Optimizing the Detection of Bipolar II Disorder in Outpatient Private Practice: Toward a Systematization of Clinical Diagnostic Wisdom

Hagop S. Akiskal, M.D., and Franco Benazzi, M.D.

Received April 5, 2004; accepted Dec. 17, 2004. From the International Mood Center, University of California, San Diego, and the VA Medical Center, Department of Psychiatry, San Diego, Calif. (Dr. Akiskal); and Hecker Psychiatry Research Center, Ravenna and Forli, Italy, and the Department of Psychiatry, National Health Service, Forli, Italy (Dr. Benazzi).

Drs. Akiskal and Benazzi report no financial or other relationships relevant to the subject matter of this article.

Corresponding author and reprints: Hagop S. Akiskal, M.D., VA Hospital, 3350 La Jolla Village Dr. (116-A), San Diego, CA 92161 (e-mail: hakiskal@ucsd.edu).

Background: We review a clinical diagnostic approach to validate a redefinition of bipolar II disorder (BPII), which bypasses several conservative steps in the DSM-IV Mood Module of the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) to make detection of BPII more "clinician-friendly."

Method: 563 consecutive private outpatients presenting with a DSM-IV–diagnosed major depressive episode (MDE) were included in the analyses. We used a modified SCID-CV in a semistructured way, used a duration of hypomania ≥ 2 days (rather than the 4-day floor cutoff recommended), did not follow the SCID-CV's stem (mood) skip-out instruction, focused more on past history of overactive behavior rather than mood change, and assessed hypomanic features both outside and during index MDE. Validation of BPII so-defined against major depressive disorder (MDD) was undertaken in the Washington University tradition. The study was conducted from June 1999 to December 2003.

Results: BPII occurred in 56.8% of patients. Compared with MDD, BPII had a significantly earlier index age and age at onset of first MDE and higher rates of atypical features, depressive recurrences, hypomanic symptoms during MDE, trait mood lability, and bipolar family history ($p = .0000$ for all variables).

Conclusions: Our experience suggests that when probing history for past hypomanic episodes, behavioral activation should be inquired first, thereby facilitating the patient's subsequent recall of euphoria and/or irritability during such activated periods. Information from significant others or past records is also crucial. In light of these clinical procedures, BPII emerged as more prevalent than MDD. We submit that clinicians have the distinct advantage of intimate knowledge of their patients, which, coupled with the procedures outlined herein, can maximize the yield of BPII diagnoses.

(J Clin Psychiatry 2005;66:914–921)

The pioneering study of Dunner and colleagues[1] delineated bipolar II disorder (BPII) in patients hospitalized for depressive episodes with history of less-than-manic features that had not required hospitalization. BPII first made formal entry into the DSM-IV[2] nearly 2 decades later, as a major depressive episode irrespective of hospitalization, plus history of hypomanic episodes without marked impairment in adaptive function. DSM-IV-TR[3] cites a community prevalence of bipolar II disorder of 0.5% based on Regier et al.[4] and Weissman et al.[5] Recent studies have reported much higher figures, finding a community prevalence of BPII 7 to 10 times higher than that of previous studies.[6–8] Yet, continuing clinical underdiagnosis of bipolar disorders is rampant, and this is particularly true for BPII.[9–12]

A PubMed/MEDLINE search (accessed Nov. 18, 2004) found 197 references for *bipolar II* and over 19,000 for *bipolar I* and *mania*. This gross neglect of BPII in the literature is due to several factors, all of which appear related to diagnostic ascertainment procedures for hypomania.[9,13–15] Low reliability of BPII diagnosis[16,17] is an important limitation of past studies. New studies have reported good reliability of diagnosis made by trained clinicians using semistructured interviews.[18,19] Frequency of BPII in outpatients with a major depressive episode (MDE) has been found to range from 30% to 60%.[9,20–25]

In this article, we review and integrate our experience reported in a series of analyses in the Ravenna-San Diego collaborative study[26–28] to validate a definition of BPII based on a minimum 2-day duration of hypomania and assessment methods of hypomania that do not strictly adhere to the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) guidelines[29] on how to elicit hypomanic mood change. As in our previous work, each of the foregoing procedures led to an incre-

ment in diagnostic accuracy; in the present analyses, we sought to find out the prevalence of BPII based on the cumulative clinical wisdom gained from combining these procedures.

METHOD

Overview of Diagnostic Procedures

The methodology of the series of analyses that form the basis of the present overview was designed by both authors. Many authorities now believe that mood disorder patients in tertiary care centers are not representative of the usual patients treated in clinical practice.[10,11,13,30,31] Private practice seems to be the preferred choice of affectively ill patients in Italy and in some settings in the United States.[13] Most people can visit a private psychiatrist in Italy, thereby reducing a selection bias related to income.

