Eur Arch Psychiatry Clin Neurosci (2012) 262:3–11
DOI 10.1007/s00406-011-0228-0

ORIGINAL PAPER

Diagnostic criteria for bipolarity based on an international sample of 5,635 patients with DSM-IV major depressive episodes

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Received: 9 September 2010 / Accepted: 20 July 2011 / Published online: 5 August 2011

Abstract To assess the clinical validity of individual DSM-IV criteria for hypomania. In an international sample of 5,635 patients with major depressive episodes (Bridge Study), DSM-IV criteria for hypomania (stem questions, number and quality of symptoms, duration and exclusion criteria) were systematically assessed and their validity analysed on the basis of clinical data including family history, course, and other clinical characteristics. Three stem questions for hypomania, irritability, elevated mood and the added question of increased activity, showed comparable validity. The results support the current DSM-IV requirement for a higher symptom threshold (4 of 7 hypomanic symptoms) in cases of irritable mood. Longer durations of hypomanic episodes were associated with higher scores on all validators. The results did not support the DSM-IV durational requirements for hypomanic episodes (4 days) and manic episodes (7 days). Brief hypomanic episodes of 1, 2 or 3 days were valid and would meet validity criteria for inclusion. The three exclusion criteria in DSM-IV (hypomania due to the use of antidepressants or of other substances, or to other medical conditions) were found to exclude patients with bipolar depression and should therefore not be retained. These results support several revisions of the DSM-IV concept of hypomanic episodes: specifically, the inclusion of increased activity as a gate question, the inclusion of 1 or 2 to 3-day episodes and the elimination of all exclusion criteria.

Keywords Hypomania · Diagnosis · DSM criteria · Validity · Bridge study

For the Bridge Study Group.

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Introduction

Epidemiological studies have reported lifetime prevalence rates for major mood disorders of 20% (NCS-R (USA) conducted over ten years [11]), 27.45% (EDSP Study (Munich) ten years) [18] and 23.6% (NEMESIS (Netherlands) 3 years) [5, 7]. All three studies identified 80–90% of such cases as DSM major depressive disorders (MDD) and only about 10–20% as bipolar disorders (BPD). However, recent re-analyses of the EDSP Study [21] and the NCS-R [4] have demonstrated that this simple

dichotomy is questionable and that hypomanic syndromes that do not meet DSM-IV criteria for bipolar-II are present in about 40% of subjects with DSM-IV MDD. Each of these longitudinal epidemiological studies applied the comprehensive international diagnostic interview (CIDI), which is tailored to the DSM-IV and hence cannot provide detailed information about the validity of the diagnostic criteria for hypomanic episodes used for the definition of bipolar-II disorders. To address this limitation in the studies, we report results from the large, multinational Bridge Study, which applied a descriptive, bottom-up approach to assess for hypomania and included an operationally defined alternative set of diagnostic criteria for bipolarity in patients presenting with a major depressive episode [3].

Methods

The Bridge Study (Bipolar Disorders: Improving Diagnosis, Guidance, and Education) is a cross-sectional diagnostic investigation of 5,635 depressed patients carried out in 18 countries in Europe, Asia and North Africa between April 2008 and May 2009. A total of 521 community- and hospital-based psychiatrists recruited consecutively all adult patients who came for evaluation with a diagnosis of major depressive episode according to DSM-IV criteria [6]. At the study evaluation, participating psychiatrists completed an assessment covering patients' clinical features, sociodemographic variables, diagnosis, medical history, treatment and comorbid psychiatric disorders. Separate sections on hypomania/mania, and the MINI DSM-IV diagnostic interview [12] were applied. These methods enabled a diagnosis of bipolar disorder to be assigned when justified by three different diagnostic algorithms: DSM-IV-TR, modified DSM-IV (no exclusion criteria applied) and a new bipolarity specifier [3, 6]. Finally, each patient completed the Hypomania Checklist for self-assessment [18]. The study was carried out by Sanofi-Aventis in co-operation with an advisory board [4, 6, 11, 13, 21].

