How Many Criteria Should Be Required to Define the *DSM-5* Mixed Features Specifier in Depressed Patients?

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Abstract

Background: During the past 2 decades, there has been intense interest in the clinical significance of the concurrence of manic symptoms in depressed patients. *DSM-5* introduced a mixed features specifier for both bipolar depression and major depressive disorder. Studies of the *DSM-5* mixed features specifier have generally found a low prevalence of mixed depression. One approach toward increasing the sensitivity of the *DSM-5* mixed features criteria is to lower the classification threshold. In the present study, we examine the impact of lowering the *DSM-5* diagnostic threshold from 3 to 2 criteria on the prevalence and validity of the *DSM-5* mixed features specifier for depression.

Methods: Four hundred fifty-nine psychiatric patients in a depressive episode were interviewed by a trained diagnostic rater who administered semistructured interviews including the *DSM-5* Mixed Features Specifier Interview. The patients were rated on clinician rating scales of depression, anxiety, and irritability and measures of psychosocial functioning, suicidality, and family history of bipolar disorder.

Results: When the *DSM-5* diagnostic threshold was lowered from 3 to 2 symptoms, the prevalence of mixed features based on the *DSM-5* majority of episode time frame tripled from 3.9% to 13.1% (n = 60). Based on a past week time frame, the prevalence of mixed features more than doubled from 9.4% to 22.9% (n = 105) upon lowering the threshold from 3 to 2 criteria. However, there was no difference between the patients with 2 mixed features and patients with 0 or 1 mixed features on family history of bipolar disorder, psychosocial impairment, presence of comorbid disorders, age of onset, or history of suicide attempts or psychiatric hospitalization.

Conclusions: The results of the present study do not support lowering the *DSM-5-TR* diagnostic threshold for the mixed features specifier in depressed patients from 3 to 2 criteria.

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More than a century ago, Kraepelin described an admixture of manic and depressive symptoms in patients with manic-depressive illness.[1] During the past 2 decades, there has been intense interest in the clinical significance of concurrent manic symptoms in depressed patients. Depressed patients with manic symptoms are more frequently diagnosed with bipolar disorder than major depressive disorder (MDD).[2–6] The presence of manic symptoms in depressed patients is associated with more frequent episodes of depression,[4,7] more comorbid anxiety disorders,[8–10] more substance use disorders,[9–13] increased suicidality,[3,9,12,14,15] greater likelihood of lifetime hospitalization,[7] more severe symptoms,[3,4] greater impairment in functioning,[4,13,16] and poorer response to treatment.[7,17–22] The link between mixed depression and bipolar disorder[23] is supported by the aforementioned research showing that mixed features are more common in patients with bipolar depression than MDD, and, among patients with MDD, those with mixed features have an elevated family history of bipolar disorder.[3,5,13,24,25] Treatment guidelines have cautioned against using antidepressants in depressed patients with mixed symptoms due to an increased likelihood of initiating the onset of mania,[26–28] thereby indicating that the accurate classification of mixed features is clinically important.

Because of the clinical significance of mixed features in depressed patients, there has been interest in how best to characterize them. Differences in which symptoms should be included as mixed features, and the number of symptoms required to identify patients with mixed features, contribute to the wide variation in the prevalence of mixed

Clinical Points

- Studies of the *DSM-5-TR* mixed features specifier have generally found a low prevalence of mixed depression.
- One approach toward increasing the sensitivity of the *DSM-5-TR* mixed features criteria is to lower the classification threshold.
- In a study of 459 depressed patients, the results did not support lowering the *DSM-5-TR* diagnostic threshold for the mixed features specifier from 3 to 2 criteria.

features in depressed patients. [5,6,8,10,12,29–34] *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) introduced a mixed features specifier for both bipolar depression and MDD.[35] There has been criticism of the *DSM-5* criteria because they do not include features that are often considered to indicate the mixed state (eg, agitation, irritability, distractibility).[36–45] While some studies supported the validity of the *DSM-5* definition,[8,10] there has nonetheless been concern that the *DSM-5* definition lacks sensitivity and underrecognizes mixed depression. Indeed, studies of the *DSM-5* mixed features specifier generally found a low prevalence of mixed depression in patients with bipolar depression,[6,8,31,33,34,46] patients with MDD,[6,32,33,46] and samples including an admixture of patients with bipolar disorder and MDD.[3,10,33]

