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ORIGINAL PAPER

Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity

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Abstract The definitions of bipolar-I (BP-I) and bipolar-II (BP-II) disorders are currently under revision by the APA and by the WHO. We provide evidence of a revised set of criteria for bipolar disorders and major depressive disorder (MDD) which could serve to strengthen the construct and predictive validity of both disorders and enable more incisive studies of treatments and courses of both disorders. In the diagnostic Bridge Study of 5,635 patients with major depressive episodes from 18 countries (Europe, North Africa, Near East and Far East) leading psychiatrists in each country assessed a pre-specified group of symptoms, illness course, family history and duration of episodes; these data allowed tests of several definitions of bipolarity. The primary revised specifier diagnosis of BP-I disorder included manic episodes based on an additional category A criterion (increased activity/energy) and did not apply any exclusion criteria. The revised BP-II disorders included hypomanic episodes of 1–3 days. Family history and illness course validators (history of mania/hypomania among first degree relatives, 2 or more lifetime episodes and first symptoms having occurred before age 30) discriminated clearly between patients with bipolar-I or bipolar-II disorders meeting bipolarity specifier criteria and those with MDD. Specifier definitions provided better discrimination between MDD and the two bipolar subgroups. Patterns of concurrent comorbidities also differed significantly between patients meeting criteria for MDD compared with those meeting bipolar specifier criteria. Comorbidity patterns differed between bipolar-I and bipolar-II patients. This study provides evidence for the validity of modified (specifier) BP-I and BP-II definitions that incorporate illness course and family history which reduce ambiguities of major depressive episodes between bipolar-I and bipolar-II disorders and MDD.

Keywords Bipolar-II · Bipolar-I · Hypomania · Definitions · Validity · Comorbidity

The study was conducted for the Bridge Study Group.

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Introduction

The diagnostic classification of mood disorders is in a state of flux. Three recent epidemiological studies from both

Europe and the United States [1–3] which applied criteria for bipolarity under the diagnostic threshold of DSM-IV and ICD-10 have reported that over 40 % of persons with major depressive episodes meet modified criteria for bipolar disorders (BDs). With the exception of the Zurich Study [4], most psychiatric epidemiological data were collected with instruments tailored to the current diagnostic manuals (e.g. the CIDI), which did not include sub-threshold psychopathology.

In the diagnostic Bridge Study [BDs: Improving Diagnosis, Guidance, and Education] of 5,635 patients from 18 countries presenting for treatment with major depressive episodes, the duration and symptoms of mania were assessed using a descriptive, bottom-up approach which allows testing of multiple definitions of bipolarity. A first article of the Bridge Study compared the validity and comorbidity of DSM-IV definitions of bipolarity with a "specifier" definition that adds increased activity as a gate criterion and eliminates exclusions associated with use of an antidepressant or other medical conditions [5]. A second article assessed the validity of the diagnostic criteria for mania/hypomania [6], that is, gate questions, duration of episodes, number of symptoms and exclusions criteria. This analysis compares patients with bipolar-I (BP-I) or bipolar-II (BP-II) disorders with patients with major depressive disorders (MDD) defined by DSM-IV versus those defined by evidence-based bipolar specifier criteria and consideration of concurrent comorbidities [1]. We also consider the relevance of these results for the diagnosis and classification of both BDs and MDDs, as well as their implications for future studies and the clinical management of these discrete disorders.

Methodology

Sample and assessment

The methodology of the Bridge Study has been described in detail [5]. In summary, it is a cross-sectional diagnostic investigation of 5,635 depressed patients conducted in 18 countries in Europe, Asia and North Africa between April 2008 and May 2009. Community- and hospital-based psychiatrists recruited consecutively all adult patients seeking treatment with a diagnosis of MDE according to DSM-IV criteria [7]. At this evaluation, participating psychiatrists completed a questionnaire on patients' clinical features, sociodemographic variables, diagnosis, medical history, treatment and simultaneously comorbid psychiatric disorders. Separate sections on hypomania/mania, and the MINI International Neuropsychiatric Interview (MINI DSM-IV) diagnostic interview [8], were applied. These methods enabled a diagnosis of BD to be assigned, using two different diagnostic algorithms: DSM-IV-TR and the bipolarity specifier [5, 7]. Patients meeting all inclusion criteria except for those for BP-I or BP-II were classed as having MDD. Concurrent comorbid conditions were also assessed by the MINI [8]. The study was carried out by Sanofi-Aventis in co-operation with an advisory board.