Systematic data gathering *as part of clinical routine* in mood clinics[32] has been championed by the senior author (H.S.A.). It was therefore natural for the 2 authors to collaborate on the present project conducted in F.B.'s outpatient private practice. F.B. is a mood disorder specialist with 20 years of practice experience.

Five hundred sixty-three consecutive outpatients with an MDE, presenting voluntarily for treatment from June 1999 to December 2003, were included in the present analyses. All diagnostic procedures and instruments described in the present methodology represent the systematic clinical routine of F.B.'s specialized mood-disorder–based practice. Patients routinely sign consent forms to be under the clinical care of F.B. No further consent is required by Italian law for data analyses based on existing data in the clinical charts of patients under one's care.

As our main objective was to focus on BPII, MDE patients with past mania (a rather uncommon type of patient in the F.B. setting) were excluded. We selected patients who were psychoactive-drug–free (with the exception of occasional use of benzodiazepines) for at least 2 weeks; current comorbid substance abuse patients with severe personality pathology were also excluded in order not to confound the diagnosis of BPII and mixed states.[13] At any rate, BPII and MDD patients with such comorbidity are uncommon in F.B.'s clinical setting.[33] Finally, we excluded from consideration affectively ill patients with clinically significant general medical illness and dementia.

During the first visit, F.B. interviewed all patients using the SCID-CV[29] and the Global Assessment of Functioning scale.[2] History of hypomania was always investigated soon after having made the diagnosis of MDE. In F.B.'s clinical routine, the diagnosis of BPII is made before the assessment of such variables as atypical features and familial bipolarity, which helps to avoid a possible bias for overdiagnosing bipolar spectrum disorders related to knowledge of external validators of bipolarity such as bipolar family history.

In the process of establishing clinical reliability in F.B.'s private practice, a subsample of MDE patients (N = 15) were recalled in 48 hours and reinterviewed by a second psychiatrist practicing in the same region of Ravenna and Forli, Italy; he was blind to F.B.'s assessment results. This psychiatrist had been trained by F.B. about study interview methods and diagnosis of BPII. The κ statistic results were as follows: agreement = 86.6%, expected agreement = 50.2%, $\kappa = 0.73$, $z = 2.8$, $p = .0023$, showing substantial (0.61–0.80) agreement. This κ statistic is similar to that found in a study on the reliability of BPII diagnosis, using similar methods of semistructured interviews by trained clinicians in genetic investigations.[19]

Assessment of Hypomanic Episodes

It is well known that patients do not report spontaneously about past hypomanic episodes, because hypomanic episodes are often experienced as pleasant periods of improved functioning and/or periods without marked impairment. Indeed, patients even view them as states of normality, rather than as dysfunction or illness.[9,14] Family members and/or significant others were often present during F.B.'s interview and were very helpful in supplementing clinical information, especially during the probe for past hypomanic episodes. This approach is actually built into the SCID-CV, which admonishes the interviewer to use "all available sources of information . . . notes, the observations of family members and friends."[29(p7)]

Furthermore, the SCID-CV is partly semistructured and based on clinical evaluation (not simple yes/no answers to structured questions). Thus, the wording of the sentences could be changed when unclear to patients, or when F.B. was in doubt about their understanding. In the Mood Module, the SCID-CV skip-out instruction of the stem question about past elevated or irritable mood was not followed, as a negative answer would not allow the assessment of other past hypomanic behavior and experience. This approach provided the opportunity to probe for past signs and symptoms indicative of overactivity in a variety of domains when the answer to the stem question on mood was negative.

In our experience, patients (and family members) remember past instances of behavioral activation more easily than past elated/irritable moods. Moreover, they seemed to remember such mood with greater ease after being queried about periods of past overactivity, even when at first the answer to the mood question had been negative.[27] Eliciting elated (or irritable mood) was facilitated by queries such as, "Did you have a period when you felt like a lion?" (a common saying in Italy); "Do you feel much better in the summer?"; and "Do you feel much better right before a depression or soon after it?" When an-

swers were positive, questions on past hypomanic symptoms were rephrased, and the patient was asked to describe both behavior and mood during that period. In brief, activated behavior was necessary but not sufficient. Our diagnostic procedures always required the presence of hypomanic mood as defined by DSM-IV for the diagnosis of past hypomania occurring outside MDE; *we changed the sequence and type of questions, overactivity first, mood later, but eliciting the latter was necessary for the diagnosis of BPII*.

