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After completing this CME activity, participants should be able to:
- List several clinical features that may help physicians differentiate between bipolar depression and major depressive disorder.

Statement of Need and Purpose
Physicians responding to questionnaires in *The Journal* and related CME activities have requested information on the identification of bipolar disorder in patients who present with depression. This CME activity was designed to meet these needs. There are no prerequisites for participation in this CME activity.

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The Clinical Features of Bipolar Depression: A Comparison With Matched Major Depressive Disorder Patients

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Background: Despite a resurgence of interest in the treatment of bipolar depression, there have been few controlled studies of the clinical characteristics of this condition. Identification of any distinctive clinical "signatures" of bipolar depression would be helpful in determining treatment options in the clinical setting.

Method: From a cohort of 270 inpatients and outpatients assessed in detail during a DSM-IV major depressive episode, 39 bipolar I disorder patients were identified and closely matched with 39 major depressive disorder patients for gender, age, and the presence or absence of DSM-IV melancholic subtype. Patients were compared on a broad range of parameters including the Hamilton Rating Scale for Depression (depression severity), 54 depressive symptoms, the Newcastle Endogenous Depression Diagnostic Index, 3 family history items, 2 physical health items, the CORE scale (psychomotor disturbance), and 5 history items.

Results: Although the bipolar patients were no more severely depressed than the major depressive disorder controls, they were more likely to demonstrate psychomotor-retarded melancholic and atypical depressive features and to have had previous episodes of psychotic depression. These findings were largely duplicated even when the population was confined to those with DSM-IV melancholia.

Conclusion: The clinical admixture of psychomotor-retarded melancholic signs and symptoms, "atypical" features, and (less frequently) psychosis may provide a "bipolar signature" in clinical scenarios when there is uncertainty concerning the polarity of a depressive presentation.

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There has been a recent, albeit belated, resurgence of interest in the treatment of bipolar depression.[1] An implicit assumption of such studies is that this form of depression differs biologically from major depressive disorder (MDD), though few replicated biological distinctions have emerged.[2,3] The renewed interest in therapeutics also raises the issue of phenomenological differences between these 2 depressive syndromes. If, indeed, there are distinctive features or "signatures" of bipolar depression, then these would be helpful in determining treatment options in common clinical situations such as first-onset depression, an ambiguous past history of (hypo)mania, or the "MDD" patient with a family history of bipolar disorder. Such a "signature" would also be of benefit in the research setting, particularly in genetic linkage studies of bipolar disorder, in which there is often uncertainty whether relatives with MDD are, in fact, bipolar subjects yet to manifest mania.[4]

Despite the accepted wisdom that there are distinctive clinical characteristics of the depressed phase of bipolar disorder, there have been few formal controlled studies examining for such distinctions. Those features usually described in monographs or textbooks include psychomotor retardation ("shutdown depression"), "atypical" features (such as hypersomnia and hyperphagia), a greater likelihood of psychosis, and less anxiety.[5]

To identify features distinguishing bipolar depression and MDD, we compared a wide range of clinical phenomena in 39 closely matched pairs of bipolar and MDD patients who were assessed in detail while currently depressed.

METHOD

Inpatients and outpatients fulfilling DSM-IV[6] criteria for a major depressive episode (present for less than 2 years) were recruited from subjects attending a tertiary referral Mood Disorders Unit in Sydney, Australia, and from a number of nonspecialist psychiatric units in several Sydney teaching hospitals. Of these 270 patients, 39 fulfilled DSM-IV criteria for bipolar disorder (all bipolar I). The bipolar patients were then matched with major depressive disorder patients for the following characteristics: gender, closest age (within 5 years), and presence or absence of DSM-IV melancholic subtype.

