The Role of Psychomotor Activation in Discriminating Unipolar From Bipolar Disorders: A Classification-Tree Analysis

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ABSTRACT

Objective: Multiple studies indicate that bipolar disorders are often underrecognized, misdiagnosed, and incorrectly treated. The aim of the present report is to determine which combination of clinical, demographic, and psychopathological factors and corresponding cutoff scores best discriminate patients with unipolar disorder from those with bipolar disorders.

Method: The study sample includes outpatients and inpatients (N = 1,158) participating in 5 studies carried out in the United States and Italy between October 2001 and March 2008, one of which was a randomized clinical trial. Diagnostic assessment was carried out with the SCID, which allows diagnoses to be made according to *DSM-IV-TR* criteria.

Using an exploratory statistical approach based on a classification tree, we employed 5 mania spectrum factors and 6 depression spectrum factors derived from the Mood Spectrum Self-Report Instrument (MOODS-SR) in combination with demographic and clinical characteristics to discriminate participants with unipolar versus bipolar disorders.

Results: The *psychomotor activation* factor, assessing the presence of thought acceleration, distractibility, hyperactivity, and restlessness for 1 or more periods of at least 3 to 5 days in the lifetime, identified subgroups with an increasing likelihood of bipolar disorder diagnosis. Mixed instability and suicidality contributed to further subtyping the sample into mutually exclusive groups, characterized by a different likelihood of receiving a diagnosis of bipolar disorder. Of the demographic and clinical characteristics included in the analysis, only sex proved to be useful to improve the discrimination.

Conclusions: The psychomotor activation factor proved to be the most potent discriminator of those with unipolar versus bipolar diagnoses. The items that constitute this factor, together with those that constitute the mixed instability, suicidality, and euphoria factors, might be useful in making the differential diagnosis.

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Multiple studies indicate that bipolar disorders are often underrecognized, misdiagnosed, and incorrectly treated. Indeed, a series of reports suggests that the typical patient with bipolar disorder waits between 7 and 10 years after first seeking treatment to receive a correct diagnosis.[1–6] The most common problem in making the differential diagnosis of bipolar disorders is its overlapping boundaries with schizophrenia, schizoaffective disorder, personality disorders, substance use disorders, and, above all, unipolar depressive disorder.[7] A major barrier to accurate diagnosis is that, with the exception of cases of severe mania, patients typically present for evaluation and treatment when they are depressed. In this cross-sectional evaluation context, their history of subtle (or not so subtle) manifestations of mania and hypomania are often not queried or, if they are, these features are often not acknowledged by patients or family members who often see these features as positive aspects of the patient's personality.[8] The consequences of the failure to arrive at the correct diagnosis include increased hospitalization, morbidity, and risk of suicide.[3] On the other hand, Zimmerman et al[9,10] have raised concerns about the emerging problem of clinicians' overdiagnosis of bipolar disorder and the possible risk of exposing patients to unnecessary side effects of mood stabilizers. They identified the clinical characteristics of patients with unipolar depression who are likely to be diagnosed with bipolar disorder, including comorbid personality disorder, drug abuse or dependence, a more chronic and severe course of illness, and greater psychosocial impairment.[11]

These reports argue for the need to diagnose bipolar disorder accurately, using thorough diagnostic evaluations, in order to minimize the risk of underdiagnosis or overdiagnosis. However, this is not always easily done in clinical practice, where sensitive assessment instruments are clearly warranted.

In the last decade, the Spectrum Collaborative Project has developed a dimensional view of the mood spectrum as a unitary phenomenon that is best understood from a longitudinal perspective.[12] This assessment gives clinical significance not only to classical symptoms of full-blown mood episodes but also to atypical symptoms, behavioral traits, and temperamental features typically associated with mood disorders, arguing that mood symptoms and traits may occur throughout life, sometimes in isolation rather than as part of a temporally circumscribed clinical syndrome.[13,14] In an earlier study based on this unitary conceptualization of mood disorders, we demonstrated that many patients with recurrent major depression without discrete lifetime hypomanic *episodes* nonetheless report the lifetime experience of hypomanic-manic *symptoms* and that the number of such symptoms reported over the course

For Clinical Use

- Our results support the role of lifetime psychomotor activation, as assessed by the Mood Spectrum Self-Report instrument, as the best discriminator of bipolar disorder from unipolar disorder.
- The mixed instability factor contributed to the discrimination of bipolar from unipolar disorder in patients with intermediate levels of psychomotor activation.
- Elevated mood (the euphoria factor) contributed to discrimination of bipolar from unipolar disorder in patients with low psychomotor activation scores.
- The suicidality factor further discriminated bipolar from unipolar disorder.

