Differences in Axis I and II Comorbidity Between Bipolar I and II Disorders and Major Depressive Disorder

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Objective: To obtain a comprehensive view of differences in current comorbidity between bipolar I and II disorders (BD) and (unipolar) major depressive disorder (MDD), and Axis I and II comorbidity in BD in secondary-care psychiatric settings.

Method: The psychiatric comorbidity of 90 bipolar I and 101 bipolar II patients from the Jorvi Bipolar Study and 269 MDD patients from the Vantaa Depression Study were compared. We used DSM-IV criteria assessed by semistructured interviews. Patients were inpatients and outpatients from secondary-care psychiatric units. Comparable information was collected on clinical history, index episode, symptom status, and patient characteristics.

Results: Bipolar disorder and MDD differed in prevalences of current comorbid disorders, MDD patients having significantly more Axis I comorbidity (69.1% vs. 57.1%), specifically anxiety disorders (56.5% vs. 44.5%) and cluster A (19.0% vs. 9.9%) and C (31.6% vs. 23.0%) personality disorders. In contrast, BD had more single cluster B personality disorders (30.9% vs. 24.6%). Bipolar I and bipolar II were similar in current overall comorbidity, but the prevalence of comorbidity was strongly associated with the current illness phase.

Conclusions: Major depressive disorder and BD have somewhat different patterns in the prevalences of comorbid disorders at the time of an illness episode, with differences particularly in the prevalences of anxiety and personality disorders. Current illness phase explains differences in psychiatric comorbidity of BD patients better than type of disorder.

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Unipolar and bipolar mood disorders are highly comorbid.[1,2] This co-occurrence of mental syndromes is important for both theoretical and clinical reasons. In investigating possible etiologic and phenomenological continuities and differences between major depressive disorder (MDD) and bipolar disorder (BD), information on patterns of comorbid disorders and the possible dependence of these patterns on illness episodes, phases, subtypes, or other factors, such as sex, is required. From a clinical perspective, presence of comorbidity has a profound impact on course, prognosis, outcome, and quality of episodes of mood disorders,[3–9] increasing health care utilization[10] and complicating treatment.[6,11–13] To date, the psychiatric comorbidity of unipolar MDD has been more extensively investigated, whereas the picture of differences in the overall pattern of comorbidity between bipolar I and II disorders and between unipolar disorder and BD still appears more fragmentary.

Half of patients with MDD in psychiatric care are estimated to suffer from a current anxiety or personality disorder, and about one fifth are estimated to have a current substance use disorder (reviewed in Melartin et al.[14]). In BD (recently reviewed in McIntyre et al.,[12] Bauer et al.,[15] and Krishnan[16]), most studies have been conducted using DSM-III-R criteria, bipolar II has almost always remained underrepresented, and the estimates of prevalence of comorbid disorders in psychiatric settings may be skewed by the imperfect recognition of BD.[17] Few studies

of BD[3,15] describe the overall pattern of current comorbidity, although the current prevalences correspond to the clinical situation better than lifetime prevalences. In clinical studies reporting current comorbidity, total Axis I comorbidity has been estimated to be 40%,[3] anxiety disorders 30%,[3,11] and substance use disorders 4% to 13%.[3,11] One study evaluated the presence of 2 current Axis I disorders in manic and mixed patients,[18] reporting lower prevalences in manic patients, supported by lower lifetime Axis I prevalences in manic patients in another study.[19] Lifetime prevalences of comorbidity in psychotic patients were highest in depressive bipolar I patients and lowest in manic patients.[20] Thus, studies suggest that current illness phase may affect prevalences of Axis I disorders in BD.

Several clinical studies have reported lifetime prevalences of comorbid DSM-IV Axis I disorders in BD,[3,4,11,15,21–23] but information is more conflicting than on current prevalences. Total Axis I lifetime comorbidity in BD patients has been estimated at about 60% to 80%,[3,9,11,15,21] or as low as 35%.[4,24,25] More specifically, estimates of lifetime prevalence of comorbid anxiety disorders vary between 42% to 56%.[3,7,11,15,22] The reported lifetime prevalences of substance use disorders in BD are higher in recent American (33%–72%)[3,10,11,15,21,23,26] than European (15%–26%)[4,9,24,25] clinical studies (for a review with older studies see Cassidy et al.[10] and Bauer et al.[15]). The prevalence of personality disorder appears higher (30%–50%) in studies focusing only on Axis II disorders[26–30] and lower (25%–33%) in studies also including Axis I disorders.[13,24,25] The picture of Axis II diagnoses may also be inflated by the presence of a current mood episode[30]; a more accurate view is most likely achieved by also using other informants.[30] However, the presence of a personality disorder may also influence the likelihood of a mood episode. No differences between bipolar I and II have been found in total Axis I[3,4,21] and substance use disorders,[3,4,21,23] but anxiety disorders have been reported to be either equally distributed[3,4,21] or even 2-fold in bipolar II.[22,23] Some gender differences in comorbidity might also exist, men having more substance use disorders[1,10] and women more anxiety disorders.[1]

