Course of Psychiatric and Substance Abuse Syndromes Co-Occurring With Bipolar Disorder After a First Psychiatric Hospitalization

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Background: Patients with bipolar disorder frequently meet criteria for other psychiatric and substance abuse diagnoses. To clarify relationships among these disorders, the authors examined the course of syndromes co-occurring with bipolar disorder for 12 months after a first hospitalization.

Method: Seventy-seven patients were recruited from consecutive inpatient admissions who met DSM-III-R criteria for bipolar disorder, manic or mixed with psychosis. The 12-month syndromal course of co-occurring DSM-III-R alcohol and drug abuse disorders, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and other anxiety disorders were longitudinally recorded.

Results: The rates of all syndromes, except other anxiety disorders, were elevated. OCD demonstrated an interval course that frequently mirrored the course of the bipolar disorder. The courses of PTSD and substance abuse syndromes were separate from that of the bipolar disorder in many of those with both syndromes. Alcohol and drug abuse syndromes were strongly correlated.

Conclusion: The obsessive-compulsive syndrome may represent an alternative expression of bipolar disorder in some patients. In contrast, PTSD appears to represent a truly separate disorder, which is possibly more prevalent in bipolar patients due to a shared risk factor. Substance abuse does not appear to simply result from attempts at self-medication or from the impulsivity of mania. These results suggest that future studies examining the course of syndromes co-occurring with bipolar disorder are warranted.

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Patients with bipolar disorder frequently meet diagnostic criteria for other psychiatric and substance abuse syndromes.[1–10] For example, the lifetime prevalence of co-occurring drug and alcohol abuse exceeds 60%.[1] Similarly, anxiety disorders,[2,4–8] including posttraumatic stress disorder (PTSD)[2] and obsessive-compulsive disorder (OCD),[2,4–6,9] occur in bipolar patients at unexpectedly high rates. It is unknown whether these syndromes represent truly separate illnesses (i.e., true comorbidity) that, perhaps due to a shared risk factor, occur excessively in bipolar patients, or, alternatively, whether these syndromes simply reflect variability in the presentation of bipolar disorder itself.[10]

One way to begin evaluating relationships of co-occurring syndromes with bipolar disorder is by studying the chronology and course of each diagnosis.[2–4,10] In preliminary work, we found that the onset of substance abuse, PTSD, and other anxiety disorders, except OCD, typically predated the onset of the bipolar illness by more than 1 year.[2–4] These findings suggested that these syndromes may be separate disorders that occur at higher rates than expected. However, an alternative interpretation is that these antecedent syndromes are prodromes of incipient bipolar illness. Longitudinal data of the course of these syndromes in patients with bipolar disorder might clarify these diagnostic relationships.

With these considerations in mind, we examined the course of substance abuse syndromes, PTSD, OCD, and other anxiety disorders in 77 patients with bipolar disorder during the 12 months after a first psychiatric hospitalization. Studying patients at the onset of their illness controls for the uncertain effects of illness chronicity and improves the validity of age-at-onset estimates.[2–5,11] To determine whether co-occurring syndromes represent separate disorders or instead variable expression of bipolar disorder, we examined (1) the chronology of syndrome onset, (2) the course of syndromes during the 12-month posthospital interval relative to the course of the bipolar illness, and (3) correlations among co-occurring syndromes. Syndromes representing separate psychiatric disorders would be expected to have a different onset and a separate course from the bipolar illness and would not be expected to correlate with other co-occurring diagnoses.

Table 1. Co-Occurring Syndromes in 77 Patients With Bipolar Disorder, Manic or Mixed With Psychosis, at the Index Evaluation and Additional Diagnoses That Occurred During the 12-Month Follow-Up Assessments*

	Alcohol Abuse		Drug Abuse		PTSD		OCD		Other Anxiety Disorder	
Diagnosis	N	%	N	%	N	%	N	%	N	%
Index evaluation	25	32	31	40	13	17	12	16	13	17
New case[a]	1	1	0	0	0	0	0	0	0	0
Index missed case[b]	3	4	4	5	3	4	0	0	1	1
Total cases	29	38[c]	35	45[c]	16	21[c]	12	16[d]	14	18
Expected cases[e]	11	14	9	12	1	1	2	3	17	22

*Abbreviations: OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder.
[a]Co-occurring diagnoses developing during the follow-up interval.
[b]Co-occurring diagnoses identified during follow-up that were not identified at the index evaluation, but in which the onset preceded the index hospitalization.
[c]Significantly greater than expected: $p < .001$.
[d]Significantly greater than expected: $p < .005$.
[e]Calculated from rates from the Epidemiologic Catchment Area Study weighted for age, sex, and race for this sample.

