Original Research

Mixed Features in Patients With a Major Depressive Episode: the BRIDGE-II-MIX Study

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ABSTRACT

Objective: To estimate the frequency of mixed states in patients diagnosed with major depressive episode (MDE) according to conceptually different definitions and to compare their clinical validity.

Method: This multicenter, multinational cross-sectional Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX study enrolled 2,811 adult patients experiencing an MDE. Data were collected per protocol on sociodemographic variables, current and past psychiatric symptoms, and clinical variables that are risk factors for bipolar disorder. The frequency of mixed features was determined by applying both *DSM-5* criteria and a priori described Research-Based Diagnostic Criteria (RBDC). Clinical variables associated with mixed features were assessed using logistic regression.

Results: Overall, 212 patients (7.5%) fulfilled DSM-5 criteria for MDE with mixed features (DSM-5-MXS), and 818 patients (29.1%) fulfilled diagnostic criteria for a predefined RBDC depressive mixed state (RBDC-MXS). The most frequent manic/hypomanic symptoms were irritable mood (32.6%), emotional/mood lability (29.8%), distractibility (24.4%), psychomotor agitation (16.1%), impulsivity (14.5%), aggression (14.2%), racing thoughts (11.8%), and pressure to keep talking (11.4%). Euphoria (4.6%), grandiosity (3.7%), and hypersexuality (2.6%) were less represented. In multivariate logistic regression analysis, RBDC-MXS was associated with the largest number of variables including diagnosis of bipolar disorder, family history of mania, lifetime suicide attempts, duration of the current episode > 1 month, atypical features, early onset, history of antidepressant-induced mania/ hypomania, and lifetime comorbidity with anxiety, alcohol and substance use disorders, attention-deficit/hyperactivity disorder, and borderline personality disorder.

Conclusions: Depressive mixed state, defined as the presence of 3 or more manic/hypomanic features, was present in around one-third of patients experiencing an MDE. The valid symptom, illness course and family history RBDC criteria we assessed identified 4 times more MDE patients as having mixed features and yielded statistically more robust associations with several illness characteristics of bipolar disorder than did DSM-5 criteria.

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Corresponding author: Giulio Perugi, MD, Clinica Psichiatrica Università Di Pisa, Via Roma 67, 56100, Pisa, Italy (giulio.perugi@med.unipi.it). **M**ajor depression with manic or hypomanic symptoms has a moderate diagnostic stability¹ and is commonly called mixed depression.^{2,3} Frequency of mixed depression in bipolar I, bipolar II, and major depressive disorder (MDD) ranges between 20% and 70%, depending on setting, samples, interview methods, and instruments used to assess intradepression manic or hypomanic symptoms.⁴ Compared with nonmixed depression, mixed depression is more common in bipolar disorders and is more frequently associated with a family history of bipolar disorders, younger age at onset, longer duration, worse outcome, and poorer response to treatments.^{5–12}

Several definitions of mixed depression have been proposed.^{5–9,13–19} Some of these require a minimum of 2 or 3 intradepression manic/hypomanic symptoms; others also require specific manic/hypomanic symptoms, such as psychomotor agitation (agitated depression). Definitions that require 3 or more symptoms have been the most utilized in clinical research.^{6,13,20} A categorical definition of mixed depression, however, is problematic because the distribution of intradepression manic and hypomanic symptoms between bipolar disorder and MDD is not bimodal.^{21–25}

In DSM-5,²⁶ subthreshold nonoverlapping symptoms of mania in a major depressive episode (MDE) are identified using a "mixed features" specifier. The inclusion of fewer symptoms of the opposite polarity in all bipolar subtypes and MDD implicitly recognizes the existence of a mood spectrum, establishing a link between bipolar disorder and MDD.27-31 This unitary model of mood disorders suggests that affective states are distributed across a continuum ranging from pure major depression to pure mania. An implication of this model is the frequent occurrence of mixed states, in which patients present mood episodes sharing both depressive and manic features. The goal of the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX study was to provide a reliable estimate of the frequency of mixed states in a large international sample of patients diagnosed with MDE according to several sets of criteria and to compare the clinical validity of the main definitional criteria.

