Features Associated With the Delayed Initiation of Mood Stabilizers at Illness Onset in Bipolar Disorder

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Background: Whether delays in the initiation of appropriate pharmacotherapy for bipolar illness negatively affect course, outcome, or lifetime suicide risk remains at issue.

Method: Lifetime affective syndromes and the initial emergence of affective symptoms were assessed by lifecharting in 56 DSM-IV bipolar patients. Lifetime treatment interventions were recorded by clinical interview with corroboration via record reviews. Lag times to the initiation of a mood stabilizer (after initial symptom onset and/or first lifetime affective episode) were assessed relative to functional outcome and lifetime suicide attempts.

Results: Mean ± SD lag time from initial affective symptoms until first mood stabilizer treatment was 9.8 ± 9.4 years. A greater number of years from symptom onset to first mood stabilizer was associated with poorer past year social functioning ($r = –0.35$, $p = .008$), more annual hospitalizations ($r = 0.38$, $p = .004$), and a greater likelihood for making a lifetime suicide attempt (odds ratio = 7.26, 95% confidence interval = 1.62 to 32.59; Wald $\chi^2 = 6.69$, $df = 1$, $p = .010$). Delayed mood stabilizer initiation was linked with poorer outcomes in these domains regardless of initial index episode polarities of mania versus depression. Prolonged delays to bipolar diagnoses and mood stabilizer initiation were associated with earlier ages at affective symptom onset ($p < .03$) and milder severity of initial symptoms ($p = .003$). Psychotherapy initiation often preceded mood stabilizer introduction by ≥ 8 years.

Conclusion: Delays in the initiation of mood stabilizer pharmacotherapy at illness onset, even for relatively mild symptoms at illness onset and regardless of index episode polarity, may confer an elevated risk for suicidal behavior, poorer social adjustment, and more hospitalizations in bipolar disorder. Greater surveillance screening for bipolar illness in patients who first present for psychotherapy may help to diminish these adverse outcomes.

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Although bipolar disorder remains highly prevalent in the general population, delays of 8 years or longer have been reported from the time of initial symptom onset until the formal diagnosis of an affective disorder.[1,2] Relatively little is known about the extent to which delays until beginning appropriate treatment may influence the course, morbidity, and mortality of bipolar patients. Among first-episode schizophrenia patients, prolonged duration of untreated psychosis prior to initiating antipsychotic pharmacotherapy appears related to slower remissions and prolonged morbidity in some studies,[3–5] but not others.[6] Among bipolar patients, outcome with lithium may be poorer when treatment is begun only after lengthy periods of untreated illness[7] or after the passage of several episodes,[8–13] although findings in this area have been variable.[2] Importantly, since suicide risk for bipolar patients may be highest in the first few years of illness,[14,15] delay in mood stabilizer treatment could correspond to a time window of greatest susceptibility to suicide.

The present study was designed to test the hypothesis that functional outcome would be poorer and lifetime suicide attempt histories would be disproportionately elevated among bipolar patients for whom treatment with

lithium, divalproex, or carbamazepine was substantially delayed after initial symptom onset. We hypothesized that delays to mood stabilizer initiation would be associated with poorer outcome regardless of the polarity (manic or depressive) of the index episode. We also sought to identify features associated with prolonged time delays from affective symptom onset until (1) the diagnosis of bipolar disorder and (2) initiation of a first mood stabilizer.

METHOD

Patient Sample

Subjects in the current study included 56 adult patients consecutively evaluated from the Bipolar Disorders Research Clinic of the New York Presbyterian Hospital who met a DSM-IV definition of bipolar I (N = 46), bipolar II (N = 7), or bipolar disorder not otherwise specified (NOS) (N = 3). Diagnoses were established using the Structured Clinical Interview for DSM-IV, Patient Version (SCID-P).[16] Interviews were conducted by trained and experienced research assistants who had formal training and extensive experience in administering the SCID-P. All SCID-P interviews and assigned diagnoses were reviewed by a senior research psychiatrist prior to subject enrollment.

Lifetime affective episodes, traced to the initial onset of manic or depressive symptoms, were documented using the retrospective Life Chart Method (LCM).[17] We have previously used this methodology,[18] and it yielded adequate interrater reliability (intraclass correlation coefficients of 0.79–0.88) for identifying lifetime episodes of mania and depression. Additional information was obtained from semistructured interviews regarding pharmacotherapies and other treatment interventions over time. Efforts were made to obtain corroboration from family members, prior medical or pharmacy records, and/or patients' treating psychiatrists, which occurred in nearly all cases. Potential subjects for whom LCM data or comprehensive medication histories could not be ascertained with reasonable confidence were not included in the study group.

