Overdiagnosis of Bipolar Disorder Among Substance Use Disorder Inpatients With Mood Instability

Joseph F. Goldberg, M.D.; Jessica L. Garno, Ph.D.; Ann M. Callahan, M.D.; Denise L. Kearns, B.A., R.N.; Barry Kerner, M.D.; and Sigurd H. Ackerman, M.D.

Background: Among substance use disorder (SUD) patients, mood instability and high-risk behaviors may suggest the presence of bipolar disorder. However, active substance abuse impedes efforts to diagnose bipolar illness validly in patients with mood complaints.

Method: The authors retrospectively reviewed records for 85 adults admitted sequentially over a 1-year period (August 1, 2005, to July 31, 2006) to a private inpatient dual-diagnosis unit for substance abuse/dependence and mood disorders. A senior research psychiatrist conducted diagnostic interviews based on DSM-IV criteria to ascertain current and lifetime manic or hypomanic episodes during abstinent periods.

Results: Only 33% of subjects with suspected bipolar diagnoses (28/85) met DSM-IV criteria for bipolar I or II disorder. DSM-IV bipolar patients were significantly older ($p = .029$) and more likely to have made past suicide attempts ($p = .027$), abused fewer substances ($p = .027$), and were less likely to abuse cocaine ($p < .001$) than those failing to meet DSM-IV criteria. Inability to affirm bipolar diagnoses most often resulted from insufficient DSM-IV "B" symptoms associated with mania or hypomania (55% or 45/82), inability to identify abstinent periods for assessing mood symptoms (36%, 29/81), and inadequate durations of manic/hypomanic symptoms for DSM-IV syndromic criteria (12%, 10/84). Patients not meeting DSM-IV criteria were most often presumed to have bipolar disorder solely on the basis of the presence of mood instability, although this feature held little predictive value for DSM-IV bipolar diagnoses.

Conclusions: Many patients with active SUDs who are diagnosed in the community with bipolar disorder may not actually meet DSM-IV criteria for bipolar I or II disorder. Caution must be exercised when attempting to diagnose such patients, particularly when mood instability or cocaine use is present.

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Received Dec. 16, 2007; accepted Mar. 17, 2008. From the Department of Psychiatry, Mount Sinai School of Medicine, New York, N.Y. (Dr. Goldberg) and the Affective Disorders Research Program, Silver Hill Hospital, New Canaan, Conn. (Drs. Goldberg, Garno, Callahan, Kerner, and Ackerman and Ms. Kearns).

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Dr. Goldberg is a consultant for Eli Lilly and GlaxoSmithKline and is a member of the speakers/advisory boards for Abbott Laboratories, AstraZeneca, Eli Lilly, and GlaxoSmithKline. Dr. Callahan is a member of the speakers/advisory boards for Pfizer, AstraZeneca, and Cephalon. Drs. Garno, Kerner, and Ackerman and Ms. Kearns have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Corresponding author and reprints: Joseph F. Goldberg, M.D., 128 East Ave., Norwalk, CT 06851 (e-mail: Joseph.goldberg@mssm.edu).

During the past 15 years, a growing number of observational studies and community-based surveys have pointed to the frequency with which unipolar depression may be overdiagnosed relative to bipolar illness among mood disorder patients.[1–3] Simultaneously, the field has witnessed a dramatic broadening of the construct of bipolar illness beyond its *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) operational definition, encompassing a more heterogeneous range of mood-related problems thought to exist along a spectrum of severity.[4] Perhaps partly in response to the historical underrecognition of bipolar disorder relative to schizophrenia[5] or unipolar depression[3] in the United States, diagnoses of bipolar disorder have risen sharply in the past decade.[6] However, the rigor with which clinicians arrive at a diagnosis of bipolar disorder, in the context of its broader differential diagnosis, has received little study.

