaired Stratified by Baseline HDRS-28 Subgroups[a,b]



[a]Log rank $\chi^2_2 = 6.0$, $P = .05$. Final % remaining impaired: clinically depressed (89%, n = 11, HDRS-28 score range = 15–32); subsyndromal (30%, n = 11, HDRS-28 score range = 9–14); normal (35%, n = 11, HDRS-28 score range = 1–6). [b]Visit 0 corresponds to "baseline visit" in text, denoting the time of symptomatic recovery.
Abbreviation: HDRS-28 = Hamilton Depression Rating Scale (28-item version).

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except for item 22 (fatigability; $\chi^2 = 4.46$, $P = .035$). Separate analyses of the 3 medication classes revealed no significant medication effects on recovery (anticonvulsants: direct effect $\chi^2_1 = 1.32$, $P = .25$, interaction $\chi^2_1 = 0.93$, $P = .33$; antipsychotics: direct effect $\chi^2_1 = 0.05$, $P = .83$, interaction $\chi^2_1 = 0.005$, $P = .92$; lithium: direct effect $\chi^2_1 = 0.88$, $P = .35$, interaction $\chi^2_1 = 0.18$, $P = .67$).

We performed the same survival analysis done with the HDRS using the YMRS. The YMRS score at baseline did not predict functional recovery ($\chi^2 = 0.25$, $P = .61$), nor did it affect the main finding when it was included as an additional covariate with the HDRS score in the multiple survival regression model (HDRS $\chi^2 = 6.6$, $P = .010$; YMRS $\chi^2 = 0.00$, $P = .99$).

DISCUSSION

Our results suggest that, in patients with bipolar I disorder, the presence of subsyndromal depressive symptoms is associated with (1) persisting functional impairment at the time of recovery from a manic episode and (2) a longer time course to eventual functional recovery compared to patients without such symptoms. Furthermore, a "dose-response" relationship was additionally seen in that the greater the baseline depressive symptom score, the more delayed the functional recovery. Even relatively low levels of depressive symptoms (HDRS scores 7–14) were associated with slower recovery compared to those with HDRS scores 0–6. These are subsyndromal depressive symptoms below the threshold for usual clinical concern.

To our knowledge, this is the first prospective study examining the relationship between the presence or severity of depressive symptoms (after recovery from an acute mania) and time to functional recovery. Functional recovery following a manic episode has been consistently shown to lag substantially behind syndromal or symptomatic recovery from that episode.[17] The reasons for this remain largely unexplored. Our study suggests that even relatively low-level depressive symptoms may contribute, in part, to functional outcome.

Research in bipolar disorder over the last 15 years has demonstrated that depression is the dominant pole of bipolar disorder.[30–32] Our cross-sectional findings are consistent with an increasing body of data suggesting that depressive symptoms in general are associated with functional disability. In their analysis of psychosocial disability in the National Institute of Mental Health Collaborative Depression Study cohort of patients with bipolar I and II disorders (which evaluated longitudinal course and outcome), Judd et al[33] demonstrated both the greater effect of depressive symptoms than manic symptoms on psychosocial disability as well as the incremental effect of depressive symptoms. In a prior cross-sectional study also utilizing the LFQ, we demonstrated a significant positive correlation between the severity of subsyndromal depressive symptoms and the degree of role impairment in the Stanley Foundation Bipolar Network cohort.[21] Our data in a bipolar population support the results of similar studies of subsyndromal depressive symptoms and work (and social function, in some studies) disability in the unipolar population[34–36] and in other bipolar populations.[37] Whether measured as subsyndromal symptoms or incomplete remission after a depressive episode, the findings are the same as in bipolar disorder—that depressive symptoms not rising to the level of a depressive episode are associated with poorer functional outcome. Findings from one longitudinal sample revealed in a secondary analysis that depressive symptoms were more disabling than hypomanic symptoms, that the effect of depression was incremental in clear stepwise fashion, and that shifts in depressive intensity over time correlated with changes in function.[18] Our results are consistent with these findings and additionally show that depressive symptoms at one point in time may have a predictive relationship to long-term functional recovery.