Definitions of subgroups of mood disorders

Table 1 presents the DSM-IV definitions for BP-I and BP-II disorders and the specifier definitions (S) for bipolarity (BP-I-S and BP-II-S); the specifier criteria included hypomanic episodes of 1 or more days, added increased

Table 1 Definitions of BP-I and BP-II disorders

	DSM-IV BP-I	BP-I-S (specifier)	DSM-IV BP-II	BP-II-S (specifier)
Distinct period (days)	7+ days	7+ days	4+ days	1+ days
A.1. Elated/irritable mood	+	+	+	+
2. Increased activity or energy	−	+	−	+
B. Seven symptoms	3+/4+	3+/4+	3+/4+	3+/4+
C. Symptoms not meeting mixed episode	Not assessed	−	Not assessed	–
D. Marked impairment or hospitalisation or psychotic	+	+	−	−
		Marked impairment or hospitalisation		–
E. Episode not due to somatic treatment	+	−	+	−

Criterion A2: new valid gate question (see Bridge Study paper on diagnostic criteria [6])

Criterion B: 3+/4+ symptoms as in DSM-IV mania

Criterion C: not assessed in the Bridge Study

Criterion D: psychotic symptoms of mania were not assessed in the Bridge Study

Criterion E: not applied on the basis of results of paper on diagnostic criteria [6]

activity/energy as a gate question in addition to elated mood or irritability and did not apply the exclusion criterion E of DSM-IV-TR (manic/hypomanic episode not due to the direct physiological effects of a substance or a general medical condition). The Bridge Study did not assess concurrent mixed syndromes and psychotic symptoms of mania. All DSM-IV MDE patients without a BP-I or BP-II diagnosis were classified as having MDD or MDD-S, respectively.

Statistical methods

The association between an assigned diagnosis of MDD or BD according to two sets of diagnostic concepts was measured by odds ratios. As validators we used demographic, family history, illness course, as well as clinical and comorbidity characteristics. Stepwise multiple logistic regression analyses were then conducted on those variables which proved significant in the bivariate analyses.

Results

BP-I and BP-II comparisons with MDD

Table 2 compares the three subgroups of major mood disorders defined by the criteria listed in Table 1. DSM-IV classified 12.2 % of MDE patients as having BP-I, 3.8 % as having BP-II and 84.0 % as having MDD. In comparison, specifier (S) criteria identified 23.9 % as BP-I ($N = 1{,}348$) and 23.1 % as having BP-II-S ($N = 1{,}299$), resulting in identification of 53 % of the sample of all patients with MDEs classified as having MDD-S. Approximately two-thirds of patients were female, a proportion that did not differ across diagnostic subgroups or between DSM and bipolar S criteria.

Validity of BP-I-S and BP-II-S disorders

Table 2 lists a number of characteristics which are generally used as clinical validators for diagnostic concepts [9, 10]. For both diagnostic schemes (DSM-IV and specifier), for variables which were significantly higher based on bivariate odds ratios in BD than MDD, the BP-I/MDD difference was larger than the BD-II/MDD difference. Further, the magnitude of the odds ratio was consistently greater between the groups diagnosed by the bipolar S criteria. Proportions and associated odds ratios were generally similar for BP-I and BP-II; but a family history of mania and the number of lifetime episodes ≥ 2 were both greater for BP-I than BP-II subjects.

The specifier classification not only identified more depressive patients as suffering from BP-I-S and BP-II-S disorders but also yielded stronger differences between bipolar and MDD-S disorders, therefore providing improved validity compared with DSM-IV diagnoses. Removing "sub-threshold" bipolars from the DSM-IV MDD group led to substantive decreases in the rates of bipolar characteristics among MDD-S patients. For example, family history for mania decreased from 13.7 to 6.2 %. Similar changes occurred among MDD-S defined patients for illness course variables: age at onset, number of episodes, illness progression and seasonality.

Concurrent comorbidity of BP-I, BP-II and MD disorders

Comorbidity patterns differed markedly between DSM-IV BP-I and BP-II patients (Table 3): BP-II patients had significantly greater comorbidity with most subgroups of anxiety disorders, except panic disorder and social phobia. Comorbidity rates for substance use disorders were similar for BP-I and BP-II patients.

Compared to DSM-IV MDD, patients with DSM-IV BP-I did not differ in comorbidity for any of the assessed other disorders. Only suicide attempters were more common among BP-I patients (35.6 vs. 27.1 %) among MDD patients. DSM-IV BP-II patients showed significant comorbidity with anxiety disorders (especially OCD, panic with agoraphobia and social phobia) and binge eating but not with suicide attempts (Table 2).

In contrast, applying the specifier criteria, patients with BP-II-S showed significantly higher comorbidity rates than BP-I-S in anxiety disorders except social phobia.

