Increased Activity or Energy as a Primary Criterion for the Diagnosis of Bipolar Mania in DSM-5: Findings From the STEP-BD Study

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Objective: DSM-5 describes "a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy" as a primary criterion for mania. Thus, increased energy or activity is now considered a core symptom of manic and hypomanic episodes. Using data from the Systematic Treatment Enhancement Program for Bipolar Disorder study, the authors analyzed point prevalence data obtained at the initial visit to assess the diagnostic validity of this new DSM-5 criterion. The study hypothesis was that the DSM-5 criterion would alter the prevalence of mania and/or hypomania.

Method: The authors compared prevalence, clinical characteristics, validators, and outcome in patients meeting the DSM-5 criteria (i.e., DSM-IV criteria plus the DSM-5 criterion of increased activity or energy) and those who did not meet the new DSM-5 criterion (i.e., who only met DSM-IV criteria).

Results: All 4,360 participants met DSM-IV criteria for bipolar disorder, and 310 met DSM-IV criteria for a manic or hypomanic episode. When the new DSM-5 criterion of increased activity or energy was added as a coprimary symptom, the prevalence of mania and hypomania was reduced. Although minor differences were noted in clinical and concurrent validators, no changes were observed in longitudinal outcomes.

Conclusions: The findings confirm that including increased activity or energy as part of DSM-5 criterion A decreases the prevalence of manic and hypomanic episodes but does not affect longitudinal clinical outcomes.

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To enhance the accuracy of diagnosis and facilitate earlier detection in clinical settings, the diagnostic criteria for bipolar disorder in DSM-5 emphasize changes in activity or energy as a core symptom of mania or hypomania (criterion A) in addition to changes in mood. In contrast, DSM-IV criteria included increased goal-directed activity or psychomotor agitation as one of several secondary criteria (criterion B). Other changes from DSM-IV to DSM-5 criteria include the new specifier "with mixed features," which can be applied to episodes of mania or hypomania when depressive features are present, as well as to episodes of depression when features of mania or hypomania are present.

Elevated activity or energy is a key symptom of mania (1). Psychomotor pressure and increased motor activity have been described in 85%−95% of mania cases (1), and previous studies supporting the inclusion of "increased activity or energy" in criterion A noted that it was as important as elevated mood in the clinical picture of mania (2, 3). In DSM-III-R, elevated motor activity was the most prevalent symptom in subjects diagnosed with a manic episode (4), and other studies noted that this symptom was more prevalent in individuals with bipolar disorder than in subjects with schizophrenia or healthy comparison subjects (4). Angst et al. (3), after evaluating a subsample of 591 subjects with bipolar disorder from a 20-year cohort of 4,547 subjects, proposed that overactivity, which is directly associated with increased activity or energy, should be included as a key criterion of hypomania in addition to euphoria and irritability. In addition, changes in energy and activity are more likely than changes in mood to be noticeable and/or documented by patients and family members.

In diverse studies that have used factor analysis to investigate the phenomenology of mania, hyperactivity and increased energy have been described as key factors across the entire spectrum of mania severity, suggesting that elevated motor activity is not only a key clinical feature of mania

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but is also more important than mood changes (5–9). In patients with bipolar II disorder or major depressive disorder, Benazzi and Akiskal (8) noted that "energized-activity" and "irritability-racing thoughts"—but not euphoria—were cardinal symptoms for the diagnosis of hypomania. Similarly, Benazzi (7) reported that hyperactivity was the most common symptom retrospectively identified by patients with bipolar II disorder as well as the one most strongly associated with this diagnosis; in that study, no association between hyperactivity and euphoria or irritability was observed. Moreover, Akiskal et al. (6) proposed new diagnostic criteria for mania, suggesting that psychomotor activation was the key criterion for mania, while mood changes (elation, depression, anxiety, etc.) were hierarchically less important than psychomotor activation for diagnosis.