The matched pairs were compared on a broad range of clinical measures comprising the Hamilton Rating Scale for Depression (17-item) (severity of depression),[7] 54 depressive symptoms (methodology described in Parker et al.[8]), the Newcastle Endogenous Depression Diagnostic Index,[9] 3 family history items (depression, other mental illness, suicide), 2 physical health items (cardiovascular or cerebrovascular/cerebral disease), the CORE scale[10–12] for rating objective behavioral features of psychomotor disturbance (the 18-item CORE scale comprises 3 subscales [agitation, retardation, and noninteractiveness]; a total CORE score of 8 or more is indicative of melancholia), and 5 historical characteristics (age at first episode, age at first suicide attempt, history of suicide attempt, history of self-injury, and history of psychotic features in past episodes). The research was approved by the responsible Institutional Ethics Review Committee; all patients gave written informed consent. Dimensional data were compared using paired Student t tests. Categorical data were compared with McNemar tests. All values are expressed as mean ± SD unless otherwise indicated.

RESULTS

Of the 39 patients with DSM-IV bipolar disorder, 25 were women and 14 were men; their mean ± SD age was 43.9 ± 15.1 years. Twenty of the bipolar patients fulfilled DSM-IV criteria for melancholic subtype for their current major depressive episode. The matched group of 39 patients with MDD was not significantly different in age when compared with the bipolar group (43.6 ± 13.7 years; p = .47). Thirteen (33%) of the bipolar subjects and 21 (54%) of the MDD subjects were inpatients at the time of assessment (not significant; p = 0.13).

Comparison of Matched Bipolar (N = 39) and MDD (N = 39) Patients

Severity of depression. There was no difference in the severity of depression between the bipolar (23.1 ± 9.4) and MDD (22.6 ± 6.6) patients on the Hamilton Rating Scale for Depression.

Symptoms. The bipolar patients scored higher on measures of "leaden paralysis," worthlessness, anticipatory anhedonia, and subjective restlessness (all $p < .05$). They were also more likely to report hypersomnia (43.6% [N = 17] vs. 18.0% [N = 7]; $p < .05$). MDD patients were more likely to report being tearful ($p < .05$). Furthermore, the Newcastle Endogenous Depression Diagnostic Index indicated that MDD patients were more likely to experience anxiety (82.1% [N = 32] vs. 25.6% [N = 10]; $p < .05$) and to blame others (38.5% [N = 15] vs. 7.7% [N = 3]; $p < .05$).

Objective signs of psychomotor disturbance (CORE scale). Bipolar patients evidenced more nonreactivity of mood, delay in verbal responses, and general slowing in their movements (all, $p < .05$). The retardation subscale score was higher in bipolar patients (4.6 ± 4.2 vs. 2.8 ± 3.1; $p < .05$), but there were no differences in the agitation or noninteractiveness subscale scores. The total CORE score was significantly higher in the bipolar patients (9.5 ± 8.4 vs. 6.6 ± 6.5; $p < .05$), indicating more marked psychomotor disturbance. Consistent with this, the Newcastle Endogenous Depression Diagnostic Index rated more bipolar patients as demonstrating depressed psychomotor activity (71.8% [N = 28] vs. 41.0% [N = 16]; $p < .05$).

Historical features. Bipolar patients had more frequently experienced hallucinations or delusional beliefs during previous depressive episodes (38.7% [N = 15] vs. 10.3% [N = 4]; $p < .05$).

Comparison of Matched DSM-IV Melancholic Bipolar (N = 20) and Melancholic MDD (N = 20) Patients

Age. There was no significant difference in age between the matched pairs of melancholic bipolar and MDD patients (41.4 ± 13.3 years vs. 42.0 ± 13.1 years).

Severity of depression. There was no difference in the severity of depression between the melancholic bipolar (26.6 ± 8.9) and MDD (26.7 ± 5.9) patients on the Hamilton Rating Scale for Depression.

Symptoms. Melancholic bipolar patients, compared with melancholic MDD patients, complained more of an-

ticipatory anhedonia ($p < .05$). They were also more likely to experience hypersomnia (45.0% [N = 9] vs. 10.0% [N = 2]; $p < .05$) and persistent and unvarying mood (45.0% [N = 9] vs. 0% [N = 0]; $p < .05$). Melancholic MDD patients had more marked initial insomnia ($p < .05$). The Newcastle Endogenous Depression Diagnostic Index indicated that melancholic MDD patients were more likely to experience anxiety (75.0% [N = 15] vs. 10.0% [N = 2]; $p < .05$).