Patients had a mean ± SD age of 40.8 ± 12.8 years; 37.9% were female, and 76.8% were white. At the time of assessment, subjects had a mean lifetime illness duration of 19.1 ± 11.4 years.

Study Instruments

Overall functional outcome in the year prior to the assessment was rated using an 8-point index developed by Levenstein and colleagues[19] that ranges from 1 (adequate functioning) to 8 (uniformly poor functioning in all areas). This measure takes into account a subject's work and social adaptation, life disruptions, self-support, psychiatric symptoms, and rehospitalization. Social adjustment in the year prior to assessment was evaluated using a 5-point index developed by Strauss and Carpenter[20] that reflects the frequency and scope of an individual's monthly social interactions during the preceding year. We have used each of these scales successfully in previous outcome studies of bipolar disorder.[21–23] Lifetime suicide attempt histories were identified using the SCID-P in conjunction with a semistructured interview that we developed.[24] Analyses regarding suicide attempt histories were based on subjects whose suicidal behaviors were deemed by the authors as having unambiguous intent to cause death (that is, self-injurious or potentially self-injurious acts associated with an acknowledged intent to end one's life).[25]

All subjects provided written informed consent to participate in the current study, which was conducted under a broader protocol designed to comprehensively assess diagnostic and clinical-psychopathologic features of bipolar patients. The study protocol was approved by the Committee on Human Rights of the Weill Medical College of Cornell University-New York Presbyterian Hospital.

Statistical Analyses

Mean group differences were analyzed using t tests or, in the case of small sample sizes, Mann-Whitney tests. Data are presented as mean ± SD unless otherwise indicated. Simple bivariate associations were examined using Pearson correlations. Logistic regression analysis was used to assess the strength of association between dichotomous outcome measures (e.g., the presence of a lifetime suicide attempt) and continuous or interval-independent variables (e.g., years from illness onset to mood stabilizer initiation). Corresponding odds ratios (ORs) with 95% confidence intervals (CIs) were obtained along with Wald chi-square statistics. Linear regression analyses were used to assess the relative strength of association among 2 or more independent variables and a continuous dependent variable. Data were analyzed using SPSS for Windows, Version 10.0 (SPSS, Inc., Chicago, Ill.). All statistical tests were 2-tailed, with an alpha level of .05.

RESULTS

Subjects had a mean age at affective symptom onset of 21.7 ± 9.6 years (range, 7–63 years). Bipolar illness was diagnosed at a mean age of 31.7 ± 11.5 years (range, 13–64 years), which occurred 9.9 ± 9.8 years after the initial onset of affective symptoms (range, 0–33 years). First formal psychiatric diagnoses for the study group occurred at a mean age of 27.5 ± 12.0 years (range, 10–64 years) and involved a primary affective disorder in the majority of instances (N = 55; depression in 17 [30.9%], bipolar disorder in 26 [47.3%], and other disorders in 12 [21.8%]). DSM-IV rapid cycling in the past year was evident in 12 (21.4%) of 56 subjects. Lifetime histories of comorbid alcohol abuse or dependence were evident in 18 (32.1%) of 56 subjects. The presence of a lifetime suicide attempt

Table 1. Clinical and Demographic Features Associated With Time From Initial Symptom Onset to Bipolar Diagnosis and Mood Stabilizer Initiation

	Time From Symptom Onset to Bipolar Diagnosis			Time From Symptom Onset to First Mood Stabilizer		
Variable	r	t[a]	p	r	t[b]	p
Age at symptom onset	–0.30	…	.028	–0.42	…	.001
% Female	…	1.12	.268	…	1.03	.309
% White	…	0.23	.816	…	0.89	.931
Psychosis at first episode	…	–2.38	.021	…	–2.51	.015
Acute (vs insidious) onset	…	0.54	.589	…	0.89	.380
Disability associated with first episode	…	–3.16	.003	…	–3.35	.002

[a]df = 53.
[b]df = 54.