It should be noted that mild positive mood changes may be misdiagnosed as hypomania when activity levels are not taken into account. Along these lines, focusing on increased activity rather than just elevated mood or irritability may more successfully identify hypomania in bipolar II disorder (2, 3). One issue of particular concern is that up to 40% of bipolar II patients may be erroneously diagnosed with major depressive disorder (10). This underdiagnosis of bipolar disorder, as well as the concomitant changes in diagnostic accuracy in mood disorders, is associated with diverse factors that may result in inadequate treatment (11). For instance, such individuals have an average delay of 7–10 years before they are diagnosed correctly (12). This is particularly important because misdiagnosed individuals often receive inappropriate treatments for many years—particularly antidepressant pharmacotherapy without mood stabilizers. A recent analysis from the international, multisite Bipolar Disorder: Improving Diagnosis, Guidance, and Education (BRIDGE) study that evaluated more than 5,000 subjects with major depressive disorder emphasized the benefits of improving the specificity of the hypomania diagnosis by requiring mood plus increased activity or energy for the diagnosis (13, 14).

In this study, we sought to assess the diagnostic validity of the new DSM-5 criterion of increased activity or energy levels by analyzing point prevalence data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study at the initial visit. Specifically, we evaluated differences between patients who met the DSM-5 criterion of increased activity or energy levels (in addition to meeting all DSM-IV criteria) and those who did not (that is, individuals who met DSM-IV criteria but not the more stringent DSM-5 criterion of increased activity or energy levels) regarding 1) diagnostic prevalence, 2) clinical and concurrent validators, and 3) longitudinal outcome. We hypothesized that the new DSM-5 criterion would reduce the prevalence of mania and/or hypomania.

METHOD

Data for this study were drawn from the STEP-BD study, a multicenter observational and effectiveness study with a hybrid design sponsored by the National Institute of Mental Health and conducted at 22 treatment sites (reviewed in reference 15). The main objective of STEP-BD was to determine which treatments were more effective for bipolar disorder across broad inclusion criteria. The study was approved by the institutional review board of each participating institution.

STEP-BD enrolled 4,360 outpatients from academic and nonacademic treatment settings across the United States (16). To be included in the study, patients were required to be at least 15 years old, to be able to give consent, and to meet criteria for bipolar disorder (type I, type II, or not otherwise specified), cyclothymia, or schizoaffective disorder (bipolar subtype, which incorporates manic symptoms). All participants met DSM-IV criteria for bipolar disorder. The database includes well-characterized subjects who sought outpatient treatment. All participants received a standard assessment, participated in naturalistic or randomized treatment, and provided written informed consent before entering the study.

The present analysis examined the STEP-BD data set to assess the effect of a single DSM-5 primary criterion—that of increased activity or energy levels—on diagnostic prevalence. Specifically, we compared those individuals with bipolar disorder who met the DSM-5 criterion of increased activity or energy levels (as well as meeting all DSM-IV criteria) to those who did not. We evaluated up to 1 year of longitudinal data for subjects with bipolar disorder (types I and II).

Assessments

All patients were systematically evaluated at study entry for medical and psychiatric history, presence of mood or psychotic symptoms, and other illness characteristics using the Mini-International Neuropsychiatric Interview and the Affective Disorders Evaluation adapted from the Structured Clinical Interview for DSM-IV Axis I Disorders (17, 18). Of the 4,360 patients originally enrolled in the STEP-BD study, 310 met DSM-IV criteria for a manic or hypomanic episode at study entry. This was determined using DSM symptoms assessed via the Clinical Monitoring Form, an assessment tool focused on symptoms and treatment status that was the primary data collection tool for clinical evaluations in the STEP-BD study. The Clinical Monitoring Form is used to record clinician-rated symptoms over the course of the previous week; symptoms were counted as present if the patient had a score ≥1 on that item. Notably, individual symptoms were used instead of categorizations by clinicians in order to facilitate understanding of how change in individual symptom criteria might alter diagnosis. Interrater reliability among the STEP-BD physicians for DSM-IV manic and depressive symptoms was high (intraclass correlation coefficients, 0.83–0.99) (19).