The goal of this analysis of the Bridge Study data was limited to assessing the clinical validity of the individual DSM-IV criteria for hypomania. We applied clinical validators which could be assessed at the initial interview, such as a family history of hypomania/mania (assessed by a direct, simple question), age of onset and course (recurrence, progression, free intervals, seasonality) and additional clinical characteristics, e.g. mood lability, psychotic features, comorbidity, resistance to treatment and hospitalisation. Family history among first degree relatives, although strongly supported by published studies, has one limitation as a validator, as it tends to be under-reported both by patients and by controls (false negatives), consequent to incomplete information, particularly in a one visit appointment.

A DSM-IV diagnosis of mania and hypomania requires a distinct episode of elevated, expansive, or irritable mood (criterion A). As in the Zurich Study, in the Bridge Study, we added increased activity as a third A criterion because patients are more likely to recognise changed levels of activity (at least as prominent in bipolar disorder as mood changes) whereas some persons lack self awareness of their changes in mood. Because the data were collected when the patients were evaluated, all information on previous history is by definition retrospective. The study is therefore a descriptive one.

The analyses conducted were based on the structure of DSM-IV, which distinguishes the following diagnostic elements of bipolarity:

– presence of a distinct period with the following criteria:

  A1: persistently elevated, expansive, or irritable mood
  A2: duration of episode: at least 4 days
  B: number of manic symptoms
  C-E: consequences
  F: exclusion criteria:

    F1) episode due to antidepressants
    F2) episode due to other substances
    F3) episode due to another medical condition

The analyses focus on (1) the Category A criteria ('gate' questions for hypomania, including also increased activity, (2) the duration of hypomanic episodes (assessed as 1, 2–3 days, 4–6 days, 7 days or more and 1 month or more in length)), (3) the number and quality of symptoms, and (4) the three exclusion criteria F.

Statistics

Groups were statistically compared using $\chi 2$—tests for percentages and Kruskal–Wallis tests for continuous variables. The analysis involved many tests of statistical significance, raising the problem of type I errors, i.e. of tests being statistically significant by chance alone. We offer a correction for multiple comparisons, but we nevertheless present the uncorrected p-values because, by showing only corrected values, important findings may be missed. A Bonferroni-corrected threshold for statistical significance is reported with each table. The correction can be applied by simply raising the level of statistical significance to this threshold. All tests were two-sided. Analyses were carried out in Stata 10.2 for Windows.

Results

Gate questions (criterion A1): irritability, elevated mood and (new) increased activity

The recruiting psychiatrists answered three gate questions about their patients' current clinical status with yes/no responses: (1) episode of elevated mood, (2) episode of irritability, (3) episode of increased activity (work, social, motor). Since patients could present with any or none of the three criteria, eight subgroups were possible. Of the 5,602 patients with major depressive episodes, 3,618 (64.6%) met one or more of the three criteria; of those, 1,021 patients were assessed positively on only one gate question; the remaining 2,597 met two or three. Irritability was reported three times more often than euphoria/elevation or increased activity alone.

Of special interest are patients with a major depressive episode who met only one of the three gate questions. A total of 610 (10.9%) were assessed as exclusively irritable (i.e. not euphoric/elevated etc.), 211 (3.8%) as exclusively more active and 200 (3.6%) as exclusively euphoric/elevated in mood (Table 1). In addition, we defined a pure depressed group of 1,984 patients with major depressive disorder (group 0 in Table 1) who scored negatively on all three gate questions. As shown in Table 1, this group differed significantly ($P < 0.0001$) from the three positive groups with regard to most of the validators and clinical characteristics of bipolarity, with the exception of a history of suicide attempts ($P < 0.09$). Group 0 also differed significantly in its total score on the Hypomania Checklist 32.

Depressed patients with irritable mood did not differ statistically from those with euphoria or increased activity in the validators (statistics not shown). There was no statistical difference in terms of family history and course between the three positive groups. Patients with irritable mood experienced fewer episodes of hypomania while taking antidepressants but manifested more mood lability and mixed states.

