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*Published in:*
American Journal of Psychiatry

*DOI:*
10.1176/appi.ajp.2016.15091119



*Publication date:*
2016

# Mixed Depression in Bipolar Disorder: Prevalence Rate and Clinical Correlates During Naturalistic Follow-Up in the Stanley Bipolar Network

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**Objective:** DSM-5 introduced the "with mixed features" specifier for major depressive episodes. The authors assessed the prevalence and phenomenology of mixed depression among bipolar disorder patients and qualitatively compared a range of diagnostic thresholds for mixed depression.

**Method:** In a naturalistic study, 907 adult outpatients with bipolar disorder participating in the Stanley Foundation Bipolar Network were followed longitudinally across 14,310 visits from 1995 to 2002. The Inventory of Depressive Symptomatology–Clinician-Rated Version (IDS-C) and the Young Mania Rating Scale (YMRS) were administered at each visit.

**Results:** Mixed depression, defined as an IDS-C score ≥15 and a YMRS score >2 and <12 at the same visit, was observed in 2,139 visits (14.9% of total visits, and 43.5% of visits with depression) by 584 patients (64.4% of all patients). Women were significantly more likely than men to experience subthreshold hypomania during visits with depression (40.7% compared with 34.4%). Patients with one or more mixed depression visits had more symptomatic visits and fewer euthymic visits compared with those with no mixed depression visits. DSM-5-based definitions of mixed depression (ranging from narrower definitions requiring ≥3 nonoverlapping YMRS items concurrent with an IDS-C score ≥15, to broader definitions requiring ≥2 nonoverlapping YMRS items) yielded lower mixed depression prevalence rates (6.3% and 10.8% of visits, respectively) but were found to have similar relationships to gender and longitudinal symptom severity.

**Conclusions:** Among outpatients with bipolar disorder, concurrent hypomanic symptoms observed during visits with depression were common, particularly in women. The DSM-5 diagnostic criteria for depression with mixed features may yield inadequate sensitivity to detect patients with mixed depression.

*Am J Psychiatry 2016; 173:1015–1023; doi: 10.1176/appi.ajp.2016.15091119*

Mixed states, characterized by concurrent manic and depressive symptoms, were described as early as ancient Greece, with the modern concept emerging through the late 19th-century writings of Emil Kraepelin (1). More recently, DSM-IV operationalized the "mixed episode," requiring full criteria for a depressive and manic episode to be met simultaneously. However, many argued that subsyndromal mixed states, which fall outside the strictly defined DSM-IV mixed episode, are common, may portend worse outcomes than pure depression or mania, and warrant classification as distinct clinical states (2–5). Recognizing the importance of subsyndromal mixed presentations, DSM-5 replaced the mixed episode with the "mixed features" specifier, defined by the presence of at least three nonoverlapping opposite-pole symptoms in the context of a syndromal depressive, hypomanic, or manic episode.

We previously characterized the prevalence of mixed hypomania in more than 900 patients with bipolar disorder participating in the Stanley Foundation Bipolar Network (5). Mixed hypomania was defined as the presence of mild to severe depressive symptoms accompanying hypomania. Mixed hypomania was present in 57% of 1,044 visits with hypomania and occurred more often in women than men.

There has been growing interest in the phenomenology and clinical implications of the opposing mixed state—that is, manic or hypomanic symptoms during a depressive episode. Mixed depression, variably defined, has been identified in 21%–76% of depressed patients (2, 3, 6–10) and has been associated with such adverse clinical outcomes as suicide attempt history (2, 3, 9), younger onset age (2, 6, 9), and longer episode duration (3, 9). The present study replicates the methodology of

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our previous work (5) and assesses the prevalence and correlations of depression with concurrent subthreshold hypomanic symptoms in 907 prospectively followed patients with well-characterized bipolar disorders. In addition, the prevalence and correlations of DSM-5-defined major depressive episodes with mixed features are examined in the same cohort.

## METHOD

Details of the methods and procedures used in the Stanley Bipolar Network have been described elsewhere (11). All patients provided written informed consent through procedures approved by their individual institutions before entering the Stanley Bipolar Network study.

### Sample

A total of 907 patients volunteered for a naturalistic follow-up study conducted from 1995 to 2002 involving prospective assessment of clinical state and medication use. Patients meeting DSM-IV criteria for bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified, or schizoaffective disorder–bipolar type were included. The Stanley Bipolar Network also enrolled patients in various embedded clinical trials, and patients could transfer from clinical trials to the naturalistic follow-up study (11, 12). Included in this report are those enrolled only in the naturalistic follow-up study; patients who participated in other trials were excluded in the event that specific inclusion or exclusion criteria would bias the likelihood of co-occurrence of symptoms.

### Procedures

All patients underwent diagnostic evaluation with the Structured Clinical Interview for DSM-IV. Patients were seen monthly on average, with medication changes made as needed. At each visit, mania and depression symptoms were assessed prospectively with the Young Mania Rating Scale (YMRS) (13) and the Inventory of Depressive Symptomatology–Clinician-Rated Version (IDS-C) (14, 15). Across four U.S. and three non-U.S. sites, interrater reliability was regularly assessed, and rater training was reinforced as needed to maintain consistent performance (kappa values were 0.7 for the YMRS and 0.85 for the IDS-C). The analyses include all naturalistic follow-up study visits at which both the YMRS and IDS-C assessments were completed. Less than 0.5% of total visits were excluded due to missing one scale; no visits were missing both symptom scales.