METHOD

Subjects

Patients were recruited from consecutive psychiatric admissions to the University of Cincinnati Hospital as part of a larger study of first-episode psychosis.[2,3,11] As we have described elsewhere in detail,[2,3,11] the University hospital serves a primarily poor, urban population including indigent care, although it also treats University of Cincinnati students. For this analysis, patients were included if they (1) were aged 15 to 45 years old; (2) met DSM-III-R criteria for bipolar disorder, manic or mixed with psychosis; (3) had no prior psychiatric hospitalizations and minimal prior treatment[2,11]; (4) could communicate in English; (5) resided within the Cincinnati metropolitan area; and (6) provided written informed consent after the study was explained. Patients were excluded if psychotic symptoms resulted entirely from acute intoxication or withdrawal from drugs or alcohol or from a medical illness as described previously.[2,3,11]

All new psychiatric admissions were reviewed, and 254 potential study subjects were identified. Eighty-four (33%) of these patients met inclusion criteria for this analysis, and of these, 77 (92%) provided written informed consent and are the subjects of this report. Patients who refused consent did not significantly differ from the remaining subjects on any demographic variable.

Diagnostic Assessments

Axis I psychiatric diagnoses were assessed at the index hospitalization and 12-month follow-up visit using the Structured Clinical Interview for DSM-III-R, Patient version (SCID-P)[12] performed by psychiatrists experienced with the SCID-P and with good interrater reliability for principal ($\kappa = 0.94$) and co-occurring ($\kappa > 0.90$) diagnoses.[2,3,11] To complete the SCID-P, information was obtained from the patient, medical records, clinicians, and family members when available. The second SCID-P was performed by a different psychiatrist than the first, thereby providing an independent evaluation; however, the second assessment was not blind to the first, as all available materials were reviewed at that time.

Bipolar disorder was defined a priori as the principal syndrome, and the SCID-P hierarchy was ignored for co-occurring syndromes.[2] To facilitate analyses, alcohol abuse and dependence were combined as *alcohol abuse syndromes*, and drug abuse and dependence were similarly combined.[2–6,11] Panic disorder with or without agoraphobia, agoraphobia, social phobia, simple phobia, and generalized anxiety disorder were combined as *other anxiety disorders*.[2] Although classified as anxiety disorders in DSM-IV, PTSD and OCD were analyzed separately due to the relatively high rates of these syndromes in previous reports.[2,4–6,9] Syndromes were defined as *current* if present in the previous month.[14] Co-occurring syndromes beginning during the follow-up interval (*new cases*), and those identified during follow-up that were not identified at the index evaluation, but that began prior to the index hospitalization (*index missed cases*) were included in analyses (Table 1).

Age at onset was defined as that time when patients endorsed enough symptoms to meet DSM-III-R syndrome criteria for a diagnosis. For bipolar disorder, this was the first full affective episode. Age at onset estimates demonstrated good interrater reliability (intraclass correlation coefficient, ICC > 0.90).[2,3] Co-occurring syndromes were defined as *antecedent* if the age at onset predated the bipolar disorder age at onset by more than 1 year.[2,3]

Expected Rates of Co-Occurring Syndromes

Since the community rates of alcohol and drug abuse, PTSD, OCD, and other anxiety disorders for Cincinnati are not available, the expected rates of these syndromes (except PTSD) were approximated by applying the Epide-

miologic Catchment Area (ECA) study lifetime prevalence rates[13] adjusted for the age, sex, and race distribution of our sample. For PTSD, we applied sex-weighted community rates from the report by Helzer et al.[14]

Relationships Between Bipolar Disorder and Co-Occurring Syndromes

Follow-up visits were scheduled for 2, 6, and 12 months after discharge; the rationale for these intervals is described elsewhere.[13] Sixty (78%) of the 77 patients completed the entire 12-month study, and 66 (86%) had at least 1 follow-up visit. The 60 completers were significantly less likely than 17 noncompleters to have a co-occurring drug abuse syndrome (33% vs. 65%; $\chi^2 = 5.4$, df = 1, p = .02).