Table 1. Sociodemographic and Clinical Characteristics of Study Populations

Variable	Kupfer et al[35]	Sbrana et al[36]	Frank et al[33]	Pini et al[37]	Maj[a]
N	330	146	337	238	107
Age, mean (SD) range, y	41.4 (11.8) 19–67	39.9 (12.0) 19–66	38.8 (12.1) 18–65	42.2 (12.1) 18–68	46.0 (12.8) 20–69
Female, %	63.3	61.6	71.2	67.6	56.1
Inclusion criteria					
Sex	M/F	M/F	M/F	M/F	M/F
Age, y	Adult	Adult	18–66	Adult	Adult
Mood disorder	Bipolar	Any	Unipolar	Any	Any
Phase	Any	In remission	Acute	In remission	In remission
Interview	SCID	SCID	SCID	SCID	SCID
Diagnosis, n					
Unipolar	NA	82	337	113	39
Bipolar I	249	55	NA	62	43
Bipolar II	69	9	NA	63	25
Bipolar NOS	12	NA	NA	NA	
Site	United States	Italy	United States, Italy	Italy	Italy

[a]Unpublished data.
Abbreviations: *DSM-IV-TR* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, F = female, M = male, NA = not applicable, SCID = Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders.

of a lifetime is related to the number of lifetime depressive symptoms reported.[15,16] To further increase the potential utility of this assessment and to better understand the constituent parts of the mood spectrum, we examined the factor structure of the lifetime mania/hypomania spectrum and the lifetime depressive spectrum. Using a classical exploratory factor analysis, we identified 5 factors of the lifetime manic/hypomanic spectrum and 6 factors of the lifetime depressive spectrum.[17,18] This, in turn, led us to consider whether any of these factors or combinations of factors could, first, discriminate individuals with a diagnosis of bipolar disorder from those with a unipolar diagnosis and could ultimately be used to identify prospectively those depressed patients likely to develop mania or hypomania in the future and thus reduce the long delay to correct diagnosis experienced by the majority of individuals with bipolar disorder.

The aim of the present report is to determine which combination of demographic, clinical, and lifetime psychopathology factors derived from the Mood Spectrum Self-Report Instrument (MOODS-SR)[16] and corresponding cutoff scores best discriminated patients with unipolar disorder from those with bipolar disorders.

METHOD

Sample

The sample consisted of 1,158 adult outpatients and inpatients with a diagnosis of unipolar or bipolar disorder, as determined by the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition (SCID-I/P),[19] participating in 5 studies conducted in the United States and Italy between October 2001 and March 2008. All studies were approved by the local ethics committees, and patients signed a written informed consent to participate. The demographic and clinical characteristics of this cross-national study sample are presented in Table 1. Of the 587 patients with bipolar disorders, 232 (39.5%) were acutely ill at the time of assessment with the MOODS-SR. The polarity of the current episode was depressive (N = 161), hypomanic (N = 18), manic (N = 41), and mixed (N = 12). Of the 571 patients with unipolar disorder, 337 (59.0%) were acutely ill at the time of assessment.

Measures

All study participants' diagnoses were confirmed by SCID-I/P conducted by experienced research clinicians. Participants completed the Lifetime MOODS-SR[16] at their baseline evaluation. The MOODS-SR consists of 154 items exploring depressive and manic/hypomanic mood, cognition, and energy symptoms and 7 items that explore the degree of impairment associated with the specific symptoms in each of the 7 domains. Each item is coded as present or absent for 1 or more periods of at least 3 to 5 days in the respondent's lifetime. Only the 154 symptom items are used for the scoring. The instrument and the scoring algorithm can be downloaded from the Web site,

Table 2. Content and Range of Scores of the 11 Mood Spectrum Factors Included in the Classification-Tree Analysis[a]