One source of diagnostic uncertainty may involve the frequency with which bipolar or other mood disturbances are accompanied by substance use disorders (SUDs).[7] In the case of co-occurring affective symptoms and substance misuse, diagnostic evaluation requires a longitudinal assessment of historical periods of abstinence from substances in order to assess the nature and extent of affective symptoms. Most individuals with substance-induced mood disorders have recognizable histories of affective disorders unrelated to alcohol or drug abuse,[8] although existing studies in this area have seldom addressed

FOR CLINICAL USE

- Only a minority of active cocaine and other substance use disorder patients who are thought to have bipolar disorder by community providers actually meet formal DSM-IV criteria for bipolar I or II disorder.
- Careful screening for a suspected diagnosis of bipolar disorder in substance use disorder patients with mood symptoms requires the identification of lifetime abstinent periods in which to assess mood, with careful attention to the associated DSM-IV criteria for mania or hypomania, including cognitive, behavioral, speech-language, motor, and sleep disturbances.

potential differences between unipolar versus bipolar disorders. Hasin and colleagues[9] devised a structured research interview that was reported to facilitate accurate diagnoses of affective disorders among individuals with SUDs; however, those authors reported a substantially lower degree of interrater reliability among interviewers attempting to diagnose bipolar disorder ($\kappa = 0.40$) than among those attempting to diagnose unipolar mood disorders ($\kappa = 0.70$).

Naturalistic studies of patients seeking treatment for SUDs illustrate the difficulty of screening for bipolar disorder. One retrospective chart review among male inpatients with SUDs (predominantly alcoholism) found that among those identified with comorbid bipolar disorder on admission, about half had previously not been identified as having bipolar disorder as outpatients in the community.[10] Another recent report suggested that only a minority of adults with substance use disorders who were previously identified in the community as having bipolar disorder in fact met formal DSM-IV criteria for bipolar I or II disorder (43%).[11]

The present study was designed to further investigate the aforementioned findings using a larger sample size and to better characterize clinical features in patients with co-occurring SUDs and mood disorders who did versus did not meet formal DSM-IV lifetime criteria for bipolar I or II disorder. Our goals were to (1) determine the prevalence of bipolar I or II disorder among SUD inpatients who had been identified in the community as having bipolar disorder, (2) identify obstacles for determining the presence or absence of a bipolar diagnosis, and (3) describe features that differentiate SUD patients whose suspected diagnoses of bipolar disorder could or could not be affirmed.

METHOD

Hospital records were reviewed for 85 adults (aged 18–59 years) who were admitted sequentially over a 1-year period from August 1, 2005, to July 31, 2006, to a specialized 16-bed dual-diagnosis mood and substance use disorders inpatient unit at Silver Hill Hospital in New Canaan, Conn. Patients were included in the study group if they carried a diagnosis of bipolar disorder from their outpatient psychiatrist and received a provisional or rule-out admission diagnosis of bipolar disorder based on their initial reported history. For the study group as a whole, mean ± SD age was 34.7 ± 11.3 years, and 53% (N = 45) were female. Fifty-eight percent (N = 49) were employed full-time, 4% (N = 3) were employed part-time, and 39% (N = 33) were unemployed on admission. All subjects had private health insurance or Medicare, and none had Medicaid.

All patients underwent formal, systematic diagnostic interviews conducted by a senior research psychiatrist (J.F.G.) with expertise in bipolar disorder who was trained and experienced in administration of the Structured Clinical Interview for the DSM-IV.[12] These interviews assessed the current and lifetime presence of DSM-IV "A" criteria (i.e., periods of abnormally and persistently elevated, expansive, or irritable mood) and the 7 associated "B" criteria for a manic or hypomanic episode: (1) inflated self-esteem or grandiosity, (2) decreased need for sleep, (3) increased or rapid speech, (4) flight of ideas or racing thoughts, (5) distractibility, (6) increased goal-directed activity of psychomotor agitation, and (7) excessive involvement in pleasurable activities with high potential for painful consequences.[13] Possible manic or hypomanic symptom constellations were evaluated relative to lifetime periods of abstinence from drugs or alcohol. In addition, subjects were asked during diagnostic interviews if they had periods of "rapid alternations in mood or 'mood swings' in response to daily life stresses" as an indicator of *mood instability*.