METHOD

The BRIDGE-II-MIX study was a cross-sectional diagnostic effort comprising 239 hospital-based or community psychiatrists. The study was conducted in Bulgaria, Egypt, Morocco, the Netherlands, Portugal, Russia, Spain, and Turkey between June 2009 and July 2010. In each country, centers were selected to reflect the psychiatric healthcare provision for each country so that the patient care would be representative of the country's practice and regional diversity. Each center was expected to

- Major depression with manic or hypomanic symptoms is frequently observed in clinical practice.
- The application of a valid evidence-based RBDC set of symptoms, illness course, and family history criteria identifies about 30% of MDE patients as having mixed states. Such diagnostic assessments provide stronger associations with several illness characteristics of bipolar disorder than DSM-5 criteria.
- DSM-5 "mixed features" specifier, based on excluding "overlapping" mood symptoms, such as psychomotor agitation, irritability, and mood lability, may leave many patients with mixed depression undiagnosed, and, perhaps, inadequately treated.

enroll 10 to 20 patients consecutively, consulting for an MDE during a 3-month recruitment period. The study, completely independent from the previous BRIDGE study,³² was primarily focused on the prevalence and definition of mixed features in a totally different sample of patients with MDE.

The study enrolled adults aged 18 years and older with MDE according to *DSM-IV-TR* diagnostic criteria at the time of the consultation. Each center maintained an anonymous screening log of the patients consulting so that the rate of participation could be estimated. Reasons for nonparticipation were precoded (refusal to participate, acute nonpsychiatric condition or emergency event, patient unable to complete the questionnaire, and other). Screening logs were completed at each site from study initiation until the last patient was included in the site.

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment; http://www.wma.net) and the Good Epidemiology Practice and the International Epidemiologic Association (IEA) European Federation (http://ieaweb.org). Good Epidemiologic Practice (GEP)– IEA Guidelines were followed for proper conduct of epidemiologic research, as well as pertinent national, legal, and regulatory requirements. Written informed consent was obtained from each patient. In each country, the protocol was approved by the local ethics committee.

Data Collection

In a single consultation, participating psychiatrists completed a structured case report form for each patient, incorporating inclusion criteria, sociodemographic variables (age, gender, marital status), inpatient or outpatient status, history of psychiatric symptoms (mood symptoms, postpartum depression, suicide attempts), and previous psychiatric hospitalizations. Features of the current depressive episode, including bipolar symptoms listed in the *DSM-IV-TR* diagnostic criteria for bipolar disorder, known risk factors for bipolar disorder, previous response to antidepressants, psychiatric comorbidity, current treatment, and functional status determined by the investigator using the Global Assessment of Functioning (GAF) were assessed.³³ The same sequence of completing and entering the evaluation into the case report form was followed at each site.

The psychiatrists consecutively recruited all adults with a diagnosis of MDE according to *DSM-IV-TR* criteria. Because of the widely separated locations of the countries and the psychiatrists participating within them, the steering committee viewed it unfeasible to provide specific live training for the psychiatrists at the participating centers. Instead, the evaluation packet was explicitly 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.

The primary objective was to establish the frequency of depressive mixed states (MXS), which was defined as the proportion of patients fulfilling: (1) DSM-5 criteria for MDE with mixed features (DSM-5-MXS), (2) DSM-5 subthreshold criteria for MDE with mixed features (subthreshold DSM-5-MXS), and (3) research-based diagnostic criteria for depressive MXS (RBDC-MXS). DSM-5 criteria require the presence for at least a week of an MDE and at least 3 of the following (nonoverlapping) hypomanic symptoms: (1) elevated, expansive mood, (2) inflated self-esteem or grandiosity, (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or subjective experience that thoughts are racing, (5) increase in energy or goal-directed activity, (6) increased or excessive involvement in activities that have a high potential for painful consequences, and (7) decreased need for sleep. For the definition of subthreshold DSM-5-MXS, we required the presence of an MDE plus 2 nonoverlapping hypomanic symptoms. RBDC-MXS were defined by the presence of an MDE plus 3 of the following 14 hypomanic symptoms for at least a week: irritable mood, emotional/mood lability, distractibility, psychomotor agitation, impulsivity, aggression (verbal or physical), racing thoughts, more talkative/pressure to keep talking, hyperactivity, increased energy, risky behavior, grandiosity, elation, and hypersexuality. Since data collection took place before the DSM-5 was published, the DSM-5 criteria were applied retrospectively by the authors on the basis of the case report forms.

