



Research report

The Bipolarity index: a clinician-rated measure of diagnostic confidence

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ABSTRACT

Background: The Bipolarity Index is a clinician-rated scale that rates cardinal features of the disorder across five domains: signs and symptoms, age of onset, course of illness, response to treatment, and family history. We tested the Index in routine clinical practice to identify the optimal cut-off for distinguishing bipolar from non-bipolar disorders.

Method: Sequential patients in a private practice were rated with the Bipolarity Index ($n=1903$) at intake. Diagnoses were made with the MINI-6.0.0 International Neuropsychiatric Interview according to DSM-IV-TR criteria, except that cases of antidepressant-induced mania and hypomania were included in the bipolar group. A subset completed the self-rated Mood Disorder Questionnaire (MDQ) ($n=1620$) or Bipolar Spectrum Diagnostic Scale (BSDS) ($n=1179$).

The primary analysis compared Bipolarity Index scores for bipolar vs. non-bipolar patients using receiver operator curves (ROC) to determine the optimal cut-off score. Secondary outcomes repeated this analysis with the MDQ, MDQ-7 (using only the symptomatic items of the MDQ) and BSDS.

Results: At a cut-off of ≥ 50 , the Bipolarity Index had a high sensitivity (0.91) and specificity (0.90). Optimal cut-offs for self-rated scales were: MDQ: ≥ 7 (sensitivity 0.74, specificity 0.71); MDQ-7: ≥ 6 (sensitivity 0.77, specificity 0.77); BSDS: ≥ 12 (sensitivity 0.71, specificity 0.77).

Limitations: The study utilized one rater at a single practice site; the rater was not blinded to the results of the MINI.

Conclusion: The Bipolarity Index can enhance the clinical assessment of mood disorders and, at a score ≥ 50 has good sensitivity and specificity for identifying bipolar disorders.

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1. Introduction

The diagnosis of bipolar disorder is a topic of controversy, with studies supporting both under-diagnosis (Akiskal et al., 2006; Benazzi, 1997; Dubovsky et al., 2011; Hantouche et al., 1998; Hirschfeld et al., 2005; Hirschfeld et al., 2003; Kim et al., 2008; Manning et al., 1997) and over-diagnosis (Goldberg et al., 2008; Zimmerman et al., 2008 and Zimmerman et al., 2010) of the condition. Underlying this debate is an inherent uncertainty in the diagnosis, which depends on the detection of manic symptoms that are too often poorly recalled, or, at the onset of the condition, have not yet appeared (Angst, 2006 and Látalová, 2012).

Ideally, clinical assessment balances sensitivity and specificity in a manner optimized for a specific purpose. For example, sensitivity would be favored in clinical practice and specificity in a research setting. Several studies illustrate how difficult this balance is to achieve with current diagnostic criteria. In the DSM-5 field trials, two centers renowned for their expertise in bipolar disorder produced disparate results when applying the bipolar I criteria, with reliability measures considered “very good” at one center and “questionable” at the other (Regier et al., 2013). In the NIMH Collaborative Depression Study, which rigorously screened for bipolar disorder, 10% of subjects originally diagnosed as unipolar were found to have bipolar disorder after a 10-year follow-up (Coryell et al., 1995). A 20-year follow-up study of patients hospitalized for unipolar depression found that 39% had converted to bipolar disorder (Angst et al., 2005).

Acknowledging diagnostic uncertainty and recognizing patients who are at risk for diagnostic conversion to bipolar disorder is a start to resolving this dilemma. In 2004, Sachs et al. created the Bipolarity

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The Bipolarity Index

Directions: Circle the bulleted items that are positive in the patient's history. Score each of the five sections by circling the highest number (0–20) for which there is at least one positive item. The final score is the sum of all five sections.