Same-visit scores on the IDS-C and YMRS were used to define mixed depression. For the purposes of this analysis, definitions for depression, hypomania and mania, and mixed depression were intentionally inclusive. On the IDS-C, mild depression is indicated by a score of 15–24, moderate depression by a score of 25–34 (symptoms presumably adequate to meet DSM-IV criteria for a major depressive episode), and severe depression by a score ≥35. A YMRS score ≥12 is considered reflective of at least mild hypomania (symptoms presumably adequate to meet DSM-IV criteria for hypomania). Importantly, IDS-C and YMRS scores serve as measures of overall symptom severity but not of symptom pervasiveness or duration, and in that sense the scores provide only indirect approximations of the presence or absence of DSM-defined syndromal mood episodes. In the present analysis, we defined depression as the presence of an IDS-C score ≥15 and a YMRS score <12; hypomania or mania as a YMRS score ≥12; and euthymia as an IDS-C score <15 and a YMRS score <12. Depression was subdivided into pure (IDS-C score ≥15, YMRS score ≤2) and mixed (IDS-C score ≥15, YMRS score >2 and <12) depression.

In addition, we applied DSM-5 criteria for a major depressive episode with mixed features to our sample, to examine a DSM-5-based construct of mixed depression. To this end, visits with depression were defined as described above (IDS-C score ≥15, YMRS score <12). The DSM-5 "with mixed features" criteria were met if at least three YMRS items were scored ≥1 during depressed visits. Individual YMRS items that directly overlapped with IDS-C items or were not reflective of DSM-5 criteria A or B symptoms for mania were not counted toward this definition, to maintain consistency with DSM-5 criteria. Therefore, three YMRS items were excluded from our DSM-5-based definition, with one (item 5, "irritability") considered to be overlapping with IDS-C items and two (item 10, "appearance," and item 11, "insight") failing to map onto DSM-5-based symptoms. YMRS item 2 ("increased motor activity/energy") was permitted as a non-overlapping mood elevation symptom based on the opinion that it primarily assesses elevated energy, a feature specific to mood elevation. This item was considered distinct from IDS-C item 24 ("psychomotor agitation"), which assesses non-goal-directed restlessness or agitation (a potential feature of both depression and mood elevation). An additional DSM-5-based definition requiring only two YMRS items scored ≥1 was also examined. Exploratory analyses were also performed that required an IDS-C score ≥25 to align more closely with syndromal depression.

### Statistical Analysis

Analyses were performed with SPSS, version 21 (IBM, Armonk, N.Y.). The primary analyses were of repeated measures, using generalized estimating equations to investigate the likelihood of experiencing subthreshold hypomania (i.e., mixed symptoms) during visits with depression. All models included a dichotomized indicator of subthreshold hypomania (YMRS score >2 and <12) as the dependent variable, a dichotomized indicator of depression (IDS-C score ≥15) as the independent variable, and study week as a linear covariate, to control for the effect of time on mood symptom severity. The predictor variables of interest for this study were gender, given our previously demonstrated relationship between gender and mixed hypomania (5), and bipolar subtype, given associations between bipolar II diagnosis and mixed depression in some (2, 8), but not all (7), previous studies. Analogous methods were used to assess gender and diagnosis effects on DSM-5-defined mixed depression.

**TABLE 1. Distribution of Diagnostic Subtypes and Gender in a Study of Mixed Depression in Bipolar Disorder: Participants With and Without Visits With Depression[a]**

| | Patients With No Visits With Depression (N=135 [14.9%]) | | Patients With One or More Visits With Depression (IDS-C score ≥15, YMRS score <12) (N=772 [85.1%]) | | Total (N=907 [100%]) | |
|---|---|---|---|---|---|---|
| Characteristic | N | % | N | % | N | % |
| Bipolar I disorder | 102 | 15.0 | 578 | 85.0 | 680 | 100.0 |
| Bipolar II disorder | 27 | 14.4 | 160 | 85.6 | 187 | 100.0 |
| Bipolar disorder not otherwise specified | 3 | 16.7 | 15 | 83.3 | 18 | 100.0 |
| Schizoaffective disorder–bipolar type | 3 | 13.6 | 19 | 86.4 | 22 | 100.0 |
| Female[b] | 57 | 11.3 | 449 | 88.7 | 506 | 100.0 |
| Male | 78 | 19.5 | 323 | 80.5 | 401 | 100.0 |

[a] YMRS=Young Mania Rating Scale; IDS-C=Inventory of Depressive Symptomatology–Clinician-Rated Version.
[b] Significant difference between groups, p=0.001.