At each visit, interviewers concentrated on times when symptoms or function improved or worsened, and in conjunction with the SCID-P, the criteria for the bipolar disorder and co-occurring syndromes were reviewed. If the criteria for a syndrome were no longer met, the date when that occurred was recorded. Similarly, if the syndrome later returned, that date was also recorded.

The relationships between the course of the bipolar disorder and each of the co-occurring syndromes was reviewed in "best-estimate" meetings held after the completion of the 12-month visits for all patients.[11] These meetings included at least 2 psychiatrists or a psychiatrist and Ph.D.-level psychologist, in addition to research assistants, and involved reviewing all assessments from the index hospitalization and follow-up evaluations, the 12-month diagnostic interview, and all available clinical records.[11] Information from these multiple sources was compared and a consensus among the research team members was obtained for the interval syndrome relationships to be classified into operationally defined categories. These categories were based on the resolution of syndromes, i.e., the decrease in symptom endorsement whereby DSM-III-R criteria were no longer met for a current disorder. For bipolar disorder, syndrome resolution was defined as the resolution of DSM-III-R manic, depressive, and psychotic syndromes for at least 1 month. Resolution of the psychotic syndrome was based on the DSM-III-R criteria for schizophrenia, i.e., no longer demonstrating any characteristic symptom of the DSM-III-R A criterion for schizophrenia and having fewer than 2 DSM-III-R-defined residual symptoms.[11] Syndrome resolution of the co-occurring disorders was defined as at least 1 month of failure to meet full DSM-III-R criteria for that diagnosis. Syndrome resolution used in this analysis is defined differently than syndromic recovery that is described elsewhere,[11] as this analysis is concerned with the relationships among current syndromes rather than recovery per se.

The specific categories for interval course relationships were operationalized as follows:

1. *Index misdiagnosis:* A diagnosis of a co-occurring syndrome at the index evaluation that was not endorsed at the second SCID-P evaluation and was not evident during the follow-up interval.
2. *Both syndromes continuously:* No resolution of either the bipolar disorder or co-occurring syndrome throughout the interval.
3. *Syndromes cycle together:* Bipolar disorder and co-occurring syndromes both resolve within 1 month of each other.
4. *Co-occurring syndrome without bipolar disorder:* More than 1 month of the co-occurring syndrome after bipolar disorder resolution.
5. *Bipolar disorder without co-occurring syndrome:* More than 1 month of the bipolar disorder after the resolution of the co-occurring syndrome.

When subjects met criteria for more than 1 category, the description that predominated during the follow-up interval was chosen. To evaluate the reliability of this process, we repeated best-estimates for 29 patients who had at least 1 co-occurring diagnosis. These patients had a total of 52 co-occurring diagnoses, and agreement on categorization occurred in 47 (90%) of those ($\kappa = 0.87$).

Finally, the term *comorbidity* originally referred to the concurrent presence of 2 discrete disease entities with differing etiologies.[15] As an attempt to recapture this definition, given that the etiologies of psychiatric disorders are unknown, we also incorporated a strict definition of comorbidity. Specifically, in the 66 patients with at least 1 follow-up visit, co-occurring syndromes were identified that were antecedent *and* exhibited an interval course independent from the bipolar disorder (categories 4 and 5 listed previously). These were designated as *narrowly defined comorbidity,*[10,15] and the rates were compared with the expected rates in those 66 patients.