We also identified the proportion of patients fulfilling criteria for bipolar disorder according to the *DSM-IV-TR* and bipolarity specifier proposed by Angst et al.^{32,34} The bipolarity specifier attributes a diagnosis of bipolar disorder to patients who experienced an episode of elevated mood or 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

Table 1. Demographic Variables and Rates of Mixed State and Bipolarity According to Different Criteria Set by Country of Origin in a Sample of 2,811 Subjects With MDE

					Diagnostic Distribution						
		Demogr	aphic Variables			Subthreshold	Bipolar	Bipolar			
	Patients, n	Male	Age,	Inpatients,	DSM-5-MXS,	DSM-5-MXS,	RBDC-MXS,	DSM-IV-TR,	Specifier, ^a		
Country	(%)	Sex, %	Mean (SD), y	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Bulgaria	300 (10.7)	24.7	49.6 (13.8)	120 (40.0)	16 (5.3)	50 (16.7)	98 (32.7)	49 (16.3)	129 (43.0)		
Morocco	294 (10.5)	38.1	38.8 (11.4)	42 (14.3)	18 (6.1)	40 (13.6)	71 (24.1)	61 (20.7)	109 (37.1)		
The Netherlands	198 (7.0)	37.4	48.5 (14.7)	6 (3.0)	14 (7.1)	28 (14.1)	66 (33.3)	23 (11.6)	72 (36.4)		
Portugal	303 (10.8)	23.4	45.2 (14.1)	3 (1.0)	24 (7.9)	50 (16.5)	122 (40.3)	72 (23.8)	172 (56.8)		
Russia	900 (32.0)	28.0	45.7 (13.6)	520 (57.8)	23 (2.6)	62 (6.9)	104 (11.6)	105 (11.7)	311 (34.6)		
Spain	182 (6.5)	32.6	49.5 (13.6)	15 (8.2)	30 (16.5)	47 (25.8)	77 (42.3)	32 (17.6)	106 (58.2)		
Turkey	317 (11.3)	30.6	38.0 (11.6)	20 (6.3)	13 (4.1)	38 (12.0)	109 (34.4)	44 (13.9)	100 (31.5)		
Egypt	317 (11.3)	43.2	37.8 (11.1)	5 (1.6)	74 (23.3)	117 (36.9)	171 (53.9)	78 (24.6)	171 (53.9)		
Total	2,811 (100)	31.2	44.0 (13.8)	731 (26.0)	212 (7.5)	432 (15.4)	818 (29.1)	464 (16.5)	1,170 (41.6)		

^aBipolar specifier according to criteria proposed by Angst et al.^{32,34}

Abbreviations: DSM-5-MXS = DSM-5 criteria for depressive mixed states, MDE = major depressive episode, RBDC-MXS = research-based diagnostic criteria for depressive mixed states, SD = standard deviation.

Table 2. Frequency of Mixed States and Bipolarity According to Different Definitions in 2,811 Patients With MDE

		Statistics				
Variable	n	%	95% CI			
Depressive mixed state						
<i>DSM-5</i> criteria (MDE + 3 nonoverlapping hypomanic criteria)	212	7.5	6.6-8.5			
<i>DSM-5</i> subtreshold criteria (MDE+2 nonoverlapping hypomanic criteria)	432	15.4	14.0–16.7			
RBDC (MDE + 3 or more hypomanic symptoms)	818	29.1	27.4-30.8			
Diagnostic distribution						
DSM-IV-TR bipolar	464	16.5	15.2-17.8			
DSM-IV-TR bipolar I	288	10.2	9.1-11.4			
DSM-IV-TR bipolar II	176	6.3	5.4-7.2			
Bipolar specifier ^a	1,170	41.6	39.8-43.5			
Bipolar I specifier	707	25.2	23.4-26.9			
Bipolar II specifier	463	16.5	15.1-17.8			
and 1 10 11 1 11 1	11 4	1	37 34			

^aBipolar specifier according to criteria proposed by Angst et al.^{32,34} Abbreviations: CI = confidence interval, MDE = major depressive episode, RBDC = research-based diagnostic criteria.

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outpatient treatment; no minimum duration was required and no exclusion criteria were applied.

Statistical Analysis

Frequency estimates were determined with 95% confidence intervals. Univariate comparisons of previous pharmacologic treatments between an assigned diagnosis of depressive MXS were conducted by contingency tables, and group differences were presented as odds ratios with 95% confidence intervals (CIs). The association between an assigned diagnosis of depressive MXS and patient characteristics was explored using multiple logistic regression analysis. The patient characteristics chosen a priori included variables known to be associated with a diagnosis of bipolar disorder.^{28,35-40} These variables were gender (female), current age (younger), age at first symptoms < 30 years, ≥ 3 prior mood episodes, history of suicide attempts, hypomania/mania among first-degree relatives, manic/hypomanic switches while taking antidepressant medications, psychotic features, duration of current depressive episode >1 month, current atypical depressive symptoms, mood lability, and problematic substance/ alcohol use. Logistic regression was performed to assess the association of these variables with assigned depressive MXS diagnosis, and the strength of the associations was presented as odds ratios with 95% CIs.