Total number of manic symptoms by gate questions

Figure 1 presents the medians, quartiles and ranges of the total number of manic symptoms for each of the eight permutations of the three gate questions. The more complex the permutation of the gate questions, the higher the number of diagnostic hypomanic symptoms. For example, the depressed patients with irritable mood alone had a median of only two hypomanic symptoms, those with only elevated mood or increased activity had three, and the

Table 1 Major depressive episode patients—clinical characteristics of pure groups: irritable mood, increased activity, elated mood

	Major depressive episodes					
	Positive gate question for mania					
	None	Irritability only	Increased activity only	Elevated mood only		
	(0)	(1)	(2)	(3)	*P* (0 vs. 1/2/3)	*P* (1–3)
N	1984	610	211	200		
	%	%	%	%		
Family history of hypomania	4.6	10.6	14.1	15.1	0.0005	0.16
Early onset <30 years	34.3	43.3	37.0	47.0	0.0005	0.11
≥2 mood episodes	51.7	66.8	65.7	73.4	0.0005	0.17
Free intervals	53.7	62.7	64.7	68.0	0.0005	0.45
Recurrence	64.6	79.6	77.3	82.5	0.0005	0.43
Hospitalisation	23.4	28.4	23.2	36.3	0.0005	0.14
Seasonality	13.9	26.4	25.6	28.6	0.0005	0.74
Hypomanic switches	1.6	29.8	32.2	36.0	0.0005	0.0005
Mixed state	15.2	43.2	33.2	25.6	0.0005	0.0005
Mood lability	16.1	43.2	33.5	31.8	0.0005	0.004
AD non-responder	17.6	25.5	22.3	16.7	0.0005	0.04
Atypical depression	15.9	25.3	20.4	23.0	0.0005	0.34
History of suicide attempts	22.3	26.3	19.4	26.9	0.09	0.10
HCL-32 total score	7.2	10.5	14.1	14.6	0.0005	0.0001

Bonferroni threshold $P = 0.0018$

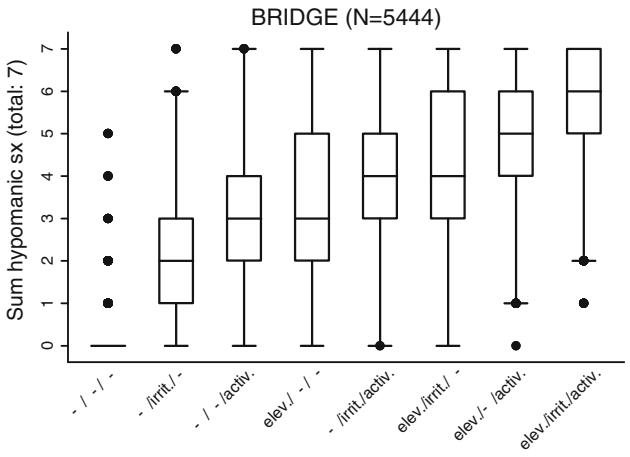

Fig. 1 Box plot of the sum of hypomanic symptoms (Total: 7) by permutation of gate questions. Shown are medians, 25th and 75th percentiles, upper and lower adjacent values and outliers, *sx* symptoms, *irrit* irritable mood, *activ* increased activity, *elev* elevated mood

combined groups had four, five or six symptoms. Figure 1 also indicates that the DSM-IV symptom threshold for caseness for a hypomanic episode in the depressed patients with irritable mood (4 or more of 7 manic symptoms) would exclude about 80% of the 610 subjects. And the current threshold of 3 of 7 symptoms would exclude 50% of the depressed patients with euphoria or increased activity alone as cases.

Hypomanic episodes with 3 of 7 symptoms and consequences by gate questions

The following analyses include all major depressive episode patients assessed positively on the gate questions for hypomania, having 3 of 7 manic symptoms and meeting DSM-IV criteria C, D, E (consequences) for a hypomanic episode (Table 2).

