ORIGINAL ARTICLE

Prevalence and Characteristics of Undiagnosed Bipolar Disorders in Patients With a Major Depressive Episode

The BRIDGE Study

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Context: Major depressive disorder, the most common psychiatric illness, is often chronic and a major cause of disability. Many patients with major depressive episodes who have an underlying but unrecognized bipolar disorder receive pharmacologic treatment with ineffective regimens that do not include mood stabilizers.

Objective: To determine the frequency of bipolar disorder symptoms in patients seeking treatment for a major depressive episode.

Design: Multicenter, multinational, transcultural, cross-sectional, diagnostic study. The study arose from the initiative Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE).

Setting: Community and hospital psychiatry departments.

Patients: Participants included 5635 adults with an ongoing major depressive episode.

Main Outcome Measures: The frequency of bipolar disorder was determined by applying both *DSM-IV-TR* criteria and previously described bipolarity specifier criteria. Variables associated with bipolarity were assessed using logistic regression.

Results: A total of 903 patients fulfilled *DSM-IV-TR* criteria for bipolar disorder (16.0%; 95% confidence interval, 15.1%-17.0%), whereas 2647 (47.0%; 95% confidence interval, 45.7%-48.3%) met the bipolarity specifier criteria. Using both definitions, significant associations (odds ratio >2; $P<.001$) with bipolarity were observed for family history of mania/hypomania and multiple past mood episodes. The bipolarity specifier additionally identified significant associations for manic/hypomanic states during antidepressant therapy, current mixed mood symptoms, and comorbid substance use disorder.

Conclusions: The bipolar-specifier criteria in comparison with *DSM-IV-TR* criteria were valid and identified an additional 31% of patients with major depressive episodes who scored positive on the bipolarity criteria. Family history, illness course, and clinical status, in addition to *DSM-IV-TR* criteria, may provide useful information for physicians when assessing evidence of bipolarity in patients with major depressive episodes. Such an assessment is recommended before deciding on treatment.

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MAJOR DEPRESSIVE DISORDERS (MDDs) are considered to be the most frequently encountered form of mental illness.[1] The Global Burden of Disease study[2] identified depression as having the third greatest impact in terms of disability-adjusted life-years in Europe and the greatest impact of all physical and mental diseases in the Americas. It is one of the most frequent medical causes of lost productivity in the workplace and is associated with considerable social and functional impairment.[3,4]

Although recurrent major depressive episodes (MDEs) are characteristic of pure MDD (unipolar depression), they also occur frequently in patients with bipolar disorder. Because depressive episodes are generally more frequent and distressing than hypomanic episodes in bipolar disorder, patients usually seek treatment for depression, which is more easily diagnosed by the physician, whereas in patients with hypomanic or subthreshold bipolar features, the disorder may be unrecognized or misdiagnosed as unipolar MDD.[5,6] Several studies[7-9] have indicated that bipolar features can be detected, if looked for carefully, in approximately one-quarter of patients diagnosed with MDD. Other studies, but not all, suggest that the true rate

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of bipolar features in MDD may be closer to 50%.[5,10-13] Recent large studies have reported rates of bipolar features in MDEs in the range of 40%. In a survey of patients with bipolar disorder, Hirschfeld et al[14] reported that two-thirds were initially misdiagnosed with MDD and that these patients had consulted a mean of 4 physicians for their mood symptoms before receiving a definitive diagnosis of bipolar disorder.

The issue of underrecognized features indicative of bipolar disorder among patients with ostensibly unipolar depression is of high clinical importance but is controversial, largely consequent to the limited empiric data in the literature. Such potential misdiagnosis has important consequences for care because such patients are at increased risk for suicide, and their condition might deteriorate or become treatment refractory[15] if bipolar symptoms are not managed appropriately. These patients do not respond adequately to treatment with antidepressants alone, which may aggravate bipolar symptoms or trigger a manic or hypomanic episode.[16] Such patients may be more appropriately treated with mood stabilizers or with certain atypical antipsychotics.[17]