**TABLE 2. Distribution of Diagnostic Subtypes and Gender in a Study of Mixed Depression in Bipolar Disorder: Participants With and Without Mixed Depression Symptoms During Visits With Depression[a]**

| | Patients With Visits With Pure Depression Only (IDS-C score ≥15, YMRS score ≤2) (N=188 [24.4%]) | | Patients With One or More Visits With Mixed Depression (IDS-C score ≥15, YMRS score >2 and <12) (N=584 [75.6%]) | | Total (N=772 [100%]) | |
|---|---|---|---|---|---|---|
| Characteristic | N | % | N | % | N | % |
| Bipolar I disorder | 135 | 23.4 | 443 | 76.6 | 578 | 100.0 |
| Bipolar II disorder | 43 | 26.9 | 117 | 73.1 | 160 | 100.0 |
| Bipolar disorder not otherwise specified | 7 | 46.7 | 8 | 53.3 | 15 | 100.0 |
| Schizoaffective disorder–bipolar type | 3 | 15.8 | 16 | 84.2 | 19 | 100.0 |
| Female | 101 | 22.5 | 348 | 77.5 | 449 | 100.0 |
| Male | 87 | 26.9 | 236 | 73.1 | 323 | 100.0 |

[a] YMRS=Young Mania Rating Scale; IDS-C=Inventory of Depressive Symptomatology–Clinician-Rated Version.

To examine the profiles of individual YMRS and IDS-C item scores as functions of mixed or pure depression status, we performed two separate multivariate analyses of covariance, with the individual YMRS and IDS-C item scores as dependent variables in each model, respectively, and with mixed or pure depression status as the dichotomous independent variable.

## RESULTS

We identified 907 naturalistic follow-up study outpatients (506 of them women; the mean age was 41.2 years [SD=11.6]) with bipolar I disorder (N=680), bipolar II disorder (N=187), bipolar disorder not otherwise specified (N=18), or schizoaffective disorder–bipolar type (N=22) who experienced a visit where the YMRS and IDS-C assessments were both completed. Across a period of almost 7 years, the median follow-up was 15 months (mean=22.7 months, SD=22.9).

### Patient Visits

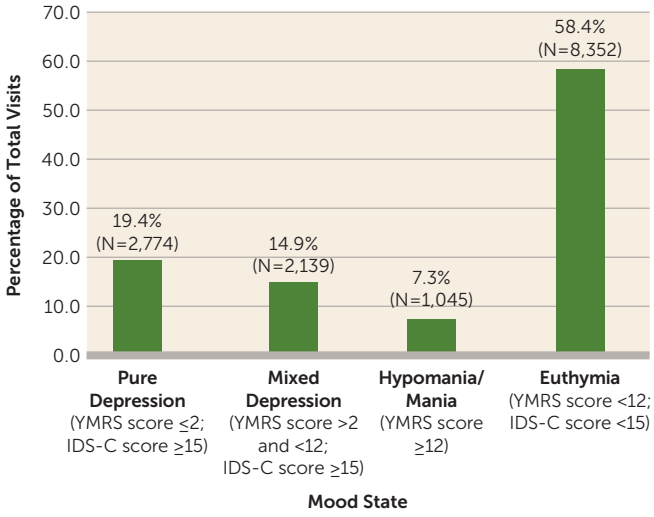
A total of 14,310 visits by 907 participants were included for analysis. Eighteen visits that were included in the original mixed hypomania analysis (5) were excluded because of missing YMRS scores. This resulted in the exclusion of one participant from the original analysis (5) because the participant had no visits where both the IDS-C and YMRS assessments were completed. For all 907 participants, the median number of visits was 16 (mean=22.9, SD=20.1). In the 25%–75% middle quartiles of the population, the mean number of visits was 28 (range=6–34).

Of the 907 participants, 772 had at least one pure or mixed depression visit. The remaining 135 had no visits classified as depressed. Among the 772 individuals who experienced at least one depressed visit, 75.6% (N=584) experienced at least one visit with mixed depression. Table 1 summarizes the diagnostic and gender distribution for participants with no depressed visits, for those with at least one depressed visit, and for all participants. Table 2 summarizes the diagnostic and gender distribution for participants with only pure depression visits, for those with at least one mixed depression visit, and for all participants who experienced a visit with pure or mixed depression.

### Distribution by Visit Type

Among 14,310 visits, the majority (58.4%; N=8,352) were characterized as euthymic, 34.3% (4,913 visits) were characterized as depressed (19.4%, or 2,774 visits, were pure depression; 14.9%, or 2,139 visits, were mixed depression), and 7.3% (1,045 visits) were characterized as hypomanic or manic (Figure 1). Among 584 patients with one or more mixed

**FIGURE 1. Affective States in 907 Patients During 14,310 Visits in a Study of Mixed Depression in Bipolar Disorder**[a]




[a] IDS-C=Inventory of Depressive Symptomatology–Clinician-Rated Version; YMRS=Young Mania Rating Scale.

depression visits, only three patients contributed ≥20 mixed depression visits to the total, with the majority of patients (66%) contributing ≤3 mixed depression visits. The mean YMRS total score during 2,139 mixed depression visits was 5.7 (SD=2.4), and the mean score during 2,774 pure depression visits was 0.7 (SD=0.9). The prevalence of concurrent hypomanic symptoms (YMRS score >2 and <12) did not differ significantly across visits with mild, moderate, and severe depression. Hypomanic symptom severity (YMRS total score) also did not differ significantly across categories of depression severity.

In total, 584 patients with one or more mixed depression visits contributed 10,286 visits to the database, while 323 patients with no mixed depression visits contributed only 4,024 visits. Overall, patients with one or more mixed depression visits were more likely to have visits with depression or hypomania and were less likely to have visits with euthymia compared with patients with no mixed depression visits ($\chi^2$=1,596.228, df=2, p<0.001) (Figure 2A).