Preadmission history data were also gathered by discussion with patients' outpatient treating clinicians as well as through mandatory meetings with immediate family members. Evidence to support or refute DSM-IV diagnoses of bipolar I or II disorder were reviewed by consensus conference among the authors to establish best-estimate confidence in lifetime diagnoses of bipolar I or II disorder based on a review of DSM-IV symptom criteria. Reasons for an inability to affirm the presence or absence of bipolar I or II diagnoses were identified and considered

Table 1. Demographic and Clinical Characteristics of Patients Diagnosed With Comorbid Substance Use Disorder and Bipolar Disorder

Feature	Subjects Meeting DSM-IV Bipolar Disorder Criteria (N = 28)	Subjects Failing to Meet DSM-IV Bipolar Disorder Criteria (N = 57)	Risk Ratio	95% CI	t	χ^2	df	p Value
Gender, N (%)								
Male	11 (39)	29 (51)	1.60	0.64 to 4.01	…	1.013	1	.314
Female	17 (61)	28 (49)						
Ethnicity, N (%)								
White	24 (86)	53 (93)	2.21	0.51 to 9.58	…	1.163	1	.281
Nonwhite	4 (14)	4 (7)						
History of suicide attempt, N (%)[a]								
Present	13 (52)	14 (26)	3.02	1.12 to 8.16	…	4.913	1	.027
Absent	12 (48)	39 (74)						
Required medication for detoxification, N (%)[a]								
Yes	4 (16)	17 (32)	2.48	0.74 to 8.36	…	2.231	1	.135
No	21 (84)	36 (68)						
Age, mean ± SD, y	39.0 ± 10.6	32.6 ± 11.2	…	…	2.22	…	76	.029
Age at onset for mood diagnosis, mean ± SD, y	27.3 ± 10.1	23.2 ± 10.8	…	…	1.31	…	70	.195
Age at onset for first substance abuse, mean ± SD, y	20.7 ± 10.5	17.8 ± 9.3	…	…	1.28	…	70	.204
No. of hospitalizations, mean ± SD	2.1 ± 2.4	2.3 ± 3.1	…	…	0.36	…	76	.722
No. of substances, mean ± SD	2.1 ± 1.1	2.8 ± 1.3	…	…	2.25	…	82	.027

[a]Complete data were available on suicide attempt histories for 25 of 28 subjects with bipolar disorder and on the necessity of medication for detoxification in 53 of 57 bipolar disorder subjects.
Abbreviation: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.
Symbol: … = not applicable.

in subsequent analyses. For cases in which a patient was readmitted during the 1-year study period, the later record was used and information was culled from the discharge summary and original records from the earlier admission. All inpatient treatment was administered under naturalistic conditions by the same psychiatrist for all patients (J.F.G.).

Information regarding age at onset, past and current treatments, hospitalizations and detoxifications, and related clinical features were harvested from clinical charts, obtained originally by the treating psychiatrist as well, with corroboration from nursing notes and social work histories.

Statistical analyses were conducted using SPSS version 11.5 (SPSS Inc., Chicago, Ill.). Dichotomous variables were analyzed by χ^2 tests with accompanying risk ratios and 95% confidence intervals. Continuous variables were compared using independent t tests. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for individual DSM-IV–associated B criteria for mania or hypomania and the presence of a lifetime manic or hypomanic episode. All statistical tests were 2-tailed with an α level of .05. Analyses were not corrected for multiple comparisons due to their exploratory, hypothesis-generating nature.

A waiver for informed consent to conduct the present chart review was obtained from the Western Institutional Review Board (Olympia, Wash.).

RESULTS

Table 1 summarizes demographic and clinical characteristics of patients who did (N = 28; 33%) or did not (N = 57; 67%) meet lifetime DSM-IV criteria for bipolar I disorder (16/85 subjects) or bipolar II disorder (12/85). Importantly, subjects who in fact met DSM-IV criteria for bipolar disorder with an SUD were significantly more likely to have made a lifetime suicide attempt as compared to those who failed to meet DSM-IV criteria for bipolar disorder; they also were significantly older and abused fewer substances as compared to those not meeting DSM-IV bipolar disorder criteria.