Consequent to these concerns about the reliability of differential diagnosis of MDD and bipolar disorder and the substantially different treatment approaches indicated for each condition, several initiatives to develop modified criteria for bipolar disorder and to reanalyze relevant large data sets have been undertaken. Angst et al[11,18] developed and validated bipolarity specifier criteria that consider family history and illness course. Specifier criteria for bipolar I disorder included manic episodes with a further gate question (increased activity/energy) and did not apply any exclusion criteria. In a validation study (J.A., J.-M.A., C.L.B., G.P., E.V., and A.H.Y., unpublished data, April 2008) with the current Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE) sample, family history of mania and course validators (eg, early onset and recurrence) provided greater sensitivity in identification of patients with bipolar features than did *DSM-IV* diagnostic criteria. Recent reanalyses[12,13] of 2 large epidemiologic studies that applied bipolar specifier–type criteria have reported rates positive for these modified criteria of approximately 40% in community-dwelling individuals with MDD diagnosed according to *DSM-IV* criteria. Each of the reanalyses found evidence for an increased validity for some, but not all, of the broader bipolar concept variables compared with the *DSM-IV* classification. The primary objective of this study was to determine the frequency of bipolar symptoms in patients consulting a psychiatrist for a current MDE. Bipolarity was defined both on the basis of the *DSM-IV-TR* criteria and by the bipolarity specifier criteria.[11] Secondary objectives were to describe the rates of bipolar disorder by these 2 sets of criteria in a generalizable group of patients with MDEs and to describe comorbidity and other clinical characteristics.

METHODS

STUDY DESIGN

This multicenter, cross-sectional diagnostic study was conducted by 521 hospital-based or community psychiatrists in 18 countries in Asia, Europe, and Africa between April 1, 2008, and April 30, 2009. Sanofi-aventis clinical research liaison staff in the respective countries aided in identifying a key senior psychiatrist to coordinate the participation by country. Once selected, that psychiatrist chose participating centers that were both psychiatric departments of hospitals/clinics and independent psychiatric practices. Their selection was intended to provide a representative impression of the health care practices in each country. In each center, 10 to 20 patients were to be included in the study. The psychiatrists in turn consecutively recruited all adults with a diagnosis of MDE according to *DSM-IV* criteria who were seeking evaluation and treatment. At this evaluation, the participating psychiatrists completed the questionnaire that the steering committee had developed on patients' clinical features and sociodemographic variables. Written patient consent was obtained after the individual had received detailed written and verbal information and the existence of a major depressive syndrome according to *DSM-IV* criteria was confirmed. In each study center, all potentially suitable patients were consecutively screened for study inclusion and asked to participate.

Because of the widely separated locations of the countries and the psychiatrists participating within them, the steering committee viewed it unfeasible to provide specific training for the selected psychiatrists at the participating centers. The evaluation packet was structured to use skills that fully trained psychiatrists would have and routinely apply in conducting an initial evaluation of an acutely ill patient. No rating scales requiring calibration with a standard were incorporated. For these reasons, the investigative psychiatrists were instructed to follow their usual practice, as training might have altered these practices and been seen as a biasing factor.

PATIENTS

The study included patients aged 18 years or older fulfilling *DSM-IV-TR* diagnostic criteria for a current MDE at the time of the evaluation, which was systematically confirmed with a checklist.[19] Each center maintained an anonymous patient screening registry of all included patients with an MDE so that the rate of participation could be estimated. Exclusion criteria were acute psychiatric or nonpsychiatric emergencies, prominent somatic illness, or inability to complete the 32-item revised Hypomania Checklist.[20]

DATA COLLECTION

Patients were evaluated at a single assessment with the participating psychiatrist, who completed a case report form for each patient, incorporating inclusion criteria, sociodemographic variables (age, sex, and marital status), inpatient or outpatient status, history of psychiatric symptoms (mood symptoms, postpartum depression, and suicide attempts), previous psychiatric hospitalization, features of the current depressive episode, bipolar symptoms listed in the *DSM-IV-TR* diagnostic criteria for bipolar disorder (J.A., J.-M.A., C.L.B., G.P., E.V., and A.H.Y., unpublished data, April 2008), known risk factors for bipolar disorder, previous response to antidepressants, current treatment, and functional status determined by the physician using the Global Assessment of Functioning.[21] Comorbidity was assessed using the Mini International Neuropsychiatric Interview[22] and diagnosed using symptom checklists by *DSM-IV TR* criteria for substance abuse and addiction, panic disorders, obsessive-compulsive disorders, social phobias, generalized anxiety disorders, eating disorders, borderline personality disorders, and attention-deficit/hyperactivity disorder (results to be reported elsewhere). Separate sections on hypomania/mania and the Mini International Neuropsychiatric Interview *DSM-IV* di-

agnostic interview were applied. Patients' diagnosis on inclusion to the study was entered as bipolar disorder, type I/type II: yes/no.

A family history of mania, hypomania, or bipolar disorder in parents, siblings, or children was assessed using questions addressing this item in the case report form. Patients completed the 32-item revised Hypomania Checklist themselves.