Some epidemiologic studies have assessed differences in comorbidity between MDD and BD. The study with the largest number of bipolar subjects[2] reported those with MDD to have more comorbid Axis I and total anxiety disorders than those with BD, in contrast to other epidemiologic findings.[1,31,32] In these studies, substance use disorders were more prevalent, up to 60%, in BD.[1,32] In the epidemiologic studies in which differences in only a single comorbid disorder were reported, BD patients had twice as much panic disorder,[33] obsessive-compulsive disorder,[34] social phobia,[8] and substance use disorders[35] as MDD patients. However, no clinical study has, to our knowledge, compared the overall comorbidity profile of unipolar and bipolar mood disorders; only 2 clinical studies on anxiety disorders were available.[36,37] Both studies reported lifetime anxiety to be more prevalent in MDD, in one (comparing psychotic patients) 92% in MDD and 79% in BD,[37] and in the other (made retrospectively and based on patient charts) 48% in MDD, 48% in bipolar II, and 12.5% in bipolar I.[36] One genetic study with a mixed sample of acute and euthymic patients reported several distinct anxiety disorders to be more prevalent in BD.[38] On Axis II, MDD patients may have more cluster C, and BD patients more cluster B, personality disorders.[27,39] The overall picture of MDD-BD differences is conflicting and fragmentary due to variation in diagnostic, inclusion, and exclusion criteria; treatment settings; and time periods investigated and because focusing on single comorbid disorders may result in inflated estimates of prevalence.[14] Thus, the existence and quality of differences in the overall comorbidity of mood disorders or bipolar I and II remain uncertain.

In the present study, we investigated bipolar I, bipolar II, and MDD patients in secondary-care psychiatric settings, with previously undiagnosed patients included. We aimed to obtain a comprehensive view of the differences in current comorbidity with all types of incident illness episodes. We hypothesized (1) BD to have more alcohol dependence, anxiety, and cluster B personality disorders, (2) MDD to have more cluster C personality disorders, and (3) the current illness phase to markedly affect the comorbidity of BD patients.

METHOD

The patients in this report came from 2 separate but comparable cohorts: those with BD from the Jorvi Bipolar Study (JoBS) and those with MDD from the Vantaa Depression Study (VDS). Both are collaborative research projects of the Mood Disorder Research Unit of the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki, Finland, with the last author as the principal investigator. JoBS was carried out with the Department of Psychiatry, Jorvi Hospital, and VDS was carried out with the Department of Psychiatry of the Peijas Medical Care District, both a part of Helsinki University Central Hospital (HUCH). The Ethics Committee of HUCH approved the study protocols in 1996 (VDS) and 2001 (JoBS).

The baseline findings and detailed methodology of JoBS and VDS have been reported elsewhere.[14,17] A summary of the methodology is provided in Table 1. In brief, patients were screened for MDD (VDS) or BD (JoBS) in an acute mood episode. After a positive screen, or suspicion of an incident episode, the patient was fully informed about the study project and a written informed consent was obtained. In the second phase, we made a diagnosis using all available information from face-to-face inter-

Table 1. Methods Used in the Jorvi Bipolar Study (JoBS) and the Vantaa Depression Study (VDS)