| I. Episode Characteristics | |
|--|---|
| 20 | • Acute manic or mixed episode with prominent euphoria, grandiosity or expansiveness and no significant medical or other secondary etiology. |
| 15 | • Acute mixed episode or dysphoric or irritable mania with no significant medical or other secondary etiology. |
| 10 | • Hypomanic episode with no significant medical or other secondary etiology; or • Cyclothymia with no significant medical or other secondary etiology; or • A manic episode within 12 weeks of starting an antidepressant. |
| 5 | • A hypomanic episode within 12 weeks of starting an antidepressant • Episodes with characteristic symptoms of hypomania, but symptoms, duration, or intensity are subthreshold for hypomania; or • A single MDE with psychotic or atypical features (atypical is ≥ 2 of the following: hypersomnia, hyperphagia or leaden paralysis of limbs); or • Any postpartum depression. |
| 2 | • Recurrent unipolar major depressive disorder (≥ 3 episode); or • History of any kind of psychotic disorder (i.e., presence of delusions, hallucinations, ideas of reference or magical thinking). |
| 0 | • No history of significant mood elevation, recurrent depression or psychosis. |
| II. Age of Onset (first affective episode or syndrome) | |
| 20 | • 15 to 19 years. |
| 15 | • Before age 15 or between age 20 and 30. |
| 10 | • 30 to 45 years. |
| 5 | • After age 45. |
| 0 | • No history of affective illness (no episodes, cyclothymia, dysthymia or bipolar-NOS). |
| III. Course of Illness & Associated Features | |
| 20 | • Recurrent, distinct manic episodes separated by at least 2 months of full recovery. |
| 15 | • Recurrent, distinct manic episodes with incomplete inter-episode recovery; or • Recurrent, distinct hypomanic episodes with full inter-episode recovery. |
| 10 | • Any substance use disorder (excluding nicotine/cafeine); or • Psychotic features only during acute mood episodes; or • Incarceration or repeated legal offenses related to manic behavior (e.g. shoplifting, reckless driving or bankruptcy). |
| 5 | • Recurrent unipolar MDD with ≥ 3 or more major depressive episodes; or • Recurrent, distinct hypomanic episodes without full inter-episode recovery; or • Borderline personality disorder, anxiety disorder (including PTSD and OCD), eating disorder; or history of ADHD with onset before puberty; or • Engagement in gambling or other risky behaviors with the potential to pose a problem for patient, family or friends; or • Behavioral evidence of perimenstrual exacerbation of mood symptoms. |
| 2 | • Baseline hyperthymic personality when not manic or depressed; or • Marriage 3 or more times (including remarriage to the same individual); or • In two or more years, has started a new job and changed jobs after less than a year; or • Has more than two advanced degrees. |
| 0 | • None of the above. |
| IV. Response to Treatment | |
| 20 | • Full recovery within 4 weeks of therapeutic treatment with a mood stabilizer. |
| 15 | • Full recovery within 12 weeks of therapeutic treatment with a mood stabilizer or relapse within 12 weeks of discontinuing treatment; or • Affective switch to mania (pure or mixed) within 12 weeks of starting a new antidepressant or increasing dose. |
| 10 | • Worsening dysphoria or mixed symptoms during antidepressant treatment subthreshold for mania (exclude worsening that is limited to known antidepressant side effects such as akathisia, anxiety or sedation); or • Partial response to one or two mood stabilizers within 12 weeks of therapeutic treatment; or • Antidepressant-induced new or worsening rapid-cycling course. |
| 5 | • Treatment resistance: lack of response to complete trials of 3 or more antidepressants; or • Affective switch to mania or hypomania with antidepressant withdrawal. |
| 2 | • Immediate, near-complete response to antidepressant withdrawal within 1 week or less. |
| 0 | • None of the above, or no treatment. |
| V. Family History | |
| 20 | • At least one first-degree relative with clear bipolar disorder. |
| 15 | • At least one second-degree relative with clear bipolar disorder; or • At least one first-degree relative with recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder. |
| 10 | • First-degree relative with recurrent unipolar MDD or schizoaffective disorder; or • Any relative with clear bipolar disorder or recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder. |
| 5 | • First-degree relative with clear substance use disorder (excluding nicotine/cafeine); or • Any relative with possible bipolar disorder. |
| 2 | • First-degree relative with possible recurrent unipolar MDD; or • First-degree relative with anxiety disorder (including PTSD and OCD), eating disorder or ADD/ADHD. |
| 0 | • None of the above or no family history of psychiatric disorders. |
| ← Total score (0 – 100). Add the highest number in each section. A score ≥ 50 indicates a high probability of bipolar disorder. | |

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Fig. 1. The Bipolarity Index.

Index to provide a quantitative estimate of diagnostic confidence in bipolar disorder (Sachs, 2004). The scale is based on the work of Robins and Guze, who proposed a method of validating psychiatric disorders based on five illness dimensions: signs and symptoms, age of onset, course of illness, response to treatment, and family history

(Robins and Guze, 1970). The Bipolarity Index uses ordinal scales to assess each of these dimensions (see Methods and Fig. 1).