OUTCOME MEASURES

The primary evaluation criterion was the frequency of bipolar disorder. This was determined as the proportion of patients fulfilling criteria for bipolar disorder according to the *DSM-IV-TR* criteria and the bipolarity specifier proposed by Angst et al.[11,18] This bipolarity specifier attributes a diagnosis of bipolar disorder in patients who experienced an episode of elevated mood, an episode of irritable mood, or an episode of increased activity with at least 3 of the symptoms listed under Criterion B of the *DSM-IV-TR* associated with at least 1 of the 3 following consequences: (1) unequivocal and observable change in functioning uncharacteristic of the person's usual behavior, (2) marked impairment in social or occupational functioning observable by others, or (3) requiring hospitalization or outpatient treatment. No minimum duration of symptoms was required and no exclusion criteria were applied. Bipolar-specifier criteria include all cases meeting *DSM-IV* criteria for bipolar I and II disorders as well as additional cases excluded by *DSM-IV* exclusionary criteria (eg, symptoms occurring during antidepressant treatment).

STATISTICAL ANALYSIS

The target number of patients to be included in the study was estimated using a priori power calculations based on an anticipated 7% prevalence of *DSM-IV* bipolar I disorder (the most restrictive diagnostic category) in patients with MDD (the prevalence rate reported in an epidemiologic study from France[8]), used to determine this prevalence in each participating country with a precision of ±3%. This required enrollment of at least 300 patients in each country to yield a total sample size of approximately 6000 patients. Frequency estimates were determined with 95% confidence intervals (CIs). All statistical analyses were 2-sided, and a probability level of .05 was established as statistically significant.

The association between an assigned diagnosis of bipolar disorder according to *DSM-IV-TR* or the bipolar-specifier criteria and patient characteristics was explored using logistic regression analysis. We chose 15 characteristics known to be associated with a diagnosis of bipolar disorder.[13,17,23-28] Each item was required to assess a variable relatively independent of all others. These variables were (1) sex; (2) age younger than 30 years at development of first symptoms; (3) seasonality of mood episodes; (4) 2 or more previous mood episodes; (5) history of suicide attempts; (6) hypomania/mania among first-degree relatives; (7) previous response to antidepressant therapy with mania/hypomania or mood lability (2 items); (8) duration of current depressive episode of 1 month or less; (9) current depressive symptoms atypical, mixed, or psychotic; and (10) current psychiatric comorbidities. Sex was included because MDD is approximately 2 times more prevalent in women,[25] whereas bipolar disorder has a comparable prevalence in men and women.[24] In addition, 3 control variables were included: inpatient vs outpatient status, geographic region from which the sample was drawn (Central Europe [reference group in logistic regression], East Europe, Iberia, Arabic countries, or East Asia), and a dichotomous variable specifying whether a patient had been recruited using a screening registry. An analog univariable, followed by a multivariable stepwise logistic regression analysis, was performed to assess the association of these variables with assigned bipolar diagnosis. The strength of the associations is presented as odds ratios (ORs) with 95% CIs.

ETHICS

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment), Good Epidemiologic Practice, and the International Epidemiological Association European Federation Guidelines for proper conduct of epidemiologic research, as well as pertinent national legal and regulatory requirements. Written informed consent was obtained from each patient. The protocol was submitted to and approved by the appropriate local ethics committee in each country. Each patient's name was replaced by a number in the study database to ensure confidentiality and conformed to the relevant national legislation.

RESULTS

STUDY SAMPLE

In all, 509 investigators participated in the study. The number of investigators per country ranged from 11 in Korea to 109 in Spain. Practice sites for the psychiatrists included hospitals (60.5%), psychiatric outpatient services (22.5%), and the community (17.0%). The mean proportion of patients who were ever hospitalized for the full sample was 34.4%, ranging from 11.9% in Portugal to 73.7% in Ukraine (**Table 1**). A total of 5635 patients agreed to participate and provided complete data; these constituted the full analysis population. The screening registry was not used systematically in China, Taiwan, Georgia, Iran, Morocco, and Egypt. For centers that used the screening registry as specified in the protocol, the proportion of screened patients included in the study was 57.5%. No significant difference was observed in the sex distribution between included (n=2357) and nonincluded (n=3328) patients in the screening registry, although included patients were slightly younger than those who were not included (mean [SD] age, 43.8 [13.8] vs 44.1 [13.7] years; $P<.01$). Demographic features were generally similar across countries (Table 1).

FREQUENCY OF BIPOLAR DISORDERS

Per *DSM-IV-TR*, 903 patients (16.0%; 95% CI, 15.1%-17.0%) fulfilled criteria for bipolar disorder, of whom 685 (12.2%; 95% CI, 11.3%-13.0%) met criteria for bipolar I disorder and 218 (3.9%; 95% CI, 3.4%-4.4%) met criteria for bipolar II disorder. In contrast, according to the bipolarity specifier, 2647 patients (47.0%; 95% CI, 45.7-48.3) met criteria for a bipolar diagnosis. All patients who met *DSM-IV-TR* criteria for bipolar disorder also fulfilled the criteria of the bipolarity specifier. Both by *DSM-IV-TR* and bipolarity specifier criteria, fewer than 20% of bipolar-positive patients had symptoms for less than 4 days.