Demographic and Clinical Variables

Age, sex, race, educational achievement, and socioeconomic status (the highest employment level, determined by job title, prior to the onset of affective symptoms) were recorded. Mood-incongruent psychosis was defined on the basis of DSM-III-R criteria and previous recommendations.[11,16] A general rating of psychiatric impairment was obtained using the Global Assessment Scale (GAS)[17] by trained research assistants (ICC = 0.73). Treatment compliance was scored as full compliance, partial noncompliance, or total noncompliance as described elsewhere.[11,18] New affective episodes were recorded by identifying switches from different affective states (e.g., mania to depression) or by identifying a new episode that occurred after a euthymic period of at least 2 weeks, as described in detail elsewhere.[11]

Statistical Analysis

Analyses were performed using the Statistical Analysis System for the Personal Computer (SAS Institute, Cary,

Table 2. Relationships Between Bipolar and Co-Occurring Syndromes During the 12-Month Interval After a First Psychiatric Hospitalization in 66 Patients With at Least 1 Follow-Up Visit

	Alcohol Abuse (N = 26)		Drug Abuse (N = 28)		PTSD (N = 14)		OCD (N = 9)		Other Anxiety Disorder (N = 12)	
Relationship	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%
Index misdiagnosis[b]	1	4	0	0	0	0	3	33	1	8
Both syndromes continuously	9	35	9	32	3	21	1	11	5	42
Syndromes cycle together	2	8	2	7	2	14	4	44	0	0
Co-occurring syndrome w/o bipolar disorder	0	0	6	21	6	43	0	0	4	33
Bipolar disorder w/o co-occurring syndrome	14	54	11	39	3	21	1	11	2	17

[a]Some percentages do not total to 100% due to rounding.
[b]Patients who received the comorbid diagnosis at the index assessment, but additional information suggested the diagnosis was not warranted.

N.C.). Logistic regression models were employed to identify significant associations of diagnoses of co-occurring syndromes with age, sex, race, education, socioeconomic status, mood-incongruent psychosis, and affective state (mixed or manic). Adjusted odds ratios (ORa) and 95% confidence intervals (CI) were calculated for dichotomous dependent variables. Correlations were calculated using contingency tables and the phi (ϕ) statistic.

For alcohol and drug abuse syndromes, which were common, Kaplan-Meier survival curves[19] were employed to estimate the probability of interval alcohol and drug abuse syndromes, scored as present at the time after discharge that patients met criteria for an active drug or alcohol abuse syndrome. Logistic regression models were used to identify potential predictors of interval alcohol or drug abuse syndromes. Similar models were calculated to evaluate associations between interval alcohol and drug abuse syndromes and other important interval variables, specifically, treatment noncompliance and interval manic and depressive episodes.

RESULTS

General Sample Characteristics

In this sample, there were 43 men (56%) and 34 women (44%). Thirty-seven (48%) were African American, and 35 (46%) were white with 5 (6%) from other ethnic groups. The mean ± SD age was 25 ± 6 years with a mean age at onset of bipolar disorder of 22 ± 6 years. Nineteen (25%) were students, 37 (48%) were unskilled laborers or unemployed, and the rest (N = 21, 27%) had various levels of skilled or professional employment. The mean educational level was 12 ± 2 years. Twenty-nine patients (38%) were in a mixed state, and 57 (74%) had mood-incongruent psychosis. The mean ± SD GAS score was 36 ± 13.

Only 4 (7%) of the 60 12-month completers had their principal diagnosis changed. Three were switched to a diagnosis of schizoaffective disorder, bipolar type due to persistent psychosis after resolution of mood syndromes. The other patient, originally diagnosed with mixed-state bipolar disorder and co-occurring PTSD, was changed to a principal diagnosis of PTSD.

