A History of Substance Abuse Complicates Remission From Acute Mania in Bipolar Disorder

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Background: Substance abuse frequently complicates the course of bipolar illness, promotes mixed states, and contributes to poor outcome in mania. Preliminary open trials suggest that anticonvulsant mood stabilizers may enhance remission rates and outcome for bipolar patients with substance abuse. This study compared remission patterns for mixed or pure manic episodes among bipolar inpatients with or without substance abuse histories.

Method: Hospital records were retrospectively reviewed for 204 DSM-III-R bipolar I inpatients. Clinical features were compared for those with or without substance abuse/dependence histories predating the index manic episode. Time until remission was analyzed by Kaplan-Meier survival analysis. Naturalistic treatment outcome with lithium or anticonvulsant mood stabilizers was compared for those with or without past substance abuse.

Results: Past substance abuse was evident in 34% of the bipolar sample and comprised most often alcoholism (82%), followed by cocaine (30%), marijuana (29%), sedative-hypnotic or amphetamine (21%), and opiate (13%) abuse. Substance abuse was more common among men ($p < .05$) and those with mixed rather than pure mania ($p < .05$). Remission during hospitalization was less likely among patients with prior substance abuse ($p < .05$), especially alcohol or marijuana abuse, and among mixed manic patients with past substance abuse ($p < .05$). Bipolar patients with substance abuse histories who received divalproex or carbamazepine remitted during hospitalization more often than did those who received lithium as the sole mood stabilizer ($p < .05$).

Conclusion: These findings support previous reports suggesting that bipolar patients with past substance abuse have poorer naturalistic treatment outcomes, but may show a better response to anticonvulsant mood stabilizers than lithium.

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Substance abuse is common among patients with bipolar disorder and more often co-occurs with bipolar illness than any other Axis I disorder.[1] In addition, outcome during maintenance treatment with lithium carbonate appears to be poorer among bipolar[2–6] or bipolar spectrum[7] patients who have comorbid substance abuse. By contrast, preliminary data from noncontrolled studies have suggested that the clinical response to anticonvulsant mood stabilizers such as divalproex may be superior to that of lithium among substance-abusing bipolar patients.[6,8] Clinicians often assume that acute affective episodes in bipolar illness are prolonged or less likely to remit when alcohol or other drug abuse complicates the clinical picture. However, little empirical information is available about the natural course of treatment and remission in dual-diagnosis bipolar disorders. In part, this gap in knowledge exists because bipolar patients with comorbid substance abuse are often excluded from randomized clinical trials or other treatment outcome studies.[6,8,9]

The purpose of the current investigation is to describe the clinical characteristics and pharmacotherapies prescribed for a large bipolar inpatient cohort with or without histories of substance abuse. We sought to confirm prior reports that substance abuse arises more often in mixed mania than pure mania.[6,10] In addition, specific forms of monosubstance or polysubstance abuse are examined in relation to their prevalence, as well as to possible delays in remission from the index manic episode. Finally, we report on patterns of affective symptom remission from acute manic episodes in bipolar patients with versus without substance abuse histories during routine naturalistic inpatient treatment at one institution.

The following research questions were addressed:

1. Is substance abuse more common among mixed than pure manic bipolar inpatients?
2. What forms of comorbid substance abuse are most prevalent among bipolar inpatients?
3. Does a history of substance abuse delay the remission of affective symptoms in an acute manic episode?
4. Are there differences in naturalistic treatment outcome with lithium versus anticonvulsant mood stabilizers in bipolar patients with substance abuse?

METHOD

Patient Sample

The sample consisted of 204 patients consecutively hospitalized for bipolar I manic episodes on a general acute care adult inpatient unit at the Payne Whitney Clinic, New York Hospital, New York, N.Y., from 1991–1995. Charts were retrospectively reviewed and diagnoses were confirmed by 2 of us (J.F.G., J.L.G.) using DSM-III-R criteria for bipolar I disorder. Patients with a past history or current symptom profile suggestive of a diagnosis of schizophrenia, schizoaffective disorder, or a primary severe personality disorder were excluded from the study cohort.

