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After studying this article, you should be able to:

- Identify probabilistic differences in depressive presentations between patients with bipolar disorders and those with major depressive disorder

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Comparing the Phenomenology of Depressive Episodes in Bipolar I and II Disorder and Major Depressive Disorder Within Bipolar Disorder Pedigrees

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ABSTRACT

Objective: In a prior study of bipolar disorder pedigrees, we demonstrated distinct clinical differences between depressive episodes in bipolar disorder and major depressive disorder (MDD), including differentiation between these conditions using the Probabilistic Approach to Bipolar Depression. The aim of this retrospective study was to compare the phenomenology of the most severe lifetime depressive episodes between bipolar I (BP-I) and II (BP-II) disorder subtypes and MDD in these pedigrees.

Method: Patients with *DSM-IV* diagnoses of BP-I (n = 202), BP-II (n = 44), and MDD (n = 120) from bipolar disorder pedigrees were assessed using the Diagnostic Interview for Genetic Studies between 1998 and 2012. Multivariate logistic regression was used to identify distinguishing clinical features. The utility of the Probabilistic Approach in distinguishing BP-I and BP-II depression from MDD was assessed.

Results: BP-I differed from MDD in terms of greater rates of psychomotor retardation ($P < .05$) and psychotic features ($P < .05$). BP-II was distinguished from MDD ($P < .01$) by the greater likelihood of mixed features. Patients with BP-II had a greater likelihood of mixed features ($P < .001$) and a lesser likelihood of psychomotor retardation ($P < .05$) compared to those with BP-I. The Probabilistic Approach significantly differentiated both BP-I and BP-II from MDD ($P < .01$ to $P < .001$, depending on cutoff) but did not robustly distinguish between BP-I and BP-II.

Conclusions: First, the differentiation of BP-II from both BP-I depression and MDD in terms of the presence of mixed symptoms is of particular interest given the current debate over "mixed specifiers" for these conditions in *DSM-5*. Second, the Probabilistic Approach to Bipolar Depression was demonstrated for the first time to significantly distinguish both bipolar disorder subtypes from MDD.

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There has been growing interest, albeit controversial, in distinguishing between the phenomenology of bipolar depression and major depressive disorder.[1–4] Although major nosologic systems such as *DSM* and *ICD* do not describe differences between these syndromes, there is increasing consistency between the substantial number of studies on this issue in recent decades.[5–7] In response to that growing literature, a taskforce of the International Society for Bipolar Disorders, led by one of the authors of this article (P.B.M.), proposed a "probabilistic" (or

Clinical Points

- Bipolar disorder often remains undiagnosed or misdiagnosed as major depressive disorder for many years. Identifying differences in depressive presentations between these 2 conditions may facilitate earlier diagnosis, as well as improved outcomes for patients.
- Young depressed patients with psychomotor retardation, psychotic symptoms, or mixed features should be further assessed for evidence of a potential bipolar I or II disorder.

likelihood) approach rather than a categorical distinction between bipolar depression and MDD, arguing that while there is no "point of rarity" between the 2 presentations, there is, rather, a differential likelihood of experiencing the above symptoms and signs of depression.[8] This Probabilistic Approach to Bipolar Depression[1,9] proposed that the following features are more common in bipolar I depression: "atypical" depressive features such as hypersomnia, hyperphagia, and leaden paralysis; psychomotor retardation; psychotic features and/or pathological guilt; and mixed features. Furthermore, it proposed that bipolar depressed patients were more likely to have an earlier age at onset of their first depressive episode, more prior depressive episodes, shorter depressive episodes, and a family history of bipolar disorder.

There would be substantial clinical and heuristic advantages in identifying phenomenological distinctions between these depressive presentations. In the clinical arena, it is not uncommon to see young patients presenting with severe depressive episodes, with uncertainty for the clinician about whether this represents MDD or rather the first phase of bipolar disorder, which most commonly first presents with 1 or more depressive episodes. In the research setting, delineation of a "bipolar depressive pattern" would be potentially advantageous in reducing the heterogeneity of depressive samples in therapeutic or mechanistic research.

In 2011, we reported on the first validation of this Probabilistic Approach, using a sample independent of our prior bipolar depression studies.[10] The study examined the proposed features in bipolar disorder and MDD samples from a large well-phenotyped collection of bipolar disorder pedigrees. As the MDD subjects in such families likely represent both "genetic" and "sporadic" (nongenetic) forms of depression, this study represented a stringent test of the Probabilistic Approach, as any clinical distinctions may be attenuated by the genetic similarity of bipolar and MDD subjects. The study, which examined a combined BP-I and BP-II sample, found that bipolar depression was characterized by significantly higher rates of psychomotor retardation, difficulty thinking, early morning wakening, morning worsening, and psychotic features. Furthermore, the Probabilistic Approach yielded a positive predictive value ranging from 74% to 82%, depending upon the threshold employed.[10]