At follow-up visits, standardized clinical assessments were similarly performed using the Clinical Monitoring Form. Data were examined during a 1-year period (at baseline, 6 months, and 12 months). It should be noted that the present analysis assessed the impact of a single DSM-5 primary criterion A symptom—that of increased activity or energy levels—on diagnostic prevalence, clinical validators, and 12-month outcome; it did not include psychomotor agitation as a primary

TABLE 1. Baseline Demographic and Clinical Variables for Patients With Mania or Hypomania Who Did and Did Not Meet DSM-5 Criteria (N=310)[a]

Variable	Did Not Meet DSM-5 Criteria (N=150)		Met DSM-5 Criteria (N=160)				
	Mean	SD	Mean	SD	t	df	p
Age (years)	37.4	11.7	40.0	12.4	1.82	281	0.07
Age at first depressive episode (years)	16.9	8.8	17.4	10.2	0.50	281	0.62
Age at first manic or hypomanic episode (years)	19.1	9.0	19.9	9.9	0.69	284	0.49
	N	%	N	%	χ^2	df	p
Diagnosis at study entry					1.02	2	0.60
Bipolar I disorder	107	71	110	69			
Bipolar II disorder	34	23	43	27			
Other	9	6	7	4			
DSM-IV major depressive disorder[b]	67	45	40	26	12.50	1	<0.001
Episode type (clinician rated)							
Depression	6	4	4	3			
Mania	21	14	40	25			
Hypomania	51	34	61	38			
Mixed or cycling	61	41	39	24			
Continued symptoms	9	6	12	8			
Roughening	1	1	2	1			
Recovering	1	1	2	1			
Female	85	63	99	66	0.28	1	0.60
Caucasian	116	90	136	93	0.93	1	0.33
Hispanic	6	5	12	8	1.52	1	0.22
Income >$20,000 a year	37	28	70	47	10.07	1	0.002
At least some college	101	75	119	79	0.64	1	0.42
Employed full-time	33	25	47	31	1.49	1	0.22
Family history of bipolar disorder							
First-degree relative	43	29	40	26	0.50	1	0.48
First- or second-degree relative	71	48	78	50	0.09	1	0.77
Comorbidity (history)							
Obsessive-compulsive disorder	19	13	34	22	4.34	1	0.04
Panic disorder	60	41	65	43	0.04	1	0.85
Personality disorder	7	5	11	7	0.66	1	0.42
Posttraumatic stress disorder	19	22	11	15	1.36	1	0.24
Social phobia	37	26	32	21	0.89	1	0.35
Suicide attempt	71	49	67	43	0.98	1	0.32
Episodes							
Manic (≥10)	84	67	93	67	0.00	1	0.96
Depressive (≥10)	84	66	101	70	0.51	1	0.48
Symptoms							
Delusions	5	3	5	3	0.01	1	0.91
Hallucinations	12	8	11	7	0.15	1	0.70
Substance abuse							
Alcohol							
Past	58	44	58	41	0.39	1	0.53
Current	13	10	17	12	0.27	1	0.60
Drugs							
Past	45	34	36	25	2.89	1	0.09
Current	12	9	9	6	0.86	1	0.35
Medications							
Anticholinergics	0	0	2	1	1.89	1	0.17
Antidepressants	64	43	80	50	1.67	1	0.20
Antipsychotics	30	20	43	27	2.03	1	0.15
Anxiolytics	5	3	2	1	1.52	1	0.22
Benzodiazepines	46	31	45	24	0.24	1	0.62
Hypnotics	7	5	12	8	1.08	1	0.30
Mood stabilizers	99	66	116	73	1.54	1	0.21
Stimulants	5	3	4	3	0.19	1	0.66

[a] All patients met DSM-IV criteria for mania or hypomania; those who met DSM-5 criteria additionally met the new criterion of increased energy or activity. Values for the two groups are point prevalence values. Episode types are clinician-derived categorizations made at the patient visit. All p values are nominal values, and none would be significant after Bonferroni correction except DSM-IV depression.