The Bipolarity Index has been applied in global clinical trials and other research settings (Campos et al., 2010; Del Debbio et al., 2007; Ford et al., 2013; Loebel et al., 2014; Mosolov et al., 2014;

Saatcioglu et al., 2011; Sachs et al., 2012a; Sachs et al., 2012b and Serhadli et al., 2008). Although some authors have recommended its use in clinical practice (Allilaire, 2010 and Phelps et al., 2008), there is no published data describing its use in routine clinical practice. This study presents the first report of performance metrics for the Bipolarity Index in an unselected clinical population.

2. Methods

2.1. Sample

Sequential patients from an outpatient psychiatric practice specializing in mood disorders who presented for intake between November 2009 and December 2014 with the principal author (C. Aiken) were included in the initial sample ($n=1903$). Patients with the following diagnoses were excluded from analysis: schizophrenia ($n=8$), schizoaffective ($n=20$), mental retardation ($n=3$), dementia ($n=3$), and psychiatric disorder due to a general medical condition ($n=16$). Two patients were excluded due to inability to participate in a full psychiatric interview, leaving 1851 patients for the final analysis.

2.2. Procedures

All subjects were interviewed with the MINI-6.0.0 International Neuropsychiatric Interview to validate the diagnoses (Sheehan et al., 1998) in those less than age 18 ($n=82$) the MINI-KID was used (Sheehan et al., 2010). A subset of these patients completed the self-rated Mood Disorder Questionnaire ($n=1620$) (Hirschfeld et al., 2000) and Bipolar Spectrum Diagnostic Scale ($n=1179$) (Ghaemi et al., 2005). The Mood Disorder Questionnaire was modified to the Mood Disorder Questionnaire-7 version by including only the 13 symptomatic items (Benazzi, 2003). Information about past mood states was gathered from close friends or relatives using modified versions of these self-rated scales in 889 patients (48%) (Aiken C, manuscript in preparation). Final diagnoses were made using DSM-IV-TR criteria, including a minimum of four days duration for hypomania. The bipolar-NOS category was limited to patients with antidepressant-induced mania or hypomania who did not otherwise qualify for a full diagnosis of DSM-IV-TR bipolar disorder (in DSM-5 these patients would be categorized as full bipolar disorder).

In conducting the MINI, patients were asked all sub-items on the mania scale in addition to the core-criteria of elevated or irritable mood. In cases where sub-items for mania were endorsed but the core symptoms were denied, the core symptoms on the MINI were revisited using hyperactivity in place of elevated mood (Akiskal and Benazzi, 2005).

2.3. The Bipolarity Index

The Bipolarity Index (Fig. 1) is a clinician-rated instrument that is scored using all available clinical information for each of the five dimensions on a 0–20 ordinal rating, where higher scores correspond to items considered most characteristic of bipolar disorder. The weighting of items on the ordinal scale was obtained by Delphi method using a panel of experts (Sachs G., Baldassano C., Ghaemi S.N. and Demopoulos C.) to achieve consensus rankings and as such has high face validity.

The Bipolarity Index was scored at the end of the intake assessment using all available clinical information. We applied standardized definitions for atypical depression (≥ 2 of the following: hypersomnia, hyperphagia, leaden paralysis of limbs) and recurrent depression (≥ 3 episodes) provided by the scale. In identifying sub-threshold hypomania, we included patients with

behavioral evidence of manic states (e.g. frequent impulsivity) who did not endorse DSM-IV symptoms of hypomania, and those with a recurrent pattern of hypomanic symptoms that did not cross the DSM-IV threshold for diagnosis.

Age of onset (Section II) was assessed by asking the patient to recall the first age at which their manic or depressive symptoms appeared. We used DSM-IV definitions to assess the disorders in Section III. Response to treatment (Section IV) was assessed using the Clinical Global Impression Scale for Improvement (Guy, 1976).

Family history was assessed by interviewing the patient with Section V of the Bipolarity Index. This section assigns greater weight to relatives who have “documented bipolar illness” than to those with “behavioral evidence suggesting bipolar disorder.” Clinical judgment was used to differentiate these two categories. The “documented bipolar illness” category was used when there was strong evidence for bipolar disorder in a relative but historical diagnostic standards or cultural factors would have limited the recognition of the diagnosis. For example, patients describing a relative as having symptoms of bipolar disorder who had been diagnosed with schizophrenia prior to 1970 (Wing, 1971).

2.4. Statistical analysis

Receiver operator curves (ROC) have been used since the 1940s to identify cut-off points with the optimal balance of sensitivity and specificity for a diagnostic test. The curves are created by comparing test results for those who have the diagnosis in question to those who do not. For our primary analysis, we compared Bipolarity Index scores for patients with DSM-IV bipolar disorder (bipolar I, bipolar II and cyclothymia) to those with a non-bipolar diagnosis. As a secondary analysis, we performed the same procedure with the Mood Disorder Questionnaire-7 and the Bipolar Spectrum Diagnostic Scale.