Compared to MDD-S patients with BP-I-S had higher comorbidity with social phobia, OCD, binge eating, ADHD, alcohol, substance use disorders and suicide attempts. Similarly, BP-II-S patients had significantly higher rates for each of the comorbid disorders including binge eating but not eating disorder. Both bipolar specifier groups also displayed significantly more frequent ADHD and borderline personality disorders in comparison with the MDD-S group.

In Table 4, we show gender differences for comorbidity according to the specifier definitions; similar rates were found for men and women (Table 4), but substance use disorders were twice as high in men. Consistent with other data, suicide attempt rates were somewhat higher in women (BP-I-S 42.4 % and BP-II-S disorders 31.7 %) when compared to 33.4 and 22.9 %, respectively, in men.

Overall, concurrent comorbidities were more sharply demarcated between bipolar and MDD patients applying the specifier classification than by DSM-IV classification.

Results from the more conclusive stepwise multiple logistic regression analyses are shown in Table 5. Compared to the DSM-IV TR diagnoses, the groups defined by

Table 2 BP-I, BP-II and MDD defined by DSM-IV versus bipolar specifier (S): family history, course and clinical characteristics

Groups	DSM-IV						Bipolar specifier (S)					
	1	2	3	1 versus 2	1 versus 3	2 versus 3	4	5	6	4 versus 5	4 versus 6	5 versus 6
Diagnosis	BP-I *N*, %	BP-II *N*, %	MDD *N*, %				BP-I-S *N*, %	BP-II-S *N*, %	MDD-S *N*, %			
Total *N*	685	218	4,732				1,348	1,299	2,988			
	%	%	%	OR 95 % CI	OR 95 % C.I.	OR 95 % CI		%	%	OR 95 % CI	OR 95 % CI	OR 95 % CI
Gender[a]												
Females	57.4	65.4	65.4	**0.7**	**0.7**	1.0	58.8	64.7	66.9	**0.7**	**0.7**	0.9
				0.5–0.98	**0.6–0.8**	0.7–1.4				**0.6–0.8**	**0.6–0.8**	0.8–1.1
Males	42.6	44.6	44.6				41.2	35.3	33.1			–
F/M	1.35	1.89	1.89				1.43	1.96	2.02			–
Family history and course												
FH+ mania[a]	32.9	24.5	**13.7**	**1.5**	3.1	**2.1**	33.6	22.2	**6.2**	**1.8**	**7.6**	**4.2**
				1.1–2.2	2.6–3.7	**1.5–2.9**				**1.5–2.1**	**6.3–9.2**	**3.4–5.2**
First symptoms <30[a]	21.6	20.2	**14.05**	1.1	2.3	**1.6**	20.7	21.0	**10.15**	0.9 0.8–1.1	**3.4**	**2–0**
				0.7–1.7	1.9–2.8	**1.1–2.3**					**2.9–4.0**	**1.7–2.5**
Hospitalised[a]	69.5	30.3	**35.8**	**6.2**	4.6	**0.6**	70.6	32.9	**28.7**	**5.0 4.3–6.0**	**6.6**	0.9
				4.4–8.8	3.8–5.5	**0.3–0.8**					**5.7–7.7**	0.7–1.0
First episode[a]	3.8	10.1	**22.8**	**0.3**	0.1	**0.4**	3.2	12.6	**30.8**	**0.2 0.2–0.3**	**0.1**	**0.3**
				0.2–0.6	0.1–0.2	**0.2–0.6**					**0.0–0.1**	**0.2–0.4**
No. of episodes ≥2[a]	90.8	79.8	**67.0**	**3.0**	5.3	**2.0**	92.9	78.7	**56.55**	**3.5 2.8–4.6**	**11.5**	**3.2**
				1.9–4.6	4.1–7.0	**1.4–2.8**					**9.2–14.4**	**2.7–3.8**
Illness progression[a]	92.2	89.9	**77.2**	**3.3**	8.2	**2.7**	96.8	87.4	**69.2**	**4.3 3.1–6.1**	**15.3**	**3.5**
				1.8–6.0	5.5–12.3	**1.7–4.2**					**11.1–21.0**	**2.8–4.2**
Episode length ≤1 month	45.0	29.4	27.9	2.0 (1.4–2.7)	2.1 (11.8–2.5)	1.1 (0.8–1.5)	43.0	29.5	**24.4**	**1.8 (1.5–2.1)**	2.3 (2.0–2.7)	1.3 (1.1–1.5)
Free intervals[a]	85.4	81.9	**64.7**	0.7	3.5 2.8–4.3	**2.5**	84.1	74.45	**57.6**	**1.8 1.5–2.1**	**4.2**	**2.4**
				0.5–1.1		**1.7–3.6**					**3.6–4.9**	**2.0–2.7**
Clinical characteristics												
Seasonality[a]	37.3	39.4	**27.0**	1.0	1.7	**1.7**	43.5	37.4	**18.3**	**1.3 1.1–1.5**	**3.6**	**2.8**
				0.7–1.3	1.4–2.0	**1.3–2.4**					**3.1–4.2**	**2.4–3.3**
Mood lability[a]	54.05	48.4	**35.55**	1.3	2.2	**1.7**	62.3	50.0	**22.2**	**1.6 1.4–1.9**	**6.1**	**3.7**
				0.9–1.7	1.8–2.6	**1.3–2.3**					**5.2–7.0**	**3.1–4.3**
Mixed state[a]	44.9	38.5	**29.0**	1.2	1.9	**1.6**	47.6	42.6	**18.95**	**1.3 1.1–1.5**	**3.7**	**2.9**
				0.9–1.7	1.6–2.3	**1.2–2.2**					**3.2–4.3**	**2.4–3.3**