RESULTS

Study Sample

In all, 239 psychiatrists participated in the study. The number of psychiatrists per country ranged from 18 in Egypt to 62 in Spain. Of the psychiatrists involved in the study, 237 returned their "site questionnaire." Practice settings were community-based (26%), dispensary (23%), or hospitalbased (48%) during 19 months on average. The locations of practices were almost entirely urban. The mean proportion of patients who were hospitalized out of the full sample was 26.0% and ranged from 3% in the Netherlands to 57.8% in Russia (Table 1). In total, 2,811 patients agreed to participate and provided complete data; these patients constituted the full analysis population. Demographic features were generally similar across countries.

Frequency of Mixed Depression and Bipolarity

Whereas 212 patients (7.5%) fulfilled *DSM-5* criteria for *DSM-5-*MXS, 432 patients (15.4%) met criteria for subthreshold *DSM-5-*MXS, and 818 patients (29.1%) met criteria for a RBDC-MXS (Table 2). All patients who met *DSM-5-*MXS or subthreshold *DSM-5-*MXS criteria also fulfilled the criteria of RBDC-MXS. The proportion of patients meeting any diagnostic criteria for MXS was lowest in Russia (less than half the value of the total sample) and highest in Egypt (Table 1).

According to *DSM-IV-TR*, 464 patients (16.5%) fulfilled criteria for bipolar disorder, of whom 288 patients (10.2%) met criteria for bipolar I disorder and 176 patients (6.3%) for bipolar II disorder. Using the bipolarity specifier, 1,170 patients (41.6%) met criteria for a bipolar diagnosis (707 patients [25.2%] for bipolar I and 463 patients [16.5%] for bipolar II).

					Sub	threshold			
	Total Sample,		DSM-5-MXS,		DSM-5-MXS,		RBDC-MXS,		
	N=2,811		1	n=212		n=432		n=818	
Hypomania Symptoms	n (%)	95% CI	%	95% CI	%	95% CI	%	95% CI	
Irritable mood	915 (32.6)	31.2-33.7	81.1	75.5-86.3	75.0	70.8-78.9	84.2	81.8-86.7	
Emotional/mood lability	837 (29.8)	28.4-31.0	80.7	75.0-86.3	63.7	59.3-68.3	74.3	71.4-77.3	
Distractibility	686 (24.4)	23.3-25.6	69.8	63.7-75.9	63.4	59.0-68.3	66.0	62.7-69.2	
Psychomotor agitation	453 (16.1)	15.0-17.3	58.5	51.4-65.1	48.1	47.7-56.3	48.0	44.6-51.6	
Impulsivity	408 (14.5)	13.4-15.6	66.0	59.9-72.6	55.1	50.5-60.0	45.0	41.7 - 48.4	
Aggression (verbal or physical)	399 (14.2)	13.1-15.3	50.0	42.9-56.6	40.0	35.4-44.9	42.5	39.1-45.8	
Racing thoughts	332 (11.8)	10.8-12.9	59.9	53.3-66.0	41.0	36.3-45.6	62.3	58.9-65.4	
More talkative/pressure to keep talking	321 (11.4)	10.7-12.2	87.7	83.0-91.5	63.7	59.3-68.3	36.4	33.0-40.0	
Hyperactivity	226 (8.0)	7.3-8.8	65.6	59.0-72.2	43.3	38.7-47.7	26.4	23.3-29.5	
Increased energy	190 (6.8)	6.1-7.4	66.0	59.4-72.2	42.1	37.5-47.0	21.9	19.0-24.9	
Risky behavior	205 (7.3)	6.5-8.1	50.0	42.9-58.1	42.6	38.0-47.2	23.3	20.4-26.2	
Grandiosity	105 (3.7)	3.2-4.4	36.3	29.7-42.9	22.5	18.5-26.8	12.6	10.4-14.9	
Euphoria	130 (4.6)	4.0-5.3	44.8	38.2-51.9	28.2	23.8-32.9	15.4	12.8-18.1	
Hypersexuality	74 (2.6)	2.1-3.2	19.8	14.6-25.5	13.4	10.4-16.9	8.7	6.7-10.5	
Abbreviations: CI = confidence interval, I	DSM-5-MXS	= <i>DSM-5</i> crit	eria for	depressive n	nixed st	ates, MDD =	major	depressive $S = DSM_{-}5$	

Table 3. Distribution of Hypomania Symptoms in the Sample of 2,811 Subjects With MDD and According to Different Mixed State Diagnosis

subthreshold criteria for depressive mixed states.