Relatively few studies have directly compared BP-I and BP-II depressive subtypes to MDD. Benazzi[11] reported more atypical and mixed symptoms in BP-II patients compared to MDD cases. Hantouche and Akiskal[12] reported similar findings, with more hypersomnia and "psychomotor activation" in BP-II subjects. Parker and Fletcher,[13] however, found minimal differences between BP-II and MDD, concluding that prior reported differences may have reflected differences in age, gender, and severity. Rastelli et al[14] reported that BP-II subjects were more likely to have simultaneous insomnia and hypersomnia, more than 5 prior mood episodes, and an earlier age at onset. Bega et al,[15] using data from the National Epidemiologic Survey on Alcohol and Related Conditions, reported higher rates of every symptom assessed in BP-I versus BP-II cases. Others have reported a greater prevalence of psychotic symptoms, psychomotor retardation, and hospitalization among BP-I compared to BP-II depressed patients.[15–18]

In this study, our aim was to examine differences in BP-I, BP-II, and MDD in the aforementioned bipolar disorder pedigree sample,[10] examining both a broad range of depressive symptoms and the utility of the Probabilistic Approach in distinguishing between these subgroups.

METHOD

A total of 1,128 participants were recruited from multigenerational bipolar disorder pedigrees as part of the ongoing Australian Bipolar Disorder Molecular Genetics Study, conducted in partnership between the University of New South Wales, Black Dog Institute, Neuroscience Research Australia, the Garvan Institute of Medical Research, and Macquarie University, from 1998 to 2012. Data from the Family Interview for Genetic Studies[19] and the Diagnostic Interview for Genetic Studies version 2.0[20] were reviewed by 2 senior research psychiatrists (who did not perform the initial interviews) to derive *DSM-IV*[21] diagnoses in accordance with best-estimate diagnostic methodology.[22] The study was approved by the Human Research Ethics Committee of the University of New South Wales and complies with the guidelines of the Australian National Health and Medical Research Council. Written informed consent was obtained after participants read a complete description of the study. A prior publication from our group reported on this same sample, focusing on overall differences between patients with bipolar disorder (BP-I and BP-II combined) and those with MDD.[10] Clinical characteristics and symptoms during the most severe lifetime major depressive episode were compared between the 3 diagnostic groups, as were features associated with the Probabilistic Approach. The 9 Probabilistic Approach symptoms and features were hypersomnia, hyperphagia, weight gain, psychomotor retardation, delusions and hallucinations, pathological guilt, mixed features, early onset (< 25 years) and multiple (at least 5) depressive episodes (note that all subjects also shared a positive family history of bipolar disorder). The presence of mixed features was also assessed after excluding "overlapping" symptoms such as distractibility, agitation, and irritability, reflecting the shift toward a mixed features specifier in *DSM-5*,[23]

Table 1. Demographic and Clinical Characteristics[a]

Characteristic	BP-I (n = 202)	BP-II (n = 44)	MDD (n = 120)	BP-I vs MDD		BP-II vs MDD		BP-I vs BP-II	
				OR[b]	95% CI	OR[c]	95% CI	OR[b]	95% CI
Gender, n (%)									
Male	77 (38.3)	11 (25.6)	37 (30.8)	1.00	…	1.00	…	1.00	…
Female	124 (61.7)	32 (74.4)	83 (69.2)	0.72	0.44–1.16	1.30	0.59–2.84	0.55	0.26–1.16
Age, median (IQR), y									
At interview	48.8 (37.2–8.7)	42.5 (32.3–55.2)	49.6 (30.5–63.3)	0.99	0.98–1.01	0.99	0.96–1.00	1.02	0.99–1.05
At first MDE	23 (17–31)	20 (14–27)	20.5 (16–28)	1.01	0.99–1.04	0.98	0.95–1.02	1.03	0.99–1.08
At most severe MDE	33 (25–42)	31.5 (21–43)	28 (21–41)	1.02	0.99–1.03	0.99	0.97–1.02	1.02	0.98–1.05
5 or more MDEs, n (%)[d]	68 (50.4)	9 (37.5)	23 (26.4)	**2.82*****	**1.57–5.06**	1.67	0.64–4.33	1.69	0.69–4.12
Duration of most severe MDE, n (%)									
Less than 3 mo	105 (55.8)	22 (52.4)	70 (64.8)	1.00	…	1.00	…	1.00	…
3–6 mo	45 (23.9)	10 (23.8)	18 (16.7)	1.67	0.89–3.11	1.77	0.71–4.39	0.94	0.41–2.15
More than 6 mo	38 (20.2)	10 (23.8)	20 (18.5)	1.27	0.68–2.35	1.59	0.65–3.90	0.79	0.35–1.83
Treatment, n (%)									
Sought help	173 (85.6)	35 (79.5)	94 (78.3)	1.65	0.92–2.96	1.07	0.46–2.52	1.53	0.67–3.52
Prescribed medication	158 (78.2)	30 (68.2)	84 (70.0)	1.54	0.92–2.57	0.92	0.44–1.93	1.67	0.82–3.43
Received ECT	27 (20.8)	7 (15.9)	15 (12.5)	1.84	0.97–3.48	1.32	0.50–3.50	1.39	0.58–3.33
Any treatment	174 (86.1)	37 (84.1)	96 (80.0)	1.55	0.85–2.83	1.32	0.52–3.33	1.17	0.48–2.89
Hospitalized	99 (49.0)	15 (34.1)	32 (26.7)	**2.64*****	**1.62–4.31**	1.42	0.67–2.99	1.86	0.94–3.67
Suicide history									
Ever attempted suicide, n (%)	67 (33.2)	13 (29.5)	34 (28.3)	1.25	0.77–2.06	1.06	0.49–2.26	1.18	0.58–2.40
No. of attempts, n (%)									
1	33 (55.00)	5 (41.7)	23 (67.6)	1.00	…	1.00	…	1.00	…
2	145 (21.2)	3 (25.00)	45 (11.8)	2.44	0.71–8.36	3.45	0.58–20.5	0.70	0.15–3.37
3 or more	19 (28.8)	4 (33.3)	7 (20.6)	1.89	0.68–5.23	2.62	0.55–12.55	0.72	0.17–3.00
Age at first attempt, median (IQR), y	27 (17–37)	18 (15–22)	17 (16–23)	**1.05***	**1.00–1.11**	0.98	0.90–1.07	1.08	0.99–1.17