VARIABLES ASSOCIATED WITH A DIAGNOSIS OF BIPOLAR DISORDER

The variables most strongly associated with a diagnosis of bipolar disorder according to *DSM-IV* (**Figure 1**A)

Table 1. Demographic Features of the Study Sample

Country	Patients, No.	Hospitalized, %	Age, Mean (SD), y	Male Sex, %	No. (%)	
					Bipolar *DSM-IV-TR*	Bipolar Specifier
Bosnia	200	46.5	46.3 (10.9)	32.5	45 (22.5)	111 (55.5)
Bulgaria	300	46.0	49.8 (12.5)	36.5	56 (18.7)	171 (57.0)
China	727	45.9	39.7 (14.4)	39.1	105 (14.4)	290 (39.9)
Egypt	306	24.2	37.7 (12.8)	49.0	42 (13.7)	144 (47.1)
Georgia	254	18.5	46.5 (15.0)	32.9	39 (15.4)	103 (40.6)
Germany	251	59.4	48.0 (12.3)	36.8	29 (11.6)	102 (40.6)
Iran	313	37.4	38.4 (12.3)	33.9	57 (18.2)	169 (54.0)
Korea	212	25.5	45.0 (14.5)	27.8	15 (7.1)	55 (25.9)
Macedonia	224	26.8	47.5 (13.3)	28.6	29 (12.9)	107 (47.8)
Morocco	317	20.8	39.7 (11.5)	38.3	55 (17.4)	148 (46.7)
The Netherlands	220	12.7	46.1 (13.7)	40.0	28 (12.7)	81 (36.8)
Pakistan	265	37.0	38.2 (12.0)	50.4	60 (22.6)	158 (59.6)
Portugal	311	11.9	45.9 (13.0)	25.7	45 (14.5)	172 (55.3)
Slovakia	297	57.6	48.4 (13.2)	38.0	50 (16.8)	166 (55.9)
Spain	655	25.5	47.2 (13.9)	33.1	100 (15.3)	324 (49.5)
Taiwan	420	14.8	45.3 (12.7)	27.2	64 (15.2)	149 (35.5)
Ukraine	297	73.7	46.9 (13.1)	29.6	65 (21.9)	156 (52.5)
Vietnam	66	37.9	40.7 (11.1)	51.5	19 (28.8)	41 (62.1)
Total	**5635**	34.4	44.1 (13.7)	35.5	903 (16.0)	2647 (47.0)