Mania-Hypomania Spectrum Factors			Depressive Spectrum Factors		
Factor	Score Range	Characteristics	Factor	Score Range	Characteristics
Psychomotor activation	1–14	Increased energy levels and activity, crowded or racing thoughts, shifting interests, talkativeness	Depressive mood	1–22	Depressed mood, loss of interests, loneliness, and anhedonia
Mixed instability	1–8	Sexual promiscuity, alcohol-related mood changes and irritability, frequently changing jobs, residences, friends, and hobbies	Psychomotor retardation	1–14	Psychomotor retardation in different areas of daily activities, physical weakness, and tiredness
Spirituality/mysticism/psychoticism	1–7	Ecstatic experiences and psychotic symptoms of mania	Suicidality	1–6	Suicidal ideation, plans, and attempts
Mixed irritability	1–7	Irritability associated with the use of medications and medical illnesses	Drug-/illness-related depression	1–5	Tendency to feel depressed when ill or after having taken substances
Euphoria	1–5	Mood elevation, high sense of humor, feeling persistently good or high	Psychotic spectrum features	1–6	Paranoid thoughts and hostility
			Neurovegetative symptoms	1–12	Sleep disturbance and sex and eating problems

[a]Data from Cassano et al.[17,18]

www.spectrum-project.org. Twelve items belonging to the rhythmicity/vegetative function domain were not used for the 2-factor analyses described below or for the analyses reported in the present article.

Five mania/hypomania factors (*psychomotor activation, mixed instability, spirituality/mysticism/psychoticism, mixed irritability,* and *euphoria*) were derived in a factor analysis of 68 mania/hypomania spectrum items (including 6 items exploring manic neurovegetative features)[18] and 6 depression factors (*depressive mood, psychomotor retardation, suicidality, drug/illness-related depression, psychotic spectrum features*, and *neurovegetative symptoms*) were derived in a second factor analysis of 74 depression spectrum items (including 12 items exploring depressive neurovegetative features).[17] The content of these factors is summarized in Table 2.

Demographic and clinical characteristics that in previous research proved to play a relevant role in the unipolar/bipolar distinction,[7] such as sex, age at onset, and anxiety comorbidity, were collected as part of the SCID-I/P.

Statistical Analyses

To determine which combination of clinical, demographic, and psychopathological factors and corresponding cutoff scores best distinguished persons with bipolar from unipolar disorders, data were analyzed using a chi-squared automatic interaction detection (CHAID) procedure. The CHAID is an exploratory procedure that derives decision trees to predict a categorical classification from a number of predictor variables. Different from discriminant analysis, CHAID is a nonparametric technique that does not rely on assumptions about linear relationships between the dependent and the independent variables. The classification tree is a graphic representation of a series of decision rules.[20] Beginning with a root node that includes all cases, the tree branches and grows iteratively by identifying optimal cutpoints for key discriminating variables in the predictor set. The best discriminating predictor is selected first, and then subsequent predictors are entered into the procedure if they contribute significantly to subtyping cases into homogeneous groups. The tree grows until a stopping criterion is met or no further significant improvement in correct classification of study participants is possible. In the terminal nodes (the "leaves" of the tree), a grouping of cases is obtained, such that the cases are as homogeneous as possible with respect to the value of the dependent variable. We also examined the importance to the classification-tree model for each of the spectrum factors and demographic and clinical variables. This measure is expressed in percentages and indicates how strongly a variable acts as a primary predictor.

In order to validate the classification tree so obtained, a cross-validation procedure was used.[21] All analyses were carried out using SPSS, version 17.0 (SPSS, Inc, Chicago, Illinois).

RESULTS

The MOODS-SR *psychomotor activation* factor was identified by the iterative classification-tree procedure as the factor best discriminating participants with a bipolar disorder diagnosis from those with a unipolar disorder diagnosis.

The scores of 0 to 7, 8 to 9, 10 to 11, and ≥12 on psychomotor activation distinguished 4 subgroups with an increasing likelihood of bipolarity (27.5%, 61.1%, 80.5%, and 96.5%, respectively), or, in other words, with increasing positive predictive value (Figure 1). In the 2 extreme groups, the cutoff score of 12 or more separated a subgroup consisting of 96.5% of patients with bipolar disorder, and a cutoff score of 7 or less distinguished a subgroup consisting of 72.5% of patients with unipolar disorder. Both these subgroups were better discriminated than in the original sample, which comprised 50.7% with bipolar and 49.3% with unipolar disorder. Discrimination was further improved in the subgroup with low psychomotor activation with consideration of sex, euphoria, and anxiety comorbidity.