One approach toward increasing the sensitivity of the *DSM-5* mixed features specifier criteria is to lower the classification threshold. The *DSM-5* definition requires the presence of 3 or more symptoms (out of a list of 7) for the majority of days of the depressive episode. We have previously demonstrated that lowering the time frame requirement from the majority of days of the episode to the past week doubled the prevalence of mixed depression, and the past week time frame was as valid as the majority of days time frame.[47]

In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project,[48] we examine the impact of lowering the *DSM-5* diagnostic threshold from 3 to 2 criteria on the prevalence and validity of mixed depression. Previous studies have found that as many, if not more, depressed patients report 2 co-occurring manic symptoms as 3 or more manic symptoms.[8,10,29,31,49,50] However, little research has directly examined whether a 2-symptom threshold is valid. In the present report, we compare 3 groups of depressed patients: 0–1 *DSM-5-TR* mixed features, 2 mixed features, and 3 or more mixed features (the *DSM-5-TR* threshold) on variables that have previously been found to distinguish patients with and without mixed depression, such as family history of bipolar disorder, age of onset, number of episodes of depression, suicidality, symptom severity, comorbidity with other psychiatric disorders, and impairment in functioning.

METHODS

Four hundred fifty-nine patients with current *DSM-IV/DSM-5-TR* MDD or bipolar disorder (current episode depressed) presenting for an intake evaluation at the Rhode Island Hospital Department of Psychiatry partial hospital program were interviewed by a trained diagnostic rater who administered a modified version of the Structured Clinical Interview for *DSM-IV*[51,52] supplemented with questions from the Schedule for Affective Disorders and Schizophrenia (SADS)[53] and the borderline personality disorder section of the Structured Interview for *DSM-IV* Personality.[54] The interview included items from the SADS assessing episode duration, symptom severity, suicidal ideation, psychosocial functioning, and lifetime history of suicide attempts and psychiatric hospitalizations. Additional questions were included to rate the items on the 17-item Hamilton Depression Rating Scale (HAMD),[55] Hamilton Anxiety Rating Scale (HAMA),[56] and Young Mania Rating Scale (YMRS).[57] A family history of bipolar disorder was based on information provided by the patient. The interview followed the guide provided in the Family History Research Diagnostic Criteria[58] for all first-degree family members.

Details regarding interviewer training and diagnostic reliability are available in other publications from the MIDAS project, which have documented high reliability in diagnosing mood disorders.[59,60] The Rhode Island Hospital institutional review committee approved the research protocol, and all patients provided informed, written consent.

The *DSM-5* Mixed Features Specifier Interview (DMSI) assesses the 7 criteria of the mixed features specifier (elevated mood, inflated self-esteem, increased talkativeness, thought racing, increased energy or goal-directed activity, increased activity with potentially painful consequences, decreased need for sleep). The *DSM-5* specifier requires the presence of at least 3 mixed features for the majority of the depressive episode. The probes of the DMSI inquire about symptom presence and severity for the past week and determine if the symptom is present for the majority of the depressive episode. The interrater reliability of the DMSI was examined in 27 patients, and the κ coefficient of agreement in diagnosing the *DSM-5* mixed features specifier was 1.0.

Data Analysis

We compared 3 groups of patients: those meeting the current *DSM-5-TR* threshold (ie, 3 or more features), those with 2 *DSM-5-TR* features, and those with fewer than 2 features. If the patients with 2 features were indistinguishable from patients with 3 or more features and differed in expected ways from the patients with fewer than 2 mixed features, this would support lowering

the *DSM-5-TR* diagnostic threshold. Categorical variables were compared by χ^2 test and continuous variables by *t* test. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed for categorical variables.