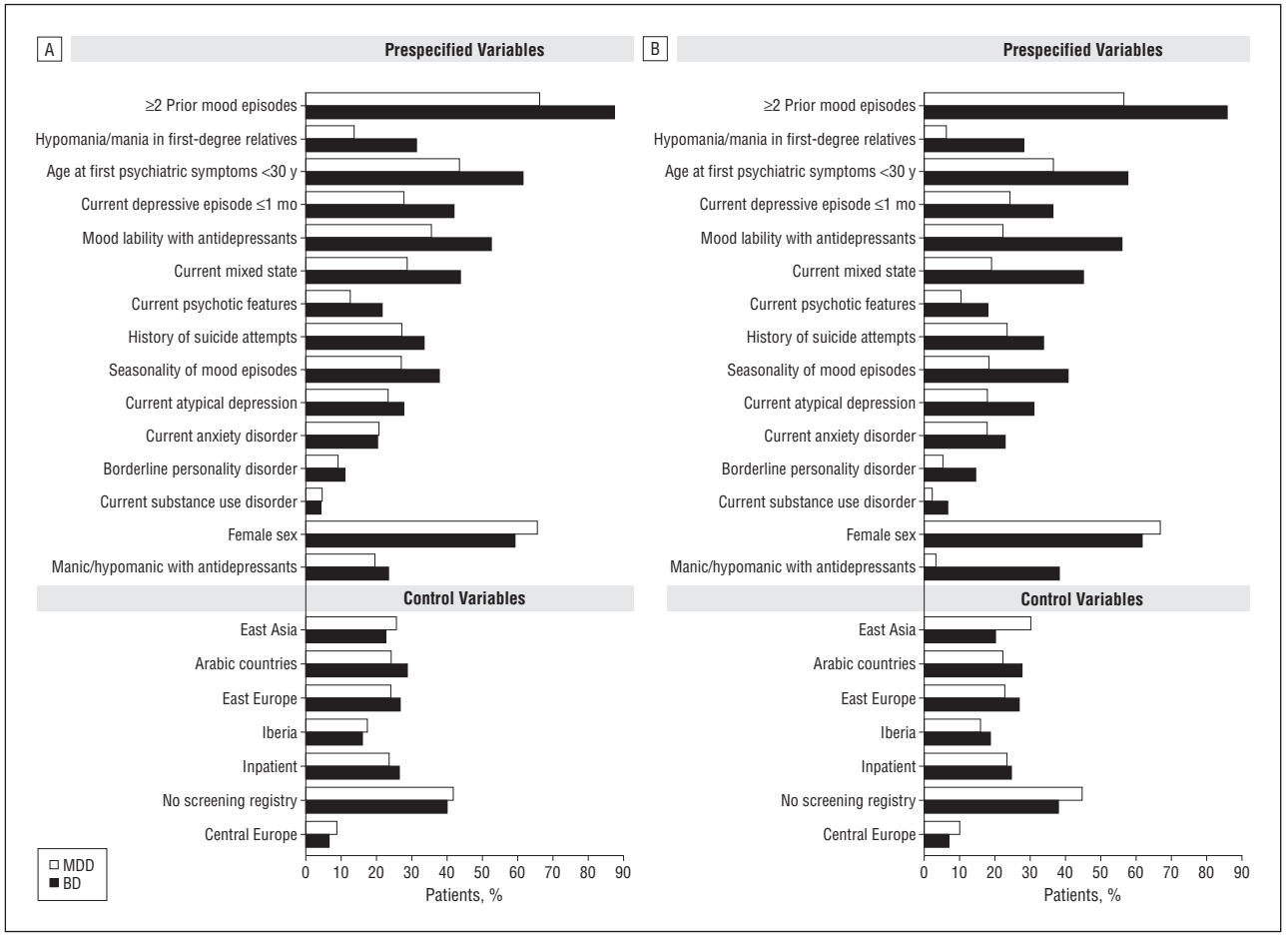

Figure 1. Frequency of 15 prespecified characteristics of bipolarity between bipolar and pure major depressive disorder (MDD) according to 2 definitions: *DSM-IV-TR* (A) and bipolarity specifier (B). BP indicates bipolar disorder.

and bipolar-specifier (Figure 1B) criteria compared with a diagnosis of unipolar depression were a family history of mania, at least 2 prior mood episodes, first psychiatric symptoms before age 30 years, mania/hypomania during antidepressant therapy, and current mixed state. For all variables, the ORs were greater per bipolar-specifier

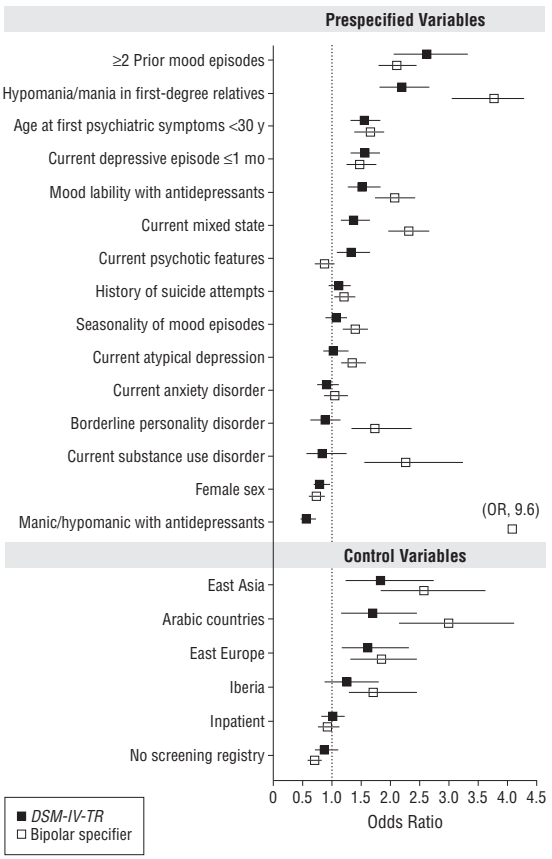

Figure 2. Multivariable logistic regression. Association of 15 prespecified characteristics of bipolarity with bipolarity-specifier and *DSM-IV-TR* criteria and vs nonbipolar major depressive disorder. Data are presented as a Forest plot, showing odds ratios (ORs) with 95% confidence intervals. The vertical dashed line indicates the point of no difference between the 2 criteria sets for bipolar disorder vs cohort individuals without features of bipolar disorder.

criteria than for *DSM-IV-R* criteria. The univariate differences in control variables were small and clinically insignificant.

In multivariable logistic regression analysis (**Figure 2**), 7 risk factors, including a family history of mania, at least 2 mood episodes in the past, and the occurrence of first psychiatric symptoms before age 30 years, were identified as independent risk factors for bipolar disorder when defined using either the *DSM-IV-TR* or bipolar-specifier criteria. Additionally, comorbid substance use disorder, borderline personality disorder, and a history of development of mania or hypomania during antidepressant therapy were associated with the bipolar-specifier features.