In women, the subgroup endorsing 0 or 1 euphoria items over their lifetime had a higher likelihood of unipolar disorder compared to the subgroup endorsing ≥ 2 items (84.7%

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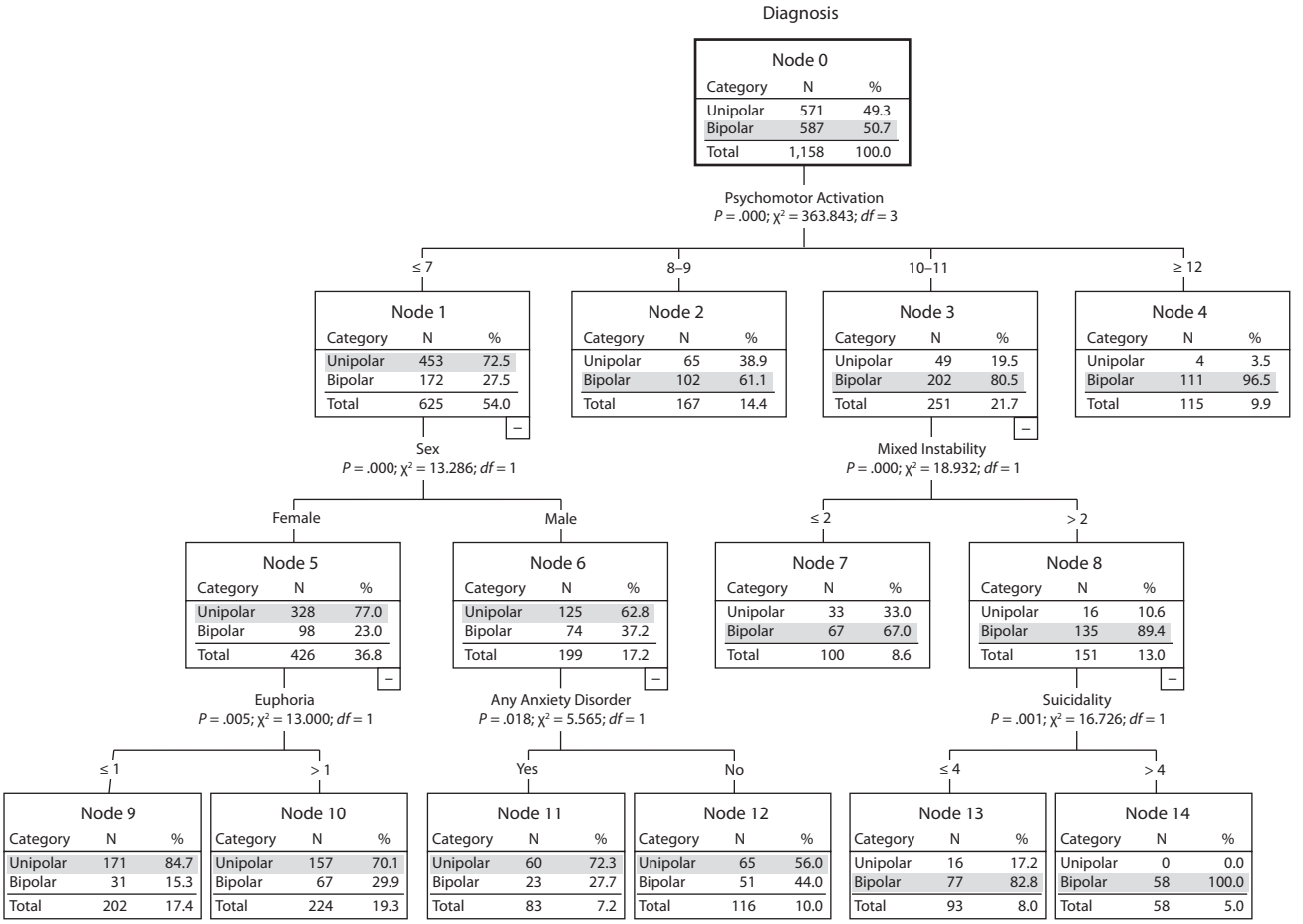
Figure 1. Results From CHAID Analyses for Discrimination of Patients With Bipolar Disorder From Those With Unipolar Disorder[a,b,c]



[a]The scores reported in the row characterize specific subgroups of patients. The cutoff points are determined using the χ^2 statistic, with a Bonferroni correction to the probability level. [b]The shaded diagnosis is the most frequent in each node. [c]All *P* values are adjusted for Bonferroni corrections.
Abbreviation: CHAID = chi-squared automatic interaction detection.

vs 70.1%). In men, the unipolar disorder diagnosis was more likely in the presence of anxiety comorbidity (72.3% vs 56.0%).