Patients with DSM-5-MXS were most likely to be diagnosed as DSM-IV-TR bipolar disorder (27.8% vs 11.9%; OR = 2.8, 95% CI, 2.3–3.5) and diagnosed as meeting bipolarity specifier criteria (93.4% vs 37.4%; OR = 23.7, 95% CI, 13.7-40.9) compared to those without DSM-5-MXS. Similarly, patients with RBDC-MXS more frequently received a diagnosis of bipolar disorder according to DSM-IV-TR (32.4% vs 13.6%; OR = 3.0, 95% CI, 2.4-3.8) and bipolarity specifier criteria (71.1% vs 29.5%; OR = 5.9, 95% CI, 4.9-7.1) compared to those without RBDC-MXS.

Frequency of Hypomanic and Manic Symptoms

In the total sample, the most frequent manic/hypomanic symptoms (Table 3) were irritable mood (32.6%), emotional/ mood lability (29.8%), distractibility (24.4%), psychomotor agitation (16.1%), impulsivity (14.5%), aggression (14.2%), racing thoughts (11.8%), and pressured speech (11.4%). Euphoria (4.6%), grandiosity (3.7%), and hypersexuality (2.6%) were infrequently present.

In the DSM-5-MXS subset, the most common symptoms were pressured speech (87.7%), irritable mood (81.1%), emotional/mood lability (80.7%), distractibility (69.8%), impulsivity (66.0%), increased energy (66.0%), and hyperactivity (65.6%). Racing thoughts (59.9%) and psychomotor agitation (58.5%) were also present in more than 50% of these patients. In subthreshold DSM-5-MXS, irritable mood (75.0%), pressure to keep talking (63.7%), emotional/mood lability (63.7%), distractibility (63.4%), and impulsivity (55.1%) were the most common symptoms. In RBDC-MXS, the most frequent manic/hypomanic symptoms were irritable mood (84.2%), emotional/mood lability (74.3%), distractibility (66.0%), and racing thoughts (62.3%).

Variables Associated With MXS According to Different Diagnostic Definitions

In multivariate logistic regression analysis, the variables most strongly associated with a diagnosis of DSM-5-MXS (Table 4) compared to patients without such a diagnosis were a DSM-IV-TR diagnosis of bipolar disorder, presence of psychotic features, duration of the current episode > 1 month, history of mania/hypomania while taking antidepressants, presence of comorbid anxiety disorders, alcohol and substance use disorders, attention-deficit/hyperactivity disorder (ADHD), and borderline personality disorder. The presence of a diagnosis of subthreshold DSM-5-MXS was associated with the same variables with the exception of the presence of psychotic features and lifetime comorbidity with ADHD. Among patients with subthreshold DSM-5-MXS, a lifetime history of suicide attempts and of at least 3 prior mood episodes was significantly elevated. A diagnosis of RBDC-MXS was associated with a much larger number of variables: DSM-IV-TR diagnosis of bipolar disorder, family history of mania/hypomania, greater lifetime number of suicide attempts, duration of the current episode > 1 month, atypical features, onset of first depressive episode before 30 years of age, history of mania/hypomania while taking antidepressants, and lifetime comorbidity with anxiety disorders, alcohol and substance use disorders, ADHD, and borderline personality disorder.

The multivariate logistic regression demonstrated specific associations of RBDC-MXS definition with lifetime suicide attempts (OR = 1.34), family history of hypomania/mania (OR = 1.33), atypical features (OR = 1.72), and onset of first depressive episode before 30 years of age (OR = 1.40). The single variable specifically associated with DSM-5-MXS definition in comparison with RBDC-MXS is the presence of psychotic features (OR = 2.18) (Table 4).

Drug Treatment

Overall, 82% of the full sample were currently receiving antidepressant treatment (Table 5). Mood stabilizers were prescribed for 798 patients (28.4%), including 127 DSM-5-MXS patients (59.9%), 223 subthreshold DSM-5-MXS patients (51.6%), and 374 RBDC-MXS patients (45.7%).