ROCs were generated using ROCKIT software (Metz et al., 1998) and fitted with the proper-binormal model. The optimal cut-off score was chosen using the Youden index, which corresponds to the maximum sum of the sensitivity and specificity (Pepe, 2004; Perkins and Schisterman, 2006).

3. Results

Patient characteristics of the final sample are presented in Table 1. Mean scores for the Bipolarity Index, Mood Disorder Questionnaire-7, and Bipolar Spectrum Diagnostic Scale are listed by DSM-IV diagnostic group in Table 2.

3.1. Receiver operator curves

Fig. 2 shows the ROC for the Bipolarity Index when it is used to compare scores of bipolar vs. non-bipolar patients. The Area Under the Curve (AUC), which provides an estimate of how well the scale distinguishes bipolar from non-bipolar diagnoses, was

Table 1
Demographic characteristics ($n=1851$).

| Age, mean \pm SD | 37 \pm 15 | Percent (%) |
|---|-------------|-------------|
| Female | 1127 | 60.89 |
| Male | 724 | 39.11 |
| Caucasian | 1614 | 87.20 |
| African American | 194 | 10.48 |
| Hispanic | 25 | 1.35 |
| Asian | 16 | 0.86 |
| Native Hawaiian or other Pacific islander | 1 | 0.05 |
| American Indian or Alaska native | 1 | 0.05 |
| Other race | 0 | 0.00 |

0.97 (where 1 = a perfect scale and 0.5 = a useless scale). The cut-off point on the Bipolarity Index with the highest Youden index (1.81) was 50, and this corresponded to a sensitivity of 0.91 and specificity of 0.90.

Table 3 shows ROC characteristics for the Bipolarity Index, Mood Disorder Questionnaire-7 and Bipolar Spectrum Diagnostic Scale.

Table 2
Bipolarity Index and self-report measures by diagnostic group.

| Diagnosis | Percent (%) | Bipolarity Index mean \pm SD | Mood Disorder Questionnaire, mean \pm SD | Bipolar Spectrum Diagnostic Scale, mean \pm SD |
|-------------------------------------|-------------|--------------------------------|--|--|
| Bipolar I | 17.50 | 79 \pm 12 | 9 \pm 3 | 16 \pm 7 |
| Bipolar II | 22.10 | 60 \pm 11 | 8 \pm 3 | 15 \pm 6 |
| Cyclothymic disorder ^a | 1.30 | 56 \pm 11 | 8 \pm 3 | 13 \pm 4 |
| BP-NOS ^b | 2.70 | 51 \pm 13 | 5 \pm 3 | 9 \pm 5 |
| Major depression, recurrent | 30.20 | 37 \pm 11 | 4 \pm 3 | 8 \pm 6 |
| Major depression, \leq 2 episodes | 14.42 | 27 \pm 10 | 4 \pm 3 | 7 \pm 6 |
| Dysthymic disorder ^a | 0.32 | 24 \pm 5 | 3 \pm 2 | 2 \pm 2 |
| Substance use disorder ^a | 0.59 | 18 \pm 9 | 3 \pm 3 | 4 \pm 4 |
| ADHD ^a | 4.38 | 12 \pm 9 | 5 \pm 3 | 5 \pm 6 |
| Personality disorder ^a | 0.11 | 12 \pm 3 | 5 \pm 0 | 5 \pm 0 |
| Adjustment disorder ^a | 0.76 | 5 \pm 7 | 2 \pm 3 | 6 \pm 4 |
| Other disorder ^a | 5.62 | 13 \pm 11 | 3 \pm 2 | 4 \pm 4 |

^a Without a comorbid mood disorder.

^b Antidepressant-induced mania or hypomania.