Non–mutually exclusive reasons for the inability to affirm lifetime bipolar I or II diagnoses included failure to meet a sufficient number of DSM-IV–associated B criteria symptoms for mania or hypomania (45/82 evaluable subjects, or 55%), failure to meet DSM-IV duration criteria for mania or hypomania (10/84 evaluable subjects, or 12%), an inability to identify abstinent periods in which to evaluate the presence and nature of mood symptoms

(29/81 evaluable subjects, or 36%), and the identification of mood episodes that occurred solely within a 4-week period following significant substance misuse (i.e., mood disorders secondary to intoxication or withdrawal states, per criteria specified in DSM-IV) (51/81 evaluable subjects, or 63%). At the time of admission, 80% of patients (N = 68) themselves expressed concern about, or believed that they had, a diagnosis of bipolar disorder. Only 37% of patients who believed themselves to have bipolar diagnoses (25/68) actually met DSM-IV criteria for bipolar I or II disorder. However, 25 of 27 DSM-IV bipolar subjects with complete data (93%) indicated belief on their own part about having a diagnosis of bipolar disorder.

Rates of achieving DSM-IV bipolar I or II diagnoses did not differ significantly for subjects whose predominant mood state was manic (3/26 DSM-IV bipolar subjects [12%] vs. 4/51 not meeting DSM-IV criteria [8%]), depressed (15/26 DSM-IV bipolar subjects [58%] vs. 18/51 not meeting DSM-IV criteria [35%]), or mixed (8/26 DSM-IV bipolar subjects [31%] vs. 7/51 not meeting DSM-IV criteria [14%]). However, for the remaining 22 subjects for whom a predominant mood polarity at hospitalization could not be determined (e.g., due to "irritability" or "mood swings" as the sole affective characteristics), none met DSM-IV criteria for bipolar I or II disorder.

Naturalistic pharmacotherapy at the time of hospitalization was similar between the 28 DSM-IV bipolar I or II subjects and the 57 subjects who failed to meet DSM-IV criteria for mania or hypomania. Bipolar subjects were receiving a mean ± SD of 2.0 ± 1.3 psychotropic medications, as compared to 1.8 ± 1.1 medications among the subjects who failed to meet DSM-IV bipolar I or II criteria (nonsignificant). Subjects in either group had most commonly been taking an antidepressant (48% [13/27] of bipolar subjects and 53% [29/55] of subjects who failed to meet DSM-IV bipolar disorder criteria), and/or an anticonvulsant mood stabilizer (i.e., divalproex, carbamazepine, or lamotrigine; 59% [16/27] of bipolar subjects and 40% [22/55] of subjects who failed to meet DSM-IV bipolar I or II criteria), an atypical antipsychotic (48% [13/27] of bipolar subjects and 45% [25/55] of subjects failing to meet DSM-IV criteria), and lithium (12% [3/26] of bipolar subjects and 11% [6/54] of those failing to meet DSM-IV criteria) (nonsignificant for all analyses). Use of an anticraving drug (e.g., naltrexone or acamprosate) was infrequent and not significantly different between the 2 groups (7% [2/27] of bipolar subjects and 4% [2/55] of subjects not meeting DSM-IV criteria). Pharmacologic detoxification from alcohol, sedative-hypnotics, or opiates during the index hospitalization was needed by 16% (4/25) of patients with bipolar disorder and 32% (17/53) of those who failed to meet DSM-IV bipolar I or II criteria, although this difference was not statistically significant.

Table 2 depicts the distribution of mood states and associated DSM-IV B criteria for mania or hypomania. As can be seen, patients who met DSM-IV criteria for bipolar I or II disorder were significantly more likely than those who did not to have mood elevation, decreased need for sleep, rapid speech, flight of ideas or racing thoughts, distractibility, and increased goal-directed activity. The groups did not differ significantly in lifetime prevalence rates of irritable mood, grandiosity, or engagement in high-risk behaviors. By contrast, subjects who did not meet DSM-IV bipolar I or II criteria were significantly more likely to have mood instability.

Table 2 also presents the sensitivity, specificity, and positive and negative predictive values of individual DSM-IV B criteria lifetime symptoms associated with mania or hypomania relative to research lifetime diagnoses of bipolar I or II disorder. Notably, mood elevation demonstrated the highest combined positive and negative predictive values, followed by racing thoughts, increased goal-directed activity, and decreased need for sleep. These characteristics were relatively infrequent among patients who failed to meet DSM-IV bipolar I or II criteria. Mood instability per se, identified in over 70% of patients failing to meet DSM-IV criteria for bipolar disorder, was relatively uncommon in patients with true bipolar disorder and had the lowest positive predictive value of any symptom for diagnosing bipolar disorder. Similarly, *irritability*—hypothesized by some as a key differentiator of bipolar from unipolar depression[14]—showed a relatively low positive predictive value for diagnosing bipolar I or II disorder.