[b] Symptoms from the Clinical Monitoring Form were used to determine whether patients met DSM-IV criteria for major depressive disorder at the initial study visit.

mania criterion. The specific question from the Clinical Monitoring Form used for this analysis involved the presence of more goal-directed activity than usual over the past week. A secondary analysis using data from the Clinical Monitoring Form examined patients' current clinical status as an indicator of mood state as assessed by the evaluating clinician. Only patients listed as experiencing a manic, hypomanic, or mixed episode were included, except as otherwise noted.

TABLE 2. Associations Between Primary DSM-5 Manic Symptoms in Patients With Bipolar Disorder in the STEP-BD Sample (N=3,684)

	Goal-Directed Activity				Elevated Mood			
	No	Yes	Total	Odds Ratio	No	Yes	Total	Odds Ratio
Elevated Mood				14.56				
No	3,010	84	3,094					
Yes	416	169	585					
Total	3,426	253	3,679					
Irritability				3.82				6.12
No	2,452	101	2,553		2,359	203	2,562	
Yes	961	151	1,112		735	387	1,122	
Total	3,413	252	3,665		3,094	590	3,684	

Statistical Analysis

Demographic characteristics were compared between those who met the DSM-5 criterion and those who did not using chi-square tests for categorical variables and t tests for continuous ones. To examine changes in symptoms over the course of the first year in the study, linear mixed models were used with a first-order autoregressive covariance structure with time and group in a factorial model with restricted maximum-likelihood estimates. Bonferroni post hoc tests were used to examine significant omnibus effects. The significance threshold was set at 0.05, two-tailed. All analyses were performed using IBM SPSS Statistics, version 21.0.0.2 (IBM, Armonk, N.Y.).

RESULTS

Table 1 summarizes the demographic and clinical characteristics of the 310 patients who were experiencing a manic or hypomanic episode at study entry based on symptoms from the Clinical Monitoring Form. All 310 patients met DSM-IV criteria for a manic or hypomanic episode, and 52% also met the stricter DSM-5 criteria (that is, DSM-IV criteria plus the additional DSM-5 criterion of increased activity or energy levels). Patients were evaluated in groups determined by whether they met DSM-5 criteria (N=160) or did not (N=150). The prevalence of mania and hypomania was 8.3% by DSM-IV criteria and 4.3% by DSM-5 criteria. Clinical and demographic comparisons showed that on average, the DSM-5 group had a higher annual income, more comorbidity with obsessive-compulsive disorder, and less DSM-IV-diagnosed major depressive disorder than those who did not meet DSM-5 criteria (Table 1). Only the difference with major depressive disorder remained significant after Bonferroni correction.

When all patients with available data were included, increased activity was associated with elevated mood (χ^2=526.30, $p<0.001$; odds ratio=14.56) and irritability (χ^2=112.02, $p<0.001$; odds ratio=3.82). Elevated mood and irritability were also related (χ^2=409.50, $p<0.001$; odds ratio=6.12) (Table 2). The odds ratio was highest for increased activity and elevated mood. In an analysis in which the three symptoms were combined, the association between elevated mood and increased motor activity was significant whether patients had irritability (χ^2=131.66, $p<0.001$; odds ratio=8.00) or not (χ^2=314.45, $p<0.001$; odds ratio=18.88). Furthermore, all three of the primary symptoms of mania—changes in mood, increased energy or activity, and irritability—were present in 62% of patients who met DSM-5 criteria for mania or hypomania. Sixty-nine percent of patients who were not experiencing a manic or hypomanic episode displayed none of the three primary manic symptoms (Table 3).

No differences in clinical rating scales were observed at 1-year follow-up between those who met DSM-5 criteria at baseline and those who did not (Figure 1). Specifically, no between-group differences in Global Assessment of Functioning (GAF) scores were observed at baseline, at 6 months, or at 12 months. For the overall sample, a significant improvement in GAF scores from baseline was observed at 6 months ($p<0.001$) and at 12 months ($p=0.003$). Similarly, Clinical Global Impressions scale scores did not differ between groups at any time point, but scores had improved significantly from baseline at 6 months ($p<0.001$) and at 12 months ($p<0.001$).