Manic symptom profiles

The hypomanic symptom profiles for patients grouped by gate questions are shown in Table 2. Consistent with the findings reported in the previous section, subjects with three positive gate questions had the highest scores on each of the seven diagnostic symptoms, the most prevalent of which were increased activity/agitation, increased talkativeness and less need for sleep.

Consequences of hypomanic behaviour

The results in Table 2 indicate the systematic increase of consequences across the subgroups of patients with major depressive episodes, i.e. the higher the number of positive gate questions, the steeper the rates of impairment, of ambulatory treatment and of hospitalisations.

It is interesting that a change in behaviour was observed in 50 to 80%, whereas marked impairment rates were lower (20 to 65%) and almost identical to rates of ambulatory treatment.

Clinical validity

A positive family history for hypomania/mania strongly increased with the quality and number of gate questions. Similar trends are present in course characteristics, early onset, recurrence, illness progression and seasonality. The independent self-assessment of hypomania by the patients confirmed the trends found in the psychiatric interview data.

Clinical validity of symptom thresholds for caseness

We conducted an additional analysis (not shown) applying a symptom threshold of 2 or more of 7 manic symptoms that confirmed the increase in bipolar caseness. For most clinical characteristics, there was a trend to slightly better validity using the higher (3 +/7) compared to the lower (2 +/7) symptom threshold, but the latter still differed markedly from the pure MDD group (0 group) in the validators. However, the differences between the two diagnostic thresholds seemed inconclusive therefore, we make no choice between the two.

Duration of hypomanic episodes as a diagnostic criterion

In all patients with a major depressive episode, the length of potential hypomanic episodes (identified only by the gate questions) was assessed as 1 day, 2–3 days, 4–6 days, 7 or more days and 1 month or more. As a consequence of missing data for pure MDD cases, the total N was 3,635. Hypomania of 2–3 days duration was more common than episodes of 4–6 days' duration (Table 3). The rates for the validators and clinical characteristics for bipolarity increased in direct relationship to the duration of hypomanic episodes. However, all bipolar durational subgroups, including those subjects whose hypomanic episodes lasted only one day, differed significantly from the pure MDD group without hypomanic features.. Patients' self-assessment of the number of days spent in hypomania over the past year resulted in a median of 20 days for each of the different episodes lengths (1 day, 2–3 days, 4–6 days, 7 + days). These results indicate that a definition of a minimum hypomanic episode duration of 2 or 4 days is an arbitrary choice, and one not based on data.

Table 2 Major depressive episode patients meeting the following three diagnostic criteria: gate question, consequences and 3 out of 7 symptoms of mania