Bipolar subjects abused a mean ± SD of 2.1 ± 1.1 substances, as compared to more (2.8 ± 1.3) among patients who failed to meet DSM-IV bipolar I or II diagnoses ($t = 2.248$, $df = 82$, $p = .027$). Cocaine abuse or dependence was significantly more common among patients who failed to meet DSM-IV bipolar disorder criteria (38/56, or 68%) than in patients who did meet DSM-IV bipolar disorder criteria (6/27, 22%) ($\chi^2 = 15.230$, $df = 1$, $p < .001$). No significant or near-significant differences emerged between the 2 diagnostic groups in prevalence rates of abuse or dependence involving other stimulants (9/56 [16%] not meeting DSM-IV bipolar disorder criteria vs. 3/28 [11%] meeting criteria), alcohol (32/56 [57%] not meeting DSM-IV criteria vs. 18/28 [64%] meeting DSM-IV criteria), cannabis (24/56 [43%] not meeting DSM-IV criteria vs. 12/28 [43%] meeting DSM-IV criteria), sedative-hypnotics (22/56 [39%] not meeting DSM-IV criteria vs. 9/28 [32%] meeting DSM-IV criteria), opiates (25/56 [45%] not meeting DSM-IV criteria vs. 8/28 [29%] meeting DSM-IV criteria), or hallucinogens (5/56 [9%] not meeting DSM-IV criteria vs. 1/28 [4%] meeting DSM-IV criteria).

A final series of analyses were undertaken in light of the fact that DSM-IV criteria do not permit making a

Table 2. Distribution of Individual Manic or Hypomanic Symptoms in Subjects Meeting or Not Meeting DSM-IV Criteria for Bipolar Disorder[a]

Variable	Subjects Meeting DSM-IV Bipolar Disorder Criteria (N = 28), N/N (%)	Subjects Failing to Meet DSM-IV Bipolar Disorder Criteria (N = 57) , N/N (%)	χ^2 (df)	p Value	Sensitivity	Specificity	PPV	NPV
DSM-IV "A" criteria								
Mood elevation	20/25 (80)	5/54 (9)	39.534 (1)	< .001	0.80	0.91	0.80	0.91
Irritable mood	8/21 (38)	17/54 (31)	0.298 (1)	.585	0.38	0.69	0.32	0.74
Mood instability[b]	7/25 (28)	42/55 (76)	16.938 (1)	< .001	0.28	0.24	0.14	0.42
DSM-IV "B" criteria								
Grandiosity	3/22 (14)	4/56 (7)	0.815 (1)	.367	0.14	0.93	0.43	0.73
Decreased need for sleep	18/24 (75)	11/56 (20)	22.278 (1)	< .001	0.75	0.80	0.62	0.88
Rapid speech	11/18 (61)	11/55 (20)	10.886 (1)	.001	0.61	0.80	0.50	0.86
Flight of ideas/racing thoughts	18/20 (90)	10/55 (18)	32.335 (1)	< .001	0.90	0.82	0.64	0.96
Distractibility	7/18 (39)	2/55 (4)	15.593 (1)	< .001	0.65	0.02	0.17	0.14
Increased goal-directed activity	20/25 (80)	8/56 (14)	32.999 (1)	< .001	0.80	0.86	0.71	0.91
High risk behavior	13/22 (59)	23/55 (42)	1.883 (1)	.170	0.59	0.58	0.36	0.78

[a]Denominators vary in individual analyses, as shown, based on availability of complete data.
[b]Not a DSM-IV symptom of bipolar disorder.
Abbreviations: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; NPV = negative predictive value; PPV = positive predictive value.