Table 2 continued

Groups	DSM-IV			Bipolar specifier (S)								
	1	2	3	1 versus 2	1 versus 3	2 versus 3	4	5	6	4 versus 5	4 versus 6	5 versus 6
Racing thoughts	20.9	16.5	**13.0**	1.3	1.7	1.3	21.2	19.7	**8.5**	1.1 0.9–1.3	**2.9**	**2.6**
				0.9–1.9	1.4–2.1	0.9–2.0					**2.4–3.4**	**2.1–3.2**
Atypical depression with 2/3 somatic symptoms[a]	28.95	22.9	**23.2**	**1.4**	1.4	1.0	34.0	27.9	**17.6**	**1.3 1.1–1.6**	**2.5**	**1.8**
				1.0–2.1	1.1–1.6	0.7–1.4					**2.1–2.9**	**1.5–2.2**
Psychotic[a]	24.7	10.1	**12.4**	**2.9**	2.2	0.8	23.5	11.95	**10.25**	**2.3 1.8–2.8**	**2.6**	1.2
				1.8–4.7	1.8–2.7	0.5–1.3					**2.2–3.1**	0.9–1.5
Suicide attempts[a]	**35.6**	25.7	27.1	**1.6**	**1.5**	0.9	**38.9**	28.5	23.1	**1.6**	**2.1**	**1.3**
				1.1–2.3	**1.2–1.8**	0.6–1.3				**1.4–1.9**	**1.8–2.5**	**1.1–1.5**

Statistics: BP-I groups (1 and 4) (differed in all variables significantly from groups 3 and 6, respectively)

Clinically relevant values are marked in bold

[a] Variables entered into the stepwise multivariate logistic regression

specifier criteria varied both in size and in the odds ratios for the chosen validators. Allocation of patients with DSM-IV MDD to the bipolar specifier groups reduced the ORs between BP-I and BP-II disorders; however, differences between the MDD and bipolar subgroups increased or remained stable. For example, a positive family history of mania applying specifier criteria doubled the differences, whereas differences in course characteristics remained stable. In addition, several characteristics of bipolarity (mood lability, mixed states and seasonality) tended to be higher in the specifier groups. The same pattern of greater differences applying specifier criteria held true for some comorbid conditions: atypical depression, substance/alcohol use disorders and borderline personality disorders.

Discussion

These results from 5,635 patients evaluated by practising psychiatrists in 18 countries provide pragmatic guidance for clinicians and investigators regarding illness features that fundamentally distinguish MDD, BP-I disorder and BP-II disorder. BP-I patients compared with BP-II patients had significantly higher rates of family history of mania/hypomania, lifetime number of episodes, illness progression, seasonality of episodes, mood lability and mixed episodes. A subset of concurrent anxiety comorbidities was significantly more frequent among BP-II than BP-I patients: GAD, panic disorder, OCD and anxiety disorder. Most of these variables are sufficiently quantifiable and reliable by standard clinical evaluation procedures that they could serve as discriminators for formal diagnostic differentiation between BP-I and BP-II forms of BD. The preponderance of anxiety disorders among BP-II versus BP-I patients suggests that treatment approaches with BP-II disorders should include specific anxiety focused procedures. In contrast, non-anxiety comorbidities did not differ between BP-I and BP-II disorders.