Table 2. Clinical Correlates of Time From Symptom Onset to Mood Stabilizer Initiation

Variable	r	t	df	p
Overall outcome[a]	0.12	…	…	.378
Work functioning	0.08	…	…	.580
Social adjustment	–0.35	…	…	.008
Mean no. of hospitalizations per year ill	0.38	…	…	.004
Lag time in lifetime suicide attempters (vs nonattempters)	…	2.96	38	.005
Lag time in those with lifetime comorbid alcohol abuse/dependence (vs those with no alcohol abuse/dependence)	…	1.92	54	.061

[a]Assessed using the scale of Levenstein et al.[19]

occurred in 16 (40.0%) of 40 subjects with evaluable data on suicide attempts. First lifetime suicide attempts occurred a mean of 8.6 ± 6.6 years after the initial onset of affective symptoms.

First lifetime affective episodes received some form of psychiatric treatment in 38 (67.9%) of 56 subjects; 30 (53.6%) of 56 received pharmacotherapy during their first affective episode. When we considered which mood stabilizers were those first prescribed for the entire study group, lithium was the agent most frequently used first (38 [67.9%] of 56 subjects), followed by divalproex sodium (15 [26.8%] of 56 subjects) and other novel anticonvulsants and/or atypical antipsychotics such as olanzapine (3 [5.4%] of 56 subjects). The mean time from initial symptom onset to any psychiatric treatment (typically psychotherapy alone) was 2.1 ± 8.6 years, while the time until first mood stabilizer treatment was 9.8 ± 9.4 years. First episodes were deemed functionally disabling (as judged by impairment in school, social, or work functioning) in 32 (57.1%) of the 56 subjects. Time to first treatment intervention was shorter when functional impairment during a first episode was present (0.5 ± 2.7 years) rather than absent (5.5 ± 12.2 years) ($t = 2.69$, $df = 54$, $p = .010$). Time from the initial onset of affective symptoms until first mood stabilizer treatment did not differ significantly between the bipolar I and bipolar II subjects (Mann-Whitney: $p = .248$), nor did the bipolar I and II subjects differ in the presence of a lifetime suicide attempt (Fisher exact test: $p = .283$). The bipolar I and II subjects were therefore pooled in subsequent analyses.

Table 1 summarizes clinical and demographic features associated with time from the initial onset of affective symptoms until (1) diagnosis of bipolar disorder and (2) introduction of a first mood stabilizer. Longer lag times until receiving a bipolar diagnosis were significantly associated with an earlier age at illness onset. In addition, lag times to diagnosis were significantly longer among subjects whose initial episodes were nonpsychotic (mean lag time = 11.6 ± 9.9 years) rather than psychotic (mean = 4.7 ± 7.5 years) and among subjects whose initial episode was judged as functionally nondisabling (mean lag time = 14.4 ± 10.5 years) rather than disabling (mean lag time = 6.6 ± 7.9 years).

Longer durations from the initial onset of affective symptoms until the introduction of a first mood stabilizer were significantly more common in subjects with an earlier age at illness onset, as well as in those who were nonpsychotic (mean = 11.6 ± 9.4 years) rather than psychotic (mean = 4.6 ± 7.7 years) and for whom initial episodes were nondisabling (mean = 14.3 ± 9.8 years) rather than disabling (mean = 6.5 ± 7.8 years).

Correlates between lag time from symptom onset to mood stabilizer initiation and functional and clinical outcome features are summarized in Table 2. Lengthy periods from initial symptom onset to mood stabilizer initiation were not significantly associated with global functional outcome, but were significantly associated with poorer social adjustment in the past year and a greater number of hospitalizations per year ill. In addition, lag time in years from symptom onset to first mood stabilizer treatment was associated with a substantially increased risk for a lifetime suicide attempt (OR = 7.26, 95% CI = 1.62 to 32.59; Wald $\chi^2 = 6.69$, $df = 1$, $p = .010$). On the basis of data from the 40 subjects for whom complete data were available on lifetime histories of unambiguous suicide attempts, mean lag times to first mood stabilizer treatment were significantly longer for subjects who eventually made a suicide attempt (N = 17; 12.2 ± 8.4 years) as compared with those with no suicide attempt (N = 23; 4.8 ± 7.4 years). Longer durations from symptom onset until first mood stabilizer use were also evident among subjects who developed comorbid alcohol abuse or dependence (N = 18; 13.3 ± 9.7 years) as compared with those without alcohol abuse or dependence (N = 38; 8.2 ± 8.9 years), although this difference fell short of statistical significance.

Delays to Mood Stabilizer Initiation and Index Episode Polarity

We separately examined outcome measures relative to lag times to mood stabilizer initiation for subjects whose index episode polarity was either manic or depressed. For subjects whose initial index episode polarity was manic (N = 19), the number of years until mood stabilizer initiation (mean = 9.5 ± 11.2) was modestly but significantly associated with a greater number of hospitalizations/years ill ($r = 0.27$, $p = .044$), but no significant association emerged with social functioning ($r = 0.15$, $p = .270$).