### Bipolar Subtype

Eighty-five percent of patients with bipolar I disorder and 85.6% of patients with bipolar II disorder experienced at least one depressed visit (Table 1). Among patients with bipolar I disorder or bipolar II disorder who experienced at least one depressed visit, 76.6% and 73.1%, respectively, also experienced a visit with mixed symptoms (Table 2). Patients with bipolar I or bipolar II disorder had similar likelihoods of experiencing a visit with depression and of experiencing mixed symptoms during visits with depression.

### Gender Differences in Experience of Mixed Depression

Women were more likely than men to experience visits with pure or mixed depression (Table 1; Wald $\chi^2$=10.144, p=0.001). In addition, the likelihood of experiencing concurrent hypomanic symptoms was significantly greater for women experiencing depression (40.7%) than for men experiencing depression (34.4%) (gender-by-depression interaction, Wald $\chi^2$=8.47, p=0.004). For women, the probability of concurrent hypomanic symptoms was 25.3% in 4,424 visits without depression, and the probability was 40.7% in 3,325 visits with depression (Wald $\chi^2$=61.496, p<0.001). For men, the probability of concurrent hypomanic symptoms was 28.0% in 4,375 visits without depression, and the probability was 34.4% in 2,186 visits with depression (Wald $\chi^2$=7.674, p=0.006) (Figure 3A).

### Individual Symptom Profiles of Mixed Depression Visits

As expected, visits with mixed depression yielded higher scores on all YMRS items compared with visits with pure depression (p<0.001 for all items), and certain mood elevation symptoms were especially prominent in mixed depression visits (effect of mixed depression status: lambda=0.311, F=978.266, df=11, p<0.001, controlling for study week and gender). The largest differences were for "irritability" (Cohen's d=1.2), "language–thought disorder" (Cohen's d=1.1), "speech–rate and amount" (Cohen's d=0.9), and "increased motor activity/energy" (Cohen's d=0.9) (Figure 4). There were significant differences between mixed depression and pure depression visits for most IDS-C items (effect of mixed depression status, lambda=0.809, F=43.157, df=26, p<0.001, controlling for study week and gender), although all effect sizes were small with the exception of "mood (irritable)" (Cohen's d=0.5).

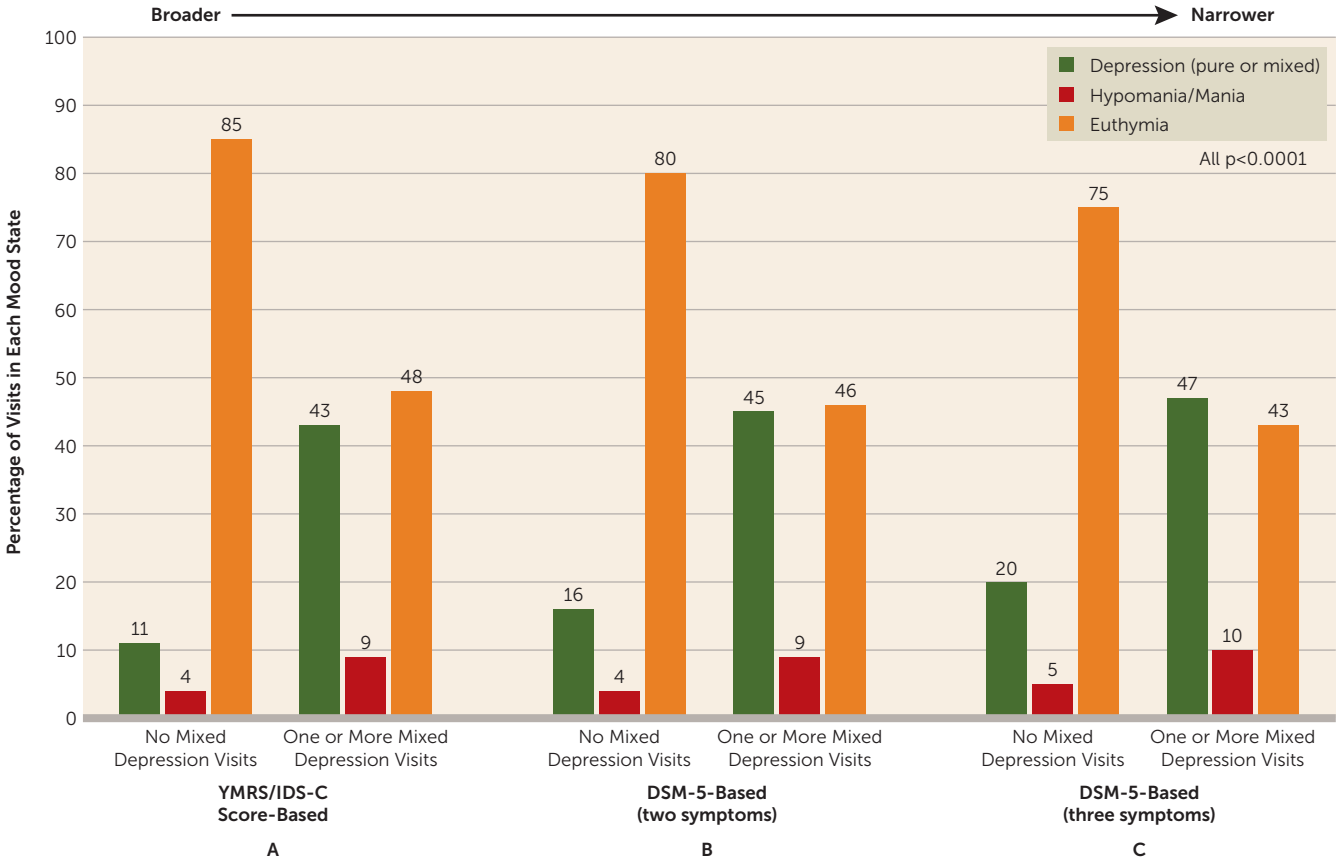
### Relationship of Mixed Hypomania to Mixed Depression