Distinctions between mixed and pure manic episodes at index admission were made using a modification of the Cincinnati Criteria.[11] Specifically, patients were rated as having a mixed manic episode if they met full DSM-III-R criteria for a bipolar I manic episode and had at least 2 prominent DSM-III-R symptoms of major depression.

We sought to examine the relationship between remission from acute mania and substance abuse or dependence that was past or recent (> 3 weeks prior to admission), rather than concurrent, for 2 reasons. First, because of the methodologic limitations of a chart review, we wished to minimize the potential diagnostic confound of substance-induced mood disorders or poorly confirmed diagnoses of bipolar I disorder for which DSM-III-R criteria could not be reliably ascertained. Second, we were interested in determining whether past abuse of psychoactive substances would contribute to a poorer immediate outcome from an acute manic episode. Models of behavioral sensitization and kindling[12,13] would suggest the possibility that previous repeated central nervous system (CNS) exposures to substances such as cocaine or alcohol might hasten relapse or induce refractory affective states. Mechanistically, if past substance abuse were found to impair subsequent remission from acute mania, this would lend further support to the theories about the longitudinal role of psychoactive drugs in the course of bipolar disorders.

Pharmacotherapy with lithium, anticonvulsant mood stabilizers (divalproex or carbamazepine), neuroleptics, benzodiazepines, or other agents was administered by patients' hospital psychiatrists according to the patients' clinical conditions, rather than by randomized assignment. Nearly all patients (> 95%) received adjunctive benzodiazepines and/or neuroleptics on at least 2 occasions during the course of their hospitalization. Although treatment was not controlled for by protocol, data were obtained regarding medication use, daily dosing, compliance, and serum blood levels (where appropriate) throughout each patient's index hospitalization. "Therapeutic" blood levels adopted for the current study were as follows: lithium ≥ 0.8 mEq/L, valproate ≥ 50 mmol/L, or carbamazepine ≥ 8 mmol/L.

Approval for the research protocol was obtained from the Committee on Human Rights of New York Hospital-Cornell University Medical College.

Assessment of Substance Abuse and Affective or Psychotic Symptoms

Substance abuse histories were routinely obtained by clinical interview for all patients by the admitting psychiatrist. A history of drug or alcohol abuse or dependence, prior to admission, was rated by the authors from the admission hospital records and from additional clinical material obtained through daily physician progress notes, toxicology screens, information from family members as reflected in social work and nursing notes, and chart notes from other members of the treatment team. Data were not systematically available to differentiate a diagnosis of substance abuse from substance dependence.

Data on affective and psychotic symptoms during the index hospitalization were rated from a review of daily hospital records for each patient as well as admission and discharge summaries, using standardized criteria from the DSM-III-R. We obtained adequate interrater reliability on ratings of individual manic and depressive symptoms (median $\kappa = 0.68$; range, 0.42–1.00). The severity of symptoms at the time of admission and at weekly intervals thereafter was rated by 2 of the authors (J.F.G., J.L.G.) from clinical chart material using the Clinical Global Impressions (CGI) Improvement and Severity scales.[14] Interrater reliability was obtained using week-by-week CGI scores obtained on a pilot sample, prior to implementation of the CGI in this study (median intraclass correlation coefficient = 0.71; range, 0.44–0.88). Information on age at onset, past suicide attempts, and past treatment compliance was abstracted from hospital admission forms completed on all patients by their admitting psychiatrists; corroboration of this material was obtained by supplemental, detailed clinical history documented in daily progress notes, social work notes, and discharge summaries. This methodology has been used successfully in previous studies by our group.[15,16] *Remission* was defined by patients' receiving a CGI Severity score of 2 (borderline mentally ill) or 1 (not at all mentally ill) for at least 1 week.