Table 4. Logistic Regression for 13 Variables

	<i>DSM-5-</i> MXS, n=212			Subthreshold <i>DSM-5-MXS</i> , $n = 432$				RBDC-MXS, n=818				
Variable	Wald	OR	95% CI	Р	Wald	OR	95% CI	Р	Wald	OR	95% CI	Р
Age, y	0.19	1.00	0.98-1.01	.66	0.42	1.00	0.99-1.01	.52	0.63	1.00	0.99-1.01	.43
Gender	0.71	1.16	0.82 - 1.64	.40	0.44	0.92	0.78 - 1.18	.51	1.99	1.16	0.95 - 1.41	.16
Bipolar DSM-IV-TR	18.69	2.30	1.58-3.36	<.0001	33.88	2.41	1.79-3.25	<.0001	40.68	2.33	1.80-3.03	<.0001
First-degree family history	2.05	1.31	0.91-1.89	.15	3.17	1.30	0.97-1.73	.07	5.306	1.33	1.04 - 1.70	.02
Lifetime suicide attempts	0.45	1.13	0.79-1.60	.50	4.28	1.32	1.02 - 1.71	.038	6.99	1.34	1.08 - 1.66	.008
Psychotic features	15.01	2.18	1.47-3.24	<.0001	2.12	1.25	0.93-1.68	.15	1.37	1.17	0.90-1.51	.24
Current episode > 1 month	33.70	2.60	1.88-3.59	<.0001	44.50	2.20	1.74 - 2.77	<.0001	12.15	1.40	1.16-1.69	<.0001
Atypical features	0.13	1.10	0.65 - 1.86	.72	0.17	0.91	0.60 - 1.40	.677	9.98	1.72	1.23-2.41	.002
3 or more episodes	1.97	1.32	0.90-1.96	.16	3.90	1.32	1.00 - 1.73	.048	0.27	1.06	0.86-1.31	.60
Onset of first depressive episode	1.10	1.22	0.83 - 1.80	.31	2.79	1.28	0.96-1.71	.09	8.09	1.40	1.11 - 1.77	.004
Switches on antidepressants	23.19	2.49	1.72-3.61	<.0001	31.91	2.33	1.74-3.13	<.0001	33.09	2.15	1.65-2.79	<.0001
Anxiety disorders	10.45	1.73	1.24 - 2.42	.001	15.63	1.65	1.29-2.11	<.0001	35.25	1.82	1.49-2.22	<.0001
Eating disorders	0.040	1.05	0.64 - 1.74	.84	1.02	0.80	0.52-1.23	.31	0.03	0.97	0.68-1.38	.86
Alcohol/substance use disorders	9.99	2.92	1.50-5.68	.002	17.26	3.06	1.80 - 5.18	<.0001	7.94	2.04	1.24-3.35	.005
ADHD	3.85	2.03	1.00 - 4.11	.05	2.36	1.62	0.87-3.02	.12	3.78	1.77	1.00 - 3.13	.05
Borderline personality disorder	21.26	2.77	1.80 - 4.28	<.0001	34.80	3.00	2.08 - 4.31	<.0001	32.28	2.81	1.97 - 4.02	<.0001

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CI = confidence interval, DSM-5-MXS = DSM-5 criteria for depressive mixed states, OR = odds ratio, RBDC-MXS = research-based diagnostic criteria for depressive mixed states, Subthreshold DSM-5-MXS = DSM-5 subthreshold criteria for depressive mixed states.

Table 5. Current Treatments in Total Sample and MDE-MXS According to Different Diagnostic Definitions

	Total Sample	DSM-5-MXS	Subthreshold	OR (CI)					
Τ	(N = 2,811),	(n=212),	(n=432),	(n=818),	DOM 5 MYC	Subthreshold	DDDC MYC		
Treatment	n (%)	n (%)	n (%)	n (%)	DSM-5-MAS	DSM-5-MAS	KBDC-MAS		
Antidepressants	2,305 (82.0)	151 (71.2)	327 (75.7)	632 (77.3)	0.5 (0.4-0.7)	0.6 (0.5-0.8)	0.7 (0.5-0.8)		
Antipsychotics	964 (34.3)	119 (56.1)	211 (48.8)	339 (41.4)	2.7 (2.0-3.5)	2.1 (1.7-2.5)	1.6 (1.3-1.8)		
Mood stabilizers	798 (28.4)	127 (59.9)	223 (51.6)	374 (45.7)	4.3 (3.2-5.7)	3.3 (2.7-4.1)	3.1 (2.6-3.7)		
ECT	46 (1.6)	12 (5.7)	17 (3.9)	22 (2.7)	4.5 (2.3-8.9)	3.3 (1.8-6.1)	2.3 (1.3-4.1)		
More than 3 drugs	920 (32.7)	120 (56.6)	213 (49.3)	340 (41.6)	2.9 (2.2-3.9)	2.3 (1.9–2.8)	1.7 (1.5–2.1)		
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Abbreviations: CI = confidence interval, *DSM*-5-MXS = *DSM*-5 criteria for depressive mixed states, ECT = electroconvulsive therapy, MDE = major depressive episode, MXS = mixed states, OR = odds ratio, RBDC-MXS = research-based diagnostic criteria for depressive mixed states, Subthreshold *DSM*-5-MXS = *DSM*-5 subthreshold criteria for depressive mixed states.

Atypical antipsychotics were prescribed for 964 of the full sample (34.3%), including 119 *DSM*-5-MXS patients (56.1%), 211 subthreshold *DSM*-5-MXS patients (48.8%), and 339 RBDC-MXS patients (41.4%).