An important result of these analyses is that criteria that distinguish BP-I and MDD are generally consistent with those distinguishing BP-II and MDD, albeit more robust for the BP-I versus MDD comparisons. This observation supports the current DSM-IV-TR approach of applying the same criteria for BP-I and BP-II diagnoses in contrast to MDD diagnoses. The magnitude of BP-I versus MDD differences was generally larger than that for BP-II versus MDD.

Current concepts of MDDs are over-inclusive [11]. A strength of DSM-IV-TR and bipolar specifier criteria bipolar classifications is that they are not. In fact, specifier classification yielded consistently stronger differences between BP-I-S and BP-II-S compared to MDD-S disorders than did DSM diagnoses. Therefore, one application of

Table 3 Simultaneous comorbidity of mood disorder subgroups

Groups	DSM-IV criteria						Revised by bipolar specifier criteria (S)					
	1	2	3	2 versus 1	1 versus 3	2 versus 3	4	5	6	5 versus 4	4 versus 6	5 versus 6
Diagnosis	BP-I	BP-II	MDD				BP-I-S	BP-II-S	MDD-S			
N	685	218	4,732				1,348	1,299	2,988			
	%	%	%	OR 95 % CI	OR 95 % CI	OR 95 % CI	%	%	%	OR 95 % CI	OR 95 % CI	OR 95 % CI
Generalised anxiety disorder[b]	**6.0**	**11.9**	9.2	**2.2**	0.6	1.3	7.9	**10.7**	8.6	**1.4**	0.9	**1.3**
				1.3–3.6	0.4–0.9	0.8–2.1				**1.04–1.8**	0.7–1.2	**1.1–3.6**
Panic disorder[b]	7.6	11.0	9.0	1.6	0.8	1.3	8.3	**11.9**	7.9	**1.5**	1.1	**1.6**
				0.9–2.6	0.6–1.2	0.8–2.0				**1.1–1.9**	0.8–1.4	**1.2–2.0**
Panic disorder with agoraphobia	4.1	**7.3**	3.9	**2.0**	1.0	**2.0**	4.2	**5.2**	3.5	1.2	1.2	**1.5**
				1.1–3.8	0.6–1.6	**1.1–3.4**				0.9–1.8	0.8–1.7	**1.1–2.1**
Social phobia	5.0	**8.3**	5.0	1.7	1.0	**1.7**	6.1	**7.2**	3.75	1.2	**1.6**	**1.9**
				0.9–3.1	0.6–1.4	**1.1–2.8**				0.9–1.6	**1.2–2.2**	**1.4–2.6**
Obsessive–compulsive disorder	5.9	**11.5**	5.45	**2.2**	1.0	**2.3**	6.1	**8.5**	4.35	**1.4**	**1.4**	**1.9**
				1.3–3.7	0.7–1.4	**1.4–3–6**				**1.04–1.9**	**1.1–1.8**	**1.4–2.5**
Any anxiety disorder[a,b]	**16.9**	**27.5**	20.1	**1.9**	0.8	**1.5**	19.5	**25.8**	17.7	**1.4**	1.1	**1.6**
				1.3–2.8	0.6–0.99	**1.1–2.1**				**1.2–1.7**	0.9–1.4	**1.3–1.9**
Eating disorder	0.7	1.4	0.85	1.9	0.8	1.6	0.7	1.2	0.7	1.5	0.9	1.4
				0.5–8.3	0.3–2.1	0.5–5.4				0.7–3.3	0.4–2.1	0.7–2.8
Binge eating	5.1	**9.6**	5.5	1.8	0.9	**1.7**	7.5	**8.0**	3.8	1.00	**2.1**	**2.1**
				0.99–3.2	0.6–1.4	**1.1–2.8**				0.8–1.3	**1.6–2.8**	**1.6–2.8**
Attention-deficit/hyperactive disorder	1.0	0.9	0.6	1.0	1.3	1.5	1.0	**1.2**	0.3	1.2	**3.1**	**3.8**
				0.2–5.1	0.5–3.1	0.3–6.3				0.6–2.4	**1.3–7.5**	**1.6–9.1**
Alcohol use disorder	2.8	3.3	3.2	1.3	0.8	1.1	**5.2**	4.3	1.75	0.9	**2.9**	**2.4**
				0.5–3.1	0.5–1.3	0.4–2.3				0.6–1.3	**2.0–4.2**	**1.6–3.7**
Substance use disorders	1.8	1.4	1.65	0.8	1.0	0.8	**2.6**	2.4	0.9	0.9	**2.7**	**2.5**
				0.2–2.9	0.5–1.8	0.2–2.7				0.6–1.5	**1.6–4.6**	**1.4–4.3**
Substance or alcohol use disorder[b]	4.0	4.7	4.4	1.2	0.8	1.1	**6.85**	6.0	2.5	0.9	**2.7**	**2.4**
				0.6–2.6	0.5–1.3	0.5–2.2				0.7–1.3	**1.9–3.8**	**1.7–3.4**
Borderline personality disorder[b]	10.8	11.6	9.1	1.1	1.1	1.3	**15.2**	**13.8**	4.9	0.9	**3.4**	**2.9**
				0.7–1.8	0.8–1.5	0.8–2.1				0.7–1.1	**2.7–4.3**	**2.2–3.7**