Table 1. Demographic Characteristics of Bipolar Patients With Versus Without Substance Abuse Histories

Characteristic	No Substance Abuse (N = 135)	Any Substance Abuse (N = 69)	Statistic t	Statistic χ^2	df	p
Mean age at index (y)	39.6	41.5	0.9		201	NS
Married at index, %	30	18		5.5	2	< .07
Female, %	62	48		3.9	1	< .05
White, %	72	74		1.3	4	NS

Table 2. Clinical Characteristics of Bipolar Patients With Versus Without Substance Abuse Histories[a]

Characteristic	No Substance Abuse (N = 135)	Any Substance Abuse (N = 69)	Statistic t	Statistic χ^2	df	p
Psychotic at index, %	71	74		0.3	1	NS
Mixed mania at index, %	56	74		6.0	1	< .02
History of medication noncompliance, %	38	53		4.1	1	< .05
Suicidal ideation at index, %	35	54		6.7	1	< .01
History of suicide attempts prior to index, %	27	28		0.0	1	NS
Family history of affective disorder, %	71	60	1.9		1	NS
No. of prior hospitalizations, mean ± SD	3.7 ± 4.0	4.2 ± 5.1	0.8		195	NS
CGI Severity at index, mean ± SD	5.9 ± 1.0	5.8 ± 1.0	0.6		202	NS
No. of depressive symptoms, mean ± SD	2.5 ± 2.2	2.9 ± 1.9	1.2		202	NS
No. of manic symptoms, mean ± SD	4.0 ± 1.3	4.1 ± 1.3	0.1		202	NS
Length of hospital stay, mean ± SD, d	37.9 ± 64.1	32.4 ± 23.1	0.7		202	NS
Age at first affective episode, mean ± SD, y	26.7 ± 12.1	26.5 ± 12.3	0.1		193	NS

[a]Abbreviation: CGI = Clinical Global Impressions scale.

Statistical Analyses

Rates of substance abuse between the mixed and pure manic subgroups were analyzed by chi-square analyses. Mean differences between interval variables were analyzed by t tests. Rates of remission for bipolar patients with versus without substance abuse were analyzed by Kaplan-Meier survival analyses with log-rank statistics. Logistic regression analysis was conducted to examine the strength of association among 2 or more independent variables and remission, from which odds ratios (ORs) with 95% confidence intervals (CIs) and Wald χ^2 analyses were determined. An alpha level of .05 and 2-tailed statistical tests were used in all analyses. The current sample size allowed for detection of medium group differences with power of > .80.

RESULTS

Clinical Features of Bipolar Patients With or Without Substance Abuse

The demographic and clinical characteristics of the bipolar sample for those with and without histories of substance abuse/dependence are summarized in Tables 1 and 2. Those with substance abuse/dependence histories were significantly more likely to be male and tended more often to be divorced, separated, or widowed. In addition, dual-diagnosis bipolar patients were significantly more likely to have histories of medication noncompliance and suicidal ideation at the time of the index manic episode. The presence of a substance abuse/dependence history was significantly more common among bipolar patients with mixed mania (51 of 127 mixed manic patients, or 40%) than pure mania (18 of 77 pure manic patients, or 23%) ($\chi^2 = 6.0$, df = 1, $p < .02$).

Of the 127 mixed manic patients, the mean ± SD number of current depressive symptoms did not differ between those with past substance abuse/dependence (3.7 ± 1.5) and those without past substance abuse/dependence (4.0 ± 1.7) (t = 1.0, df = 125, p = .34). In addition, the mean ± SD number of manic symptoms during the index episode did not differ between the mixed bipolar patients with (3.8 ± 1.3) versus without (3.7 ± 1.3) substance abuse/dependence (t = 0.6, df = 125, p = .57). The mean ± SD overall duration of hospitalization was not longer for mixed manics with (31.5 ± 23.6 days) versus without (40.3 ± 83.5 days) substance abuse/dependence histories (t = 0.9, df = 125, p = .39).