Using the Clinical Monitoring Form to show point prevalence, clinicians categorized the type of episode a patient was currently experiencing at the initial visit. Figure 2 illustrates the prevalence of DSM-5 diagnosis by episode type. Of the 310 patients who met DSM-IV criteria for a manic or hypomanic episode, 112 (36%) were experiencing a hypomanic episode, 61 (20%) were experiencing a manic episode, and 100 (32%) were experiencing a mixed episode; the remaining 37 (12%) patients were in cyclothymic and other states. For those characterized as hypomanic, 54% met DSM-5 criteria. Sixty-six percent of patients characterized as manic and 39% characterized as being in a mixed episode met DSM-5 criteria. The distribution of DSM-IV criterion A symptoms is summarized in Table 3.

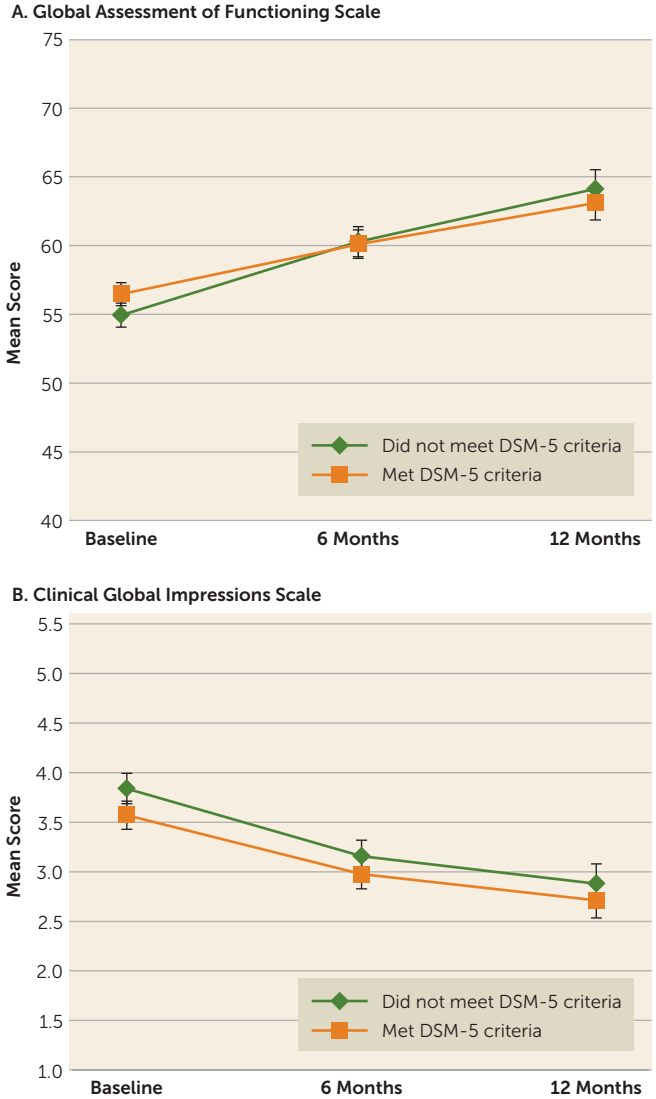
It should be noted that patients met entry criteria into the STEP-BD study for bipolar disorder through methods other than the Clinical Monitoring Form, but many of these patients would not have met full mania

TABLE 3. Prevalence of Mania Symptoms, by Group, in the STEP-BD Sample (N=3,663)[a]

	Symptom and Prevalence (%)								
Mania Criteria	None	Irritability	Elevated Mood	Activity	Elevated Mood and Irritability	Activity and Irritability	Activity and Elevated Mood	Activity, Elevated Mood, and Irritability	N
Met neither DSM-IV nor DSM-5 criteria	68.7	19.8	3.6	1.4	5.2	0.5	0.4	0.4	3,354
Did not meet DSM-5 criteria	0.0	19.5	17.4	0.0	63.1	0.0	0.0	0.0	149
Met DSM-5 criteria	0.0	0.0	0.0	0.0	0.0	11.9	26.3	61.9	160

[a] The patients included in this analysis had data available on all three symptoms of interest.