To further broaden the assessment of mental overactivity, the SCID-CV structured question on racing thoughts was supplemented by Koukopoulos and Koukopoulos'[34] definition of *crowded thoughts* ("head so continuously full of ideas that the patient is unable to stop thinking"), modified from a similar description by Kraepelin.[35]

The DSM-IV 4-day minimum duration of hypomania for BPII diagnosis was not followed, because for this cutoff "there were no data to support the minimum duration criteria for hypomania."[36(p5)] Instead, at least 2 days of hypomania were required for the diagnosis of BPII, following previous reports supporting this cutoff.[9,14,21,32,37,38] In our setting, most BPII patients report more than 1 episode of hypomania, which increases reliability of ascertainment.[9]

Scoring Hypomanic Signs and Symptoms *During* Clinical Depression

Presence of hypomanic symptoms was also systematically assessed *during* the index MDE. Such assessment cannot be done if we were to strictly follow the SCID-CV structure. Hypomanic symptoms had to have lasted at least 1 week, to have appeared during the MDE, and to have been present at the time of the interview. A categorical definition of MDE plus concurrent hypomanic symptoms (depressive mixed state [DMX]) was used, requiring ≥ 3 hypomanic symptoms. This categorical definition of DMX has received clinical, psychometric, and family history validation.[26,28,39–42] We carried this further to the evaluation of all major depressions, including those without history of discrete hypomanic episodes.[28]

In our assessments, we first used the SCID-CV to screen for the presence of *intraepisode* hypomania. To improve detection and assessment of specific hypomanic symptoms during MDE, we supplemented the SCID-CV with the Hypomania Interview Guide, Current Assessment Version.[43] The utility of assessing MDE for intraepisode hypomanic activation—obviously euphoria is not one of the components of such activation—lies in the fact that assessing such activation during the presenting *index* MDE does not depend on the vagaries of memory for *history* of hypomanic episodes,[27] thereby serving as a screen or proxy for such episodes in the past. The optimum specificity and sensitivity in our work[39,43] has been achieved by irritable mood, racing/crowded thoughts, and psychomotor agitation. The presence of such intraepisode signs and symptoms would suggest the need for further probing for past discrete episodes of hypomania, necessary for the DSM-IV construct of BPII. In this article, we adhere to this convention.

Ancillary Measures

Bipolar (types I and II) family history was investigated with the Family History Screen (FHS),[44] a structured interview for psychiatric history of first-degree relatives, which interviews the patient and often one knowledgeable first-degree relative. The threshold for the diagnosis of mania and hypomania, the sine qua non for bipolar disorder, was assigned for first-degree relatives on the basis of Weissman and colleagues' unpublished version of the FHS (reference 44 and personal communication): History of elated and/or activated episodes which departed significantly from one's routine, with at least some functional impairment. The FHS is a screening tool, which does not take the place of more comprehensive family history interviews. Given an aggregate median sensitivity of 67.6, specificity of 87.6, and median interrater reliability of $\kappa = 0.80$ for the FHS (requiring 5–20 minutes), it is the instrument to be preferred over research-elaborate family history interviews in private practice for feasibility reasons. Although we did not undertake the reliability of the FHS in F.B.'s private practice, we did check on the probands' family history information by interview of significant others and/or the affected relative whenever feasible. Again, obtaining data beyond this is unrealistic in private practice.

Mood lability, a personality trait associated with BPII, was assessed by using 2 of the items of the Mood Lability Scale validated prospectively for its specificity for BPII[45]: "Mood often changes, happiness to sadness, without my knowing why," and "I have frequent ups and downs in mood, with and without apparent cause." If at least 1 answer was positive, mood lability was recorded as present.

Depressive recurrence was set at a cutoff level of ≥ 5 on the basis of prior work showing its association with bipolar disorder.[46,47]

Validation and Statistics

The validity of BPII diagnosed in our experience is best tested by comparing it with MDD on variables often reported to distinguish bipolar disorders from MDD, including age at onset, depressive recurrences, atypical features, hypomanic symptoms present *during* MDE, trait mood lability, and bipolar family history.* Most of these variables are based on validating principles for psychiatric diagnosis in the spirit of the Washington University

*References 8, 14, 15, 26–28, 39, 40, 45, 48–50.

Table 1. Comparison Between Patients With Bipolar II Disorder (BPII) and Major Depressive Disorder (MDD)

Variable	BPII (N = 320)	MDD (N = 243)	t/z	df	p
Index age, mean (SD), y	41.6 (13.4)	46.6 (14.9)	4.1	561	.0000
Female, N (%)	219 (68.4)	148 (60.9)	1.8		.0643
Age at onset of first MDE, mean (SD), y	22.8 (10.6)	31.9 (14.0)	8.7	561	.0000
Index GAF score, mean (SD)	50.5 (9.1)	50.9 (9.4)	0.5	561	.6108
≥ 5 MDEs, N (%)	260 (81.2)	140 (57.6)	6.1		.0000
Index DSM-IV atypical features, N (%)	176 (55.0)	75 (30.8)	5.7		.0000
Trait mood lability, N (%)	201 (62.8)	82 (33.7)	6.8		.0000
Bipolar (I and II) family history, N (%)	161 (50.3)	42 (17.2)	8.0		.0000

Abbreviations: GAF = Global Assessment of Functioning scale, MDE = major depressive episode.