To determine the relative contributions of past substance abuse/dependence and depression in the development of suicidal ideation during the index episode, we conducted separate analyses comparing the presence or absence of suicidal ideation for mixed manic patients with or without a substance abuse/dependence history and for pure manic patients with or without a substance abuse/dependence history. Among the 127 mixed manic patients, 36 (71%) of the 51 with a substance abuse/dependence history had current suicidal ideation, while suicidal ideation was evident for 47 (62%) of the 76 mixed manic patients with no substance abuse/dependence history (continuity-corrected $\chi^2 = 0.7$, df = 1, p = .41). Among the 77 pure manic patients, none (0%) of the 18 with past substance abuse/dependence had current suicidal ideation, while 1 (2%) of the 59 pure manic patients without past substance abuse/dependence had current suicidal ideation (continuity-corrected $\chi^2 = 0.4$, df = 1, p = .53).

Treatment Intensities

Bipolar patients with versus without substance abuse/dependence histories did not differ significantly in

Table 3. Forms of Substance Abuse in Mixed and Pure Manic Inpatients

	Total Sample (N = 204)		Mixed Mania (N = 127)		Pure Mania (N = 77)		χ^2	
Substance	N	%	N	%	N	%	(df = 1)	p
Alcoholism	58	28	43	34	15	20	4.9	< .03
Cocaine[a]	25	12	18	14	7	9	1.2	NS
Marijuana[a]	21	10	15	12	6	8	0.9	NS
Opiates[a]	9	4	8	6	1	1	2.8	NS
Other[a,b]	15	7	14	11	1	1	6.7	< .01
Any abuse	69	34	51	40	18	23	6.0	< .02
Polydrug abuse	32	16	24	19	8	10	2.5	NS

[a]For cocaine, marijuana, and other abuse, total N = 203 (mixed mania: N = 126; pure mania: N = 77), and for opiate abuse, total N = 202 (mixed mania: N = 126; pure mania: N = 76), due to incomplete data for 2 subjects.
[b]"Other" substance abuse includes hallucinogens, amphetamines/stimulants, or sedative-hypnotics, combined due to small sample sizes.

the frequencies with which they received any lithium (96 [71%] of 135 without substance abuse vs. 56 [81%] of 69 with substance abuse) or any divalproex and/or carbamazepine (55 [41%] of 135 without substance abuse vs. 25 [36%] of 69 with substance abuse) while hospitalized. Similarly, patients with versus without substance abuse/dependence histories did not differ significantly in their mean ± SD peak serum lithium levels (1.0 ± 0.3 vs. 1.1 ± 0.4 mEq/L, respectively), serum valproate levels (51.4 ± 24.8 vs. 62.1 ± 18.9 mmol/L, respectively), or serum carbamazepine levels (7.9 ± 2.6 vs. 9.0 ± 2.0 mmol/L, respectively). Mean peak dosages of lithium were higher for patients with than without substance abuse/dependence histories (1461 ± 1261 mg/day vs. 1158 ± 400 mg/day, respectively; t = 2.3, df = 150, p < .03). No significant differences were found between patients with versus without substance abuse/dependence histories in their mean ± SD peak dosages of divalproex (1005 ± 457 vs. 1073 ± 496 mg/day, respectively) or carbamazepine (644 ± 378 vs. 561 ± 159 mg/day, respectively).

Patterns of Substance Abuse Among Bipolar Inpatients

Data are presented in Table 3 regarding the frequencies of substance abuse/dependence histories for the overall bipolar sample, subdivided for the mixed and pure manic inpatients. Among the full sample of 204 bipolar patients, 34% (N = 69) had histories of any form of substance abuse. Alcoholism was the most frequent drug of abuse (28%; N = 58), followed by cocaine (12%; 25 of 203 subjects with complete data), marijuana (10%; 21 of 203 subjects with complete data), opiates (4%; 9 of 202 subjects with complete data), and other drugs (7%; 15 of 203 subjects with complete data), the latter category including hallucinogens, amphetamines/stimulants, and sedative-hypnotics.

When subtypes of drug abuse/dependence were examined separately for the 69 bipolar patients with substance abuse/dependence histories, alcohol again emerged as most common (82%), followed by cocaine (30%), marijuana (29%), other drug abuse (hallucinogens, amphetamines/stimulants or sedative-hypnotics; 21%), and opiates (13%).