It is of note that the power of depressive symptoms to predict functional outcome was exclusively associated with the 7 additional items on the extended HDRS.[27] While exploratory, analyses of the subset of items revealed fatigability to predict slower functional recovery. Because these items in general and fatigability in particular measure the "slowed down" symptoms of depression, such as fatigue, anergy, hypersomnia, as well as social withdrawal, it may be that symptoms related to lack of energy may be the most functionally disabling of the depressive symptoms for subjects with bipolar disorder.

While our data suggest an association between postmanic depressive symptoms and functional impairment, the direction of the association is uncertain. For example, it is possible that lack of functional recovery leads to depressive symptoms. This would be consistent with the results of 2 prior studies using a much longer time frame, both of which showed that functional impairment predicted future depression in bipolar populations.[11,38] This finding might imply that the relationship between depressive symptoms and function is circular; ie, depression may lead to poorer function and poorer function may then lead to increased depressive symptoms. Thus, the causal direction between depression and functional recovery is unclear and remains to be evaluated in future longitudinal studies.

The treatment implications of our findings are also unclear. The association between depressive symptoms and slower functional recovery would suggest that more aggressive treatment (psychosocial, pharmacologic, or other) of these symptoms—and perhaps, in particular, fatigability and the other depression symptoms specific to bipolar depression—might hasten the functional recovery. A pharmacologic strategy targeting energy symptoms to enhance function could be studied. Because the optimal pharmacotherapeutic approach for bipolar depression is still unknown and controversial, and beyond the scope of this article, specific pharmacologic recommendations cannot be made at this time. However, any treatment that diminishes depressive symptoms (eg, psychopharmacologic, cognitive-behavioral, environmental, and interventional) should be strongly considered. If the circular relationship between

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depressive symptoms and function is validated in future studies, then treatment should probably proceed along both paths—improving mood in order to increase function and, simultaneously, trying to help patients with bipolar disorder function better (through psychotherapy, social service help, etc) in order to diminish depressive symptoms. Additionally, it is possible that those patients who have postmanic depressive symptoms might differ fundamentally from the patients with bipolar disorder who do not have such symptoms. Although we did not find any significant differences in demographic or course of illness variables between the subjects studied compared to our larger sample, other unmeasured variables may be relevant in this regard. Future analyses may elucidate these factors.

The major limitation of this study is the small sample size available for the final analyses. Of the 209 subjects initially enrolled, 142 (68%) remained in the study to be followed over 6 months. However, of these 142, only 89 (63% of those followed for 6 months; 43% of the original 209 subjects) recovered symptomatically during the first 6 months and were enrolled in the second study phase, during which assessment for functional recovery occurred. Although our findings may be valid for the particular group of subjects studied—that is, those who, after symptomatic resolution of mania, continued to be followed over 6 months—this group represents less than half of the original sample enrolled. The current study only reports findings on a subgroup of subjects with bipolar disorder who symptomatically recover. Our data with this subgroup reveal that a large proportion of patients with bipolar disorder are not functionally recovered at the time of symptomatic recovery.

CONCLUSION

In summary, our results suggest that the presence of subsyndromal depressive symptoms soon after recovery from a manic episode (1) is associated with lower likelihood of concomitant functional recovery and (2) predicts a slower ultimate functional recovery. Future studies can focus on the direction of this relationship, as well as other predictors (eg, neuropsychological, brain imaging, life stress data) that may also play a role in contributing to persistent functional disability in the bipolar population.

Drug names: carbamazepine (Carbatrol, Equetro, and others), divalproex sodium (Depakote and others), lithium (Lithobid and others), olanzapine (Zyprexa), risperidone (Risperdal and others), valproate sodium (Depacon and others).

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Potential conflicts of interest: **Dr Gitlin** has received honoraria from Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Pfizer, Takeda, Cephalon, and GlaxoSmithKline (all unrelated to this study). **Dr Sokolski** is a member of the speaker's bureaus for AstraZeneca and Bristol-Meyers Squibb. During the past 12 months, **Dr Altshuler** has served on an advisory board for Forest. Prior to this, she has received honoraria from Abbott, Bristol-Meyers Squibb, Forest, and GlaxoSmithKline and has been a member of the speaker's bureaus for Forest, GlaxoSmithKline, and AstraZeneca. **Drs Mintz** and **Hammen** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

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