Conversely, in the subgroup with intermediate levels of psychomotor activation (a score of 10 or 11), better prediction of the classification of bipolar disorder was achieved by adding information on mixed instability and suicidality. In the subgroup with a score of > 2 on mixed instability and > 4 on suicidality (node 10), the diagnosis of bipolar disorder was virtually certain (100%). This cutoff on suicidality identifies patients who reported having made a suicide attempt that required medical attention.

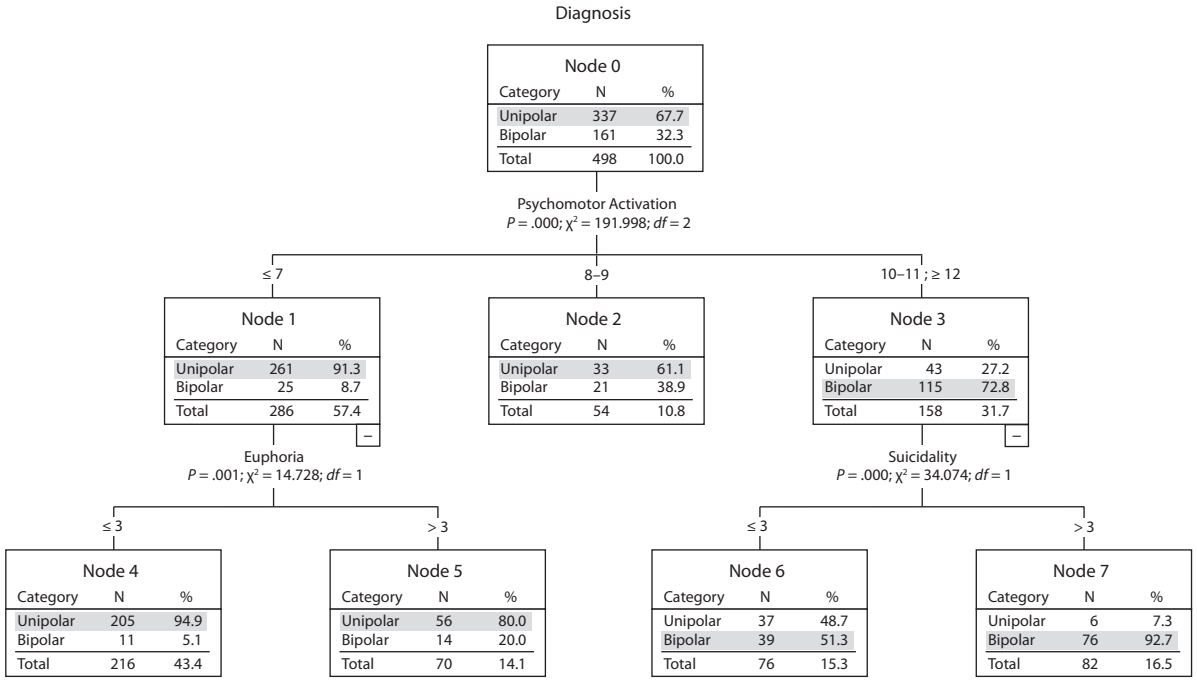
The subgroup of 167 participants with a score on psychomotor activation of 8 or 9 (14.4% of the study sample, node 2) appears to be the one in which the diagnostic discrimination is most problematic.

The extreme nodes of the tree (nodes 4, 9, and 14) were those in which the difference between patients with unipolar and bipolar disorders was maximized. Only 4 patients with unipolar depression were allocated to node 4, which included a large majority of patients with bipolar disorders, and 31 patients with bipolar disorder were allocated to node 9, in which the likelihood of unipolar disorder was the highest. Overall, the cross-validated percentage of patients allocated to the correct diagnostic group by the classification tree was 75.0% (79.3% unipolar, 70.7% bipolar).