Nine hundred twenty patients (82.0%) were currently receiving more than 3 drugs. This proportion was higher in *DSM*-5-MXS patients (32.7%; n = 120), subthreshold *DSM*-5-MXS patients (49.9%; n = 213), and RBDC-MXS patients (41.6%; n = 340) than in patients without MXS.

DISCUSSION

These results from a large, culturally generalizable study, conducted by practicing psychiatrists who applied a structured, comprehensive symptom, illness course, and family history assessment, indicate that *DSM-5-MXS* criteria identify fewer than half as many MDE patients as having mixed states as do RBDC-MXS criteria (Table 1). Every patient who met *DSM-5-MXS* or subthreshold *DSM-5-MXS* criteria also fulfilled the criteria of RBDC-MXS. Patients with MXS, independent of the criteria utilized, were significantly more likely to be diagnosed as bipolar by both *DSM-IV-TR* and bipolarity specifier criteria.

A subset of manic symptoms was common in these MDE patients: irritable mood, emotional/mood lability,

distractibility, psychomotor agitation, impulsivity, aggression, racing thoughts, and pressured speech. The results are consistent with previous studies on the type and frequency of intradepressive manic/hypomanic symptoms in MDE patients.^{3,5–7} In contrast, hypomanic symptoms of euphoria, grandiosity and hypersexuality are rare, which is also consistent with other studies.^{5,9} Such results indicate that taxonomic decisions in DSM-5 warrant revision of both category 1 and 2 criteria for bipolar disorders.²⁶ Typical patients with mixed depression have many characteristics of manic/hypomanic behavior, but they lack expansiveness and easy performance of activities.¹⁸ These results are consistent with previous studies indicating that excitatory symptoms during mixed depression are usually distressing; productive capabilities are diminished; restless agitation is aimless; and the risk of suicide is increased.^{15,41-44}

The *DSM-5* definition of MXS is based on excluding "overlapping" mood criteria, such as psychomotor agitation, irritability, and mood lability, the most common features of mixed depression in our sample and across the literature. Assessment of key symptomatology that facilitates discrimination among manic/hypomanic, mixed, and depressed states (both bipolar and unipolar) is hampered by the limited symptom set for symptomatic characterization of

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depression and mania in *DSM-IV* and *DSM-5*, as well as the inattention to a substantial set of symptoms in traditional rating scales (eg, Montgomery-Asberg Depression Rating Scale [MADRS] and Young Mania Rating Scale [YMRS]). *DSM-5* definition for depression with mixed features does not include mood lability, irritability, or anxiety.

Although mood lability should not be considered a specific feature, it has been observed among the core trait characteristics of bipolar disease. *Mood lability*, defined as relatively sudden, unpredictable, large changes in mood,^{45,46} is more prevalent in nonaffected relatives of bipolar disorder patients than in the general population and is predictive of bipolar evolution,⁴⁶ as well as functional impairment.⁴⁷ A mood lability construct was associated with significantly higher scores in bipolar children of bipolar parents compared with nonbipolar offspring or offspring of nonbipolar parents.⁴⁸

Analogous to mood lability, both irritability and anxiety can also be considered nonspecific features, but they have been much more commonly observed in mixed states than in mania and depression. The use of separate scales for mania and depression, which differ in approaches to item construction and scoring scheme, has contributed to the paucity of studies on the spectrum of symptomatology in bipolar disorder. The recently developed Bipolar Inventory of Symptoms Scale (BISS) provides a broader 42-symptom item range, yielding 5 factors by exploratory factor analysis: depression, mania, anxiety, irritability, and mania. The utility of the BISS in distinguishing among 4 primary clinical states in bipolar disorder (depression, mania/hypomania, mixed episodes, and recovered status) was recently reported.⁴⁹ Symptom items for irritability, mood lability, and observed anxiety were significantly more severe in mixed than in manic/hypomanic subjects and depressed subjects. Reported anxiety was significantly higher in mixed and depressed subjects than in manic subjects. Somatic anxiety was higher in mixed than in manic subjects. Conversely, items for hyperactivity, increased energy, grandiosity, sharpened thinking, delusions, and impaired insight were each significantly higher in manic than in mixed or depressed subjects. These results suggest that the DSM employment of identical sets of manic symptoms for both manic/hypomanic and mixed episode diagnoses is inconsistent with actual presentation of the 2 syndromes. Racing thoughts, mood lability, irritability, and distractibility, none of which inherently comprise elevated mood or affect, dominated in mixed episodes over other manic symptomatology such as elation or grandiosity. Levels of depression were similar in depressed and mixed states subjects, and both were significantly more depressed than manic/hypomanic subjects. Manic/hypomanic and mixed subjects did not differ on mania severity. Overall, bipolar symptom severity was significantly higher in mixed episodes compared to that in depressed or manic episodes.⁴⁹ This clinically intuitive result is not possible to ascertain when disparate scales for depression and mania are used to assess symptoms and is widely consistent with our findings.