[a]Boldface indicates statistical significance.
[b]ORs larger than 1.0 reflect higher prevalence in BP-I group.
[c]ORs larger than 1.0 reflect higher prevalence in BP-II group.
[d]Feature included in the Probabilistic Approach.
*$P < .05$.
***$P < .001$.
Abbreviations: BP-I = bipolar I disorder, BP-II = bipolar II disorder, ECT = electroconvulsive therapy, IQR = interquartile range, MDD = major depressive disorder, MDE = major depressive episode, OR = odds ratio.

which removed symptoms that commonly occur in mood episodes of either polarity.[24] For each participant, the number of endorsed features was summed, ranging from 0 to 9.

Inclusion Criteria

Inclusion in the analysis was restricted to participants with a best-estimate *DSM-IV* diagnosis of BP-I, BP-II, or MDD, the latter requiring a history of at least 2 major depressive episodes.

Statistical Analysis

Comparisons between the 3 diagnostic groups were carried out using logistic regression models, adjusted for age and gender. All symptoms were entered first as single predictors, then simultaneously in a multivariate model to identify any independent associations with diagnosis after accounting for the effects of other symptoms. All analyses were carried out using Stata version 12 on Windows XP (StataCorp).

RESULTS

A total of 366 participants met sample criteria, with 202 (55.2%) diagnosed with *DSM-IV* BP-I, 44 (12.0%) with BP-II, and 120 (32.7%) with MDD. All participants—BP-I, BP-II, and MDD—had at least 1 first-degree relative with BP-I.

Demographic and Longitudinal Clinical Characteristics

When demographic and clinical characteristics were compared between the 3 diagnostic groups, BP-I was significantly associated with a greater number of lifetime depressive episodes (OR = 2.82, $P < .001$) and with a greater likelihood of having been hospitalized during the most severe depressive episode (OR = 2.64, $P < .001$) when compared to MDD (Table 1). No differences were observed in either the prevalence or number of lifetime suicide attempts between groups.

Symptom Profile During Most Severe Depressive Episode

Compared to MDD cases, the symptom profile of BP-I patients was significantly more likely to be characterized by terminal insomnia ($P < .05$), hypersomnia ($P < .05$), psychomotor retardation ($P < .001$), difficulty thinking ($P < .05$), morning worsening ($P < .05$), and psychotic features ($P < .001$) (Table 2).

Compared to MDD cases, depression among BP-II patients was significantly more likely to feature initial insomnia ($P < .05$), excessive guilt ($P < .05$), difficulty thinking ($P < .05$), morning worsening ($P < .05$), and 3 or more mixed features ($P < .001$). Interestingly, the presence of "any" mixed features was also significantly more common in BP-II compared to MDD cases ($P < .001$). When only

Table 2. Prevalence of Depressive Symptoms During Most Severe Major Depressive Episode[a]