diagnosis of bipolar disorder in SUD patients for whom a sustained abstinence period cannot be identified (and, thus, such individuals are assumed not to have bipolar disorder, an assumption that may or may not be accurate). Recognizing the high prevalence of such patients in community treatment settings, we undertook exploratory analyses to compare characteristics of subjects for whom a period of SUD abstinence could or could not be identified. Subjects for whom a period of abstinence *could* be identified were significantly younger (mean ± SD age = 30.1 ± 10.1 years) than those without identifiable abstinent periods (mean ± SD age of 37.9 ± 11.3 years) ($t = 3.044$, $df = 78$, $p = .003$); used more substances (3.2 ± 1.1 vs. 2.1 ± 1.1, respectively; $t = 4.051$, $df = 78$, $p < .001$); more often abused cocaine (24/29 subjects with identifiable abstinence vs. 16/50 without identifiable abstinence; $\chi^2 = 18.919$, $df = 1$, $p < .001$); more often abused opiates (16/29 with identifiable abstinence vs. 16/51 without identifiable abstinence; $\chi^2 = 4.633$, $df = 1$, $p = .037$); and tended more often to be nonwhite (0/30 with identifiable abstinence vs. 6/51 without identifiable abstinence; $\chi^2 = 3.812$, $df = 1$, $p = .051$). The groups showed no significant or near-significant differences from one another in other substances, gender, employment status, current mood state, history of suicide attempts, number of hospitalizations, or age at onset of substance misuse or of mood disorder.

DISCUSSION

Consistent with prior reports in the literature,[11] the present findings indicate that only a minority of patients with alcohol abuse or dependence or SUDs suspected of having bipolar disorder actually meet formal DSM-IV criteria for a lifetime manic or hypomanic episode. The possibility remains that some patients identified in the present cross-sectional study may *subsequently* experience a first lifetime manic or hypomanic episode, although given the mean age of 35 years in the current study group, one would epidemiologically expect only a small minority to do so,[15] particularly since individuals with bipolar disorder and comorbid substance abuse typically have childhood-onset or adolescent-onset rather than adult-onset bipolar disorder.[16]

Prior literature has identified patient characteristics that may help to differentiate substance-induced depression from independent depressive disorders in patients with alcohol dependence. These include a greater likelihood among those with independent depressive disorders to have had experience with fewer drugs as well as a more extensive history of suicide attempts.[17] Both of these findings were evident in the current study group, with respect to diagnoses of true bipolar disorder. The present findings are further noteworthy for the apparent role of cocaine abuse or dependence relative to mood disturbances, insofar as cocaine use was dramatically more common in mood-unstable patients with few other signs of bipolar disorder but comparatively rare in patients with true bipolar I or II disorder. Consistent with this observation, Rosenblum and colleagues[18] noted that among methadone maintenance patients with comorbid mood disturbances who sought treatment for cocaine use, only 27% had an autonomous mood disorder that persisted during periods of abstinence. Prior data linking bipolar spectrum diagnoses with stimulant abuse have been limited by very small sample sizes or else a focus on hyperthymia or other

temperamental characteristics as a proxy for DSM-based diagnoses of bipolar disorder.[19,20] These issues highlight that, from a practical standpoint, clinicians must first pursue aggressive treatment for active cocaine use in patients with mood instability, and ascertain the formal presence of manic or hypomanic symptoms during abstinence, before diagnosing comorbid bipolar disorder. The limited efficacy of existing treatments for cocaine abuse may discourage some practitioners from acknowledging this distinction.

Usual pharmacotherapies for bipolar disorder are often less effective when accompanied by substance misuse,[21,22] leading some observers to assume the necessity for unusually aggressive or novel treatments for bipolar disorder. The present findings indicated that community practitioners undertook comparable rigor in the use of mood-stabilizing agents between subjects who did or did not meet DSM-IV criteria for bipolar illness. Clinicians may tend to pay less attention to the rigorous treatment of active substance use disorders as a prerequisite for the accurate diagnosis and effective treatment of bipolar illness. Naturalistic data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) indicate that less than half of 1% of dual-diagnosis patients with bipolar and substance use disorders receive pharmacotherapies approved by the U.S. Food and Drug Administration for the treatment of alcoholism (e.g., disulfiram or naltrexone) or drug abuse (e.g., methadone, buprenorphine).[23] At the same time, patients with comorbid bipolar and substance use disorders in the STEP-BD cohort were more likely to recover from a prospectively followed affective episode if they first achieved remission from substance abuse/dependence.[24]