Clinically relevant values are marked in bold

[a] Includes generalised anxiety disorder, panic disorder, agoraphobia, social phobia and obsessive–compulsive disorder

[b] Variables entered into the stepwise multivariate logistic regression

Table 4 Revised bipolar disorders—current comorbidity by gender

Groups	Males			Females		
	1	2	3	4	5	6
Diagnosis	BP-I-S	BP-II-S	MDD-S	BP-I-S	BP-II-S	MDD-S
N	551	455	986	786	835	1993
	%	%	%	%	%	%
Generalised anxiety disorder	6.8	**10.6**	8.1	8.6	**10.6**	8.9
Panic disorder	9.3	**10.3**	5.2	7.4	**12.4**	9.1
Panic disorder with agoraphobia	4.0	**4.2**	1.6	4.2	**5.8**	4.4
Social phobia	6.2	**6.6**	4.5	6.9	**7.55**	3.4
Obsessive–compulsive disorder	5.85	**7.7**	5.2	6.3	**9.05**	3.9
Any anxiety disorder[a]	19.2	**24.0**	16.5	19.5	**26.6**	18.2
Eating disorder	0.4	0.4	0.3	1.0	1.7	1.0
Binge eating	5.6	3.1	2.4	8.9	10.7	4.4
Attention-deficit/hyperactive disorder	1.8	1.8	0.8	0.5	1.0	0.0
Alcohol use disorder	7.9	7.35	3.1	3.2	2.7	1.1
Substance use disorder	3.3	3.1	1.5	2.1	2.1	0.6
Substance or alcohol use disorder	**9.65**	**9.64**	4.3	**4.8**	**4.1**	1.6
Borderline personality disorder	**12.8**	**11.3**	5.5	**16.8**	**15.2**	4.6
Suicide attempts—lifetime	**33.4**	22.9	16.5	**42.4**	31.7	24.1

Clinically relevant values are marked in bold

[a] Includes GAD, panic, agoraphobia, social phobia and OCD

these results is to suggest a path forward for a more homogeneous diagnosis MDD. In fact, the DSM-5 field trials indicate that the reliability of BP-I and BP-II is larger than that of MDD [12]. Such a process has important clinical implications. It should lead to improved prognosis and treatment response with antidepressants. Similarly, it could contribute to improved testing of new treatments for MDD through excluding enrolment of patients with BD characteristics whose responses to the treatments confound outcome assessments [13–15].

This analysis has uncommon strengths: including a large sample supporting sub-analyses not generally possible in research on differential diagnostic characterisation, and evidence of generally similar results across countries and cultures on all research questions for all analyses conducted to date. The Bridge Study provides evidence-based criteria to differentiate BP-I from BP-II disorders not possible with DSM-IV-TR approaches, which limit the applicable criteria to episode duration and functional impairment during manic/hypomanic episodes. Our detailed assessment of the elements of the hypomanic syndrome allows a new, broader and more precise operational specifier definition for both BP-I and BP-II disorders.

This study provides the largest systematically diagnosed group of patients experiencing (MDD-S) comprised of 2,988 patients. As hypothesised on the basis of the epidemiological data, the reduction in the number of patients meeting MDD-specifier criteria in comparison with the DSM-IV MDD group reduced the rates of bipolar characteristics among them. Family history of mania/hypomania among first degree relatives was reduced from 13.7 % in DSM-MDD patients to 6.2 % in MDD-S patients.

Although the specifier concept classified twice as many MDE patients as BP-I patients, the validators for bipolarity remained comparable between DSM-IV and specifier concepts in terms of a history of mania among first degree relatives, early onset, number of episodes, illness progression, duration of episodes and presence of free intervals. The same is true when comparing DSM-IV BP-II with BP-II-S patients, although the latter group is almost six times larger.

We conclude from these findings that BP-I and BP-II disorders defined by the specifier concept are both more valid regarding their distinction from MDD than the corresponding DSM-IV groups.