				BP-I vs MDD		BP-II vs MDD		BP-I vs BP-II	
Symptom	BP-I (n = 202)	BP-II (n = 44)	MDD (n = 120)	OR[b]	95% CI	OR[c]	95% CI	OR[b]	95% CI
Anhedonia	185 (91.6)	43 (97.7)	110 (91.7)	0.54	0.20–1.41	2.39	0.28–20.49	0.26	0.03–2.00
Appetite loss	131 (64.8)	26 (59.1)	67 (55.8)	1.52	0.94–2.45	1.19	0.58–2.43	1.32	0.66–2.64
Appetite gain[d]	26 (12.9)	8 (18.2)	17 (14.2)	0.84	0.42–1.66	1.18	0.46–3.03	0.70	0.28–1.72
Weight loss	92 (45.5)	21 (47.7)	51 (42.5)	1.13	0.71–1.80	1.26	0.62–2.56	0.91	0.47–1.79
Weight gain[d]	31 (15.4)	6 (13.6)	12 (10.0)	1.69	0.81–3.52	1.18	0.40–3.49	1.35	0.51–3.56
Initial insomnia	110 (54.5)	32 (72.7)	65 (54.2)	1.01	0.64–1.61	**2.28***	1.06–4.91	**0.44***	0.21–0.93
Middle insomnia	111 (55.0)	26 (59.1)	68 (56.7)	0.93	0.58–1.49	1.22	0.59–2.50	0.78	0.39–1.54
Terminal insomnia	110 (54.5)	25 (56.8)	52 (43.3)	**1.64***	1.03–2.62	1.90	0.93–3.91	0.87	0.44–1.72
Hypersomnia[d]	93 (46.0)	20 (45.5)	43 (35.8)	**1.65***	1.02–2.68	1.58	0.77–3.26	1.04	0.53–2.05
Agitation	98 (48.5)	27 (61.4)	56 (46.7)	1.11	0.70–1.77	1.76	0.85–3.61	0.63	0.32–1.25
Psychomotor retardation[d]	119 (58.9)	18 (40.9)	46 (38.3)	**2.43*****	1.51–3.90	1.39	0.66–2.92	**2.04****	1.04–4.02
Anergia	180 (89.1)	39 (88.6)	101 (84.2)	1.56	0.80–3.05	1.81	0.57–5.69	0.87	0.28–2.70
Guilt[d]	142 (70.3)	37 (84.1)	76 (63.3)	1.46	0.89–2.40	**2.81***	1.14–6.91	0.50	0.21–1.22
Worthlessness	158 (78.2)	38 (86.4)	91 (75.8)	1.17	0.67–2.04	2.23	0.79–6.27	0.54	0.20–1.48
Difficulty thinking	181 (89.6)	43 (97.7)	97 (80.8)	**2.07***	1.08–3.97	**10.48***	1.36–80.73	0.22	0.03–1.72
Suicidal ideation	127 (65.1)	29 (67.4)	65 (55.6)	1.37	0.85–2.21	1.74	0.82–3.72	0.83	0.40–1.72
Self-harm	62 (30.7)	11 (25.0)	27 (22.5)	1.57	0.91–2.71	1.06	0.46–2.45	1.42	0.66–3.07
Morning worsening	104 (51.5)	25 (56.8)	46 (38.3)	**1.69***	1.05–2.72	**2.13***	1.03–4.39	0.77	0.39–1.53
Evening worsening	20 (9.9)	7 (15.9)	17 (14.2)	0.76	0.37–1.58	1.11	0.41–3.03	0.66	0.25–1.72
Any psychosis[d]	57 (28.2)	9 (20.5)	17 (14.2)	**2.56*****	1.38–4.76	1.70	0.68–4.26	1.60	0.71–3.58
Any mixed features	39 (19.3)	23 (52.3)	29 (24.2)	0.67	0.38–1.18	**3.36*****	1.55–7.28	**0.21***	0.10–0.43
3+ mixed features	23 (11.4)	11 (25.0)	8 (6.7)	1.78	0.76–4.14	**4.31****	1.58–11.80	**0.41***	0.18–0.95
Any mixed features (nonoverlapping)	36 (17.8)	19 (43.2)	22 (18.3)	0.93	0.50–1.72	**3.38****	1.51–7.57	**0.27*****	0.13–0.56
3+ mixed features (nonoverlapping)	20 (9.9)	9 (20.5)	5 (4.2)	2.42	0.88–6.69	**5.87*****	1.83–18.89	0.44	0.18–1.09

[a]Values expressed as n (%) unless otherwise noted. Boldface indicates statistical significance.
[b]ORs larger than 1.0 reflect higher prevalence in BP-I group.
[c]ORs larger than 1.0 reflect higher prevalence in BP-II group.
[d]Feature included in the Probabilistic Approach.
*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviations: BP-I = bipolar I disorder, BP-II = bipolar II disorder, MDD = major depressive disorder, OR = odds ratio.

"nonoverlapping" mixed symptoms (as used in *DSM-5*) were included, both any ($P < .01$) and 3 or more ($P < .001$) mixed features were significantly more likely to be reported among BP-II patients than MDD cases.

When the 2 bipolar disorder subtypes were compared, BP-I was characterized by psychomotor retardation ($P < .01$), while BP-II was significantly associated with initial insomnia ($P < .05$) and mixed features ($P < .05$). When only nonoverlapping mixed features were included, BP-II was significantly associated with at least 1 mixed symptom ($P < .01$); no differences were found when comparing 3 or more nonoverlapping symptoms between the 2 groups.

A multivariate logistic regression was then undertaken, including the 9 symptoms for which significant differences were found at the bivariate level (Table 3). When MDD and BP-I cases were compared, psychomotor retardation ($P < .05$) and psychotic features ($P < .05$) remained significantly associated with BP-I. The presence of either at least 3, or at least 1, mixed features remained significantly associated with BP-II when compared to both MDD ($P < .01$) and BP-I ($P < .001$). Psychomotor retardation was also more commonly associated with BP-I than BP-II depression ($P < .05$).