In the present study, we addressed the validity of 3 different definitions of mixed depression and evaluated variables previously observed in mixed states in many empirical studies using multivariate logistic regression analysis.^{32,50} The variables most strongly associated with a diagnosis of DSM-5-MXS compared to patients without such a diagnosis were a DSM-IV-TR diagnosis of bipolar disorder, presence of psychotic features, duration of the current episode >1 month, history of mania/hypomania while taking antidepressants, presence of comorbid anxiety disorders, alcohol and substance use disorders, ADHD, and borderline personality disorder. These findings are widely consistent with previous literature.⁵¹⁻⁵³ RBDC-MXS was associated with the largest number of variables including diagnosis of bipolar disorder, family history of mania, lifetime suicide attempts, duration of the current episode >1 month, atypical features, onset of first depressive episode before 30 years of age, history of mania/hypomania while taking antidepressants, and lifetime comorbidity with anxiety disorders, alcohol and substance use disorders, ADHD, and borderline personality disorder. In comparison with DSM-5-MXS definition, the multivariate logistic regression demonstrated specific associations of RBDC-MXS definition with lifetime suicide, family history for hypomania/mania, atypical features, and onset of first depressive episode before 30 years of age. The sole variable specifically associated with DSM-5-MXS definition in comparison with RBDC-MXS is the presence of psychotic features. This finding indicates that the conservative definition of DSM-5 may allow for the identification of mixed features only in the most severe psychotic MDEs.

In DSM-5, the diagnosis of mixed episode has been replaced by the "mixed features" specifier.²⁶ The possibility of classifying depression "with mixed features" represents an improvement from the DSM-IV; however, the discarding of the distinct mixed affective episode diagnostic category has been criticized. A recent article on ICD-11 proposal for the classification of affective mixed states⁵⁴ suggested that a diagnostic category should be preferred to a specifier because it may increase the focus on the disorder and, as a consequence, the importance of research into the nature and treatment of the mixed states. Moreover, a specific diagnostic category is more likely to improve diagnostic sensitivity and to ensure specific treatment than is a simple specifier. The results of the present study seem to indicate not only the importance of a distinct diagnostic category, but also the importance of specific operative diagnostic criteria.

The majority of patients in the present study were currently receiving antidepressants. As expected, this proportion was slightly lower among all mixed subtypes than in the rest of the sample. In contrast, mood stabilizers, atypical antipsychotics, and ECT were more commonly prescribed in the mixed subtypes. The same trend was observed for the proportion of patients receiving more than 3 drugs, suggesting the tendency for mixed depression to be treated with combination regimens, which target specific components of mixed states.⁵⁵

This study has certain strengths and limitations. The principal strengths are the large number of patients included and the range of care settings encompassed. The study included hospital and community psychiatrists from 8 countries across 3 continents. This broad, local clinicalpractice relevant sample, which had few exclusionary criteria, increases the generalizability of the findings. Although the reliance on individual practitioners' skills may be helpful for purposes of generalizability to "routine practice" settings, the inherent tradeoff may affect diagnostic reliability. Moreover, the participating centers were not randomly selected, which may have led to a bias through the inclusion of psychiatrists with a particular interest in mixed states. However, a random selection of participants was not feasible, since lists of all practicing physicians were not in the public domain for the participating countries. A second limitation is the widely varying rates of hospitalized patients across countries, ranging from 1.0% to 57.8%, which largely reflect economically driven policies on the use of hospitalizationbased treatment.

In conclusion, this study shows that the application of an evidence-based set of symptoms, illness course, and family history RBDC criteria for mixed states identifies about 30% of MDE patients as mixed. Such diagnostic assessments provide stronger associations with several illness characteristics of bipolar disorder, which psychiatrists can readily assess in routine practice settings. These include, but are not limited to, comorbidity with substance use disorder or borderline personality disorders, development of mania/hypomania while taking antidepressants, and suicidality. Conversely, DSM-5 "mixed features" specifier may leave many patients with mixed depression undiagnosed and, perhaps, inadequately treated. We hope that the results presented here from this large BRIDGE-II-MIX study, as well as the review of strengths and limitations of methodologies to conduct studies in mixed states and the state of diagnostic ascertainment of mixed states, will encourage more investigators to plan new work in this understudied area.

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