Positive gate questions	None	irrit. only	activ. only	elev. only	irrit. + activ.	elev. + irrit.	elev. + activ.	elev. + irrit. + activ.	*P* (0 vs. 1/2/3)
	(0)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	
N	1988	177	104	110	185	126	521	1422	
	%	%	%	%	%	%	%	%	
Diagnostic symptoms									
Grandiosity	0.5	11.3	28.2	46.7	33.0	51.4	67.3	81.9	
Less need for sleep	2.4	34.7	53.1	56.8	66.5	64.9	74.2	87.9	
More talkative	1.6	28.9	61.7	72.9	65.7	80.8	89.0	93.5	
Flight of ideas	0.5	17.2	24.9	36.2	36.0	44.7	50.7	72.5	
More distractable	3.3	57.2	32.2	44.7	62.8	66.1	54.1	78.4	
Increased goal-directed or psychomotor activity	3.5	53.7	91.4	73.2	89.5	80.2	91.0	97.1	
Increased pleasure- and risk-seeking	0.5	11.4	17.7	31.7	34.2	44.1	42.3	66.4	
Consequences									
Unequivocal, observable change		37.3	38.9	47.0	56.9	62.0	69.6	82.8	
Marked impairment		38.0	20.4	24.0	38.7	49.7	30.5	65.2	
Observable by others		54.2	50.7	53.5	66.2	75.0	73.7	87.1	
Hospitalisation		11.4	6.6	11.0	11.6	21.5	18.7	39.5	
Ambulatory treatment		30.7	17.4	23.2	39.9	43.8	33.0	57.7	
Clinical validators and characteristics									
Family history of hypomania	4.6	15.5	19.4	19.4	23.1	25.6	23.5	33.4	0.0005
Course									
Early onset < 30 years	34.2	52.9	41.3	53.7	57.2	66.7	48.0	62.6	0.0005
≥2 mood episodes	51.7	74.9	72.1	80.7	77.5	84.8	82.9	91.4	0.0005
Free intervals	14.2	22.1	16.5	15	19.2	15.1	11.5	15.4	0.0005
Illness progression of mood episodes	64.6	85.7	81.7	92.7	87.3	89.6	90.5	95.3	0.0005
Seasonality of mood episodes	14.0	37.1	26.9	32.4	36.5	47.6	36.2	44.2	0.0005
Hospitalisation	1.1	21.1	11.5	19.3	15.6	27.4	23.3	42.1	0.0005
Manic/hypomanic switches	0.7	16.2	26.5	34.9	24.0	32.5	35.3	44.7	0.0005
Mood lability	16.1	58.8	33.3	40.7	55.4	66.1	46.3	61.9	0.0005
Mixed state/mood lability	15.2	55.7	35.0	32.4	54.5	54.6	33.9	52.4	0.0005
Resistance to treatment	17.6	33.3	29.4	17.6	26.9	28.0	21.1	28.5	0.0005
History of suicide attempts	22.3	33.1	25	24.8	36.3	36.8	28.5	36.5	0.008
Self-assessed hypomania	Means	Means	Means	Means	Means	Means	Means	Means	
Sum score HCL (32 items)	7.2	14.3	17.3	16.8	16.1	17.8	18.9	20.9	0.0001
Score F1-revised, HCL (20 items)	5.7	10.1	13.1	12.5	11.6	12.5	14.6	14.9	0.0001
Score F2-revised, HCL (12 items)	1.6	4.1	4.1	4.3	4.4	5.4	4.3	6.0	0.0001

Bonferroni threshold $P = 0.0018$

irrit irritable mood; *activ* increased activity; *elev* elevated mood

Exclusion criteria for bipolarity

We investigated whether DSM-IV exclusion criterion F rests on good evidence. For instance, do patients with a major depressive episode who develop hypomania under an antidepressant or other substances have unipolar or bipolar depressive disorder? We hypothesise that any causal attribution is uncertain.

In this study, 1,553 (32.8%) of 4,732 DSM-IV MDD patients met exclusion criterion F. About 1,392 (89.6%) of

Table 3 Major depressive episode patients: clinical characteristics and validators by duration of hypomanic episode

Variable	Unipolar MDD	Duration of hypomanic episodes							
		1 day	2–3 days	4–6 days	7 + days	1 month+	*P* (0 vs. 1)	*P* (0 vs. 2)	*P* (1–5)
N	1988	285	626	409	1096	1219			
	(0)	(1)	(2)	(3)	(4)	(5)			
	%	%	%	%	%	%			
Family history of hypomania	4.6	11.0	16.7	21.4	24.5	27.4	0.0005	0.0005	0.0005
Early onset <30 years	34.3	50.7	51.7	56.3	53.0	52.8	0.0005	0.0005	0.60
≥2 mood episodes	51.7	64.7	69.0	81.2	84.1	85.2	0.0005	0.0005	0.0005
Illness progression of mood episodes	64.6	75.6	78.8	89.0	90.5	92.3	0.0005	0.0005	0.0005
Seasonality of mood episodes	14.0	22.8	27.4	39.6	41.0	39.4	0.0005	0.0005	0.0005
Manic/hypomanic switches	0.7	8.7	14.0	27.1	37.9	35.2	0.0005	0.0005	0.0005
Mixed state/mood lability	15.2	36.6	42.0	44.0	48.1	41.7	0.0005	0.0005	0.002
Mood lability	16.1	28.6	39.1	50.0	57.0	53.1	0.0005	0.0005	0.0005
Resistance to treatment	17.6	22.4	22.2	26.6	25.4	25.6	0.080	0.008	0.35
Atypical depression	15.9	22.8	23.8	28.6	31.5	28.2	0.001	0.0005	0.003
History of suicide attempts	22.3	31.0	29.1	28.9	33.2	33.0	0.001	0.0005	0.33
Self-assessed highs	Means	Means	Means	Means	Means	Means			
Sum score HCL (32 items)	7.2	13.0	14.8	16.6	17.6	19.0	0.0001	0.0001	0.0001
Score F1-revised, HCL (20 items)	5.7	9.9	11.0	12.4	13.0	13.9	0.0001	0.0001	0.0001
Score F2-revised, HCL (12 items)	1.6	3.3	3.8	4.3	4.6	5.1	0.0001	0.0001	0.0001
Days/past year in hypomania (medians)	7	20	20	20	20	45	0.0001	0.0001	0.0001