Probabilistic Approach to the Diagnosis of Bipolar Depression

To assess the utility of the Probabilistic Approach in distinguishing between BP-I, BP-II, and MDD, we determined the number of positive features for each participant and calculated receiver operating characteristics for the cutoff scores that were most likely to offer the greatest clinical utility (Table 4). As the utility of the Probabilistic Approach lies in its potential to identify possible bipolar disorder cases, we prioritized higher sensitivity over specificity. Additionally, we calculated Youden *J* Index, defined as $sensitivity + (specificity - 1)$, to determine the optimal cutoff score,[25] and this was repeated for each of the 3 comparisons between diagnostic groups. Finally, a series of age- and sex-adjusted logistic regression analyses were carried out to determine if meeting probabilistic criteria differentiated between the 3 diagnostic categories (Table 5).

Using a cutoff of 3 or more items, 51.7% of MDD cases, 77.3% of BP-II cases, and 72.3% of BP-I cases were identified as potential bipolar disorder cases by the Probabilistic Approach (see Table 5). With a more stringent criterion of 5 or more features, 11.7% of MDD cases, 38.6% of BP-II cases, and 22.8% of BP-I cases were so identified.

BP-I Compared to MDD

Receiver operating characteristics are reported in Table 4. A cutoff score of 3 or more features provided the highest sensitivity and optimal Youden *J* Index. The proportion of those correctly classified fell from 63.4% as the cutoff score increased, although the low false-positive rate indicates that the majority of cases with 5 or more features were likely to fall within the BP-I group. As detailed in Table 5, those with BP-I

Table 3. Multivariate Logistic Regression Analysis Predicting Diagnosis From Depressive Symptoms[a]

				BP-I vs MDD		BP-II vs MDD		BP-I vs BP-II	
Symptom	MDD (n = 120)	BP-II (n = 44)	BP-I (n = 202)	OR[b]	95% CI	OR[c]	95% CI	OR[b]	95% CI
Initial insomnia	65 (54.2)	32 (72.7)	110 (54.5)	0.55	0.30–1.01	2.05	0.75–5.65	0.42	0.17–1.04
Terminal insomnia	52 (43.3)	25 (56.8)	110 (54.5)	1.87	1.02–3.42	1.08	0.42–2.78	1.21	0.51–2.91
Hypersomnia	43 (35.8)	20 (45.5)	93 (46.0)	1.41	0.83–2.39	2.05	0.86–4.89	0.97	0.46–2.04
Psychomotor retardation	46 (38.3)	18 (40.9)	119 (58.9)	**1.79***	**1.06–3.02**	0.86	0.37–2.01	**2.35***	**1.12–4.92**
Guilt	76 (63.3)	37 (84.1)	142 (70.3)	1.13	0.66–1.93	2.07	0.78–5.45	0.52	0.20–1.34
Difficulty thinking	97 (80.8)	43 (97.7)	181 (89.6)	1.30	0.62–2.70	4.17	0.50–34.96	0.30	0.04–2.57
Morning worsening	46 (38.3)	25 (56.8)	104 (51.5)	1.45	0.87–2.44	1.81	0.81–4.04	0.59	0.27–1.29
Any psychosis	17 (14.2)	9 (20.5)	57 (28.2)	**2.21***	**1.15–4.25**	1.09	0.39–3.0	1.73	0.73–4.10
3+ mixed symptoms	29 (24.2)	23 (52.3)	39 (19.3)	1.86	0.75–4.65	**3.99****	**1.33–11.9**	**0.36*****	**0.14–0.92**

[a]Values expressed as n (%) unless otherwise noted. Boldface indicates statistical significance.
[b]ORs larger than 1.0 reflect higher prevalence in BP-I group.
[c]ORs larger than 1.0 reflect higher prevalence in BP-II group.
*$P < .05$.
**$P < .01$.
***$P < .01$.
Abbreviations: BP-I = bipolar I disorder, BP-II = bipolar II disorder, MDD = major depressive disorder, OR = odds ratio.

Table 4. Sensitivity and Specificity of Probabilistic Approach at Different Cutoffs

	BP-I vs MDD				BP-II vs MDD				BP-I vs BP-II			
Probabilistic Approach	Sens	Spec	%[a]	*J*[b]	Sens	Spec	%[a]	*J*[b]	Sens	Spec	%[a]	*J*[b]
3 or more features	72.3	48.3	63.4	.206	77.3	48.3	56.1	.256	72.3	22.7	63.4	.05
4 or more features	48.5	69.2	56.2	.177	52.3	69.2	64.6	.215	48.5	47.7	48.4	.04
5 or more features	22.8	88.3	47.2	.111	38.6	88.3	75.0	.269	22.8	61.4	29.7	.16

[a]Percentage correctly classified.
[b]Youden *J* Index.
Abbreviations: BP-I = bipolar I disorder, BP-II = bipolar II disorder, MDD = major depressive disorder.