FIGURE 1. Clinical Rating Scale Scores at Baseline, 6 Months, and 12 Months for Patients With Mania or Hypomania Who Did and Did Not Meet DSM-5 Criteria at Baseline (N=310)[a]



[a] All patients met DSM-IV criteria for mania or hypomania; those who met DSM-5 criteria additionally met the new criterion of increased energy or activity. Error bars indicate standard error.

criteria based on the Clinical Monitoring Form questions. Of those patients previously diagnosed as manic using DSM-IV criteria based on the Clinical Monitoring Form, 45% met DSM-5 criteria for "major depressive episode with mixed features."

DISCUSSION

In this sample from the STEP-BD study, adding "abnormally and persistently increased activity or energy" as part of criterion A for hypomanic and manic episodes in DSM-5 decreased the prevalence of mania and hypomania; this change was assessed using the Clinical Monitoring Form via the additional question on increased goal-directed activity. Changes in cross-sectional diagnosis were more robust for hypomania and mixed episodes than for mania. For hypomania and mixed episodes, only 54% and 39% of patients, respectively, kept the same diagnosis of bipolar disorder using DSM-5 criteria. However, compared with DSM-IV criteria, these expanded criteria affected point prevalence at the baseline visit but did not alter clinical and concurrent validators or 1-year longitudinal outcome when examined in the context of multiple visits for a given patient.

When we examined symptoms at the baseline visit, we found that using the single DSM-5 criterion of increased activity or energy levels reduced the identified number of manic and hypomanic episodes by 48%. Interestingly, the BRIDGE study, which assessed diagnostic criteria for bipolar disorder in a sample of 5,635 patients with DSM-IV major depressive disorder, found that increased activity was a primary symptom of bipolar disorder. In that study, any of the three primary symptoms (changes in mood, increased energy or activity, and irritability) showed diagnostic validity on its own (14).

These results suggest that the DSM-5 criteria for mania and hypomania may not only affect point prevalence (and potentially prevent overdiagnosis) for both mood states but also, because of their increased ability to differentiate diagnoses, may have an impact on the treatment of mood disorders (7). Indeed, the change to criterion A was expected to decrease the overall prevalence of bipolar disorder while concomitantly improving diagnostic accuracy. The impact of requiring increased activity or energy as a criterion for the diagnosis of bipolar disorder—and its concomitant effects on treatment selection—is unclear and will require additional study.

Despite the altered point prevalence rates observed in this study when the DSM-5 criteria were used, no impact on

outcome was noted in the 1-year follow-up. The magnitude of the odds ratio for the presence of motor activity associated with elevated mood and irritability supports an association among these key manic symptoms.

Nevertheless, the study has some limitations. Specifically, time spent in any mood episode was not evaluated; rapid cycling was not evaluated; there was no diagnostic evaluation of mood disorder (only episode prevalence was analyzed); and the role of comorbidities was not taken into account. In addition, our reliance on a single question on the Clinical Monitoring Form may have limited our ability to evaluate the relationship between diagnostic changes from DSM-IV to DSM-5, although it should be noted that good interrater reliability was present across sites. It is also important to mention that the STEP-BD study only included patients in tertiary care, so the present study was not based on a population-based, random, representative sample. As a result, data comparing the prevalence of DSM-IV-diagnosed versus DSM-5-diagnosed bipolar disorder require further replication in studies with samples drawn from a more generalizable population to confirm potential prevalence changes.