The distribution of these variables was compared between patients meeting these criteria and the remaining patients with depression but without bipolar features. Both bipolar diagnostic definitions were significantly associated with several validators and characteristics of bipolar disorder. For many variables, the bipolarity-specifier definition distinguished bipolar from unipolar diagnoses more clearly than the *DSM-IV-TR* definition. Finally, only the bipolarity-specifier criteria were associated with significant comorbidity with substance use disorder and anxiety disorders. The multivariable logistic regression (Figure 2) demonstrated robust associations of the bipolar-specifier criteria with development of hypomania during antidepressant therapy (OR, 9.6) and also with a family history of hypomania/mania (OR, 3.8), which was higher than that associated with the *DSM-IV-TR* definition (OR, 2.2) (Figure 2). Geographic region was a statistically significant control variable for both definitions of bipolarity. The absence of a screening registry was negatively related to rates for bipolarity according to the bipolar-specifier, but not the *DSM-IV-TR*, definition.

Table 2. Presence of Lifetime Bipolar Symptoms in Patients Fulfilling the 2 Definitions of Bipolar Disorder and the Complete Sample of All Subjects With MDEs

	No. (%)[a]		
	MDE	Bipolar Disorder	
Symptom	Total (N=5635)	*DSM-IV-TR* (n=903)	Bipolar Specifier (n=2647)
Elevated mood	2544 (45.3)	830 (92.2)	2174 (82.5)
Irritable mood	2573 (45.8)	689 (76.6)	1906 (72.3)
Increased activity	2656 (47.3)	808 (89.9)	2223 (84.4)
Inflated self-esteem	2071 (37.6)	736 (81.6)	1855 (70.2)
Decreased sleep	2573 (46.8)	813 (90.1)	2227 (84.3)
More talkative	2777 (50.5)	829 (92.0)	2369 (89.6)
Nonstop ideas	1820 (33.1)	638 (70.8)	1653 (62.6)
Distractibility	2381 (43.3)	715 (79.3)	1954 (73.9)
Goal-directed activity	2620 (47.6)	781 (86.6)	2187 (82.7)
Psychomotor agitation	1951 (35.5)	602 (66.7)	1608 (60.8)
Pleasurable activities	1614 (29.3)	628 (69.5)	1516 (57.3)
Unequivocal change	2434 (44.2)	840 (93.1)	2173 (82.2)
Marked impairment	1768 (32.1)	670 (74.2)	1540 (58.2)
Observable by others	2714 (49.3)	855 (94.7)	2346 (88.6)
Hospitalization	916 (16.7)	431 (47.8)	850 (32.2)

Abbreviation: MDE, major depressive episode.
[a] Denominators vary for some analyses.

FREQUENCY OF *DSM-IV* BIPOLAR SYMPTOMS IN BIPOLAR PATIENTS

Rates of individual *DSM-IV-TR* bipolar symptoms are shown in **Table 2** for the total sample of patients with MDE and for the subsets of patients meeting bipolar-specifier or *DSM IV-TR* criteria for bipolar disorder. For each symptom, rates were similar for the 2 bipolar classification groups and consistently slightly higher for patients meeting *DSM-IV-TR* criteria than for those meeting bipolar-specifier criteria. However, even in the total study sample of patients presenting with an MDE, one-third to one-half experienced these symptoms. The duration of elevated and irritable mood was similar for the 2 diagnostic concepts of bipolar disorder, with more than two-thirds of patients having a hypomanic episode lasting more than 1 week. The number of patients with elevated or irritable mood lasting less than 4 days was infrequent in the *DSM-IV-TR* bipolar group, which excludes them unless they required hospitalization.

For both bipolar diagnostic concepts, the most frequent manic symptoms of Criterion B of the *DSM-IV-TR* were being more talkative, decreased need for sleep,

and increased goal-directed activity. Unequivocal changes in behavior observable by others were reported for more than 90% of *DSM-IV-TR* criteria bipolar patients and more than 80% of the bipolar-specifier criteria patients. Approximately one-half of the patients with *DSM-IV* bipolar disorder had been hospitalized for a mood disorder compared with approximately one-third of those meeting the criteria of the bipolarity specifier.

Patients whose hypomanic episodes occur in the presence of another disorder or during antidepressant therapy are excluded from the *DSM-IV-TR* diagnosis of bipolar disorder. However, in our sample, 1276 patients (23.2%) had experienced episodes of elevated or irritable mood triggered by antidepressants. These patients are eligible for the bipolar-specifier definition. Also in this sample, 1036 of 2647 patients (39.2%) in the bipolar-specifier group had previously experienced hypomanic episodes during antidepressant therapy, including 59.5% in the subgroup of 1742 patients meeting bipolar-specifier criteria who were not classified as having bipolar disorder according to *DSM-IV-TR* criteria.