Of 584 patients who had one or more visits with mixed depression, 39.0% also experienced one or more visits with mixed hypomania (YMRS score ≥12 and IDS-C score ≥15 at the same visit). In contrast, of 323 patients who never had mixed depression, only 15.2% had at least one mixed hypomania visit. Thus, experiencing mixed symptoms of one polarity increased the risk of experiencing mixed symptoms of the opposite polarity (Wald $\chi^2$=51.616, p<0.001, controlling for gender).

### DSM-5 Validation

Applying a strict three-symptom DSM-5-based definition of depression with mixed features (IDS-C score ≥15 and ≥3 nonoverlapping DSM-5-based YMRS items scored ≥1) yielded a substantially lower prevalence compared with our broader definition of mixed depression based on IDS-C and YMRS scores. Thus, only 6.3% (906/14,310) of visits by 42.2% (383/907) of patients met criteria for DSM-5-defined depression with mixed features. Gender remained a significant predictor of the likelihood of experiencing hypomanic symptoms during visits with depression (gender-by-depression interaction, Wald $\chi^2$=4.055, p=0.044), with 17.2% of women and 14.7% of men experiencing mixed depression (Figure 3C). Bipolar subtype (i.e., bipolar I or bipolar II) did

**FIGURE 2. Patient Visits Delineated by Mood State Across Patients With and Without Mixed Depression**[a]




[a] In panel A, mixed depression was defined using the broadest (Young Mania Rating Scale [YMRS] and Inventory of Depressive Symptomatology–Clinician-Rated Version [IDS-C] score-based) criteria (YMRS score >2 and <12, and IDS-C score ≥15); $\chi^2$=1,596.228, df=2, p<0.001. In panel B, mixed depression was defined using intermediate (two-symptom DSM-5-based) criteria (≥2 YMRS items scored ≥1, in conjunction with an IDS-C score ≥15 and a YMRS score <12); $\chi^2$=1,512.999, df=2, p<0.001. In panel C, mixed depression was defined using the narrowest (three-symptom DSM-5-based) criteria (≥3 YMRS items scored ≥1, in conjunction with an IDS-C score ≥15 and a YMRS score <12); $\chi^2$=1,487.432, df=2, p<0.001.

not significantly predict the presence of DSM-5-defined mixed features during visits with depression. Patients with at least one visit with three-symptom DSM-5-defined mixed depression were more likely to have visits with depression or hypomania and were less likely to have visits with euthymia, compared with patients without any mixed depression visits ($\chi^2$=1,487.432, df=2, p<0.001) (Figure 2C).

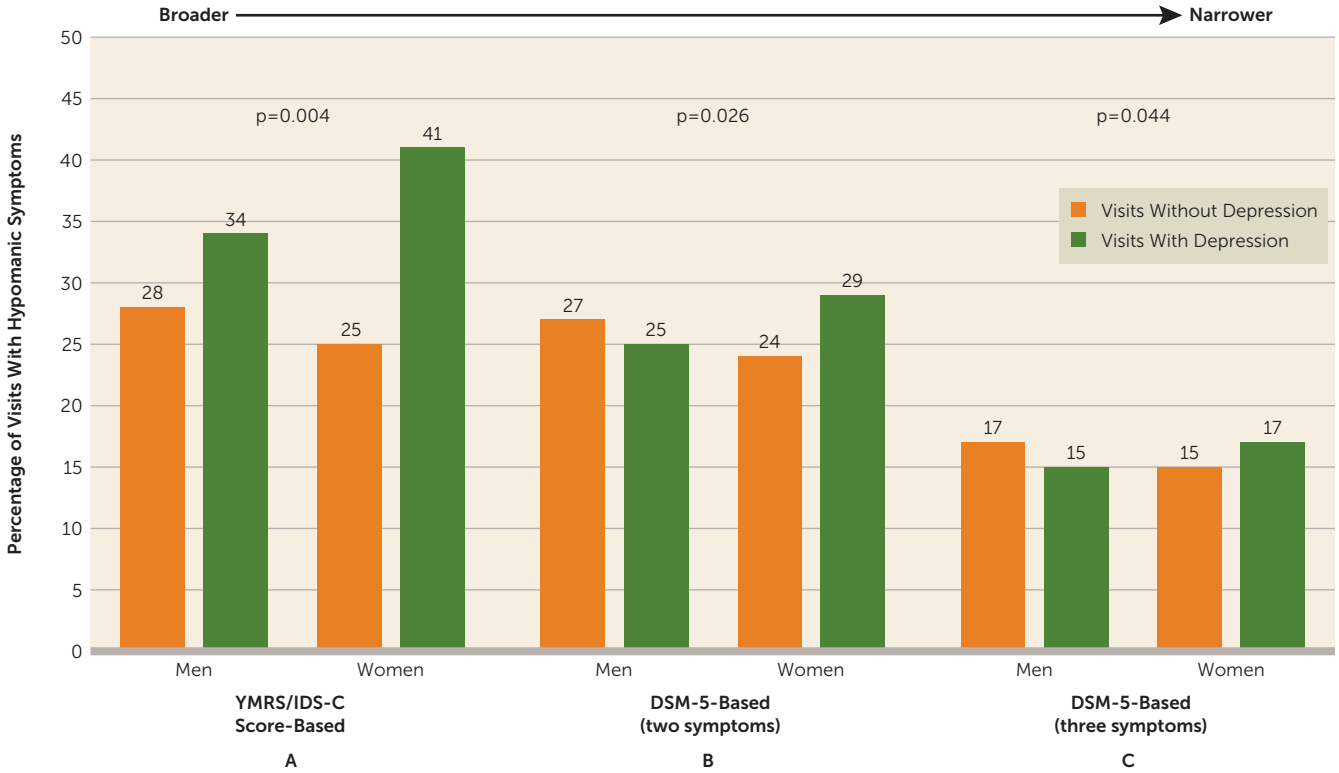
Using a more inclusive two-symptom DSM-5-based definition, the prevalence of depression with mixed features increased to 10.8% (1,550/14,310) of visits by 54.5% (494/907) of patients. Women remained more likely than men to experience mixed symptoms (defined here as ≥2 YMRS items scored ≥1) during visits with depression (gender-by-depression interaction, Wald $\chi^2$=4.945, p=0.026), with 29.2% of women and 25.5% of men experiencing hypomanic symptoms during depressed visits (Figure 3B). As with our previous definitions, bipolar subtype was not a significant predictor of hypomanic symptoms during visits with depression, and patients with at least one visit with two-symptom DSM-5-based mixed depression were more often symptomatic and less often euthymic compared with patients without any mixed depression visits ($\chi^2$=1,512.999, df=2, p<0.001) (Figure 2B).