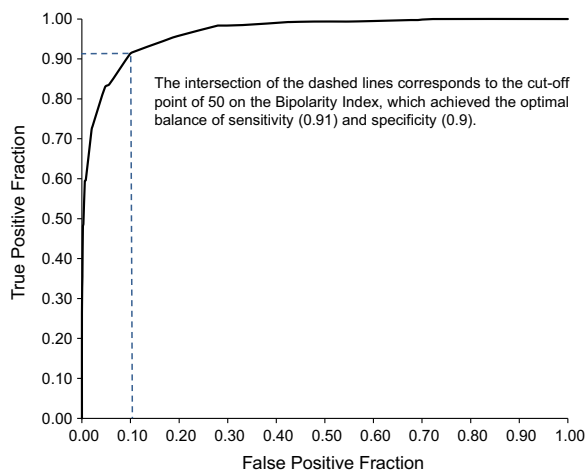


Fig. 2. Receiver operator curve for the Bipolarity Index in Bipolar vs. Non Bipolar patients

Table 3
Receiver operator curve characteristics for four bipolar rating scales.

| Scale | Cut-off | Sens | Spec | PPV | NPV | AUC |
|-----------------------------------|-----------|------|------|------|------|------|
| Bipolarity Index | \geq 50 | 0.91 | 0.90 | 0.88 | 0.93 | 0.97 |
| Mood Disorder Questionnaire | \geq 7 | 0.74 | 0.71 | 0.81 | 0.61 | 0.78 |
| Mood Disorder Questionnaire-7 | \geq 6 | 0.78 | 0.77 | 0.72 | 0.82 | 0.84 |
| Bipolar Spectrum Diagnostic Scale | \geq 12 | 0.71 | 0.77 | 0.69 | 0.79 | 0.81 |

Sens=sensitivity, Spec=specificity, PPV=positive predictive value, NPV=negative predictive value, AUC=area under the curve.

4. Discussion

The Bipolarity Index assigns a quantitative value signifying the degree to which a patient's history corresponds to the classic conception of bipolar disorder. This study suggests that a cut-off of \geq 50 provides the optimal balance between sensitivity (0.91) and specificity (0.90) for distinguishing bipolar from non-bipolar disorders with the Bipolarity Index. The area under the curve (0.97) was close to the ideal of 1, indicating the Bipolarity Index is a useful test for distinguishing bipolar from non-bipolar disorders. These results are consistent with a smaller study from Argentina which used similar methodology and arrived at a cut-off of \geq 50 for distinguishing personality disorders from bipolar disorders with the Bipolarity Index (specificity=0.88, sensitivity=0.90) (Apfelbaum et al., 2013).

This cut-off should serve as a bench-mark for interpreting the Index rather than a diagnostic rule. Patients who score close to the cut-off may be at risk for conversion to bipolar disorder or worsening on antidepressants. Higher scores reflect greater clarity in the diagnosis and may predict better outcomes with mood stabilizer treatment. For example, the STEP-BD study found that higher scores on the Bipolarity Index at intake were associated with better prognosis (Del Debbio et al., 2007).

The Bipolarity Index can also enhance a patient's collaboration with the diagnostic process. By presenting the diagnosis in probabilistic terms that logically build on evidence collected primarily from the patient, we have found that the Index can reduce the conflict that sometimes arises in conveying a bipolar diagnosis.

Among self-rated scales, the modified Mood Disorder Questionnaire-7 achieved greater sensitivity and specificity than both the full Mood Disorder Questionnaire and the Bipolar Spectrum Diagnostic Scale (although at an optimal cut-off of 6 rather than 7). This is consistent with other reports of improved performance after removal of the last two sections of the Mood Disorder Questionnaire, which assess clustering of symptoms and impairment (Benazzi, 2003; Lee et al., 2013).

4.1. Limitations

The main limitation is that the rater of the Bipolarity Index was not blind to the results of the MINI, which served as the gold standard for diagnosis. It would have been difficult to fully blind the rater to the results of the MINI since several sections of the Bipolarity Index are scored from the structured interview. This may limit the generalizability of the findings, but is ecologically consistent with the way the scale would be utilized in clinical practice.

Another limitation is the reliance on a single interviewer in one practice setting and the lack of longitudinal follow-up. A review of follow-up studies suggests that unipolar patients convert to a bipolar diagnosis at a rate of 1% per year (Angst et al., 2005). We might therefore expect to find a slightly lower cut-off point with longitudinal confirmation, and this would be a good area of future study. Future research with the scale might also identify which items are predictive of treatment response and of conversion from unipolar to bipolar disorder.

5. Conclusions

Our experience suggests the Bipolarity Index can be readily integrated into routine clinical practice. It provides a tool that both encourages systematic gathering of key diagnostic information and a scale for quantifying diagnostic confidence in bipolar disorder. Our data indicate that a cut-off of 50 on the scale

provides a good balance between sensitivity and specificity in identifying patients as having bipolar disorder with high confidence.

Conflict of interest

Disclosure of financial relationships and conflicts of interest:

1. Chris Aiken: none
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