Bonferroni threshold $P = 0.0011$

them became hypomanic under antidepressants (F1) and a further 208 under other substances or due to medical causes (criterion F2 and F3).

Lifetime switches to hypomania under antidepressants

Table 4 compares 3,137 MDD patients who experienced no switch with the three subgroups who switched; 903 patients with DSM bipolar disorder (BPD) are listed for visual comparison.

The two MDD subgroups (with switches and without switches under antidepressants (1 vs. 2) differed greatly with regard to the validators. In the group who switched, a family history for hypomania/mania was three times more common and the first symptoms occurred earlier. Similarly, patients in the AD switch group had more episodes and more free intervals between episodes, which is comparable to the BPD group. The mean scores of self-assessed hypomanic symptoms (HCL-32 R1) in the switch group were almost double those in the pure MDD group.

Lifetime switches to hypomania under other circumstances

The 144 patients whose switches were due to other substances and the 59 in whom they were due to a general medical condition (subgroups 3 and 4) also differed greatly from the pure MDD case, having higher rates of family history for hypomania, earlier onset and typical course characteristics of bipolar depression, including seasonality, mixed states and mood lability.

In the aggregate, these validity data for the three groups who developed hypomania align them much more closely with the BPD than with the pure MDD group.

Discussion

These analyses, from a large, multinational and broadly representative clinical sample, indicate that the clinical validity of increased activity as a gate criterion for bipolar disorders is comparable to that of elevated/expansive mood. The addition of activity identified an additional 6% of cases of sub-threshold hypomania among patients with a major depressive episode. The addition of increased energy/activity is currently being considered for the definition of a hypomanic episode in the proposed draft revisions to DSM-5, an option which the results of the present study support.

The lower specificity of irritability as a gate criterion of bipolarity is consistent with the findings of Rich et al. [15] in paediatric bipolar disorders and with some of the

Table 4 Pure MDD versus MDD with switch under antidepressants

Variable	MDD	MDD + switch AD	MDD + switch other subst.	MDD + switch other medical conditions	BPD	*P* (1 vs. 2)	*P* (2–4)
	(1)	(2)	(3)	(4)	(5)		
N	3137	1392	144	59	903		
	%	%	%	%	%		
Family history of hypomania	7.7	25.9	22.0	27.1	30.9	0.0005	0.58
Early onset <30 years	38.4	53.0	65.2	50.0	60.6	0.0005	0.02
≥2 mood episodes	55.8	91.2	79.0	62.1	88.1	0.0005	0.0005
Free intervals	57.2	80.6	70.4	65.5	84.5	0.0005	0.001
Illness progression of mood episodes	68.4	96.7	83.3	67.2	94.7	0.0005	0.0005
Seasonality of mood episodes	18.2	45.6	34.0	37.9	37.8	0.0005	0.02
Mixed state/Mood lability	23.7	47.4	44.6	42.9	46.0	0.0005	0.68
Mood lability	21.4	66.2	39.6	40.4	52.7	0.0005	0.0005
Resistance to treatment	17.3	34.6	25.0	12.3	21.7	0.0005	0.0005
Atypical depression	18.3	32.5	36.8	28.8	27.5	0.0005	0.47
History of suicide attempts	23.2	35.8	33.6	20.3	33.3	0.0005	0.05
Psychotic features	10.2	17.1	12.5	18.6	21.2	0.0005	0.35
Ever admitted to a psychiatric hospital	23.4	28.5	25.7	25.9	57.6	0.0005	0.67
Self-assessed highs	Means	Means	Means	Means	Means		
Sum score HCL (32 items)	9.6	18.0	19.4	16.2	20.2	0.0001	0.004
Score F1-revised, HCL (20 items)	7.5	13.3	13.2	11.6	14.6	0.0001	0.09
Score F2-revised, HCL (12 items)	2.2	4.8	6.2	4.6	5.6	0.0001	0.0001