When comparing subtypes of drug abuse/dependence in the mixed and pure manic patients, those with mixed mania were significantly more likely than those with pure mania to have alcohol abuse (43 [34%] of 127 mixed manic patients versus 15 [20%] of 77 pure manic patients; $\chi^2 = 4.9$, df = 1, p < .03) or to abuse hallucinogens, amphetamines/stimulants, or sedative-hypnotics (14 [11%] of 126 mixed manics versus 1 [1%] of 76 pure manics; $\chi^2 = 6.7$, df = 1, p < .01).

Polysubstance Abuse/Dependence

Polysubstance abuse/dependence was evident among 32 (46%) of the 69 dual-diagnosis patients and was no more common among mixed than pure manics ($\chi^2 = 0.1$, df = 1, p = .73). A history of alcoholism was found among three quarters or more of bipolar patients who also abused opiates, marijuana, cocaine, and other drugs (including sedative-hypnotics, hallucinogens, and/or amphetamines). In addition, cocaine abuse was common in half or more of bipolar patients who abused marijuana or opiates.

Among the 58 bipolar patients with alcohol abuse/dependence, 19 (33%) also abused cocaine, 15 (26%) also abused marijuana, 6 (10%) also abused opiates, and 13 (22%) also abused sedative-hypnotics, anxiolytics, and/or amphetamines. Among the 25 bipolar patients with cocaine abuse, 13 (52%) also abused marijuana, 5 (20%) also abused opiates, and 7 (28%) also abused sedative-hypnotics, anxiolytics, and/or amphetamines. Among the 21 bipolar patients with marijuana abuse, 2 (10%) also abused opiates and 6 (29%) also abused sedative-hypnotics, anxiolytics, and/or amphetamines. Finally, among the 9 bipolar patients with opiate abuse, 3 also abused sedative-hypnotics, anxiolytics, and/or amphetamines.

Substance Abuse and Remission From the Index Manic Episode

Remission from the index manic episode during hospitalization was significantly more likely to occur for those bipolar patients without substance abuse/dependence histories (99 of 135 patients, or 73%) than for those with substance abuse histories (38 of 69 patients, or 55%) ($\chi^2 = 6.9$, df = 1, p < .01). A Kaplan-Meier survival analysis revealed a nonsignificant trend for the bipolar patients with a substance abuse/dependence history to recover more slowly from the index manic episode, as compared to manic patients without a substance abuse/dependence history (log-rank statistic = 3.21, df = 1, p = .07).

We compared the rates of eventual remission of affective symptoms among bipolar patients by different sub-

types of drug abuse histories. Those with alcoholism were significantly less likely to achieve remission by the end of their hospitalization (33 of 58 alcoholic bipolar patients, or 57%) as compared to those without alcoholism (104 of 146 patients, or 71%) ($\chi^2 = 3.9$, df = 1, $p < .05$) or to those with no substance abuse (99 of 135 patients, or 73%) ($\chi^2 = 5.1$, df = 1, $p < .03$). In addition, patients with marijuana abuse were less likely to remit (9 of 21 patients, or 43%) as compared to those without marijuana abuse (127 of 182 patients with complete data, or 70%) ($\chi^2 = 6.2$, df = 1, $p < .02$) or those with no substance abuse (99 of 133 patients with complete data, or 74%) ($\chi^2 = 8.6$, df = 1, $p < .01$). When remission was examined for the 146 patients without alcohol abuse/dependence, those with marijuana abuse/dependence (N = 7) still had significantly lower remission rates (1 of 7 patients, or 14%) than those without marijuana abuse/dependence (103 of 139 patients remitted, or 74%) ($\chi^2 = 11.6$, df = 1, $p < .001$). There was also a marginally significant trend for patients with opiate abuse to have a lower rate of remission (4 of 9 patients, or 44%) as compared to those with no substance abuse (99 of 135 patients, or 73%) ($\chi^2 = 3.5$, df = 1, $p = .06$).

The proportion of those who eventually achieved remission by the end of the study period was not significantly lower for the bipolar patients with polysubstance abuse (18 of 31 patients, or 58%) as compared to those with monosubstance abuse (20 of 38 patients, or 53%) ($\chi^2 = 0.2$, df = 1, $p = .65$).