Objective signs of psychomotor disturbance (CORE scale). Melancholic bipolar patients evidenced more facial immobility, delay in initiating motor activity, and general slowing in their movements compared with the melancholic MDD patients (all, $p < .05$). The retardation subscale score was higher in the melancholic bipolar patients (6.3 ± 4.6 vs. 4.0 ± 3.5; $p < .05$), while there were no between-group differences in the agitation or noninteractiveness subscale scores. Although there was a trend for the total CORE score to be higher in the melancholic bipolar patients (12.7 ± 9.3 vs. 9.2 ± 7.1), this was not significantly different. The Newcastle Endogenous Depression Diagnostic Index rated more melancholic bipolar patients as demonstrating depressed psychomotor activity (85.0% [N = 17] vs. 50.0% [N = 10]; $p < .05$).

Table 1. Summary of Significant Symptomatic Differences Between Bipolar and Major Depressive Disorder (MDD) Patients[a]

Symptom[b]	Sample	Bipolar (N = 39)	MDD (N = 39)*
Bipolar > MDD			
"Leaden paralysis"	A	1.2 (1.3)	0.6 (0.9)
Hypersomnia, %	A, B[c]	44	18
Worthlessness	A	2.5 (0.8)	2.1 (1.0)
Persistent and unvarying mood, %	B	45	0
Anticipatory anhedonia	B	2.8 (0.4)	2.4 (0.7)
Subjective restlessness	A	1.3 (1.3)	0.7 (1.1)
Signs of psychomotor retardation (CORE scale)			
Nonreactive mood	A	1.3 (1.0)	0.8 (0.8)
Delayed verbal responses	A	0.6 (0.7)	0.3 (0.6)
General slowing of movements	A, B[c]	0.8 (0.9)	0.4 (0.6)
Facial immobility	B	1.4 (0.9)	1.2 (1.0)
Delay in initiating motor activity	B	0.7 (0.7)	0.2 (0.4)
Past history of psychotic depression, %	A	39	10
Bipolar < MDD			
Tearfulness	A	2.0 (1.4)	2.7 (1.1)
Anxiety, %	A, B[c]	26	82
Tendency to blame others, %	A	8	39
Initial insomnia	B	1.2 (1.2)	2.0 (1.1)

[a]Values expressed as mean (SD) unless otherwise noted. Abbreviations: A = melancholic and nonmelancholic subjects combined (N = 39), B = melancholic subjects only (N = 20).
[b]Symptoms were rated on a 0–3 scale (0 = not present, 1 = more than usual, 2 = much more than usual, 3 = severe).
[c]If there were significant differences between the bipolar and MDD patients in both samples A and B, as indicated in the text, only data for sample A are given.
*$p < .05$ for all comparisons.

DISCUSSION

This study demonstrated that although bipolar I patients were not more severely depressed than matched MDD patients, the bipolar patients were more likely to demonstrate both "retarded melancholic" and "atypical" depressive features and to have had previous episodes of psychotic depression (Table 1). Specifically, bipolar patients had more frequent and/or severe symptoms of worthlessness, anticipatory anhedonia, subjective restlessness, hypersomnia, and leaden paralysis than MDD patients. Objectively, bipolar patients showed more marked psychomotor retardation, but not more agitation. Consistent with these features, they were less likely than MDD subjects to show tearfulness, initial insomnia, anxiety, or a tendency to blame others. These findings were largely duplicated even when the samples were limited to those with DSM-IV–defined melancholia and provide strong support for the traditional clinical descriptions of bipolar depression.[5]

The necessity of controlling for age, sex, and melancholic status when comparing bipolar disorder and MDD cannot be overemphasized. MDD, as currently broadly defined under the DSM system (unlike the older European definitions), is considered by many to be heterogeneous.[12] Furthermore, older depressed patients are more likely to be melancholic and psychotic and to demonstrate psychomotor disturbance.[13]

Overall, the research literature comparing the clinical features of bipolar depression and MDD (tabulated in Mitchell et al.[14]) has been inconsistent, perhaps reflecting the scarcity of well-controlled studies. The only well-controlled investigation apart from our own studies has been that of Beigel and Murphy,[15] who used actimetry to demonstrate lower activity levels in bipolar subjects. In our previous study of age- and sex-matched melancholic patients from the first of our data sets,[13] we found no significant differences between bipolar and MDD patients, perhaps because an early (and limited) version of the CORE scale was employed, "atypical" features were not examined, and the diagnosis of past (hypo)manic episodes was determined retrospectively by case-note review.