For the subsample of 40 subjects with complete data on lifetime suicide attempts, lag time from first mania onset to mood stabilizer initiation was significantly longer among those who had made a lifetime suicide attempt (N = 17; mean = 8.2 ± 8.9 years) than those who had not (N = 23; mean = 2.8 ± 5.8 years) ($t = 2.35$, $df = 38$, $p = .024$).

For subjects whose initial index episode polarity was depressed (N = 34), the number of years until mood stabilizer initiation (mean = 9.9 ± 8.0) was modestly but significantly associated with a greater number of hospitalizations per year ill ($r = 0.30$, $p = .032$) and was associated with poorer social functioning at a marginal level of significance ($r = 0.26$, $p = .057$). In the subgroup of 37 subjects with complete data on lifetime suicide attempts, lag time from first depression onset to mood stabilizer initiation was again significantly longer among those who had made a lifetime suicide attempt (N = 17; mean = 11.8 ± 8.4 years) than those who had not (N = 20; mean = 3.2 ± 7.3 years) ($t = 3.29$, $df = 35$, $p = .002$).

We conducted additional regression analyses for subjects with index episode polarities of depression to differentiate the effects on outcome of lag time to initiation of mood stabilizers versus other pharmacotherapies (typically, antidepressants and/or benzodiazepines). Poor social functioning remained significantly associated with delays to initiation of mood stabilizers ($\beta = 0.482$, $p = .015$), but not with delays to initiation of other psychotropic drugs ($\beta = 0.304$, $p = .120$) ($R^2 = 0.11$). The number of hospitalizations per year ill was related to lag time to mood stabilizer initiation at a trend level ($\beta = 0.35$, $p = .08$) and was not significantly associated with time to initiation of other psychotropic drugs ($\beta = 0.07$, $p = .706$) ($R^2 = 0.10$). Lastly, a logistic regression analysis found that the presence or absence of a lifetime suicide attempt remained significantly associated with time to mood stabilizer initiation (OR = 0.789, 95% CI = 0.932 to 0.668; Wald $\chi^2 = 7.872$, $df = 1$, $p = .005$) but not with time to other psychotropic drug initiation (OR = 1.172, 95% CI = 0.989 to 1.390; Wald $\chi^2 = 3.299$, $df = 1$, $p = .069$).

Other Factors Relative to Delayed Mood Stabilizer Initiation and Outcome

Age at illness onset. Because age at illness onset was associated with an increased lag time to mood stabilizer treatment, we sought to control for the independent effects of each of these 2 variables on the 3 outcome measures described in Table 2 as being linked with delayed mood stabilizer initiation, namely, poorer social functioning, a greater number of hospitalizations per year ill, and an increased risk for suicide attempts. We first conducted a linear regression analysis to assess the relationship between social functioning (the dependent variable) and 2 independent variables (lag time to mood stabilizer initiation and age at onset). A significant association was observed between social functioning and lag time to begin mood stabilizers ($\beta = 0.41$, $p = .005$), but no significant relationship was observed with age at onset ($\beta = 0.15$, $p = .305$) ($R^2 = 0.14$). We next conducted a linear regression analysis using annual number of hospitalizations as the dependent variable. Once again, a significant association was observed with lag time to mood stabilizer initiation ($\beta = 0.41$, $p = .005$) but not age at onset ($\beta = 0.07$, $p = .606$) ($R^2 = 0.15$). A third analysis was conducted using logistic regression, in which the presence of a lifetime suicide attempt (the dependent variable) was assessed relative to age at onset and lag time to mood stabilizer therapy (the independent variables). Lag time to mood stabilizer initiation was significantly associated with the presence of a lifetime suicide attempt at a marginal level of significance (OR = 0.907, 95% CI = 0.824 to 1.001; Wald $\chi^2 = 3.870$, $df = 1$, $p = .049$), but age at onset was not (OR = 1.035, 95% CI = 0.921 to 1.162; Wald $\chi^2 = 0.342$, $df = 1$, $p = .559$).