To examine the relationship between substance abuse comorbidity and affective state at the time of hospitalization (mixed or pure manic), we separately compared remission rates for mixed manic patients with or without substance abuse/dependence and for pure manic patients with or without substance abuse histories. Among the 127 mixed manic patients, remission was less likely among those with substance abuse/dependence (55%, or 28 of 51 patients) than those without substance abuse/dependence (72%, or 55 of 76 patients) ($\chi^2 = 4.1$, df = 1, $p < .05$). Among the 77 pure manic patients, remission again was less likely in those with substance abuse/dependence (56%, or 10 of 18 patients) than those without substance abuse/dependence (75%, or 44 of 59 patients), although the difference in this smaller subsample, having less power, was not statistically significant ($\chi^2 = 2.4$, df = 1, $p = .12$).

To further clarify the relationship between mixed mania and substance abuse, we conducted a logistic regression analysis using these 2 independent variables in association with remission during hospitalization (the dependent variable). Substance abuse was significantly associated with remission (OR = 0.45, 95% CI = 0.24 to 0.84; Wald $\chi^2 = 6.3$, df = 1, $p < .02$), but mixed mania was not significant (OR = 0.92, 95% CI = 0.49 to 1.72; Wald $\chi^2 = 0.1$, df = 1, $p = .79$) when controlled for in the regression equation.

Table 4. Relationship Between Treatment Groups and Remission[a]

	Bipolar With Substance Abuse[b]			Bipolar Without Substance Abuse[c]		
Treatment	N	No Remission	Remission	N	No Remission	Remission
Lithium	26	12 (46%)	14 (54%)	54	9 (17%)	45 (83%)
Divalproex or carbamazepine alone[d]	9	1 (11%)	8 (89%)	15	3 (20%)	12 (80%)
Divalproex or carbamazepine plus lithium[e]	9	1 (11%)	8 (89%)	26	6 (23%)	20 (77%)

[a]Only patients who achieved therapeutic blood levels of mood stabilizers were included for analysis.
[b]$\chi^2 = 6.0$, df = 2, $p < .05$.
[c]$\chi^2 = 0.5$, df = 2, $p = .79$.
[d]Remission occurred for 4 of 5 dual-diagnosis patients taking divalproex alone and 4 of 4 dual-diagnosis patients taking carbamazepine alone.
[e]Remission occurred for 1 of 1 dual-diagnosis patient taking divalproex plus lithium and 7 of 8 dual-diagnosis patients taking carbamazepine plus lithium.

Naturalistic Treatment and Remission in Patients With or Without Substance Abuse Histories

For the 69 dual-diagnosis bipolar patients, rates of eventual remission or nonremission while hospitalized were compared for those who received therapeutically dosed lithium without divalproex or carbamazepine (N = 26) versus those who received therapeutically dosed divalproex or carbamazepine with lithium (N = 9) or without lithium (N = 9). Patients who achieved therapeutic blood levels of mood stabilizers (as described in the Method section) were included for analysis. Patients with versus without substance abuse/dependence did not differ in their frequencies of receiving lithium without an anticonvulsant (26/44 [59%] versus 54/95 [57%], respectively), an anticonvulsant without lithium (9/44 [21%] versus 15/95 [16%], respectively), or a combination of both during the index admission (9/44 [21%] versus 26/95 [27%], respectively) ($\chi^2 = 1.0$, df = 2, $p = .61$).

As shown in Table 4, eventual remission during hospitalization was significantly more likely for patients taking an anticonvulsant mood stabilizer, either alone or in combination with lithium, as compared to patients who took lithium without an anticonvulsant. In contrast, among bipolar patients without a history of substance abuse/dependence, no significant differences were observed in remission rates during the hospitalization for patients who received lithium as the sole mood stabilizer, divalproex or carbamazepine as the sole mood stabilizer, or the combination of lithium plus divalproex or carbamazepine.