DRUG TREATMENT

Overall, 5098 patients (90.5%) were receiving antidepressant treatment. This proportion was slightly lower among those meeting *DSM-IV* criteria for bipolar disorder (716 [79.3%]) vs those in the bipolar-specifier group (2246 [84.9%]). Mood stabilizers were prescribed for 2234 patients overall (39.7%): 625 meeting *DSM-IV-TR* criteria (69.2%), and 1638 meeting bipolar-specifier criteria (61.9%). Atypical antipsychotics were prescribed for 1546 patients overall (27.4%), 368 meeting *DSM-IV-TR* criteria (43.0%), and 1006 meeting bipolar-specifier criteria (38.0%).

COMMENT

These results are from a large, 3-continent, culturally generalizable study conducted by practicing psychiatrists. The data indicate that, whereas with application of the *DSM-IV-TR* criteria, 16.1% of patients with MDEs met criteria for either bipolar I or bipolar II disorder, this rate rose to 47% with application of the bipolarity-specifier criteria. These results suggest that bipolar features are more frequent in patients with MDE than indicated by *DSM-IV-TR* criteria. Almost half of the entire 5098 cohort presented the core symptoms of bipolarity (elevated mood, irritable mood, or increased activity), and these symptoms led to unequivocal changes in behavior that were observable by others in a similar proportion of patients.

The diagnostic specifier for bipolarity identified substantially more patients with MDE as having well-established bipolar features and provided stronger associations with several potential items that can be reliably assessed in routine care settings as indicators of bipolarity, eg, family history of bipolar disorder, comorbidity with substance use disorder, or borderline personality disorders. Our finding that no significant comorbidity between pure MDD and substance use disorder remained after removal of the bipolar-specifier group confirms the results of Zimmermann et al.[12] This suggests that the reported association between MDD and substance use disorder may be an artifact as a result of the inclusion of patients with unidentified bipolar disorder.

Indices of comorbidity of substance abuse or borderline personality disorder and mood lability or mania/hypomania during antidepressant therapy were consistently more discriminatory with the bipolar-specifier concept. Variables that performed similarly for both bipolar definitions and for unipolar depression included sex, suicidality, comorbid anxiety disorder or psychosis, and episode duration. These results, with the limitation of the substance use disorder and borderline personality associations, indicate that comorbidities per se should not be viewed as validators of a specific diagnosis. A small set of variables on family history, illness course, and consequences of antidepressant treatment provides a valid basis for ascertainment of bipolar disorder in MDEs. These data provide strong evidence that the *DSM-IV*–based opinion that antidepressant-induced mania/hypomania and affective instability are not predictive of bipolar disorder is unfounded.

Odds ratios alone provide an important but insufficient basis for inclusion of variables as diagnostic criteria. For example, although strongly differentiating patients meeting bipolar-specifier criteria from those meeting MDD criteria, the frequency of both substance use disorder and borderline personality disorder is less than 12% among the bipolar-specifier group. In contrast, mixed episodes are present in more than 40% of bipolar-specifier patients. Similarly, the frequency of mood instability is more than twice that for development of hypomania/mania during antidepressant therapy. Considering such trade-offs between general usefulness and relative risk is ultimately the responsibility of the task force developing *DSM-5*.

This study also identified a number of historical, demographic, and clinical variables associated with bipolar features. If verified by independent samples, several of the significant items reported here could justifiably be incorporated in criteria in the revised *DSM-5*, yielding more-valid criteria and ones not arbitrarily limited to cross-sectional symptomatology and unrealistic duration of presence. The strength of several of these variables, eg, mania/hypomania developing during therapy with an antidepressant or other drug, mood lability developing during antidepressant therapy, 2 or more prior mood episodes, and positive family history of mania/hypomania, is larger than that of most gate or symptom features of *DSM-IV*. Indeed, for some of these variables, eg, number of prior episodes and mood lability, *DSM-IV* has no items that even address the variable. This perspective is acknowledged in the recently posted *DSM-5* update,[29] which states that severity of illness is the key measure for improved diagnostic validity and usefulness, in contrast to the emphasis in *DSM-IV-TR* on a large number of complex, discrete syndromes. Although evidence[30-33] indicates that the minimum of 4 days of symptomatology required by *DSM-IV-TR* may exclude many "subthreshold" manic/hypomanic episodes from qualifying for bipolar diagnoses,[29-31,34] in our sample, fewer than 20% of hypomanic episodes were shorter than 4 days. Con-

versely, development of hypomania during antidepressant treatment, which precludes a *DSM-IV-TR* diagnosis of bipolar disorder, was frequently reported, including in the bipolar-specifier group who did not have bipolar disorder according to *DSM-IV-TR*.