Diagnostic classification by DSM-IV

Bonferroni threshold $P = 0.0016$

considerations raised by an ECNP expert consensus document [10]. Depressed patients with irritable mood reported on average one fewer diagnostic manic symptom than did patients with euphoria or increased activity. This observation would support the DSM-IV requirement of a larger number of diagnostic manic symptoms when only irritability is present. The data also confirm the clinical relevance of the current DSM-IV criteria for the consequences (C, D, E) of hypomania.

The finding that the duration of hypomanic episodes is systematically correlated with increasing validity is also of interest. This result was present for each of the five episode lengths we tested: 1 day, 2–3, 4–6 and 7 or more days, and 1 month or more. We conclude that the DSM-IV criteria of 4 days for hypomanic episodes and 7 days for manic episodes are not data based, and that no clear cut-off for diagnosis based on this distribution exists. Even patients with hypomanic episodes lasting only 1 day differed markedly from those with pure major depressive disorder, thus confirming the existence and validity of brief hypomania (defined by 1–3 day episodes) [1, 2]. For DSM-5, a conservative decision would be to include hypomanic episodes of 2–3 days as clinically valid. Such a decision would support concerns raised by authorities in child and adolescent psychiatry [13]. However, the data from this study clearly favour a 1-day duration with a median of 20 days of hypomania over the past 12 months.

Our results show the DSM-IV exclusion criteria F1, F2, F3 for a hypomanic/manic episode to be problematic. The data suggest that in patients with major depressive episodes, an antidepressant-induced switch occurs mainly in those with signs indicative of bipolarity (family history, onset and course). In addition, MDD patients who switched under ADs were characterised by higher rates of seasonality of episodes, mixed states, mood lability, resistance to antidepressants in the previous history, atypical depression, history of suicide attempts, psychotic features and psychiatric hospitalisation. This finding is in accordance with the lack of statistical evidence that hypomanic episodes are caused by antidepressants [8, 14]. In the proposed draft revisions to DSM-5, a switch under antidepressants has been removed as an exclusion criterion for defining a hypomanic episode. This proposed change will greatly reduce the heterogeneity of MDD and may result in greater validity of the diagnostic criteria for bipolar-I [16, 19] and especially for bipolar-II [20] disorders. These data also suggest, in agreement with numerous studies, that switches from major depressive episodes to hypomania due to other substances or other medical conditions occur mainly in

Table 5 Current DSM criteria for hypomanic episodes and the amendments suggested by the present study

Current DSM-IV criteria	Suggested amendment	Evidence
Stem questions (A1)	Add increased activity	Comparable validity in terms of
Elevated mood		Family history
Irritable mood		Course
		N of diagnostic symptoms
Episode duration (A2)	Include brief episodes of 2–3 days	Comparable validity in terms of
4 days or more		Age of onset
		Mixed states
		Treatment resistance
		Suicide attempts
		HCL scores
		Days per year in hypomania
		Slightly lower validity in terms of
		N mood episodes
		Illness progression
		Seasonality
		Hypomanic switches
		Mood lability
Exclusion criteria (F)	Drop	Excluded cases are *bona fide* bipolar cases in terms of
episode due to		
Antidepressants		Family history
Other substances		Course
Another medical condition		Suicide attempts
		HCL scores

subjects with characteristics of and a disposition for bipolarity (family history, etc.) [9, 17].