Limited data were available on the pre-index course of treatment for most of the sample. Patients who were prescribed anticonvulsant mood stabilizers at index were more likely to have had prior divalproex or carbamazepine treatment as compared to patients on no anticonvulsants

at index ($\chi^2 = 25.3$, df = 1, $p < .001$). However, pre-index use of lithium did not differ for patients who did or did not receive anticonvulsants during the index admission ($\chi^2 = 0.6$, df = 1, $p = .42$). The dual-diagnosis bipolar patients who received anticonvulsants tended to have been younger at the onset of their affective illness (mean ± SD age = 23.8 ± 11.7 years) as compared to those who received no anticonvulsants (mean ± SD age = 29.0 ± 12.3 years; $t = 1.7$, df = 64, $p < .10$).

DISCUSSION

Results from the present study are consistent with other reports in the literature which suggest that substance abuse is common in at least one third or more of bipolar patients and may be associated with a poorer course of illness. In addition, the current findings indicate that substance abuse may be linked with mixed mania, as well as increased rates of suicidal ideation and past treatment noncompliance among bipolar patients. In an earlier study of suicidality in mixed versus pure mania, we found that the impact of substance abuse contributed less to suicidality at index than did the presence of mixed mania per se.[16] The present data, in combination with those prior findings, would suggest that substance abuse is an intervening variable in the relationship between suicidality and mixed mania. Substance abuse may be a covariate of mixed mania, which in turn appears to be highly associated with suicidality among bipolar patients.[16–18]

Remission from acute manic episodes during hospitalization was significantly less common for bipolar patients with than without substance abuse histories. Previous alcoholism was the most common form of substance abuse encountered and was associated with a significantly lower proportion of those who showed clinical improvement while hospitalized. Marijuana abuse also was linked with a diminished likelihood of acute remission in the current study, even when controlling for the presence of alcohol abuse/dependence. The relationship between significant marijuana use and functional outcome in psychiatric patients as well as normal subjects has been the subject of ongoing debate.[19] An amotivational syndrome has been described in connection with frequent marijuana use, although substance abuse studies in general have not clearly documented poorer functional outcome for psychiatric patients who abuse cannabinoids. Recent preclinical data also have linked the psychological manifestations of marijuana withdrawal to abnormal elevations of corticotropin-releasing factor (CRF)[20]; and CNS-reinforcing effects of tetrahydrocannabinol exposure have been associated with mu opioid receptor mediation, comparable to that seen in heroin or other opiate abuse pathways.[21] To our knowledge, the present study is one of the first to support the connection between poorer treatment outcome and marijuana abuse in bipolar illness.

Bipolar disorder complicated by substance abuse has previously been associated with a poorer response to pharmacotherapy and more extensive impairment in psychosocial functioning.[2–4] The current findings would support the view that prior drug and alcohol abuse/dependence is associated with a lower likelihood of remission from an acute manic episode, as well as a trend toward slower symptomatic remission. None of the dual-diagnosis bipolar patients in the current study were undergoing active drug or alcohol detoxification during their index hospitalization, and none had active drug use immediately prior to admission; thus, the deleterious effects of substance abuse on acute remission from mania were not caused by acute substance withdrawal or delayed drug metabolism.

Interestingly, however, the dual-diagnosis bipolar patients had received significantly higher peak dosages of lithium as compared to those without substance abuse histories, yet the 2 groups had nearly identical mean peak serum lithium levels. The nonrandomized study design prevents one from drawing definitive conclusions about the potential significance of this observation; however, it is possible that bipolar patients with prior substance abuse may require relatively high levels of lithium to achieve adequate serum lithium levels. The hypothesis that prior substance abuse might interfere with the metabolism or distribution of lithium may warrant further study.

The current data suggesting that past substance abuse may interfere with resolution of an index manic episode may lend support to theories about behavioral sensitization and kindling secondary to alcohol or other psychoactive substance abuse in the longitudinal course of bipolar disorder.[12,13] Prior substance abuse may also contribute to the development of a more severe subtype of bipolar disorder, one involving a higher prevalence of mixed mania, suicidality, medication noncompliance, and poor social support (as reflected by a higher rate of divorce and separation among those with than without comorbid substance abuse). Bipolar patients with past histories of drug or alcohol abuse may be at greater risk for poor treatment outcome due to a range of clinical and psychosocial factors that collectively impede remission and recovery.