Alcohol abuse comorbidity. Because alcohol abuse/dependence was a near-significant correlate of delayed mood stabilizer initiation (Table 2) and could, in itself, influence varied domains of outcome, we conducted separate regression analyses to account for the relative effects of each of these features on social functioning, rehospitalization, and suicide risk. In a first linear regression model, time until mood stabilizer initiation was significantly associated with the number of hospitalizations per year ill ($\beta = 0.391$, $p = .004$) but not with a history of alcohol abuse/dependence ($\beta = 0.043$, $p = .742$) ($R^2 = 0.15$). A second linear regression model found a significant association between social functioning and time to mood stabilizer initiation ($\beta = 0.330$, $p = .016$) but not alcohol abuse/dependence ($\beta = 0.075$, $p = .576$). Last, a logistic regression analysis with suicide attempt histories as the dependent variable found a significant association maintained with both time until mood stabilizer initiation (OR = 0.901, 95% CI = 0.822 to 0.998; Wald $\chi^2 = 4.900$, $df = 1$, $p = .027$) and comorbid alcohol abuse/dependence (OR = 6.416, 95% CI = 1.215 to 33.886; Wald $\chi^2 = 4.796$, $df = 1$, $p = .029$).

Psychosis and functional impairment at illness onset. Finally, to better characterize the relative contributions toward eventual suicide attempts of lag time to mood stabilizer initiation and (1) psychosis at illness onset and

(2) functional impairment at illness onset, we conducted separate logistic regression analyses to examine the comparative strengths of association for each of these features relative to the presence or absence of a lifetime suicide attempt (the dependent variable). When suicidality was examined relative to lag time to mood stabilizer initiation and psychosis at initial illness onset, a significant association was observed between lifetime suicide attempts and lag time (OR = 0.904, 95% CI = 0.828 to 0.987; Wald $\chi^2 = 5.09$, df = 1, p =. 024) but not psychosis (OR = 0.296, 95% CI = 0.047 to 1.870; Wald $\chi^2 = 1.68$, df = 1, p = .195). The second logistic regression model revealed a significant association between suicide attempts and lag time to mood stabilizer initiation (OR = 0.833, 95% CI = 0.945 to 0.735; Wald $\chi^2 = 8.10$, df = 1, p =. 004), as well as functional disability at illness onset (OR = 12.419, 95% CI = 1.349 to 114.308; Wald $\chi^2 = 4.70$, df = 1, p = .030).

DISCUSSION

Delays of about 8 to 10 years' duration from the initial onset of affective symptoms until prescription of a first mood stabilizer were evident among bipolar patients, consistent with previous reports from patient advocacy groups[1] as well as findings from other investigators.[2,26] The present data, though preliminary due to the retrospective nature of the current study, suggest that such delays may hold implications for several aspects of clinical course and outcome. These implications include links to poorer social adjustment, a greater number of hospitalizations, a heightened risk for suicide attempts, and a trend toward development of substance use comorbidity. Delayed initiation of mood stabilizers adversely affected outcome in these domains, particularly suicide risk, regardless of an index episode polarity of mania or depression. This latter finding would support other distinctions between unipolar and bipolar depression,[27] suggesting that depressed patients who ultimately go on to manifest signs of bipolar illness may have a poorer prognosis and endure more psychosocial complications when mood stabilizer treatment is substantially delayed. This risk window becomes all the more clinically important in light of our finding that for most subjects, a first treatment encounter typically involved psychotherapy within about 2 years after initial symptom onset, while first mood stabilizer use did not occur until about 10 years after initial symptom onset. From a public health perspective, these findings highlight the importance of surveillance screening for bipolar illness among psychotherapists, who may be among the first clinicians to encounter depressed individuals with the susceptibility for bipolar disorder.

The approximate time we observed from initial symptom onset until a first suicide attempt—about 5 to 10 years after affective symptoms first arose—is consistent with other findings reported by our group on the occurrence of first versus second or third suicide attempts among bipolar patients who survive a first attempt.[24] Prolonged time from the initial onset of affective symptoms until either a diagnosis of bipolar disorder or the first use of a mood stabilizer was more common among subjects with an early age at symptom onset and subjects for whom an initial episode involved neither psychotic symptoms nor functional impairment. However, when controlled for in multifactorial analyses, age at onset per se was not associated with the negative outcome findings associated with delayed mood stabilizer therapy—a finding contrary to that reported by Ho and colleagues[28] in the case of outcome and time to first treatment for schizophrenia. Similarly, alcohol abuse comorbidity did not mitigate the observed relationship between time until mood stabilizer initiation and outcome, although both alcohol misuse and delayed mood stabilizer initiation contributed significantly to the risk for attempting suicide.