Increasing the depression threshold to an IDS-C score ≥25 reduced the prevalence of mixed depression visits to 2.6% and to 4.5% for the three-symptom and two-symptom DSM-5-based definitions, respectively (see Figure S1 and Figure S2 in the data supplement that accompanies the online edition of this article), but this threshold change did not otherwise alter the pattern of findings. Thus, women remained significantly more likely than men to experience mixed depression, whereas the effect of bipolar subtype remained insignificant, and patients with mixed depression visits compared with those without mixed depression visits had significantly more symptomatic visits.

## DISCUSSION

In a sample of 907 patients with bipolar disorder followed naturalistically across 14,310 visits, we found that 64.4% of patients experienced at least one visit with mixed depression, defined broadly as the presence of subthreshold hypomania (YMRS score >2 and <12) concurrent with at least mild depression (IDS-C score ≥15). Mixed depression defined as such was present during 14.9% of all visits over the 7-year

**FIGURE 3. Gender Differences in the Experience of Hypomanic Symptoms Across Visits With and Without Depression**[a]




[a] In panel A, mixed depression was defined using the broadest (Young Mania Rating Scale [YMRS] and Inventory of Depressive Symptomatology–Clinician-Rated Version [IDS-C] score-based) criteria (YMRS score >2 and <12, and IDS-C score ≥15) (gender-by-depression interaction, Wald $\chi^2$=8.47, p=0.004). In panel B, mixed depression was defined using intermediate (two-symptom DSM-5-based) criteria (≥2 YMRS items scored ≥1, in conjunction with an IDS-C score ≥15 and a YMRS score <12) (gender-by-depression interaction, Wald $\chi^2$=4.945, p=0.026). In panel C, mixed depression was defined using the narrowest (three-symptom DSM-5-based) criteria (≥3 YMRS items scored ≥1, in conjunction with an IDS-C score ≥15 and a YMRS score <12) (gender-by-depression interaction, Wald $\chi^2$=4.055, p=0.044).

study period. Narrower definitions, based on DSM-5 criteria for depression with mixed features, yielded lower prevalence rates of mixed depression, ranging from 2.6% to 10.8%.

Across our mixed depression definitions, diagnosis of bipolar I or II disorder did not predict the likelihood of subthreshold hypomania during visits with depression. This finding aligns with our previous study examining mixed hypomania, where we found no effect of bipolar subtype on the likelihood of experiencing depressive symptoms during visits with hypomania (5). Other studies of mixed depression reported either increased bipolar I disorder prevalence (16), increased bipolar II disorder prevalence (2, 8), or no difference in bipolar I or bipolar II prevalence (3) in patients with mixed depression compared with pure depression. Thus, bipolar subtype may not be a consistently robust predictor of mixed depression.