RESULTS

Demographic information was missing for 1 patient. The sample included 100 (21.8%) men and 358 (78.0%) women who ranged in age from 18 to 78 years (mean = 35.5, SD = 13.3). Nearly one-fourth of the subjects were married (22.9%, n = 105), and nearly half were single (45.8%, n = 210). Approximately one-fifth graduated from a 4-year college (21.8%, n = 100), and 61 (13.3%) completed graduate or professional school. The racial/ethnic composition of the sample was 72.5% (n = 333) white, 7.4% (n = 34) black, 12.6% (n = 58) Hispanic, 1.5% (n = 7) Asian, and 5.7% other (n = 26). The majority of the patients were diagnosed with MDD (89.8%, n = 412). Approximately twice as many patients were diagnosed with bipolar II (6.5%, n = 30) than bipolar I (3.7%, n = 17) disorder.

Frequency of the *DSM-5* Mixed Features Subtype and Symptoms

For both the majority of the episode and the past week time frames, the distribution of the number of mixed features was skewed (Table 1). Only 3.9% (n = 18) of the entire sample of depressed patients met the *DSM-5-TR* criteria for the mixed features specifier. More than twice as many patients met the mixed features specifier criteria during the week before the assessment (9.4%, n = 43).

For both the past week and majority of episode time frames, more patients reported 2 mixed features than 3 or more symptoms. When the *DSM-5-TR* diagnostic threshold is lowered from 3 to 2 criteria, the prevalence of mixed features based on the *DSM-5-TR* majority of episode time frame would more than triple from 3.9% to 13.1% (n = 60). Based on a past week time frame, the prevalence would more than double from 9.4% to 22.9% (n = 105).

Association Between the Mixed Features Specifier and Mood Disorder Diagnosis

Previously, we supported the validity of the *DSM-5-TR* symptom threshold for both the past week and majority of episode time frames.[47] Therefore, the subsequent analyses included patients in the mixed features group if they met the symptom threshold for either time frame.

Compared to patients with MDD, the patients with bipolar disorder were significantly more likely to meet the mixed features specifier based on the *DSM-5-TR* 3-symptom threshold (29.8% vs. 9.2%; OR 4.18; 95% CI, 2.06–8.48). The patients with bipolar disorder were also significantly more likely than patients with MDD to be diagnosed with mixed features when the threshold was lowered to include 2 or more mixed features (48.9% vs. 24.8%; OR 2.91; 95% CI, 1.58–5.38). However, when limiting the analysis to the patients with only 2 mixed features, and excluding the patients with 3 or more criteria, the difference between bipolar disorder and MDD was not significant (19.1% vs. 15.5%; OR 1.29; 95% CI, 0.59–2.79).

Table 1.

Frequency Distribution of the Number of *DSM-5* Mixed Features Specifier Criteria Based on the *DSM-5* Majority of the Days Requirement and During the Week Before Evaluation in 459 Depressed Patients

Number of *DSM-5* mixed features specifier criteria	Majority of days		Past week	
	n	(%)	n	(%)
0	214	(46.6)	186	(40.5)
1	185	(40.3)	168	(36.6)
2	42	(9.2)	62	(13.5)
3	9	(2.0)	18	(3.9)
4	5	(1.1)	16	(3.5)
5	2	(0.4)	3	(0.7)
6	1	(0.2)	5	(1.1)
7	1	(0.2)	1	(0.2)

Mixed Features and Diagnostic Comorbidity

Because the mixed features specifier was more frequent in patients with bipolar disorder, and there are differences in the rate of comorbid disorders between patients with MDD and bipolar disorder, subsequent analyses were limited to patients with MDD. The patients with 2 mixed features did not differ from the patients without mixed features in the frequency of comorbid disorders (Table 2). Compared to the patients meeting the *DSM-5-TR* symptom threshold of 3 or more mixed features, the patients with 2 mixed features had a significantly lower prevalence of social anxiety disorder, borderline personality disorder, and attention deficit disorder. No disorder was significantly more often diagnosed in patients with 2 mixed features than in patients with 3 or more mixed features.

Mixed Features, Symptom Severity, and Suicidality

Compared to the patients without mixed features, the patients with 2 mixed features had greater symptom severity, though the difference on the HAMD was not significant (Table 3).

The patients with 2 mixed features were significantly less likely to have a lifetime history of

Table 2.