One of the most striking and possibly heuristic findings in these analyses is the high comorbidity of BP-II disorders with all forms of anxiety disorders, in contrast to high comorbidity limited to social phobia and OCD for BP-I disorders, apparent using either the DSM-IV or specifier diagnostic classification. Lifetime anxiety disorders, more

Table 5 Results of multivariate logistic regression

	DSM-IV TR diagnoses			Specifier diagnoses		
	BP-I versus BP-II	BP-I versus MDD	BP-II versus MDD	BP-I-S versus BP-II-S	BP-I-S versus MDD-S	BP-II-S versus MDD-S
N	647 versus 212	591 versus 4,209	208 versus 4,452	1,229 versus 1,204	1,136 versus 2,499	1,173 versus 2,595
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Family and personal history						
Family history of mania/hypomania	5.5 (4.2–6.8)	2.1 (1.7–2.6)	1.7 (1.2–2.4)	1.5 (1.2–1.8)	5.3 (4.2–6.8)	3.4 (2.7–4.3)
First depressive symptoms <age 30		1.5 (1.2–1.9)		1.5 (1.2–1.9)	1.7 (1.4–2.2)	
More than 2 depressive episodes	2.3 (1.4–3.7)	3.7 (2.7–5.0)	1.7 (1.2–2.4)	2.7 (2.0–3.5)	4.8 (3.6–6.3)	1.6 (1.3.–1.9)
History of suicide attempts	1.5 (1.0–2.1)			1.5 (1.3–1.8)	1.5 (1.2–1.8)	
Ever hospitalised for depression	1.7 (1.4–2.2)					
Depressive episode						
Duration ≤1 month	1.7 (1.2–2.3)	1.8 (1.5.–2.1)		1.7 (1.4–2.0)	2.1 (1.7–2.6)	
Atypical depression	1.5 (1.0–2.2)			1.2 (1.0–1.5)	1.4 (1.1–1.7)	1.3 (1.1–1.5)
Mood lability		1.3 (1.0–1.5)		1.4 (1.2–1.7)	2.6 (2.1–3.1)	1.6 (1.4–2.0)
Psychotic syndrome	2.7 (1.6–4.4)	1.7 (1.3–2.1)	0.7 (0.4–1.1)[a]	1.8 (1.4–2.2)	1.7 (1.3–2.2)	
Hypomania under ADs				1.3 (1.1–1.6)	0.3 (0.2–0.4)	0.2 (0.16–0.24)
Seasonality					1.4 (1.1–1.7)	1.4 (1.2–1.7)
Mixed state		1.3 (1.1–1.6)	1.4 (1.1–1.9)		1.8 (1.5–2.2)	1.8 (1.5–2.2)
Comorbidity						
Anxiety disorder	0.5 (0.3–0.7)	0.7 (0.6–0.9)	1.4 (1.0–1.9)	0.7 (0.6–0.8)	0.8 (0.6–0.9)	1.3 (1.0–1.5)
Any substance/alcohol use disorders					2.5 (1.6–3.9)	2.2 (1.5–3.3)
Borderline personality disorder					1.4 (1.0–1.9)	1.6 (1.2–2.1)
Age	1.02 (1.006–1.032)	1.009 (1.001–1.017)		0.98 (0.97–0.99)	1.01 (1.002–1.019)	1.02 (1.01–1.03)
Sex	1.4 (1.0–2.0)	1.4 (1.2–1.7)		1.4 (1.2–1.6)	1.8 (1.5–2.1)	1.2 (1.0–1.4)

[a] Statistics: all ORs were significant with at least $p < 0.05$, with exception of psychotic syndromes: $p < 0.10$

than any other axis I condition, are highly comorbid with BDs [4]. Panic disorder is much more prevalent in patients with bipolar illness than in the general population; obsessive compulsive disorder is eight times more prevalent [16]. Concomitant anxiety disorders are associated with greater illness severity than bipolar patients without anxiety disorders [4, 17]. Additionally, anxiety disorders are predictive of poor outcomes, including lower likelihood of recovery from depression, increased risk of relapse in patients who recover from an acute episode and impaired quality of life and role function [18–21]. Social phobia, panic symptomatology and PTSD appear most associated with impaired quality of life and time to recovered status [18, 20]. None of these studies separately examined comorbidities in bipolar-I and bipolar-II patients, nor analysed discrete anxiety disorders separately. An epidemiological study in Finland found mixed mania most associated with anxiety symptomatology and poorer function [22].