We then examined the extent to which the MOODS-SR spectrum factors enabled us to distinguish unipolar disorder (N = 571) from bipolar II disorder (N = 166). The variables selected by the classification-tree procedure included psychomotor activation, mixed instability, and mixed irritability. The model was very good in ruling out bipolar II disorder and, overall, correctly classified 80.7% of cases. The risk of overdiagnosing unipolar depression as bipolar II disorder was very low (4.4%).

We carried out further analyses by restricting the sample to acutely ill patients with unipolar (N = 337) and bipolar depression (N = 161). The classification-tree analysis (Figure 2) again identified psychomotor activation as the best discriminating variable. The "risk" of bipolarity increased as a function of the psychomotor activation score from 8.7% (score ≤ 7) to 72.8% (score ≥ 10). The tree further branched

Figure 2. Results From CHAID Analyses for Discrimination of Patients With Bipolar Depression From Those With Unipolar Depression in the Acute Phase[a,b,c]



[a]The scores reported in the row characterize specific subgroups of patients. The cutoff points are determined using the χ^2 statistic, with a Bonferroni correction to the probability level. [b]The shaded diagnosis is the most frequent in each node. [c]All *P* values are adjusted for Bonferroni corrections
Abbreviation: CHAID = chi-squared automatic interaction detection.

according to the suicidality and euphoria scores. Patients with a score ≥ 10 on psychomotor activation and a history of suicidal behavior had a 92.7% probability of being diagnosed with bipolar disorder. Patients with a score ≤ 7 on psychomotor activation and a score ≤ 3 on the euphoria factor had a probability of 94.9% of being diagnosed with unipolar disorder.

Lastly, we examined the impact of clinical status on the response to the MOODS-SR in unipolar depression by comparing the scores on psychomotor activation, mixed irritability, instability, euphoria, and suicidality between those who were acutely ill at the point of MOODS-SR completion (n = 337) and those in remission (n = 234). No significant differences were found using the *t* test for euphoria, suicidality, and mixed irritability, while scores on psychomotor activation and mixed instability were significantly higher in the acutely ill group than in the group in remission (mean ± SD psychomotor activation scores: 5.1 ± 3.2 vs 4.4 ± 3.1, *t* test = 2.7, $P < .01$;. mean ± SD mixed instability scores: 1.6 ± 1.6 vs 1.1 ± 1.5, *t* test = 3.9, $P < .01$).

DISCUSSION

Compared with the broad extant literature on distinguishing clinical and psychopathological features of unipolar and bipolar disorders that have examined individual indicators of bipolar diathesis, the present report attempts to determine which combinations of factors confer a higher likelihood of bipolarity using a classification-tree analysis. Although this technique is exploratory in nature and requires confirmation in separate samples, we found evidence that the lifetime experience of *psychomotor activation* as assessed by the MOODS-SR is the most potent discriminator of the bipolar versus unipolar disorder diagnosis. In particular, the cutoff score of ≥ 12 separated a subgroup with an extremely high likelihood of bipolarity. Given the proposal of the *DSM-5* Mood Disorders Work Group to give a more prominent place to increased activity and energy in the definition of mania and hypomania with the idea that doing so might increase the correct and early identification of those with bipolar disorder (www.dsm5.org), our findings provide an important empirical confirmation of the role that the experience of psychomotor activation might play in discriminating these 2 types of mood disorders.

Our results are consistent with the recommendations of Angst et al[22] and Akiskal et al[23] that increased activity and energy are the key discriminators of the bipolarity. Both research groups have argued that the stem question on mood (euphoric or irritable) in the mania/hypomania section of the SCID-I/P and the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) is less than ideal for identifying those with a history of or current mania/hypomania. Likewise, they have pointed out the need to focus on acceleration (as opposed to agitation[24–26]) in making this discrimination.[23] For example, in the Ravenna-San Diego collaborative study, Benazzi and Akiskal[27] found that bypassing the mood question and inquiring first about the behavioral activation signs

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and symptoms of hypomania better identified those with bipolar II disorder. These authors suggest that, after such activation symptoms are elicited, patients can then be queried about mood changes, because they are likely to remember that they were irritable or euphoric during such activated periods.