Besides the potential for confusing substance-induced mood symptoms with signs of bipolar disorder, the present findings demonstrate the low diagnostic predictive value for 2 clinical features commonly assumed to be suggestive of bipolar disorder: (1) mood instability—a nonpathognomonic phenomenon seen across numerous psychiatric disorders, including borderline personality disorder, posttraumatic stress disorder, and adjustment disorders, among others, and (2) irritability in the absence of psychomotor acceleration and other associated syndromic features of mania or hypomania. Although irritability is often seen in patients with bipolar disorder,[14] it also arises in almost half of unipolar depressed patients, as described in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) cohort).[25]

It is possible that some patients in the current study who did not meet DSM-IV criteria for bipolar I or II disorder might be considered by some to have bipolar disorder not otherwise specified (NOS)—although problematic with such distinctions is their lack of construct validation or inclusion criteria for operational definitions. Empirical efforts toward such operational definitions have been scarce. Using data from the National Comorbidity Survey Replication (NCS-R), Merikangas and colleagues[26] identified "bipolar spectrum disorders" as encompassing patients with bipolar I or II disorder as well as those with at least 2 DSM-IV B criteria for hypomania, regardless of intermorbid depressive episodes—the latter (termed "subthreshold bipolar disorder") carrying a lifetime prevalence of 2.4%. Notably, lifetime SUDs were observed in a minority (35%) of NCS-R subthreshold bipolar disorder patients, with drug dependence per se arising in only 9.5%.[26] Also of note, fewer than 15% of subjects in the current study failed to meet DSM-IV criteria for bipolar disorder by virtue of an inadequate duration of manic or hypomanic symptoms, suggesting that this aspect of a potential NOS diagnosis does not robustly account for the inability to establish DSM-IV diagnoses of bipolar I or II disorder in this population.

There are a number of limitations worth noting in the present study. As in most retrospective studies, participants were subject to recall bias, although efforts were made to minimize this parameter by the acquisition of data from collateral historians and outpatient treating clinicians. Diagnostic interviews were performed by a single unblinded psychiatrist on the basis of a clinical review of DSM-IV symptom criteria; it is possible that findings might have been different had assessments been conducted by multiple interviewers using a formal research diagnostic instrument and who were blinded to study hypotheses. Notably, patient assessments occurred as part of a larger phenomenological study that sought to ascertain a group of DSM-IV bipolar subjects from among all patients admitted to the inpatient clinical service; while it is possible that biases of the interviewing psychiatrist could have led to an underdiagnosis of bipolar I or II disorder, any potential biases would more likely have erred toward inclusion of more (rather than fewer) patients with bipolar disorder. Moreover, members of the diagnostic consensus conference were experienced, doctoral-level research clinicians with prior expertise in the administration and rating of the Structured Clinical Interview for DSM-IV.[12]

The present results are further limited by the fact that they were derived from patients from a single private health care institution, drawing on a population that was mostly employed, carried private health insurance, and had been in treatment prior to admission. Hence, generalizability to other populations (e.g., individuals seen in community mental health centers, health maintenance organization members, or Medicaid recipients) is limited and replication is needed in other settings. Systematic data regarding family histories of bipolar disorder or other psychiatric conditions were available for only a small minority of patients, precluding meaningful statistical analyses. Severity of mood symptoms was not assessed using a standardized rating scale, limiting the ability to examine whether the degree of current manic or

depressive symptoms may have impacted recall of lifetime affective episodes. Finally, confidence in inpatient diagnostic assessments might have been further improved had subsequent longitudinal assessments been conducted following discharge from the hospital; resources were unavailable to conduct such additional evaluations.

The present findings suggest that among SUD patients who report mood instability and irritability, patients and clinicians alike may find themselves inclined to overcompensate for the historical underdiagnosis and underrecognition of bipolar disorder by overdiagnosing it in the absence of corroborative DSM-IV signs of a lifetime manic or hypomanic episode. High co-occurrence rates of alcohol or substance misuse with affective symptoms (particularly mood instability) create particularly difficult challenges for making accurate and rigorous lifetime diagnoses of bipolar disorder; high prevalence rates of alcohol and substance misuse in turn raise concern about the potential undertreatment of SUDs in favor of excessive and possibly unnecessary pharmacotherapy for presumed bipolar illness. At the same time, the current results affirm prior findings of an increased risk for lifetime suicide attempts in patients with true bipolar I or II disorder who have comorbid alcohol or substance abuse/dependence, underscoring the need for careful diagnostic evaluation and focused treatment when both disorders do, in fact, coexist.