The changes to existing DSM criteria suggested by our study are summarised in Table 5.

These results have both the strength and the limitation that they are based on treated patient and not epidemiological samples. This is mainly a strength as regards the clinical generalisability of the findings. Moreover, the sample is uniquely large and distributed evenly across three continents and many countries, which increases the generalisability of the results. The methods were determined by a group of experts in the diagnostic nomenclature, illness course and symptomatic characteristics of bipolar disorders; the documentation of the treating doctors' findings was standardised. No test of inter-rater reliability among the participating psychiatrists was carried out.

Conclusions

The current concept of DSM-IV major depressive disorder is problematic, because it includes over one-third of patients who actually have subthreshold bipolar disorders.

The data of the Bridge Study suggest that there should be a broader definition of a hypomanic episode and consequently of bipolar-II disorder. The addition of increased activity as a primary requirement for eligibility for diagnosis of hypomania/mania and bipolar disorder appears to be a valid and readily applicable change that would improve the accurate diagnostic identification of patients presenting with major depressive episodes. The exclusion criteria for hypomania (episode due to antidepressants, other substances or other medical reasons) are not valid and should be discontinued. Brief hypomanic episodes (1–3 days' duration) exist and have a similar validity to longer episodes. These suggested changes (Table 5) would allow much earlier recognition and treatment of bipolar disorder and reduce adverse consequences of interventions that are not indicated for bipolar disorders.

Acknowledgments The diagnostic Bridge Study was organised and sponsored by Sanofi-Aventis. We thank them for providing us with all data and derived variables for analyses without any restrictions.

Conflict of interest statement **Prof. Dr. Jules Angst** has served on the advisory board for Eli Lilly & Company, Janssen Cilag, Lundbeck, on the speakers' bureau for Eli Lilly & Company and AstraZeneca, and as a consultant for Sanofi Aventis.

J.M.A. has undertaken consultancy work for Lilly, Janssen, Sanofi-Aventis, Lundbeck, Astra Zeneca, and Bristol-Myers-Squibb; and has received honoraria form Lilly, Janssen, Lundbeck, Sanofi-Aventis,

Bristol-Myers-Squibb, Pfizer, and Novartis in relation to conference presentations.

A.G. is a statistician of JA and has no conflict of interest to declare.

C.L.B. has acted as a consultant for Pfizer, Bristol Myers Squibb, Repligen, and Merck. He has served on an advisory board of sanofi-aventis. He has received grant support from NIMH, Johnson and Johnson, and Bristol Myers Squibb.

G.P. has acted as consultant of Sanofi Aventis, Bristol Myers Squibb, Astra Zeneca, Eli Lilly, Boehringer Ingheleim; received grant/research support from Eli lilly, Astra Zeneca, Boehringer Ingheleim, Glaxo-SmithKline; is on the speaker/advisory board of Sanofi Aventis, Bristol Myers Squibb, Astra Zeneca, Eli Lilly, Boehringer Ingheleim, Glaxo-SmithKline, Pfyzer, Wyeth, Jannsen-Cilag, Lundbeck.

E.V. has acted as consultant, received grant/research support or honoraria from Almirall, Astra-Zeneca, Bristol-Myers-Squibb, Eli Lilly, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck Sharpe and Dohme, Novartis, Organon, Otsuka, Pierre-Fabre, Pfizer, Sanofi Aventis, Servier, Shering-Plough, Takeda, United Biosource Corporation, and Wyeth.

A.H.Y. has acted as a consultant, received grant/research support or honoraria from, and/or has been on the advisory boards of Sanofi-aventis, Eli-Lilly, Bristol-Myers Squibb, BCI, AstraZeneca, GSK, Janssen, Pfizer and Servier.

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