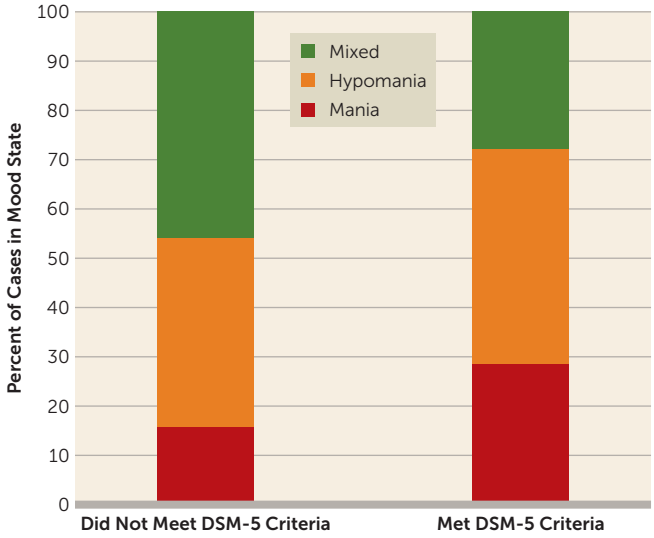
The DSM-5 criteria for mania and hypomania produced a large decrease in point prevalence, with no change in validity or other measures. The impact on point prevalence appears to be particularly remarkable. Specifically, the change in DSM-5 mania criteria reduced the frequency of mania or hypomania by nearly 50%. No difference was observed for most of the available validators when comparing the DSM-5 and DSM-IV criteria sets. Furthermore, and based on available information, a large percentage of those who did not meet DSM-5 criteria for mania now met criteria for major depressive episode with mixed features. Thus, it appears that the decision to include "mixed features" in DSM-5 was a beneficial one, as this is a key and extremely valuable specifier for making diagnoses across the continuum of mood disorders.

Indeed, depressive symptoms as well as full depressive episodes predominate in bipolar disorder; most individuals with bipolar disorder experience chronic depression much more frequently than mania or hypomania (20, 21). In a longitudinal study, Judd et al. (20, 21) observed that subjects with bipolar I disorder had depressive symptoms for 30.6% of the weeks observed, while only 9.8% of the weeks observed were spent in hypomanic or manic states. In addition, patients with bipolar II disorder had depressive symptoms for 51.9% of the weeks observed, while only 1.4% of the weeks observed were spent in a hypomanic state. Similar results have been described by the Stanley Foundation Bipolar Network, which found that individuals with bipolar disorder had depressive symptoms three times as often as they did manic or hypomanic symptoms over a 12-month period (22, 23). The present findings from the STEP-BD data set further support the persistent presence of depressive symptoms over the course of bipolar disorder.

It should be noted that only a relatively small proportion of patients in the total sample experienced a manic or hypomanic episode. Because patients with bipolar disorder spend three times as much time experiencing depressive symptoms as mania or hypomania (24), we expected to observe only a relatively small proportion of patients with mania or hypomania in a sample with broad entry criteria such as this one, especially considering that patients spent some time well and not ill. In addition, this was a long-term outpatient study, which may explain the small proportion of recruited STEP-BD participants experiencing a manic, hypomanic, or mixed episode.

Despite these limitations, taken together, our results indicate that the new DSM-5 criteria may affect the diagnostic prevalence of manic or hypomanic episodes as well as the overall diagnosis of bipolar I and II disorder. Ultimately, these differences may affect the number of individuals clinically diagnosed with bipolar disorder during initial episodes and their treatment course (i.e., whether they are treated with mood stabilizers, atypical antipsychotics, and/or antidepressants). In addition, these findings suggest that the new DSM-5 criteria may directly affect the diagnostic prevalence of both major depressive disorder and bipolar disorder by potentially increasing the first and lowering the second, while nevertheless potentially supporting their existence along a continuum. Overall, our findings suggest that the inclusion of increased activity or energy levels as a DSM-5 criterion A symptom for manic episodes decreases point prevalence rates of mania and hypomania but does not affect longitudinal clinical outcomes.