Table 2. Hypomanic Signs and Symptoms During Major Depressive Episodes (MDEs) in Patients With Bipolar II Disorder (BPII) and Major Depressive Disorder (MDD)

Variable	BPII (N = 320)	MDD (N = 243)	t/z	df	p
Elevated mood, N (%)	0 (0.0)	0 (0.0)			
Irritable mood, N (%)	194 (60.6)	92 (37.8)	5.3		.0000
Inflated self-esteem, N (%)	0 (0.0)	0 (0.0)			
Decreased need for sleep, N (%)	6 (1.8)	0 (0.0)	2.1		.0355
More talkative, N (%)	82 (25.6)	23 (9.4)	4.8		.0000
Pressure to keep talking, N (%)	0 (0.0)	0 (0.0)			
Flight of ideas, N (%)	0 (0.0)	0 (0.0)			
Racing/crowded thoughts, N (%)	239 (74.6)	133 (54.7)	4.9		.0000
Distractibility, N (%)	245 (76.5)	160 (65.8)	2.7		.0052
Increased goal-directed activity, N (%)	24 (7.5)	3 (1.2)	3.4		.0005
Psychomotor agitation, N (%)	112 (35.0)	45 (18.5)	4.3		.0000
Risky pleasurable activities, N (%)	58 (18.1)	21 (8.6)	3.2		.0013
≥ 3 hypomanic symptoms during MDE, N (%)	200 (62.5)	79 (32.5)	7.0		.0000
No. of hypomanic symptoms during MDE, mean (SD)	3.0 (1.4)	1.9 (1.3)	9.5	561	.0000

approach.[14,15,42,51–53] Validation external to clinical phenomenology is important because, to the best of our knowledge, the architects of the DSM-IV did not subject their operationalization of the BPII construct to such validation.

Means were compared by the t test, and proportions were compared by the 2-sample test of proportions. STATA Statistical Software, Release 7 (Stata Corporation, College Station, Tex.) was used. p Values were 2-tailed, and α level was .05.

RESULTS

Prevalence of BPII was 56.8% (320/563). In comparing BPII and MDD (Table 1), BPII had a significantly younger index age and age at onset of first MDE and significantly higher rates of DSM-IV atypical features, depressive recurrences, and trait mood lability.

Table 2 summarizes the data on ascertaining intra-episode hypomania (DMX) during MDE and the separation of BPII from MDD on this basis. As expected, elation and related signs and symptoms (inflated self-esteem, pressure of speech, and strictly defined flight of ideas) are absent *during* MDE. Separation of BPII from MDD is globally achieved by a significantly higher rate of DMX, mean number of hypomanic symptoms *during* MDE, as well as such individual hypomanic signs and symptoms as irritable mood, decreased need for sleep, increased talkativeness, racing/crowded thoughts, distractibility, increased agitation, and goal-directed activity.

DISCUSSION

Prevalence of Bipolar II Disorder

To the best of our knowledge, the Ravenna-San Diego collaboration involving 563 MDE patients in the present study is the largest clinical sample reporting the relative prevalence of BPII versus MDD. The French EPIDEP study[24] from 4 regions of France involving 50 experienced psychiatrists conducting systematic interviews of 492 MDE patients representing a national sample of patients (both inpatient and outpatient) reported a BPII prevalence of 22% at index interview and 40% a month later. This was in adherence to the DSM-IV definition of 4 days of hypomania.

In the present analyses from an Italian outpatient practice, we deviated from the DSM-IV construct by using a 2-day threshold for hypomania. We found a high prevalence (56.8%) of BPII. This finding is in line with the near 1:1 ratio of BPII versus MDD first reported by Akiskal and Mallya[20] in a suburban U.S. mental health center and more recently by Angst et al.[8] in the community in

the Canton of Zurich in Switzerland. The present analyses used a 2-day cutoff for hypomania, whereas Angst et al.[8] suggested no minimum duration for it; an earlier analysis by Wicki and Angst[54] from the same database had reported that most hypomanias in the community were of 1 to 3 days duration. The high prevalence rates of BPII from 4 different countries, a U.S. mental health clinic,[20] a French national clinical sample,[24] a specialized Italian private setting (present analyses), and a Swiss community setting,[8] argue against referral bias as an explanation for the high rates of this bipolar subtype reported herein.