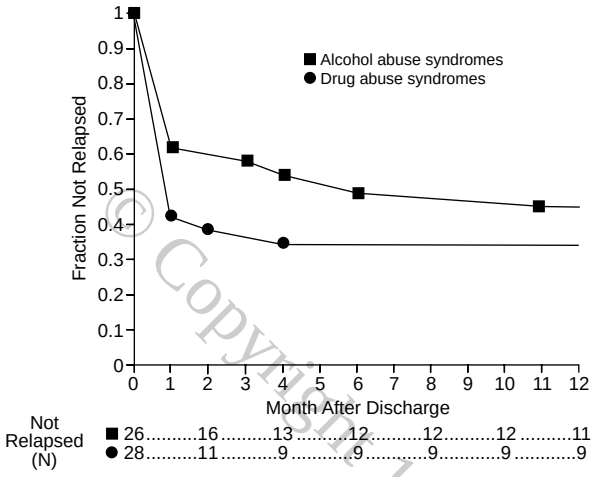
Co-Occurring Diagnoses

Alcohol abuse syndromes. Twenty-three (79%) of the 29 patients with an alcohol abuse syndrome met criteria for alcohol dependence, 19 (66%) had current alcohol abuse at the index hospitalization, and 20 (69%) had antecedent alcohol abuse. Twenty-two (76%) of these patients also met criteria for a drug abuse syndrome (ϕ = 0.48, p = .001). A lifetime diagnosis of alcohol abuse was more prevalent than expected from ECA estimates (Table 1). The mean age at onset of alcohol abuse was 17 ± 4 years. Older age (27 ± 7 vs. 23 ± 5 years; Wald χ^2 = 6.5, df = 1, p = .01) and white race (49% vs. 29%; ORa = 3.5, 95% CI = 1.1 to 11.2) were associated with an alcohol abuse syndrome.

During the follow-up interval, 54% of patients (N = 14) with a history of an alcohol abuse syndrome experienced affective episodes in the absence of alcohol abuse, although, when present, alcohol abuse was always associated with a current bipolar syndrome (Table 2). Twelve patients (18%) exhibited narrowly defined alcohol abuse comorbidity, a rate that is not significantly higher than the expected ECA case-rate of alcohol abuse in those 66 patients with at least 1 follow-up visit (N = 9, 14%).

As illustrated in Figure 1, 54% of the patients with a history of alcohol abuse and at least 1 follow-up visit (N = 26) resumed (or began, in 1 case) alcohol abuse during the 12-month interval. Logistic regression revealed that current alcohol abuse at the index hospitalization was the only predictor of interval alcohol abuse (ORa = 176.9, 95% CI = 8.5 to 999.0; p = .0008) after adjusting for age, race, sex, education, socioeconomic status, index GAS, mood-incongruent psychosis, affective state, and any history of drug abuse. Ten (71%) of the 14 patients with in-

Figure 1. Resumption of Alcohol and Drug Abuse Syndromes in Patients With Both Bipolar Disorder and Substance Abuse Syndromes During the 12 Months After a First Psychiatric Hospitalization*



*The numbers under the scale indicate the number of subjects who had not dropped out or resumed alcohol or drug abuse.

terval alcohol abuse had a current alcohol abuse syndrome at the index hospitalization. Logistic regression analyses to evaluate associations among interval alcohol abuse and other interval variables found a significant association with treatment noncompliance (ORa = 3.0, 95% CI = 1.1 to 7.9, p = .03), but not with interval affective episodes, after adjusting for age, sex, race, education, and socioeconomic status.

Drug abuse syndromes. Thirty-five patients received a lifetime diagnosis of a drug abuse syndrome, which was significantly more than expected (Table 1). This included cannabis abuse (N = 6, 17%) or dependence (N = 26, 74%), cocaine dependence (N = 6, 17%), and other drug abuse or dependence (N = 4, 11%). Seven subjects (20%) used more than 1 drug, and polysubstance dependence occurred in 4 (11%). Twenty-three patients (66%) met current drug abuse criteria at the index hospitalization, and 27 (77%) had antecedent drug abuse. The mean ± SD age at onset of drug abuse was 17 ± 3 years. Only lower education (11.7 ± 1.9 vs. 12.7 ± 2.4; Wald $\chi^2 = 3.8$, df = 1, p = .05) was associated with drug abuse.

In contrast to alcohol abuse, 21% of these patients continued to actively abuse drugs (cannabis in all cases) and still maintained resolution of the bipolar disorder (Table 2). Fifteen patients (23%) exhibited narrowly defined drug abuse comorbidity, which was higher than the expected case rate (N = 8, 12%; Fisher exact test, p = .08).