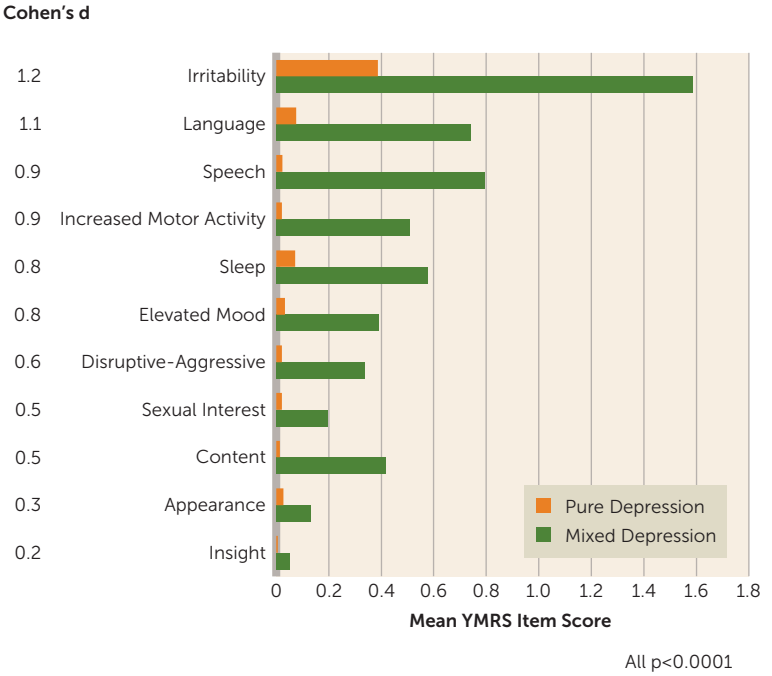
In contrast, we found that gender was a significant predictor of mixed depression across definitions, with women being more likely than men to experience subthreshold hypomania during depression visits. The effect of gender on mixed depression was similar to that demonstrated in our mixed hypomania study, in which women were more likely than men to experience depressive symptoms during hypomania visits (5). Thus, in our cohort of patients with bipolar disorder, women were more likely than men to experience mixed features in general. While some previous studies also found mixed depression to be more common in females (17, 18), many found no gender effect (3, 16, 19, 20), and one study found that mixed depression occurred more frequently in males (2). Our association of female gender with mixed depression may conflict with the expectation that certain mood elevation symptoms (e.g., irritability, agitation, and impulsivity) are more commonly endorsed by male patients during depressed and/or mixed states (5, 21). On the other hand, some have argued that such conventionally "male" symptoms may actually occur with similar or greater prevalence among female patients with depression (22). Further studies are clearly warranted to evaluate the effect of gender on mixed symptom presentations in bipolar disorder.

Visits with mixed depression compared with visits with pure depression were characterized by higher scores on all individual YMRS items, and the largest effect sizes were seen for irritability, language–thought disorder, speech, and increased motor activity. Interestingly, the latter three YMRS items were predictive of antidepressant treatment-emergent mania in an earlier Stanley Bipolar Network report (23). The present findings suggest that the presence of mixed symptoms during depression visits may signal heightened risk for

antidepressant-induced mania, warranting particular caution in clinical decision making. In contrast, mixed depression status did not robustly affect IDS-C item scores, raising the possibility that depressive-pole symptomatology may not differ substantially across pure and mixed depression states.

We found that patients with at least one mixed depression visit, compared with those with no mixed depression visits, were more likely to have at least one mixed hypomania visit. Thus, certain patients may be predisposed to experiencing mixed features in general, a concept supported by previous prospective analyses (24–26). We also found that patients with at least one mixed depression visit, compared with patients without any mixed depression visits, were more likely to experience visits with depression and/or mood elevation and were less likely to experience visits with euthymia. This finding is consistent with a growing body of evidence suggesting that mixed depression may be a predictor of more severe bipolar illness course (2–4, 19, 20, 27). The robust association with longitudinal symptom severity is noteworthy given that most patients with mixed depression in our cohort experienced only a few (≤3) such visits across their total follow-up duration. Thus, even sporadic presentations of mixed depression within individual patients may portend adverse outcomes.

**FIGURE 4. Individual YMRS Item Scores in Visits With Mixed Depression and With Pure Depression[a]**




[a] Bars represent estimated marginal means, controlling for study week and gender. Associated effect sizes (Cohen's d) are shown for each item. For the effect of mixed depression status, lambda=0.311, F=978.266, df=11, p<0.001; partial eta squared=0.689. Tests of between-subject effects indicated that the effect of mixed depression status on Young Mania Rating Scale (YMRS) item scores was significant (p<0.001) for all YMRS items.

Applying a strict three-symptom DSM-5-based definition to our data set resulted in a low prevalence rate of mixed depression visits but also yielded findings similar to those seen under our broader definitions of mixed depression. Thus, our results raise the possibility that relaxing the diagnostic criteria for the mixed features specifier (for example, requiring two rather than three mood elevation symptoms) may yield greater sensitivity for identifying patients with mixed depression. Indeed, a recent International Society for Bipolar Disorders task force report indicated that the illness characteristics associated with mixed depression states (e.g., increased prevalence of comorbidities, adverse treatment outcomes, and suicidality) appear stable across a range of diagnostic criteria for mixed states, with such clinical correlates becoming evident in the presence of as few as two nonoverlapping, opposite-pole symptoms (28).