In a more general vein, we also concur with Hirschfeld et al.[12] that bipolar disorder is underdiagnosed. Our *clinical* procedures are obviously more "sensitive" for BPII diagnosis than the *self-rated* screening in their methodology in the community in the United States. Finally, our data have greater specificity because of the external validators for bipolarity documented herein.

Duration Cutoff for Hypomania

Based on the foregoing comparison of data from 4 different studies, can we justify a particular threshold for hypomania? We submit that the present analyses challenge the DSM-IV requirement of a minimum duration of hypomania of 4 days. The latter threshold is intermediate between the 2 days (for probable) and 7 days (definite) in the *Research Diagnostic Criteria*.[55] Since 1979,[56] the first author has defended the low threshold of 2 days based on family history and prospective follow-up. Cassano et al.[21] confirmed this cutoff in a very large cohort of major depressives. International data-based consensus from 10 studies in the United States and Europe[9] and, most recently, a systematic comparison of the *Research Diagnostic Criteria* thresholds of 2 versus 7 days in the National Institute of Mental Health (NIMH) Collaborative Study[57] upheld the 2-day floor cutoff. An earlier study,[38] also from a prospective study from the NIMH study database, had shown high stability for the diagnosis of BPII based on the floor cutoff.

Reliability

Although a single psychiatrist (F.B.) conducted the interviews in the present cohort, interrater reliability had been previously established on a small subcohort. However, we did not specifically assess the reliability of the procedure to detect hypomanic signs and symptoms *during* MDE. It is nonetheless noteworthy that this procedure represents a tradition that goes back to Kraepelin's[35,42] delineation of DMX, recently endorsed by both Sato et al.[58] and Angst and Gamma.[59]

The interviews were conducted by a clinician (F.B.) who has both studied and treated mood disorders for 2 decades, using state-of-the-art structured/semistructured interviews, information from key informants, and systematic interviewing about past hypomania. We strongly concur with Dunner and Tay,[18] Simpson et al.,[19] and Brugha et al.[60] that semistructured interviews by clinicians experienced in BPII provide more valid assessment than structured interviews by research interviewers who are not clinicians.

Design Issues

One may raise the question of whether the present analyses would have given more meaningful data if we had made a straightforward comparison between DSM-IV BPII hypomania (≥ 4 days), broadened BPII (2–4 days of hypomania), and unipolar MDD. We did not do so because Judd et al.[57] already compared the analogous thresholds, finding no differences between short and long hypomanias on all external validating parameters. Speaking more specifically to the 2- to 3-day threshold versus the DSM-IV threshold of ≥ 4 days, in a manuscript in press,[61] we found them indistinguishable on external validating parameters for bipolarity, including that for family history for bipolar disorder; the shorter threshold accounted for a maximum of 1 out of 3 patients diagnosed in that study. If we subtract a third of the overall rate of 56.8% for BPII in the present study, we obtain a figure of 37%, very much in the ballpark of the 40% for DSM-IV BPII in the French national study.[24]

Criterion A of DSM-IV mania and hypomania, which always requires elevated or irritable mood, was also challenged by the present analyses, showing that overactivity in a variety of behavioral domains can be more important than mood, or can have the same level of importance as mood in mania[62] and hypomania.[8] The importance of overactivity for the diagnosis of hypomania had already been recommended by the first author in 1977.[63] Does this translate into an increment in the rate of BPII that can be justified by bipolar history as an external validator? We have indeed elsewhere shown this to be the case.[27] By reversing the SCID-CV routines, and asking about elation/irritability after eliciting overactive behaviors, the clinician can increase the prevalence of BPII by 17%.

Validating Bipolar II Disorder

Our study is founded on the general validating principles first enunciated by Robins and Guze[51] and elaborated subsequently by others.[15,52,53] Our results overall confirm that BPII, as opposed to MDD, had a significantly earlier age at onset, higher frequency of depressive recurrences, and higher rates of atypical features, trait mood lability, hypomanic symptoms *during* MDE, and, most importantly, greater familial loading for bipolar disorders. These data generally cohere with the definitional characteristics for a putative bipolar spectrum condition.[15]

Rates of family history in bipolar disorder probands in the literature typically report global rates, i.e., without distinguishing between bipolar I and II. Many have reported rates similar to ours.[17,48] For unipolar MDD pa-

tients, bipolar I family history was 1.6% in our sample (in line with previous reports[17,48]). Our figure for BPII is 15.8%, which, added to 1.6%, concurs with the 17.2% reported in Table 1. These familial data for bipolar I and II in depressive illness are compatible with a spectrum concept of affective illness.