Current Diagnoses in 412 Major Depressive Disorder Patients With 0–1, 2, or 3 or More Mixed Features

DSM-IV disorder	Mixed features absent (n = 310) n	%	2 mixed features present (n = 64) n	%	≥3 mixed features (n = 38) N	%	2 mixed features vs mixed features absent, OR (95% CI)	2 mixed features vs ≥3 mixed features[a], OR (95% CI)
Panic disorder	100	32.3	21	32.8	13	34.2	1.03 (0.58–1.82)	1.07 (0.46–2.49)
Specific phobia	27	8.7	5	7.8	3	7.9	0.89 (0.33–2.40)	1.01 (0.23–4.49)
Social phobia	90	29.0	17	26.6	19	50.0	0.88 (0.48–1.62)	**2.77 (1.19–6.43)**
Obsessive-compulsive disorder	24	7.7	3	4.7	3	7.9	0.59 (0.17–2.01)	1.74 (0.33–9.11)
Posttraumatic stress disorder	118	38.1	28	43.8	23	60.5	1.27 (0.73–2.18)	1.97 (0.87–4.46)
Generalized anxiety disorder	196	63.2	48	75.0	32	84.2	1.75 (0.95–3.22)	1.78 (0.63–5.03)
Borderline personality disorder	55	17.7	17	26.7	24	63.2	1.68 (0.90–3.14)	**4.74 (2.00–11.22)**
Attention deficit disorder	70	22.6	15	23.4	19	50.0	1.05 (0.56–1.98)	**3.27 (1.38–7.72)**
Alcohol use disorder	29	9.4	9	14.1	3	7.9	1.59 (0.71–3.54)	0.52 (0.13–2.09)
Drug use disorder	13	4.2	1	1.6	1	2.6	0.36 (0.05–2.82)	1.70 (0.10–28.04)
Any substance use disorder	38	12.3	10	15.6	4	10.5	1.33 (0.62–2.82)	0.64 (0.19–2.19)
Any eating disorder	42	13.5	9	14.1	7	18.4	1.04 (0.48–2.27)	1.38 (0.47–4.07)
Any somatoform disorder	15	4.8	5	7.8	5	13.2	1.67 (0.58–4.76)	1.79 (0.48–6.63)
Any impulse control disorder	21	6.8	6	9.4	4	10.5	1.42 (0.55–3.68)	1.14 (0.30–4.32)

[a]Boldface indicates statistical significance.

Table 3.

Functioning in Major Depressive Disorder Patients With 0–1, 2, or 3 or More Mixed Features

Domain of functioning	Mixed features absent (n = 310) Mean	SD	2 mixed features present (n = 64) Mean	SD	≥3 mixed features (n = 38) Mean	SD	2 mixed features vs mixed features absent[a], *P* value	2 mixed features vs ≥3 mixed features[a], *P* value
Suicidal ideation	1.61	1.41	1.51	1.34	1.74	1.41	.60	.43
Functioning in past week	2.77	1.06	2.83	1.02	2.97	1.00	.67	.50
Young Mania Rating Scale	2.49	2.73	4.33	3.10	5.79	4.69	**<.001**	.15
Hamilton Depression Rating Scale	18.95	5.87	20.30	6.11	21.35	5.78	.11	.40
Hamilton Anxiety Rating Scale	18.15	6.89	20.33	7.43	21.14	7.15	**.03**	.60
Age of onset of depression	19.40	11.52	18.14	11.88	16.80	12.00	.45	.60
Schedule for Affective Disorders and Schizophrenia sum of 2 anger items	3.70	2.52	4.42	2.40	4.50	2.44	**.04**	.88

	Mixed features absent (n = 310) n	%	2 mixed features present (n = 64) n	%	≥3 mixed features (n = 38) n	%	2 mixed features vs mixed features absent[a], OR (95% CI)	2 mixed features vs ≥3 mixed features[a], OR (95% CI)
Lifetime suicide attempt	82	28.3	17	29.3	19	50.0	1.05 (0.57–1.96)	**2.41 (1.03–5.65)**
Lifetime psychiatric hospitalization	95	32.8	21	35.6	17	44.7	1.13 (0.63–2.04)	1.47 (0.64–3.37)
Family history of bipolar disorder	57	22.2	13	24.1	15	42.9	1.11 (0.56–2.22)	2.37 (0.95–5.91)
Age of onset ≤18 y	172	61.0	40	69.0	28	80.0	1.42 (0.78–2.60)	1.80 (0.66–4.88)
≥3 Depressive episodes	177	67.6	42	80.8	23	74.2	2.02 (0.97–4.21)	0.69 (0.24–1.98)