Eighteen (64%) of the 28 patients with a history of a drug abuse syndrome and at least 1 follow-up visit resumed drug abuse during follow-up (Figure 1). Current drug abuse at the index hospitalization was the only predictor of interval drug abuse (ORa = 298.2, 95% CI = 14.4 to 999.0; p = .0002), after adjusting for the previously listed variables. Seventeen (94%) of the 18 patients who met interval drug abuse criteria were abusing drugs in the month prior to the index hospitalization. No significant associations were observed between interval drug abuse and treatment noncompliance or interval affective episodes.

Posttraumatic stress disorder. Sixteen patients (21%), 12 (75%) of whom were women, received a lifetime diagnosis of PTSD, which was significantly more than expected (Table 1). At the index hospitalization, 14 (88%) of these met criteria for current PTSD, and PTSD was antecedent in 10 (63%). The mean age at onset of PTSD was 14 ± 8 years. Women were significantly more likely to receive a diagnosis of PTSD (ORa = 7.0, 95% CI = 1.7 to 29.6; p = .008). PTSD was not significantly correlated with any other co-occurring syndrome. PTSD showed a separate course relative to the course of the bipolar disorder in 64% of those with both syndromes (Table 2). Six patients (9%) exhibited narrowly defined PTSD comorbidity, which was higher than the expected case rate (N = 1, 1%; Fisher exact test, p = .06).

Obsessive-compulsive disorder. Twelve patients (16%) were diagnosed with a lifetime history of OCD, which was significantly more than expected. OCD was current in 9 (75%) of these at the index hospitalization, but was antecedent to the bipolar disorder in only 25% (N = 3). The mean age at onset of OCD was 19 ± 8 years. OCD was diagnosed in 24% (N = 7) of patients with mixed state, but in only 10% (N = 5) of those with mania (ORa = 5.6, 95% CI = 1.02 to 30.3; p = .05). OCD was significantly associated with other anxiety disorders ($\phi = 0.35$, p = .001). During the follow-up period, the OCD diagnosis was dropped in 3 patients (33%) as additional information suggested it was unwarranted. Additionally, the OCD and bipolar disorder cycled together in 44%. There were no cases of OCD that persisted in the absence of an affective syndrome (Table 2), and no patients exhibited narrowly defined OCD comorbidity, which was not significantly different than the expected case rate (N = 2, 3%).

Other anxiety disorders. Fourteen patients (18%) received a lifetime diagnosis of an anxiety disorder, which was not significantly higher than expected (Table 1). This included 7 (9%) with panic disorder, 6 (8%) with social phobia, 3 (4%) with simple phobia, and 1 (1%) with generalized anxiety disorder. Three (4%) had more than 1 anxiety disorder diagnosis. Anxiety disorders were antecedent in 10 (71%) of these patients and current at the index hospitalization in 11 (79%). The mean age at onset of anxiety disorder was 12 ± 7 years. Lower socioeconomic status was associated with anxiety disorders (Wald $\chi^2 = 3.8$, df = 1, p = .05). During follow-up, anxiety and bipolar syndromes were both continuously present in 42% of those with these diagnoses, although occurred separately in 50% (Table 2). Five patients (8%) exhibited nar-

rowly defined anxiety disorder comorbidity, which was significantly lower than the expected case rate (N = 15, 23%; Fisher exact test, p = .01).

DISCUSSION

Most of the patients in this sample met criteria for 1 or more co-occurring syndrome. Alcohol and drug abuse syndromes were particularly common, were highly correlated, and exhibited rates higher than expected from ECA study prevalence estimates. The majority of patients with a history of substance abuse resumed using drugs and alcohol, typically within the first month after discharge. Since substance abuse has been associated with poor outcome,[11,20] this observation emphasizes the importance of rapidly initiating substance abuse treatment after hospitalization for mania.