It is beyond the scope of this article to examine the range of comorbidity—especially anxious comorbidity—and the associated temperament instability that, too, can serve as validation for bipolar II and the broader bipolar spectrum.[25,45,64,65] In this context, it is relevant to point out that mood lability, still deemed specific in DSM-IV-TR for borderline personality, is also one of the hallmarks of bipolar II disorder as reported herein and elsewhere.[45,63,66]

CONCLUSIONS

In sum, on the basis of the present analyses and review of findings from an increasingly sophisticated literature on BPII, we submit that DSM-IV and SCID-CV procedures are in need of revision in the diagnostic approach to BPII. These revisions pertain largely to optimizing the detection of hypomania:

1. The 2-day cutoff for hypomania appears both sensitive and valid for detecting hypomania.
2. Raising overactivity to the level of the stem question and inquiring about mood and confirming its presence thereafter can, in the hands of a clinician properly trained to recognize hypomania, significantly increase the diagnosed yield of BPII.
3. Given the vagaries of the patient's state-dependent memory of hypomania, interviewers should always inquire about intraepisode hypomanic symptoms during an index depressive episode. These patients are best regarded as having DMX. This maneuver could further help identify BPII diagnosis from the ranks of unsuspected pseudo-unipolar MDD.[28] We submit that DMX represents a "proxy" for BPII: Its presence should prompt the clinician to further probe for forgotten past episodes of hypomania that had occurred outside the frame of MDE.

Previous studies[8,9,20–24,37] from other clinical settings have reported rates of bipolar spectrum disorders ranging from 27% to 50%. We submit that the innovative clinical procedures we applied systematically and cumulatively further upgraded the foregoing figures. Our objective was to show the feasibility of conducting innovative systematic interviews to maximize the diagnosis of BPII in routine practice. The onus is now on others to replicate or refine this approach for research purposes. Are psychiatrists who report that at least 50% of depressives belong to the bipolar spectrum "bipolar zealots," or do they have methodological advantages over researchers who report more conventional figures? We think this should be judged on the basis of the overall thrust of the emerging literature on BPII.

In the French multisite collaborative study,[24] the figure of 40% for DSM-IV BPII (4 days of hypomania) could not be in doubt, because it was the aggregate average of 50 psychiatrists. The figure of 50% from earlier Memphis, Tenn., data[20] involved at least 3 experienced psychiatrists. The present figure of 56.8% based on clinical interview by 1 psychiatrist is in the same general ballpark.

The thrust of our diagnostic logic in this article is that clinicians, in their search for BPII, have a unique advantage over researchers when they conduct systematic interviews of MDE patients under their care in that clinicians have a more intimate knowledge of their patients: BPII represents a clear instance where clinical savvy and savoir faire outsmart researchers.

Baldessarini[67] has criticized the enlargement of the terrain of the bipolar spectrum on the grounds that it would encroach upon the territory of other nosologic entities, and would thereby dilute the concept of bipolar disorder for rigorous research. In clinical practice, bipolar spectrum patients are often diagnosed as Axis II and/or with substance use disorders.[13,64] Some authorities[68] have further suggested that borderline personality disorder is best conceived as antisocial and substance use disorders. As we excluded substance and alcohol use disorders and significant personality pathology from our sample, the high rates of BPII in our study cannot be faulted as an encroachment upon Axis II and substance/alcohol use territories. On the other hand, the BPII data reported here do encroach significantly upon the territory of "unipolar" MDD. In so doing, our data, based on what is possibly the largest clinical sample of major depressives systematically examined for bipolarity, favor the need for a partial return to the Kraepelinian broader concept of mood disorders.[69] This is in line with the Dunner and Tay[18] statement that clinicians with the relevant knowledge and experience of BPII outperform researchers without such knowledge and experience. What we have reported herein represents optimization of the clinical procedures that reflect such knowledge and experience.

REFERENCES

1. Dunner DL, Gershon ES, Goodwin FK. Heritable factors in the severity of affective illness. Biol Psychiatry 1976;11:31–42
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
4. Regier DA, Boyd JH, Burke JD Jr, et al. One-month prevalence of mental disorders in the United States: based on five Epidemiologic Catchment Area sites. Arch Gen Psychiatry 1988;45:977–986
5. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996; 276:293–299