Although treatment was not administered in a controlled, randomized fashion, no significant differences were observed in the selection or relative intensities of pharmacotherapy regimens for the bipolar patients with or without substance abuse histories. For the majority of patients, both with and without substance abuse, mean peak dosages and blood levels of mood stabilizers fell within a range generally considered to be therapeutic. Bipolar patients with a history of substance abuse/dependence who were treated with divalproex or carbamazepine had significantly higher rates of eventual remission as compared to those receiving treatment with lithium. This preliminary observation is consistent with previous reports in the

literature which suggest that bipolar patients with comorbid substance abuse may respond preferentially to anticonvulsant mood stabilizers than to lithium.[8] To our knowledge, double-blind, randomized medication trials have not yet been conducted specifically on populations of bipolar patients with comorbid substance abuse. Because such patients represent a significant proportion of all bipolar patients,[1] such studies would seem to be indicated in light of the current findings and those of previous investigators.[7]

The current study is limited by its retrospective design, which did not allow for precise discrimination between substance abuse and dependence. Our estimation of the prevalence of substance abuse in the present cohort is conservative, since patients who may have had bipolar illness but were acutely intoxicated at admission were excluded from the study, in order to minimize the confounding effects of a substance-induced mood disorder on the primary diagnosis and immediate outcome. Data were unavailable regarding pre-index substance abuse treatment, or the duration, age at onset, and extent of past addictive behaviors—features that may play important roles in gauging the full impact of substance abuse on the course of bipolar disorder. The chronology of onset of substance abuse in relation to bipolar illness or prior manic episodes also could not be ascertained for all patients; data in this area are especially important in the case of bipolar disorder since many manic patients engage in alcohol, cocaine, or other drug use as part of the syndrome of recklessness associated with mania.[22–24] In addition, because pharmacotherapy and other inpatient treatments in the present study were administered by patients' physicians based on clinical judgment, rather than by random assignment, caution is warranted in interpreting the data regarding medication use and patterns of remission.

Bipolar patients with substance abuse frequently present with intoxications, potentially as part of the impulsive behavior frequently associated with acute mania,[24] although little is known about the impact of active substance abuse on the course of remission from acute mania. It is possible that because we purposefully excluded intoxicated manic patients from the study sample, we may have underestimated the impact of substance abuse on the short-term course of bipolar disorder. This might be especially true for bipolar patients with cocaine abuse, in which a past history of abuse was not associated with lower remission from acute mania in the current sample; it is possible that the deleterious effects of cocaine in bipolar disorder would be more manifest in the aftermath of acute intoxication.

Bradley and Zarkin[25] found that active substance abuse comorbidity did not lengthen hospital stay for either schizophrenia or affectively ill inpatients in a large database of over 20,000 discharges in Maryland, California, and Arizona. Because of the extremely high comorbidity between substance abuse and bipolar disorder, and the methodologic complexities in accurately diagnosing and studying intoxicated bipolar patients, further research using prospective designs is needed to elucidate the effects of concurrent substance abuse on rates and patterns of symptom remission among hospitalized manic patients.

In summary, substance abuse remains a significant clinical problem in at least one third or more of hospitalized bipolar patients. The current findings would suggest that prior substantial drug and alcohol use is associated with lower rates of remission during hospitalizations for acute mania, particularly in the case of alcoholism or marijuana abuse. Bipolar patients with previous substance abuse or dependence also appear significantly more likely to have mixed than pure mania, past treatment noncompliance, and a markedly increased risk for suicidal ideation. These data would also suggest that under naturalistic conditions, pharmacotherapy with divalproex or carbamazepine (alone or in combination with lithium) may be associated with a greater degree of symptom remission and better short-term outcome than is lithium as a sole mood stabilizer. Further studies using controlled, randomized designs are needed to confirm whether anticonvulsant mood stabilizers are, in fact, superior to lithium for acute mania complicated by substance abuse or dependence.

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

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