Drug names: acamprosate (Campral), buprenorphine (Buprenex, Subutex, and others), carbamazepine (Carbatrol, Equetro, and others), disulfiram (Antabuse), divalproex (Depakote), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), methadone (Methadose, Dolophine, and others), naltrexone (Vivitrol, ReVia, and others).

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

REFERENCES

1. Lish J, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-Depressive Association (National DMDA) survey of bipolar members. J Affect Disord 1994;31:281–294
2. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003 Feb;64(2):161–174
3. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. J Clin Psychiatry 2000;61:804–808
4. Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III and IV. Psychiatr Clin North Am 1999 Sep;22(3):517–534
5. Stoll AL, Tohen M, Baldessarini RJ, et al. Shifts in diagnostic frequencies of schizophrenia and major affective disorders at six North American psychiatric hospitals, 1972–1988. Am J Psychiatry 1993;150:1668–1673
6. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996–2004. Biol Psychiatry 2007 Jul;62(2):107–114
7. Grant BF, Stinson FS, Hasin DS, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and Axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2005 Oct;66(10):1205–1215
8. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004;61:807–816
9. Hasin D, Samet S, Nunes E, et al. Diagnosis of comorbid psychiatric disorders in substance users assessed with the Psychiatric Research Interview for Substance and Mental Disorders for DSM-IV. Am J Psychiatry 2006;163:689–696
10. Albanese MJ, Clodfelter RC Jr, Pardo TB, et al. Underdiagnosis of bipolar disorder in men with substance use disorder. J Psychiatr Pract 2006;12:124–127
11. Stewart C, El-Mallakh RS. Is bipolar disorder overdiagnosed among patients with substance abuse? Bipolar Disord 2007;9:646–648
12. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-Patient Edition (SCID-I/NP). New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002
13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
14. Benazzi F. Possible bipolar nature of irritability in major depressive disorder [letter with reply]. J Clin Psychiatry 2005 Aug;66(8):1072–1073
15. Perlis RH, Miyahara S, Marangell LB, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2004;55:875–881
16. Goldstein BI, Levitt AJ. Further evidence for a developmental subtype of bipolar disorder defined by age at onset: results from the national epidemiologic survey on alcohol and related conditions. Am J Psychiatry 2006;163:1633–1636
17. Shuckit MA, Tipp JE, Bergman M, et al. Comparison of induced and independent major depressive disorders in 2,945 alcoholics. Am J Psychiatry 1997;154:948–957
18. Rosenblum A, Fallon B, Magura S, et al. The autonomy of mood disorders among cocaine-using methadone patients. Am J Drug Alcohol Abuse 1999;25:67–80
19. Camacho A, Akiskal HS. Proposal for a bipolar-stimulant spectrum: temperament, diagnostic validation, and therapeutic outcomes with mood stabilizers. J Affect Disord 2005;85:217–230
20. Maremmani I, Pacini M, Perugi G, et al. Cocaine abuse and the bipolar spectrum in 1090 heroin addicts: clinical observations and a proposed pathophysiologic model. J Affect Disord 2008 Feb;106(1–2):55–61
21. Tohen M, Waternaux CM, Tsuang MT, et al. Four-year follow-up of twenty-four first-episode manic patients. J Affect Disord 1990;19:79–86
22. Goldberg JF, Garno JL, Leon AC, et al. A history of substance abuse complicates remission from acute mania in bipolar disorder. J Clin Psychiatry 1999 Nov;60(11):733–740
23. Simon NM, Otto MW, Weiss RD, et al. Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. J Clin Psychopharmacol 2004;24:512–520
24. Weiss RD, Ostacher MJ, Otto MW, et al. Does recovery from substance use disorder matter in patients with bipolar disorder? J Clin Psychiatry 2005 Jun;66(6):730–735
25. Perlis RH, Fraguas R, Fava M, et al. Prevalence and clinical correlates of irritability in major depressive disorder: a preliminary report from the Sequenced Treatment Alternatives to Relieve Depression Study. J Clin Psychiatry 2005 Feb;66(2):159–166
26. Merikangas K, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2007;64:543–552

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