Similar questions have been raised regarding the validity of excluding "overlapping" symptoms from the DSM-5 mixed features criteria. Although the implications of permitting or excluding overlapping symptoms were not explicitly assessed in the present report, we found that irritability and increased motor activity were among the most prominent symptoms during mixed depression visits. Recently published data from a multisite, cross-sectional study of 2,811 depressed patients also demonstrated the predominance of irritability and psychomotor agitation in patients with mixed depression, even when strict DSM-5 criteria were applied, leading the authors to suggest that these symptoms may in fact be core features of mixed depression (9). In contrast, others have argued that symptoms like irritability and agitation, although highly prevalent during mixed states, are also robustly linked with conditions that frequently co-occur with mixed states (e.g., anxiety, substance use, and personality disorders) and therefore lack specificity for diagnosing mixed depression (29, 30). More research is needed to understand the complex role of overlapping symptoms in the construct of mixed depression and to consider whether including these symptoms as gateway criteria in the future will increase clinical utility.

Our study has several important strengths, including the large sample of well-characterized patients with bipolar disorder; a prospective study design; broad inclusion criteria, which optimize generalizability; and the use of standardized, validated rating scales for clinical assessment. However, the study also has noteworthy limitations, including our reliance on observational rather than controlled data, introducing clinical and demographic heterogeneity. Because of variable visit frequencies across participants, it was not possible to differentiate whether symptoms present at visits represented new or persistent mood episodes, thus limiting our interpretation of longitudinal trajectories of mixed features. Finally, our reliance on mood symptom rating scales limited

our ability to examine a strictly DSM-5-based definition of mixed depression.

In summary, among 907 bipolar disorder patients in 14,310 visits, depressive symptoms were common, and subthreshold hypomania occurred in almost half of all visits with depression. We demonstrated that women were more likely than men to experience hypomanic symptoms concurrently with depression across a range of diagnostic criteria for mixed depression. The presence of mixed depression appears to be a marker of vulnerability to mixed depression features in general and may portend a more symptomatic course of illness over time. The stability of our mixed depression construct across a range of definitions supports the possibility that broader diagnostic criteria for mixed depression may improve sensitivity while preserving clinical meaningfulness.

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Dr. Altshuler died in November 2015.

Presented at the 17th annual conference of the International Society for Bipolar Disorders, Toronto, June 3–6, 2015.

Grant support was provided by the Stanley Medical Research Institute.

Dr. Miller has received grant support from Merck and Sunovion. Dr. Suppes has received consulting fees from AztraZeneca, H. Lundbeck, Merck, and Sunovion; she has received research funding from Elan Pharma International, NIMH, Sunovion, and the VA Cooperative Studies Program; and she has received royalties from Jones and Bartlett and UpToDate. Dr. Frye has received grant support from AssureRx Health, Janssen, the Mayo Foundation, Myriad, the National Institute on Alcohol Abuse and Alcoholism, NIMH, and Pfizer; he has been a consultant to Janssen, Mitsubishi Tanabe Pharma, Myriad Genetics, Sunovion, Supernus, and Teva; and he has received CME and travel support from CME Outfitters and the American Psychiatric Association. Dr. McElroy is a consultant to or member of scientific advisory boards of Alkermes, Bracket, Corcept, Hoffmann-La Roche, MedAvante, Naurex, Novo Nordisk, Shire, Sunovion, and Teva; she is a principal or coinvestigator on studies sponsored by the Agency for Healthcare Research and Quality, Alkermes, AstraZeneca, Cephalon, Eli Lilly, Forest, the Marriott Foundation, NIMH, Naurex, Orexigen, Pfizer, Shire, Takeda, and Transcept; and she is named as an inventor on U.S. Patent No. 6,323,236 B2 (Use of Sulfamate Derivatives for Treating Impulse Control Disorders), and along with the patent's assignee, the University of Cincinnati, she has received payments from Johnson & Johnson, the exclusive rightsholder. Dr. Grunze has received grants from the National Institute for Health Research, the Medical Research Council, the Northumberland, Tyne, and Wear National Health Service Foundation Trust, and Otsuka Pharmaceuticals; he has received honoraria for speaker bureaus or advisory panels from Bristol-Myers Squibb, Desitin, Gedeon-Richter, Hoffmann-LaRoche, and Lundbeck; and he has received honoraria for presenting at sponsored CME activities from Eli Lilly, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, and Servier. Dr. Altshuler was on an advisory board for Takeda and Lundbeck and attended an editorial board meeting sponsored by Sunovion; she received an honorarium as part of the 2014 Award for Research in Mood Disorders given by the American College of Psychiatrists; she performed a medical records review for the law offices of Hughes Socol Piers Resnick and Dym; and she was principal investigator and coinvestigator on research studies sponsored by NIMH. Dr. Keck is or has been a principal or coinvestigator on research studies sponsored by Alkermes, AstraZeneca, Cephalon, GlaxoSmithKline, Eli Lilly, the Marriott Foundation, NIMH, Orexigen, Pfizer, and Shire; he has been reimbursed for consulting to Alkermes, Bristol-Myers Squibb, Forest, Merck, Otsuka, ProPhase, Shire, Sunovion, Supernus, and Teva; he is listed as a coinventor on U.S. Patent No. 6,387,956 (Methods of Treating Obsessive-Compulsive Spectrum Disorders), and he has received no financial gain from this patent. Dr. Post has been a speaker for AstraZeneca, Sunovion, and Validus. Dr. Mintz, Dr. Hellemann, Dr. Nolen, Dr. Kupka, and Ms. Leverich report no financial relationships with commercial interests.

Received Sept. 1, 2015; revision received Jan. 8, 2016; accepted Feb. 8, 2016; published online April 15, 2016.

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