In a recent overview analysis of the 3 data sets that we have now accumulated,[16] we reported that bipolar patients were more likely to receive DSM, CORE, and clinical diagnoses of melancholic and psychotic depression. The present study provides a fine-grained analysis of the most recent (the third) of those data sets. This data set incorpo-

rated additional items on "atypical" depressive features and included structured questions related to past (hypo)manic episodes. Furthermore, the present study has controlled for age, sex, and melancholic status.

The finding of a greater likelihood of melancholic symptoms and signs in bipolar depressed patients in both this study and our overview report is consistent with a number of previous publications. In addition to the Beigel and Murphy[15] study, 2 other less strictly controlled trials[17,18] have also described greater psychomotor retardation in those with bipolar depression. There have been, however, a number of studies that have reported no difference in the degree of retardation.[14,19–23]

While "atypical" features of depression, such as hypersomnia, hyperphagia, and "leaden paralysis," have been associated with bipolar depression in recent years, there have been no well-controlled data to support this. Benazzi,[24] for example, found atypical features to be more common in bipolar II disorder than in MDD in an outpatient private practice setting, but age was not controlled for, despite the MDD patients being significantly older.

Both our fine-grained and overview studies have demonstrated a greater likelihood of psychotic features in current or prior depressed episodes, as reported previously (but not invariably)[15] in uncontrolled studies.[25–27] The increased risk of psychotic features during bipolar I depression was also reported by the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression 11-year prospective follow-up of index unipolar patients who later switched to bipolar I or II status.[28,29] Of particular relevance to our own study was the finding that bipolar I "converters" were more likely to have been psychotic or hospitalized at the index depressive assessment, compared with those who continued to have a diagnosis of MDD.[28] Bipolar I "converters" also rated worse on psychic anxiety, inability to concentrate, social withdrawal, and feelings of inadequacy and discouragement.[29]

In conclusion, this closely controlled comparative study has demonstrated that bipolar depression is more likely than MDD to be characterized by psychomotor-retarded melancholic signs and symptoms, "atypical" features of depression, and (less frequently) psychosis, even when only DSM-IV–defined melancholic subjects are considered. These findings indicate that such features may suggest a "bipolar signature" of use in clinical practice scenarios in which there is uncertainty concerning the polarity of a depressive presentation. Furthermore, the intriguing and apparently characteristic admixture of atypical and retarded melancholic features in bipolar depression gives a clinical rationale for a number of reports of the particular effectiveness of the older monoamine oxidase inhibitors for such patients[30] and indicates the potential usefulness of such antidepressants if newer medications are ineffective.

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1. In this study, bipolar depressed patients were more likely than major depressive disorder patients to demonstrate the following characteristics:
a. Retarded melancholic features only
b. Agitated melancholic features only
c. Agitated melancholic features and atypical features
d. Retarded melancholic features and atypical features

2. In this study, clinical features shown to be more commonly associated with bipolar depression (in comparison to major depressive disorder) included:
a. Psychosis
b. Anorexia
c. Diminished libido
d. Irritability

3. This study clearly demonstrates that compared to major depressive disorder patients, bipolar depressed patients are:
a. More severely depressed
b. Less psychomotor retarded
c. More easily treated
d. More likely to have atypical features

4. The CORE scale measures:
a. Clinician-rated depression severity
b. Patient-rated depression severity
c. Psychomotor disturbance
d. Anxiety severity

5. The following are all signs of psychomotor retardation (as described by the CORE scale) *except*:
a. Noninteractiveness
b. Facial immobility
c. Delayed verbal responses
d. General slowing of movements

6. The following are subscales of the CORE scale *except*:
a. Agitation
b. Noninteractiveness
c. Retardation
d. Anxiety

7. Atypical depression is associated with each of the following features *except*:
a. Hyperphagia
b. Psychomotor retardation
c. Hypersomnia
d. Leaden paralysis

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