Table 5. Percentage Classified by Probabilistic Approach at Different Cutoffs[a]

				BP-I vs MDD		BP-II vs MDD		BP-I vs BP-II	
Probabilistic Approach	MDD (n = 120)	BP-II (n = 44)	BP-I (n = 202)	OR[b]	95% CI	OR[c]	95% CI	OR[b]	95% CI
3 or more features	62 (51.7)	34 (77.3)	146 (72.3)	2.79***	1.65–4.65	3.53***	1.52–8.18	0.85	0.37–1.94
4 or more features	37 (30.8)	23 (52.3)	98 (48.5)	2.26***	1.37–3.73	2.55**	1.23–5.29	0.92	0.46–1.83
5 or more features	14 (11.7)	17 (38.6)	46 (22.8)	2.53**	1.28–5.01	4.91***	2.08–11.59	0.52	0.25–1.06

[a]Values expressed as n (%) unless otherwise noted.
[b]ORs larger than 1.0 reflect higher prevalence in BP-I group.
[c]ORs larger than 1.0 reflect higher prevalence in BP-II group.
**$P < .01$.
***$P < .001$.
Abbreviations: BP-I = bipolar I disorder, BP-II = bipolar II disorder, MDD = major depressive disorder, OR = odds ratio.

were significantly more likely to have 3 or more symptoms (OR = 2.79, $P < .001$).

BP-II Compared to MDD

A cutoff of 3 or more features provided the greatest sensitivity and correctly classified 56.1% of cases (see Table 4), with moderate specificity. As the number of features increased, so did the proportion of correctly classified cases, reaching 75% with a cutoff of 5 or more items, although sensitivity decreased with a more conservative cutoff. When Youden *J* Index was calculated, 2 cutoff values (a minimum of either 3 or 5 items) had similar values, identifying both as potentially optimal cutoffs. Those with BP-II were significantly more likely to have 3 or more (OR = 3.53, $P < .001$) or 5 or more (OR = 4.91, $P < .001$) features.

BP-I Compared to BP-II

When the 2 bipolar subgroups were compared, sensitivity was highest with a cutoff of 3 or more items (see Table 4), which correctly classified 63.4% of participants. Youden *J* Index was maximized at a cutoff of 5 or more items, which correctly classified 29.7% of participants. Using logistic regression, the Probabilistic Approach did not differentiate between BP-I and BP-II at any of the 3 cutoff levels examined (Table 5).

DISCUSSION

The findings reported here add to the growing literature documenting robust differences in the phenomenology of depressive episodes between bipolar and MDD patients. This study is one of few that have directly compared both BP-I and BP-II subtypes against MDD cases, with distinct symptom profiles emerging from each of these comparisons. Compared to MDD cases, BP-I patients were characterized by greater rates of early morning awakening, psychomotor retardation, morning worsening, psychotic features, difficulty thinking, and hypersomnia. These findings are consistent with the broader literature, with numerous studies

reporting on the high rates of psychomotor retardation and other "melancholic" features,[5,23] psychosis,[26] and atypical depressive symptoms[5] in BP-I depression. Both psychomotor retardation and psychotic symptoms remained significant in the multivariate model, confirming their status as cardinal features of BP-I depression.

When compared to MDD cases, BP-II patients presented with a different symptom profile, characterized by initial insomnia, excessive guilt, difficulty thinking, morning worsening, and mixed features. The latter remained significantly associated with BP-II disorder even when restricted to nonoverlapping symptoms, consistent with *DSM-5*.[23] In the multivariate analysis, only mixed features remained significant. In our previous study,[10] mixed features did not differ significantly between MDD and BP cases; in that analysis, both BP-I and BP-II subtypes were combined. Our current findings clearly indicate that this association is robust, but specific to the BP-II cases. Although few studies have compared BP-II and MDD depression, this finding is consistent with a number of reports from Benazzi[11,27,28] and others[29] on the high rate of mixed features in BP-II depression. Given the potential difficulty of differentiating mixed features from symptoms of comorbid anxiety disorders, we carried out a follow-up analysis (data not shown), excluding any participant who met criteria for a *DSM-IV* anxiety disorder. The previously reported pattern of findings was unchanged, with the same differences observed in both the bivariate and multivariate analyses.

The nosologic significance of mixed features within bipolar depressive episodes remains a contentious issue.[29] Under *DSM-IV*, some patients may not have met the conservative threshold requiring criteria for both manic and depressive episodes to be met for 1 week, limiting the clinical usefulness of this diagnosis. In *DSM-5*, the mixed features specifier requires only 3 "nonoverlapping" symptoms from the opposite affective pole to be present,[23] consistent with Benazzi's criteria described in his research on mixed depressive episodes.[30,31] *DSM-5* also explicitly acknowledges the presence of mixed features during a unipolar depressive episode as a strong risk factor for bipolar disorder.[23] Our current findings support this position but suggest that this association is more prominent among BP-II cases, over half of whom reported mixed features during their most severe depressive episode. Angst et al[32] reported a similar finding, with mixed states more common among BP-II patients compared to MDD cases, while no differences were noted between those with BP-I and MDD. These data suggest that mixed presentations are a prominent feature of bipolar depression, particularly for BP-II, perhaps aiding clinicians in identifying patients who may warrant further assessment for a possible bipolar disorder.