6. Szadoczky E, Papp Z, Vitrai J, et al. The prevalence of major depressive and bipolar disorders in Hungary: results from a national epidemiologic survey. J Affect Disord 1998;50:153–162
7. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–151
8. Angst J, Gamma A, Benazzi F, et al. Toward a redefinition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003;73:133–146
9. Akiskal HS, Bourgeois ML, Angst J, et al. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord 2000;59(suppl 1):S5–S30
10. Ghaemi SN, Sachs GS, Chiou AM, et al. Is bipolar disorder still underdiagnosed? are antidepressants overutilized? J Affect Disord 1999;52: 135–144
11. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. J Clin Psychiatry 2000; 61:804–808
12. Hirschfeld RM, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. J Clin Psychiatry 2003;64:53–59
13. Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatr Clin North Am 1999;22:517–534
14. Akiskal HS. Classification, diagnosis and boundaries of bipolar disorders: a review. In: Maj M, Akiskal HS, Lopez-Ibor JJ, et al, eds. Bipolar Disorder. Chichester, UK: John Wiley & Sons, Ltd; 2002:1–52
15. Akiskal HS. Validating "hard" and "soft" phenotypes within the bipolar spectrum: continuity or discontinuity? J Affect Disord 2003;73:1–5
16. Rice JP, McDonald-Scott P, Endicott J, et al. The stability of diagnosis with an application to bipolar II disorder. Psychiatry Res 1986;19: 285–296
17. Coryell W. Bipolar II disorder: the importance of hypomania. In: Goldberg JF, Harrow M, eds. Bipolar Disorders: Clinical Course and Outcome. Washington, DC: American Psychiatric Press; 1999:219–236
18. Dunner DL, Tay LK. Diagnostic reliability of the history of hypomania in bipolar II patients and patients with major depression. Compr Psychiatry 1993;34:303–307
19. Simpson SG, McMahon FJ, McInnis MG, et al. Diagnostic reliability of bipolar II diagnosis. Arch Gen Psychiatry 2002;59:736–740
20. Akiskal HS, Mallya G. Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bull 1987;23:68–73
21. Cassano GB, Akiskal HS, Savino M, et al. Proposed subtypes of bipolar II and related disorders: with hypomanic episodes (or cyclothymia) and with hyperthymic temperament. J Affect Disord 1992;26:127–140
22. Benazzi F. Prevalence of bipolar II disorder in outpatient depression: a 203-case study in private practice. J Affect Disord 1997;43:163–166
23. Manning JS, Haykal RF, Connor PD, et al. On the nature of depressive and anxious states in a family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. Compr Psychiatry 1997;38:102–108
24. Hantouche EG, Akiskal HS, Lancrenon S, et al. Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study (EPIDEP). J Affect Disord 1998;50: 163–173
25. Perugi G, Akiskal HS, Lattanzi L, et al. The high prevalence of "soft" bipolar (II) features in atypical depression. Compr Psychiatry 1998;39: 63–71
26. Benazzi F, Akiskal HS. Delineating bipolar II mixed states in the Ravenna-San Diego collaborative study: the relative prevalence and diagnostic significance of hypomanic features during major depressive episodes. J Affect Disord 2001;67:115–122
27. Benazzi F, Akiskal HS. Refining the evaluation of bipolar II: beyond the strict SCID-CV guidelines for hypomania. J Affect Disord 2003; 73:33–38
28. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. J Affect Disord 2003;73:113–122
29. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, DC: American Psychiatric Press; 1997
30. Goldberg JF, Kocsis JH. Depression in the course of bipolar disorder. In: Goldberg JF, Harrow M, eds. Bipolar Disorders: Clinical Course and Outcome. Washington, DC: American Psychiatric Press; 1999:129–147
31. Post RM, Nolen WA, Kupka RW, et al. The Stanley Foundation Bipolar Network, 1: rationale and methods. Br J Psychiatry 2001;178 (suppl 41):s169–s176
32. Akiskal HS, Bitar AH, Puzantian VR, et al. The nosological status of neurotic depression: a prospective three- to four-year follow-up examination in light of the primary-secondary and unipolar-bipolar dichotomies. Arch Gen Psychiatry 1978;35:756–766
33. Benazzi F. Borderline personality disorder and bipolar II disorder in private practice depressed outpatients. Compr Psychiatry 2000;41:106–110
34. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. Psychiatr Clin North Am 1999;22: 547–564
35. Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburgh, UK: E & S Livingstone; 1921
36. Dunner DL. Diagnostic revisions for DSM-IV. In: Goodnick PL, ed. Mania: Clinical and Research Perspectives. Washington, DC: American Psychiatric Press; 1998:3–10
37. Benazzi F. Is 4 days the minimum duration of hypomania in bipolar II disorder? Eur Arch Psychiatry Clin Neurosci 2001;251:32–34
38. Coryell W, Endicott J, Maser JD, et al. Long-term stability of polarity distinctions in the affective disorders. Am J Psychiatry 1995;152:385–390
39. Benazzi F. Clinical and family history markers of bipolar II disorder [letter]. Can J Psychiatry 2003;48:208–209
40. Benazzi F. Which could be a clinically useful definition of depressive mixed state? Prog Neuropsychopharmacol Biol Psychiatry 2002;26: 1105–1111
41. Benazzi F, Akiskal HS. Clinical and factor analytic validation of depressive mixed state in outpatient private practice. Curr Opin Psychiatry 2003;16(suppl 2):S71–S78
42. Akiskal HS, Benazzi F. Delineating depressive mixed states: their therapeutic significance. Clin Approaches in Bipolar Disord 2003;2:41–47
43. Williams JBW, Terman M, Link MJ, et al. Hypomania Interview Guide (including hyperthymia). Current Assessment Version (HIGH-C). Norwood, NJ: Clinical Assessment Tools Packet, Center for Environmental Therapeutics; 1994
44. Weissman MM, Wickramaratne P, Adams P, et al. Brief screening for family psychiatric history: the Family History Screen. Arch Gen Psychiatry 2000;57:675–682
45. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from "unipolar" to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 1995;52:114–123
46. Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. Am J Psychiatry 2001;158:582–586
47. Kessing LV, Andersen PK, Mortensen PB, et al. Recurrence in affective disorder, 1: case register study. Br J Psychiatry 1998;172:23–28
48. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
49. McMahon FJ, Stine OC, Chase GA, et al. Influence of clinical subtype, sex, and lineality on age at onset of major affective disorder in a family sample. Am J Psychiatry 1994;151:210–215
50. Benazzi F. Bipolar II depressive mixed state: finding a useful definition. Compr Psychiatry 2003;44:21–27
51. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970;126: 983–987
52. Akiskal HS. External validating criteria for psychiatric diagnosis: their application in affective disorders. J Clin Psychiatry 1980;41(12, pt 2): 6–15
53. Kendler KS. Toward a scientific psychiatric nosology: strengths and limitations. Arch Gen Psychiatry 1990;47:969–973
54. Wicki W, Angst J. The Zurich Study, 10: hypomania in a 28- to 30-year-old cohort. Eur Arch Psychiatry Clin Neurosci 1991;240:339–348
55. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria for a Selected Group of Functional Disorders. 3rd ed. New York, NY: Biometrics Research Division, New York State Psychiatric Institute; 1977
56. Akiskal HS, Rosenthal RH, Rosenthal TL, et al. Differentiation of primary affective illness from situational, symptomatic, and secondary depressions. Arch Gen Psychiatry 1979;36:635–643
57. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269
58. Sato T, Bottlender R, Schröter A, et al. Frequency of manic symptoms during a depressive episode and unipolar 'depressive mixed state' as