The chronology and course data suggest substance abuse syndromes and bipolar disorder are separate conditions in many patients. First, the onset of substance abuse predated that of the bipolar disorder by more than 1 year in over 70% of those with both disorders. Second, the course of substance abuse dissociated from that of the bipolar disorder in over half of these patients, and the syndromes rarely cycled together. Nonetheless, whenever alcohol was used, it was associated with a current bipolar syndrome. Alcohol is well known to produce affective symptoms in users,[21] so it is possible that it initiates or perpetuates affective symptoms in some patients.[3,10] This suggestion is further supported by the observation that in one third of the subjects, both substance abuse and bipolar syndromes persisted together throughout the follow-up interval. It is probable that many factors contribute to the high rates of substance abuse in bipolar disorder including high base rates of substance abuse in the community, self-medication of symptoms, affective symptoms initiated or maintained by substance abuse, and risk factors that contribute to the development of both disorders.[10] These results suggest that future studies with larger numbers of subjects will be needed to separately identify risk factors for these various associations between substance abuse and bipolar disorder.

Although bipolar patients commonly meet criteria for OCD,[2–5,9] our data suggest that, in many patients, this co-occurrence reflects variability in the expression of the bipolar disorder, rather than a separate obsessive-compulsive disorder per se. In contrast to the other co-occurring syndromes, the onset of OCD usually occurred within a year of the onset of the bipolar disorder. Additionally, during follow-up, there was only a single patient in whom the course of the OCD deviated from the course of the bipolar disorder, and there were no cases of narrowly defined OCD comorbidity. Among the co-occurring syndromes, OCD was the least stable between the 2 diagnostic evaluations. Finally, OCD was significantly correlated with other anxiety disorders. The significant association with mixed states suggests that the obsessive-compulsive syndrome may represent a depressive equivalent for some bipolar patients.[9,22]

In contrast to OCD, PTSD appears to be a separate disorder in most bipolar patients. PTSD persisted in 43% of patients after resolution of the bipolar disorder, and another 21% had resolution of PTSD without resolution of the bipolar illness. Also, the onset of PTSD was antecedent to the onset of bipolar disorder in most cases. Finally, PTSD was not significantly correlated with any other co-occurring syndrome. The rates of PTSD remained elevated compared with expected rates even when restricted to cases of narrowly defined comorbidity, suggesting that the risk of PTSD is elevated in bipolar disorder, although the reason for this is unclear. However, since most cases of PTSD are antecedent to the bipolar disorder, this suggests that the trauma associated with the PTSD may place vulnerable people (e.g., those with a family history of bipolar disorder) at risk for developing mania. This finding supports behavioral sensitization models, which propose that trauma and repeated stressors induce PTSD and affective episodes.[23–25]

A number of limitations to this study must be considered when interpreting these data. First, the absolute numbers of specific co-occurring disorders were often small within the several categories of interval course, limiting conclusions that can be made. Second, although retention of subjects was generally high, patients with co-occurring drug abuse were significantly less likely to complete the study, which may bias results toward less ill subjects. Third, these hospitalized patients were acutely manic and psychotic, so that these results may not generalize to other clinical or research settings. Related to this, acutely ill patients may be unable to reliably provide information regarding psychiatric and substance abuse symptoms. However, the low rates of diagnostic disagreement between the index and 12-month assessments suggest that the effect of this limitation was minimal. Fourth, since only *syndromes* were examined, patients with no symptoms of a disorder were analyzed in the same way as those with many symptoms that just failed to meet syndrome criteria. Ideally, different disorders would be identified with pathognomonic clinical markers, but psychiatric diagnoses lack these. Instead, psychiatric diagnoses are based on symptom associations that are not random or artifactual (syndromes), even though the individual symptoms are not diagnostically discriminating.[15] Since the syndrome serves as the basic unit of psychiatric diagnosis, it was chosen as the unit of this study. Finally, our strict definition of comorbidity (i.e., narrowly defined comorbidity) may be too restrictive, implying a lack of separateness where it may actually exist. Comorbidity originally referred to the concurrent presence of 2 discrete disease entities with differing etiologies.[15] Without markers of etiology, alternative approaches must be invoked to evaluate

relationships among psychiatric disorders.[15] Our narrow definition of comorbidity based on differences in the chronology of onset and course of co-occurring syndromes is simply one such approach.

Despite its limitations, we believe this study provides a preliminary description of the relationships between bipolar disorder and co-occurring syndromes. To our knowledge, this is the first study of its kind in this patient population. We are hopeful these results will stimulate others to extend these preliminary findings and further study these complex relationships.

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