This study has strengths and limitations. The principal strengths include the large number of patients studied and the range of care settings encompassed. The study included hospital and community psychiatrists from 18 countries across 3 continents. This broad, local clinical practice–relevant sample increases the generalizability of the findings. In addition, the high percentage of patients screened who were enrolled (57.5%) constitutes a specific strength for the generalizability of results.

One limitation is that the participating centers were not randomly selected, which may have led to a bias through inclusion of psychiatrists with a particular interest in bipolar disorder. However, a random selection of participants would not have been possible because lists of all practicing physicians were not in the public domain for the participating countries. Another limitation is the widely varying rates of hospitalized patients across countries, ranging from 11.9% to 73.7%. However, these rates reflect clinical practices in the respective countries, and hospitalization rates were not associated with significant differences in rates of bipolar I diagnosis. The retrospective assessment of hypomanic symptoms may have introduced some imprecision into the estimation of their frequency. However, this is the challenge that psychiatrists face when making the differential diagnosis between MDD and bipolar disorder in clinical practice. Psychiatrists participating in the study were provided limited training regarding conduct of the interview to obtain the case report form data. However, the protocol was designed to use skills expected of fully trained psychiatrists and did not involve rating scales for which calibration of scores was needed. The use of psychiatrists for clinical assessments, rather than nonclinician raters, constitutes a strength of the study.

The bipolar features identified in this large sample of patients experiencing MDEs, consistent with several other recent studies[32,33] limited to patients with bipolar disorder who were experiencing MDEs, have important consequences for care. This cross-sectional study design is unable to identify patients in the unipolar depressive group who will subsequently develop hypomania/mania and does not provide outcome data that could serve to support the prognostic ability of the bipolar-specifier criteria.

The lack of a healthy control group raises the issue of the extent to which some "hypomanic features" may be relatively prevalent in the general population. However, the study shows that, regardless of their "normality" or "abnormality," a subset of the 15 evidence-based variables selected for evaluation made a difference in differentiating between MDD and bipolar disorder in the sample of persons with MDEs. That difference is remarkably aligned with the characteristic features of bipolar illness, including clinically independent items such as family history.

The reliability of these results can reasonably be criticized; however, at present, this is the only way to conduct large epidemiologic studies. Even post mortem, no reference standard for full validity of bipolar disorder exists. We believe that the clinical qualifications of the fully trained psychiatrists who participated in the study and the consistency of the findings across countries and cultures are indirect indicators of data quality and lack of bias.

Treatment approaches for MDD and bipolar disorder differ substantially. The importance of long-term prophylactic treatment is greater for bipolar disorder.[35] Most patients experiencing MDEs are prescribed antidepressants, as this study confirms. A recent study[36] established that, either as monotherapy or as adjunctive therapy to mood stabilizers, the benefits of antidepressants in treatment of bipolar disorder are, at most, modest and adverse consequences often ensue. The Systematic Treatment Enhancement Program for Bipolar Disorders (STEP-BD) randomized study[37] of bipolar depression found that adjunctive therapy with antidepressants had no benefits over therapy with mood stabilizers alone. Among patients initially responding to treatment with antidepressants plus mood stabilizers who were euthymic for 2 months, those randomly assigned to receive continued antidepressant treatment did not experience significantly different efficacy compared with those receiving only mood stabilizers for 1 to 3 years. Patients with rapid-cycling symptoms had worse outcomes if assigned to receive adjunctive antidepressants.[38] In a study[39] of patients who entered STEP-BD in a symptomatic state and achieved remission within 2 years of prospective follow-up, exhibiting residual symptoms of mood elevation was the principal predictor for risk of recurrence for both depressive and manic/hypomanic/mixed episodes. Paroxetine monotherapy did not produce a greater antidepressant effect than placebo in patients with bipolar depression.[40]

Prospective studies such as those briefly reviewed here could aid in validation of the clinical usefulness of bipolarity-specifier criteria. Based on these studies and the major differences in treatment guidelines for MDD and bipolar disorder, we recommend that, among patients with MDEs, the presence of bipolar features, including all those with significant predictive value reported in this study, should be investigated carefully before a decision is made to prescribe antidepressants. If patients exhibit bipolar symptoms that impair everyday functioning, treatment with a mood stabilizer or an atypical antipsychotic may be useful.[21]

In conclusion, this study shows that more than one-third of patients with MDE also have subthreshold hypomania or mania, which suggests the existence of an unrecognized bipolar subgroup that can be distinguished from pure MDD by several validators. These reliably assessable variables merit further study as potential additional criteria to establish an accurate syndromal diagnosis of bipolar disorder.

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