bipolar spectrum. Acta Psychiatr Scand 2003;107:268–274
59. Angst J, Gamma A. A new bipolar spectrum concept: a brief review. Bipolar Disord 2002(suppl 1):11–14
60. Brugha TS, Jenkins R, Taub N, et al. A general population comparison of the Composite International Diagnostic Interview (CIDI) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Psychol Med 2001;31:1001–1013
61. Benazzi F, Akiskal HS. The duration of hypomania in bipolar-II in private practice: methodology and validation. J Affect Disord. In press
62. Akiskal HS, Hantouche EG, Bourgeois ML, et al. Toward a refined phenomenology of mania: combining clinician-assessment and self-report in the French EPIMAN study. J Affect Disord 2001;67:89–96
63. Akiskal HS, Djenderedjian AM, Rosenthal RH, et al. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Am J Psychiatry 1977;134:1227–1233
64. Perugi G, Akiskal HS. The soft bipolar spectrum redefined: focus on the cyclothymic, anxious-sensitive, impulse-dyscontrol, and binge-eating connection in bipolar II and related conditions. Psychiatr Clin North Am 2002;25:713–737
65. MacKinnon DF, Zandi PP, Gershon ES, et al. Association of rapid mood switching with panic disorder and familial panic risk in familial bipolar disorder. Am J Psychiatry 2003;160:1696–1698
66. Henry C, Mitropoulou V, New AS, et al. Affective instability and impulsivity in borderline personality and bipolar II disorders: similarities and differences. J Psychiatr Res 2001;35:307–312
67. Baldessarini RJ. A plea for integrity of the bipolar disorder concept. Bipolar Disord 2000;2:3–7
68. Hudziak JJ, Boffeli TJ, Kreisman JJ, et al. Clinical study of the relation of borderline personality disorder to Briquet's syndrome (hysteria), somatization disorder, antisocial personality disorder, and substance abuse disorders. Am J Psychiatry 1996;153:1598–1606
69. Akiskal HS, Akiskal K. Reassessing the prevalence of bipolar disorders: clinical significance and artistic creativity. Psychiatr Psychobiol 1988;3:29s–36s