In general, delays to initiation of appropriate pharmacotherapy for bipolar illness appear to be less common when clear prodromal psychopathology is present than when initial symptoms are relatively mild. Similar observations were reported by Baldessarini and colleagues,[2] in which latency until beginning lithium treatment was shortest for bipolar patients who manifested signs of rapid cycling and greater overall morbidity associated with initial manic episodes. However, the current data suggest that delayed treatment initiation even for mild initial symptoms could be associated with an eventual adverse impact on longitudinal outcome. This relationship was maintained when we controlled for 2 other factors independently associated with eventual suicide attempts in this study, namely, the presence of psychosis at illness onset and functional disability at illness onset. It is also possible that delayed treatment may portend negative consequences by influencing 2 distinct periods: the time before treatment is initiated (where delay in recognition is associated with lack of treatment), and the time after treatment has begun (where poorer outcomes could arise via possible neurotoxic sequelae from the preceding duration of untreated psychopathology). This conceptual distinction holds importance from both a theoretical and a clinically pragmatic standpoint.

Contemporary theorists have speculated that lengthy durations of untreated psychosis or affective illness might worsen prognosis via direct psychotoxic effects such as apoptosis or excitotoxicity, although only limited empirical data yet exist to support or refute such hypotheses.[29,30] Norman et al.[31] found that the duration of untreated psychosis in first-episode psychotic inpatients bore no relation to performance on cognitive functioning, while the impact on negative symptoms of delayed antipsychotic pharmacotherapy has not been well described. The duration of untreated psychosis has been shown to predict the

ease with which psychotic symptoms can be initially reduced, although its effect on relapse appears less clear.[30] Delays to initiation of antipsychotic medications have also been associated with diminished quality of life among first-episode schizophrenic patients in some studies[32] but not others.[33] In other severe psychiatric conditions such as posttraumatic stress disorder, psychotoxicity has been suggested from prolonged, untreated stress-related symptoms leading to elevated glucocorticoid levels and reductions in hippocampal volume.[34]

Specifically in the case of bipolar illness, current theories about episode recurrence and long-term morbidity suggest that poorer treatment outcome may arise in part from behavioral sensitization or kindling-like mechanisms due to frequent uncontrolled episodes.[35,36] It is conceivable that because lithium and potentially other mood stabilizers may confer some degree of neuroprotection against neuronal loss,[37] time delays until their introduction could result in disease progression or clinical deterioration.

Lithium was the first mood stabilizer taken by the majority of subjects in the present study, limiting the degree to which inferences could be drawn about the differential effects of lag time to initiate lithium versus divalproex or other putative mood stabilizers. Previous work has suggested that acute antimanic response to divalproex may be less impeded by the passage of multiple episodes as compared with response to lithium.[8] Whether this observation could reflect antikindling effects of an anticonvulsant such as divalproex remains an area open to further investigation.

Limitations of the current study include the use of retrospective clinical assessments and the focus on bipolar patients drawn from an urban tertiary-care academic medical center. Treatments with mood stabilizers or other pharmacotherapies or psychotherapies occurred under naturalistic conditions rather than by random assignment, and outcomes might have differed had the immediate versus delayed introduction of specific treatments been randomly undertaken, regardless of the severity of initial symptoms. Other psychosocial factors such as family and social support, denial of illness, and access to health care could potentially have played some role in contributing to appropriate detection and management of early symptoms suggestive of bipolar disorder. However, on the basis of narrative material that emerged during the course of assessment interviews, there was no indication of any such systematic bias for subjects with shorter versus longer delays to either an appropriate diagnosis or treatment for bipolar disorder.

The present study, alongside other data,[7–13] supports the view that the first few symptomatic years of bipolar illness may represent a critical time period that may substantially influence future illness course, based on early detection and appropriate treatment intervention. Appropriate pharmacotherapy for bipolar illness may be delayed for several years after a first psychiatric presentation, as psychotherapy alone typically represents the first intervention provided to most patients. Delayed mood stabilizer initiation may worsen long-term course even when initial symptoms are of only mild or moderate severity and regardless of an index episode polarity of mania or depression. Future prospective studies are needed to help corroborate these preliminary findings. Moreover, as suicide risk may be especially high in the first 5 to 10 years after symptom onset in bipolar patients,[14,15] efforts to minimize delays in appropriate pharmacotherapy during this time window may be vital to minimize longitudinal morbidity as well as mortality.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), olanzapine (Zyprexa).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, carbamazepine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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