In our analysis, the *mixed instability* factor also contributed to the discrimination of bipolar from unipolar disorder in patients with intermediate levels of psychomotor activation. This factor might be thought of as representing some aspects of what Hantouche et al[28] and Akiskal et al[23] have referred to as the "dark" side of mania and includes behaviors that frequently lead to impaired social relations in the context of mania and hypomania. Of note, the presence of elevated mood (the *euphoria* factor) that is the main *DSM-IV-TR* criterion for mania proved to be useful only to subtype patients with low *psychomotor activation* scores.

The suicidality factor contributed to further discriminating patients with bipolar disorder, consistent with evidence that adults with bipolar disorder are at very high risk for suicidal ideation, nonfatal suicidal behaviors, and suicide.[7]

Of the demographic and clinical variables selected as putative indicators of bipolarity, including sex, age at onset, and anxiety comorbidity, only sex and comorbidity played a role in discriminating subtypes of patients with unipolar disorder among those with a score ≤7 on psychomotor activation. Women endorsing a maximum of 1 euphoria symptom over the lifetime had a higher likelihood of unipolar disorder compared to those endorsing 2 or more symptoms. In men, the unipolar disorder diagnosis was more likely in the presence of anxiety comorbidity.

Our classification-tree strategy is consistent with the probabilistic approach to the detection of bipolar disorder of Mitchell et al[29] and is partly at variance with other studies showing that self-report instruments are useful to rule out the diagnosis of bipolar disorder but not to rule it in.[30] Existing instruments designed to judge whether bipolar disorder is present or absent, such as the Mood Disorder Questionnaire and the Bipolar Spectrum Diagnostic Scale, proved to have positive predictive values in adult outpatient populations that increase as a function of the prevalence of bipolar disorder and achieve estimated values between 0.63 and 0.88 when the prevalence is 50%, as in our sample.[31]

The assignment of a number of patients with unipolar depression to the subgroups with higher scores on psychomotor activation may be interpreted either as model misclassification or as an indication that this factor captures a lifetime subthreshold bipolarity overlooked by standardized diagnostic assessments that focus almost exclusively on current symptoms. It would be highly desirable to be able to identify those patients initially diagnosed with unipolar depression who are likely to develop mania or hypomania in the future, since the most frequent course of bipolar disorder is one in which manic or hypomanic episodes follow an initial episode of depression.[32] In one of the studies used for the present report,[33] we obtained a small amount of data suggesting that such an identification may be possible. In this study, we entered data for patients with unipolar disorder diagnosed according to the SCID-I/P. During the course of this study, 9 patients (8 being treated with selective serotonin reuptake inhibitors and 1 being treated with interpersonal psychotherapy) developed an episode of mania or hypomania. When we examined their *pretreatment* factor scores, we found that 8 of 9 exceeded at least 1 of the thresholds on psychomotor activation, mixed instability, or suicidality obtained in our first classification-tree analysis, suggesting the potential of this instrument to predict the onset on mania or hypomania.

Several caveats need consideration in interpreting our results. First, the clinical status of patients has a potential impact on the reliability of their report of lifetime signs and symptoms. To this purpose, we examined the difference in factor scores between unipolar patients in the acute phase of the illness and those in remission and found no differences or differences less than 1 point on the factors that discriminate patients with unipolar disorder from those with bipolar disorder. Moreover, poor insight into mania may limit the reliability of self-report scales. However, as we demonstrated earlier, the clinical status of patients with bipolar disorder does not appear to affect the way patients complete self-report spectrum instruments.[34] Second, the impact of other indicators of bipolarity, such as the number of depressive episodes or the family history of bipolar disorder, could not be assessed, because this information was either unavailable or not collected consistently across studies.

Future directions exploring the utility of this approach include (1) a replication study in an independent sample of individuals with well-established unipolar and bipolar diagnoses, (2) confirming the predictive validity of these items (in terms of risk for hypomania or mania associated with antidepressants) in patients diagnosed with unipolar disorder, and (3) discriminating psychiatrically healthy youth with and without a family history of bipolar disorder.

If the results of our classification-tree analysis were replicated in an independent sample and if there were evidence that these items discriminate at-risk individuals, use of either the 33 items making up the *psychomotor activation, mixed instability*, *suicidality,* and *euphoria* factors or just the 14 items of the *psychomotor activation* factor might be used to develop a screening tool for identifying those with a probable diagnosis of bipolar disorder. Given the often long delay to correct diagnosis of bipolar disorder, adding such an efficient method to our diagnostic armamentarium would seem well worth the effort.

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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