[a]Boldface indicates statistical significance.

attempted suicide compared to patients with 3 or more mixed features, and the patients with 2 mixed features did not differ from the patients without mixed features. There was no difference in the level of suicidal ideation during the week before the evaluation between the 3 groups (Table 3).

Mixed Features, Psychosocial Morbidity, and Family History of Bipolar Disorder

The patients with 2 mixed features did not differ from the patients without mixed features in functioning, age of onset, history of psychiatric hospitalization, or family history of bipolar disorder. The patients with

2 mixed features also did not differ from the patients with 3 or more mixed features on any of these variables (Table 3).

DISCUSSION

For disorders that are defined by a list of features, the threshold used to distinguish disorder presence versus absence is of critical importance because it impacts the prevalence of the condition. Ideally, a diagnostic threshold would be identified by examining the frequency distribution of the number of criteria, a bimodal distribution would be found, and a point of rarity would be identified to demarcate those with and without the disorder. At the core of the categorical-dimensional debate of classification is the fact that points of rarity are rarely identified and individuals who manifest the number of criteria just below the diagnostic threshold are more similar to individuals who meet the diagnostic threshold than to individuals with none of the diagnostic criteria. Nonetheless, the categorical approach to diagnosis prevails.

The *DSM-5-TR* mixed features specifier definition has been questioned. Many have criticized the content of the *DSM-5* criteria for failing to include symptoms such as agitation, irritability, and distractibility.[36–45] Others have used a lower diagnostic threshold to define mixed features.[49,61] Given the potential treatment implications of mixed features in depressed patients, an examination of the validity of alternative diagnostic thresholds is clinically relevant.

In the present study, the frequency distribution of the number of mixed features was skewed. There was a marked reduction in the number of patients who met 2 criteria compared to 1 criterion and another large drop when going from 2 to 3 criteria. If a diagnostic threshold of 1 criterion was adopted, then the majority of patients would be considered to have mixed features. This is consistent with studies that have found that the majority of depressed patients report at least 1 mixed feature.[2,5,29,30,62] At a diagnostic threshold of 2, the prevalence of mixed features was approximately one-quarter of the patients with MDD and one-half of the patients with bipolar disorder. The prevalence of 2 or more mixed features in patients with MDD in the present study was lower than the rate reported by Benazzi[2] (42%), though his assessment of mixed features included non-*DSM-5* symptoms such as agitation, irritability, and distractibility. In contrast, Sato et al[5] reported a rate of 20%, despite also including non-*DSM* symptoms. In patients with bipolar depression, the rates of mixed features based on a cutoff of 2 have ranged from 20%[5] to nearly 70%.[25,30]

We chose to focus on the validity of lowering the threshold to 2 criteria rather than 1 criterion for 2 reasons. First, some recent treatment studies of *DSM-5* mixed depression have included patients with 2 criteria but not 1 criterion.[49,61] Second, we appreciate that for a continuously distributed variable that wherever the diagnostic threshold is established, there will be diagnostic error such that some patients who meet the diagnostic threshold do not, in fact, have the disorder and some individuals who fall below the threshold do, in fact, have the disorder. Such is the reality inherent in a phenomenologically based, rather than pathophysiologically based, classification system. For continuous variables, such as the *DSM-5-TR* mixed specifier criteria, the question is not whether diagnostic error exists upon establishing a diagnostic threshold, but rather which type of error is more palatable and correctable. Too low of a diagnostic threshold for mixed features, giving rise to more false-positive diagnoses, would potentially result in overtreatment with mood stabilizer medications and health-impairing side effects. Too high of a threshold, causing false-negative diagnoses, would potentially result in overtreatment with antidepressant medication and increased risk for initiating the emergence of a manic episode. We consider errors associated with false-negative diagnoses to be easier to correct than false-positive diagnoses. A false-negative diagnosis could be corrected, and outcome improved, by an active treatment intervention. The potential negative outcomes associated with a false-negative diagnosis include the emergence of a (hypo)manic episode or persisting mixed features. Active intervention to address these negative outcomes could include adding a mood stabilizer or stopping an antidepressant. On the other hand, the adverse consequence of a false-positive diagnosis is to remain on an unneeded medication and the possible occurrence of adverse effects from remaining on the medication.