FIGURE 2. Baseline Prevalence of Episode Types Among Patients With Mania or Hypomania Who Did and Did Not Meet DSM-5 Criteria (N=310)[a]



[a] All patients met DSM-IV criteria for mania or hypomania; those who met DSM-5 criteria additionally met the new criterion of increased energy or activity. The categories mixed, hypomania, and mania are clinician-derived categorizations made at the patient visit.

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REFERENCES

1. Cassidy F, Murry E, Forest K, et al: Signs and symptoms of mania in pure and mixed episodes. J Affect Disord 1998; 50:187–201
2. Akiskal HS, Benazzi F: Optimizing the detection of bipolar II disorder in outpatient private practice: toward a systematization of clinical diagnostic wisdom. J Clin Psychiatry 2005; 66:914–921
3. Angst J, Gamma A, Benazzi F, et al: Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders, and hypomania. J Affect Disord 2003; 73:133–146
4. Minassian A, Henry BL, Geyer MA, et al: The quantitative assessment of motor activity in mania and schizophrenia. J Affect Disord 2010; 120:200–206
5. Akiskal HS, Azorin JM, Hantouche EG: Proposed multidimensional structure of mania: beyond the euphoric-dysphoric dichotomy. J Affect Disord 2003; 73:7–18
6. Akiskal HS, Hantouche EG, Bourgeois ML, et al: Toward a refined phenomenology of mania: combining clinician-assessment and self-report in the French EPIMAN study. J Affect Disord 2001; 67:89–96
7. Benazzi F: Testing new diagnostic criteria for hypomania. Ann Clin Psychiatry 2007; 19:99–104
8. Benazzi F, Akiskal HS: The dual factor structure of self-rated MDQ hypomania: energized-activity versus irritable-thought racing. J Affect Disord 2003; 73:59–64
9. Cheniaux E, Filgueiras A, Silva RdeA, et al: Increased energy/activity, not mood changes, is the core feature of mania. J Affect Disord 2014; 152-154:256–261
10. Hirschfeld RM, Lewis L, Vornik LA: Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003; 64:161–174
11. Ghouse AA, Sanches M, Zunta-Soares G, et al: Overdiagnosis of bipolar disorder: a critical analysis of the literature. Scientific World Journal 2013; 2013:297087
12. Kupfer DJ, Frank E, Grochocinski VJ, et al: Demographic and clinical characteristics of individuals in a bipolar disorder case registry. J Clin Psychiatry 2002; 63:120–125
13. Angst J, Azorin JM, Bowden CL, et al: Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. Arch Gen Psychiatry 2011; 68:791–798
14. Angst J, Gamma A, Bowden CL, et al: Diagnostic criteria for bipolarity based on an international sample of 5,635 patients with DSM-IV major depressive episodes. Eur Arch Psychiatry Clin Neurosci 2012; 262:3–11
15. Bowden CL, Perlis RH, Thase ME, et al: Aims and results of the NIMH systematic treatment enhancement program for bipolar disorder (STEP-BD). CNS Neurosci Ther 2012; 18:243–249
16. Sachs GS, Thase ME, Otto MW, et al: Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2003; 53:1028–1042
17. Sheehan DV, Lecrubier Y, Sheehan KH, et al: The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59(suppl 20):22–33
18. First MB, Spitzer RL, Gibbon M, et al: Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P). New York, New York State Psychiatric Institute, Biometrics Research Department, 1998
19. Schneck CD, Miklowitz DJ, Miyahara S, et al: The prospective course of rapid-cycling bipolar disorder: findings from the STEP-BD. Am J Psychiatry 2008; 165:370–377
20. Judd LL, Akiskal HS, Schettler PJ, et al: A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003; 60:261–269
21. Judd LL, Akiskal HS, Schettler PJ, et al: The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002; 59:530–537
22. Altshuler LL, Post RM, Black DO, et al: Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. J Clin Psychiatry 2006; 67:1551–1560
23. Post RM, Leverich GS, Altshuler LL, et al: An overview of recent findings of the Stanley Foundation Bipolar Network (part I). Bipolar Disord 2003; 5:310–319
24. Kupka RW, Altshuler LL, Nolen WA, et al: Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disord 2007; 9:531–535