Our study also directly compared depressive symptoms between BP-I and BP-II disorders, with the former characterized by psychomotor retardation and the latter by initial insomnia and mixed features. Of particular note was that mixed features differentiated BP-I and BP-II disorders in multivariate analysis, being far more prevalent in the latter (52.3% compared to 19.3%). To our knowledge, no prior studies have directly compared rates of mixed features during depressive episodes between BP-I and BP-II patients. The current data suggest that, apart from mixed features and psychomotor retardation, the clinical features and phenomenology of depressive episodes were generally similar between BP-I and BP-II participants.

The current data also extend previous work on the Probabilistic Approach in differentiating between bipolar disorder and MDD.[10] The approach was successful in distinguishing between MDD and both subtypes of bipolar disorder, based solely on characteristics of depressive episodes, but was unable to differentiate between the 2 bipolar subtypes. Although there were some differences in the rates of individual symptoms between these subtypes, they were not sufficient to enable a distinction between subtypes based on combinations of depressive features.

Examination of receiver operating characteristics indicated some variation in the optimal cutoff when comparing bipolar subgroups with MDD. When distinguishing between BP-I and MDD cases, a cutoff of 3 or more items provided the greatest sensitivity. When BP-II was compared to MDD, 2 possible cutoffs were identified: a minimum of either 3 or 5 symptoms. The former cutoff offered the greatest sensitivity, although with a high rate of false-positives. The latter cutoff of 5 items lowered the false-positive rate considerably, although sensitivity was low. It is possible that, given the greater symptomatic similarity between MDD and BP-II (compared to the more profound differences found between MDD and BP-I), the presence of a greater number of items was necessary in order to accurately rule out MDD cases.

Finally, when BP-I was compared to BP-II, a cutoff of 5 or more items had the highest Youden *J* Index, although this was associated with lower sensitivity than smaller cutoffs. The overall findings suggest that the Probabilistic Approach was unable to robustly differentiate between the 2 bipolar disorder subtypes, which is consistent with our finding of few symptomatic differences between BP-I and BP-II in the multivariate analysis.

We elected to prioritize a cutoff that maximized sensitivity, given that the utility of the Probabilistic Approach stems from the potential to identify patients who, based on their history of depression, may warrant further assessment for a possible bipolar disorder. The current findings indicate that the Probabilistic Approach, while not diagnostic, was successful in flagging possible bipolar disorder cases and may provide practitioners with an additional tool to complement a thorough clinical assessment. The availability of appropriate treatments, and the potential implications of either delayed or inappropriate treatment, also suggests greater value in maximizing sensitivity to identify possible bipolar cases. Further assessment of such cases using methods that offer greater specificity are recommended.

Several limitations apply to the current findings, including the reliance on the retrospective assessment of depressive episodes. Confirming these results in a cross-sectional study

of currently depressed patients would further strengthen the validity of the current findings. Additionally, all participants were ascertained on the basis of a family history of bipolar disorder, which may limit the generalizability of our findings. However, we would expect this to attenuate, rather than increase, any between-group difference based on the shared genetic background. Despite this, we have still been able to identify robust differences across the 3 categories.

In conclusion, the findings of this study suggest clear differences in the symptom profile of depressive episodes between BP-I and BP-II subtypes and MDD. Further replication of these differences in larger independent datasets is necessary, particularly among patients not ascertained from within bipolar disorder pedigrees.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this activity.
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REFERENCES

1. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. *Lancet*. 2013;381(9878):1663–1671.
2. Goodwin GM, Anderson I, Arango C, et al. ECNP consensus meeting: bipolar depression. Nice, March 2007. *Eur Neuropsychopharmacol*. 2008;18(7):535–549.
3. Bowden CL. Diagnosis and impact of bipolar depression. *J Clin Psychiatry*. 2009;70(9):e32.
4. Baldessarini RJ, Vieta E, Calabrese JR, et al. Bipolar depression: overview and commentary. *Harv Rev Psychiatry*. 2010;18(3):143–157.
5. Mitchell PB, Wilhelm K, Parker G, et al. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. *J Clin Psychiatry*. 2001;62(3):212–216, quiz 217.
6. Forty L, Smith D, Jones L, et al. Clinical differences between bipolar and unipolar depression. *Br J Psychiatry*. 2008;192(5):388–389.
7. Xiang YT, Zhang L, Wang G, et al. Sociodemographic and clinical features of bipolar disorder patients misdiagnosed with major depressive disorder in China. *Bipolar Disord*. 2013;15(2):199–205.
8. Mitchell PB, Goodwin GM, Johnson GF, et al. Diagnostic guidelines for bipolar depression: a probabilistic approach. *Bipolar Disord*. 2008;10(1, pt 2):144–152.
9. Cardoso de Almeida JR, Phillips ML. Distinguishing between unipolar depression and bipolar depression: current and future clinical and neuroimaging perspectives. *Biol Psychiatry*. 2013;73(2):111–118.
10. Mitchell PB, Frankland A, Hadzi-Pavlovic D, et al. Comparison of depressive episodes in bipolar disorder and in major depressive disorder within bipolar disorder pedigrees. *Br J Psychiatry*. 2011;199(4):303–309.
11. Benazzi F. Bipolar disorder—focus on bipolar II disorder and mixed depression. *Lancet*. 2007;369(9565):935–945.
12. Hantouche EG, Akiskal HS. Bipolar II vs unipolar depression: psychopathologic differentiation by dimensional measures. *J Affect Disord*. 2005;84(2–3):127–132.
13. Parker GB, Fletcher K. Is bipolar II depression phenotypically distinctive? *Acta Psychiatr Scand*. 2009;120(6):446–455.
14. Rastelli CP, Cheng Y, Weingarden J, et al. Differences between unipolar depression and bipolar II depression in women. *J Affect Disord*. 2013;150(3):1120–1124.
15. Bega S, Schaffer A, Goldstein B, et al. Differentiating between bipolar disorder types I and II: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Affect Disord*. 2012;138(1–2):46–53.
16. Vieta E, Gastó C, Otero A, et al. Differential features between bipolar I and bipolar II disorder. *Compr Psychiatry*. 1997;38(2):98–101.
17. Brugue E, Colom F, Sanchez-Moreno J, et al. Depression subtypes in bipolar I and II disorders. *Psychopathology*. 2008;41(2):111–114.
18. Serretti A, Mandelli L, Lattuada E, et al. Clinical and demographic features of mood disorder subtypes. *Psychiatry Res*. 2002;112(3):195–210.
19. Maxwell M. *Family Interview for Genetic Studies (FIGS): a Manual for FIGS. Clinical Neurogenetics Branch, Intramural Research Program*. Bethesda, MD: National Institute of Mental Health; 1992.
20. Nurnberger JI Jr, Blehar MC, Kaufmann CA, et al. Diagnostic Interview for Genetic Studies: rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry*. 1994;51(11):849–859, discussion 863–864.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Arlington, VA: American Psychiatric Association; 2000.
22. Leckman JF, Sholomskas D, Thompson WD, et al. Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch Gen Psychiatry*. 1982;39(8):879–883.
23. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.
24. Vieta E, Valentí M. Mixed states in *DSM-5*: implications for clinical care, education, and research. *J Affect Disord*. 2013;148(1):28–36.
25. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3(1):32–35.
26. Goes FS, Sadler B, Toolan J, et al; Bipolar Disorder Phenome Group. Psychotic features in bipolar and unipolar depression. *Bipolar Disord*. 2007;9(8):901–906.
27. Benazzi F. Depressive mixed states: unipolar and bipolar II. *Eur Arch Psychiatry Clin Neurosci*. 2000;250(5):249–253.
28. Benazzi F. Mixed depression: a clinical marker of bipolar-II disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(2):267–274.
29. Malhi GS. Diagnosis of bipolar disorder: who is in a mixed state? *Lancet*. 2013;381(9878):1599–1600.
30. Benazzi F. Bipolar II depressive mixed state: finding a useful definition. *Compr Psychiatry*. 2003;44(1):21–27.
31. Benazzi F. Sensitivity and specificity of clinical markers for the diagnosis of bipolar II disorder. *Compr Psychiatry*. 2001;42(6):461–465.
32. Angst J, Gamma A, Bowden CL, et al. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. *Eur Arch Psychiatry Clin Neurosci*. 2013;263(8):663–673.

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Posttest

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1. **Which major nosologic system describes differences in clinical features of depressive episodes depending on whether the patient has major depressive disorder (MDD) or a type of bipolar disorder?**
   a. *Diagnostic and Statistical Manual of Mental Disorders (DSM)*
   b. *International Classification of Diseases (ICD)*
   c. Both the *ICD* and *DSM*
   d. Neither the *ICD* nor *DSM*

2. **Ms A is experiencing her second and most severe major depressive episode and is hospitalized. She has had early morning awakening, psychomotor retardation, difficulty thinking, and hallucinations. According to the results of this study, which diagnosis is more probable?**
   a. Bipolar I disorder
   b. Bipolar II disorder
   c. MDD
   d. None of the above

3. **Mr B is experiencing his most severe major depressive episode. He has had initial insomnia, excessive guilt, and *DSM-5* mixed features. According to the results of this study, which diagnosis is more probable?**
   a. Bipolar I disorder
   b. Bipolar II disorder
   c. MDD
   d. None of the above

4. **The authors made all of the following conclusions *except*:**
   a. The study was limited by reliance on retrospective assessment of patients' most severe depressive episodes
   b. The Probabilistic Approach is a tool that can complement but not replace a thorough clinical assessment
   c. If any features described in this study are found in a patient, no further assessment is needed for diagnosis
   d. All patients in the sample had a family history of bipolar disorder, which should have attenuated, rather than increased, between-group differences