The results of the present study do not support lowering the diagnostic threshold for mixed features to 2 criteria. Patients with bipolar disorder were not significantly more likely than patients with MDD to report 2 mixed features. There was no difference between the patients with 2 mixed features and patients with 0 or 1 mixed features on family history of bipolar disorder, psychosocial impairment, presence of comorbid disorders, age of onset, history of suicide attempts, or psychiatric hospitalization. The only significant difference between the groups was on the symptom severity measures with greater severity found in the patients with 2 mixed features. Compared to the patients who met the *DSM-5* threshold, those with 2 mixed features were less often diagnosed with attention deficit disorder, borderline personality disorder, and social anxiety disorder and less often had attempted suicide. Moreover, other differences between these 2 groups were in the expected direction (eg, family history of bipolar disorder was nearly twice as high in the patients with

3 or more mixed features), and the lack of significant differences may have been due to the small sample size of the group with 3 or more features. Finally, our prior work demonstrated that patients with 3 or more mixed features differed from patients with 2 or fewer mixed features on many of these important validators.[47]

Typically, studies examining the validity of diagnostic thresholds compare patients scoring at and above versus below various thresholds. [5,8,25] In this type of analysis, the group scoring above a low threshold includes an admixture of patients who have been added to the diagnosis positive group by virtue of lowering the threshold as well as the patients who were already in the diagnosis positive group at the higher threshold. Had we analyzed the data in this manner, we would have validated a cutoff of 2 features because the group with 2 or more features includes the patients with 3 or more features. However, when we focused on the patients who had only 2 mixed features, our findings did not support their inclusion in the mixed group.

Research investigating the optimal threshold for identifying patients with mixed features is inconsistent. Suppes and colleagues[49] examined the efficacy of lurasidone in depressed patients with 2 or 3 mixed features and found that the effect size was greater for patients with 2 symptoms. Conversely, Benazzi,[25] using a family history of bipolar disorder as the validator, found that a cutoff of 3 features produced the highest odds ratio, though this cutoff was derived from a list of 10 symptoms including some symptoms that were excluded from the *DSM-5* definition (agitation, irritability, distractibility). The BRIDGE-II-MIX study[10] analyzed the data in a manner similar to the present paper but found that the presence of 2 *DSM-5* mixed features was associated with as many validators as the presence of 3 or more mixed features. Kim et al[8] found more statistically significant correlates with a cutoff of 2 than a cutoff of 3; however, the lack of significant differences based on the higher cutoff was likely due to the small sample size of the mixed group (n = 11). The inconsistency of the findings regarding the optimal cutoff for mixed features highlights the importance of not reifying diagnostic thresholds.

Although the current study included a number of noteworthy strengths, it was conducted in a single clinical program in which the majority of the patients were white, were female, and had health insurance. Replication in samples with different demographic characteristics is warranted. Replication in a community-based nonpatient sample is also warranted. Additionally, the ratings on the clinician scales were not independent of each other. That is, the same rater completed the DMSI and the HAMA, HAMD, and YMRS. It would be preferable to have independent interviewers complete the clinician rating scales, although this was not practical in an integrated clinical research setting such as ours in which the interview is conducted primarily for clinical purposes and the use of the information for research purposes is a secondary goal.

Furthermore, the relatively small sample size of patients with MDD who met the *DSM-5-TR* mixed features criteria reduced the power to find differences compared to the group with 2 mixed features.

In conclusion, the results of the present study do not support lowering the *DSM-5-TR* diagnostic threshold for the mixed features specifier in depressed patients from 3 to 2 criteria. Given its treatment implications, future research examining the most valid diagnostic threshold for mixed features is warranted.

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