A small number of studies have examined anxiety disorders separately rather than collectively. The proportion of patients in whom the onset of anxiety disorders preceded hypomania was highest for social anxiety (95 %) compared with half for obsessive–compulsive disorder and only one quarter of patients for panic-agoraphobia [23]. The antecedent appearance of social phobia/anxiety in childhood among persons eventually diagnosed as having BDs indicates that this component part of bipolar symptomatology is a harbinger of syndromal BD, and suggests that such bipolar subtypes are more severe. Although these earlier studies support discrete, rather than agglomerated consideration of anxiety disorder, none addressed the distinct profile which we report.

Social phobia was elevated in BP-I versus MDD, but not the other anxiety conditions. In contrast, BP-II shows elevations across the spectrum of anxiety syndromes. Bipolar patients with early illness displayed significantly more fear of uncertainty and were shyer than patients with late onset than either late onset bipolar or healthy controls [24]. Population-based phenotypic and factor-analytic studies indicate two sub-components of anxiety disorders: fear diagnoses and anxiety-misery disorders [25]. In sum, these marked differences in patterns of comorbid anxiety suggest that elements of underlying pathophysiology may be involved. These differences may aid in better characterising pathophysiology as well as targeting intervention strategies for BP-I and BP-II, respectively.

Both investigators and clinicians are disadvantaged consequent to the historically low consideration of anxiety in BD. Indeed, a primary reason that recent studies that have reported linkages of BD with anxiety states, particularly social anxiety, panic disorder and PTSD use methods that assess for syndromal states, rather than focus on domain, or dimensional methodologies, is that DSM-IV-TR criteria for BD do not include any item for anxiety. Additionally, no criterion for social withdrawal, which may in part be consequent to social anxiety, is present for any BD syndrome, including for depressive episodes in BD. None of the most frequently used scales for mania has an item for anxiety. Only one of the items on the most commonly used depression scale, the MADRS, deals with anxiety. The MADRS has no item for reduced social interest.

Comparing BP-I and BP-II disorders, the patterns of *comorbidity* are relevant to clinical diagnosis and provide new information about the burden of bipolarity. This study assessed only concurrent, not lifetime comorbidity by the MINI diagnostic interview. To our surprise, the DSM-IV BP-I group did not differ much in their simultaneous comorbidity from the MDD group. For instance, we expected a clear association of BP-I disorders with substance use disorders, which was not present at all. Only generalised anxiety disorders were less strongly associated with BP-I than MDD, whereas suicide attempts were more strongly associated with BP-I than with MDD. Of interest, DSM-IV BP-II disorders were significantly associated with the full spectrum of anxiety disorders (panic with agoraphobia, social phobia, OCD) and also with binge eating.

The specifier BP-II-S group had consistently higher ORs than did the DSM-IV classification, including significant associations with all subgroups of anxiety disorders. In contrast, the BP-I-S group was only associated with social phobia and OCD but not with GAD or panic. On the other hand, binge eating and substance use disorders were clearly associated with BP-I-S and BP-II-S, as well as ADHD and borderline personality disorder. The association of both BP disorders with binge eating is interesting in the light of research, using the hypomania checklist 32, on severely obese patients seeking surgical treatment by Alciati et al. [26]. Of further interest is the strong comorbidity of BP-I-S and BP-II-S with borderline personality disorders (ORs 3.4 and 2.9, respectively). It is compatible with the results of the follow-up study by Michael Stone [27]. It is also noteworthy that the comorbidity patterns of BP-I-S and BP-II-S were reproducible across gender.

This study has *substantial strengths and some limitations*. The exceptionally large sample, standard assessment battery applied by fully trained psychiatrists, and likelihood that the lack of exclusionary criteria resulted in enrolment of bipolar patients with the full spectrum of bipolar symptomatology rather than a milder spectrum that too often characterises clinical trials all constitute major strengths. One limitation is that the study included only treated MDE patients; it may not be generalisable to untreated MDE subjects. It also did not assess psychotic manic symptoms and concurrent mixed symptoms. Our

results need confirmation by community studies assessing brief episodes (1–3 days) of hypomania.

In conclusion, the broader specifier definitions of BP-I and BP-II disorders yielded consistently valid and clinically relevant results, particularly important given the high rates of comorbid disorders in BD. The results provide novel evidence that the forms of current comorbid anxiety disorders differ substantially between bipolar-I and bipolar-II disorders, and similarly between bipolar-I and bipolar-II versus MDD patients.

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Conflict of interest **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, Lundbeck AstraZeneca and Bristol-Myers Squibb, and as a consultant for Sanofi-Aventis; 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; 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; 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, Ferrer, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck Sharpe and Dohme, Novartis, Organon, Otsuka, Pierre-Fabre, Pfizer, Roche, Sanofi-Aventis, Servier, Shering-Plough, Shire, 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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