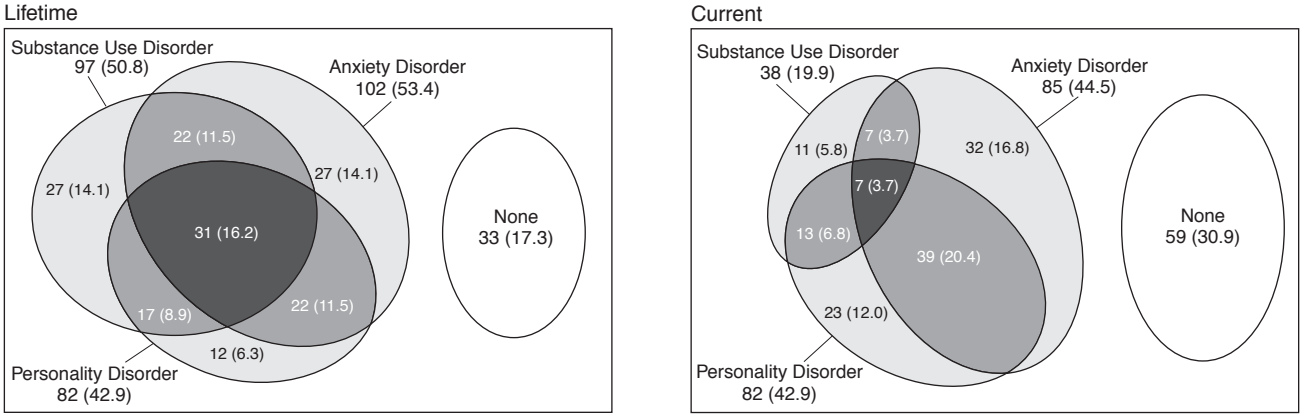
Phase	JoBS [17]	VDS [14]
Timing of screening	Jan 1, 2002–Feb 28, 2003	Feb 1, 1997–May 31, 1998
Catchment area	Adjacent cities of Espoo, Kauniainen, and Kirkkonummi (population 261,100 in 2002)	City of Vantaa (population 169,000 in 1997)
Setting	Department of Psychiatry, Jorvi Hospital, Helsinki University Central Hospital, Espoo, Finland	Department of Psychiatry of the Peijas Medical Care District, Helsinki University Central Hospital, Vantaa, Finland
Target group	All psychiatric patients aged 18–59 years (1) seeking treatment, (2) referred to treatment, or (3) already in treatment with an acute deteriorating clinical state	All psychiatric patients aged 20–59 years (1) seeking treatment, (2) referred to treatment, or (3) already in treatment with an acute deteriorating clinical state
Exclusion from screening	ICD-10 schizophrenia	ICD-10 schizophrenia, bipolar I
Screening procedure	(1) Mood Disorder Questionnaire,[50] 7/13 items positive, or (2) Clinical suspicion of BD (N = 28)	(1) Five screening questions for depression from SCAN,[40] 1 positive, or (2) Scale for Suicide Ideation,[61] score ≥ 6
Total screened	1630	806
Screened positive	546	703
Refusals	Screening 46 (2.8% of the screened), interview 49 (9.0% of positive screens)	Clinical screening, interview 161 (22.9% of eligible patients)
Diagnostic interview	After informed consent, DSM-IV (SCID-I/P[41] and SCID-II[48])	After informed consent, DSM-IV (Axis I, SCAN) and DSM-III-R (SCID-II,[47] modified to DSM-IV)
Inclusion criteria	DSM-IV BD type I or II with a new depressive, manic, hypomanic, mixed, or depressive mixed[42] episode of BD	DSM-IV MDD with a new depressive episode
Cohort	90 BD I and 101 BD II inpatients and outpatients	269 inpatients and outpatients with MDD
Diagnostic reliability	20 videotaped diagnostic interviews; kappa coefficient for BD = 1.0, bipolar I = 1.0, and bipolar II = 1.0; not tested for comorbidity	20 videotaped diagnostic interviews; kappa coefficient = 0.86 (95% CI = 0.58 to 1.00); not tested for comorbidity
Symptom assessment	Young Mania Rating Scale,[46] Hamilton Rating Scale for Depression,[43] Beck Depression Inventory,[44] Beck Anxiety Inventory[45]	Hamilton Rating Scale for Depression,[43] Beck Depression Inventory,[44] Beck Anxiety Inventory[45]

Abbreviations: BD = bipolar disorder; MDD = major depressive disorder; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID-I/P = Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition; SCID-II = Structured Clinical Interview for DSM-IV Personality Disorders.

views and psychiatric records; if the diagnosis was uncertain, other informants were contacted. A current episode of MDD was diagnosed (and BD excluded) using the World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (SCAN), version 2.0,[40] and a current episode of BD was diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders, research version with psychotic screen (SCID-I/P).[41] To exclude substance-induced mood disorder, MDD patients who were currently abusing alcohol or other substances were interviewed after 2 to 3 weeks of abstinence. Also included as bipolar II were those bipolar not-otherwise-specified (NOS) patients with recurrent hypomania of 2 to 3 days or depressive mixed states (DMX3 = 3 or more simultaneous intra-episode hypomanic symptoms present for at least 50% of the time during a major depressive episode) as defined by Benazzi and Akiskal.[42] The soft bipolar spectrum was excluded. The final study group included in the analyses consisted of 191 DSM-IV bipolar I and II patients in JoBS and 269 MDD patients in VDS, all with a current episode. The diagnosticians were 9 psychiatrists and 2 psychologists, and interrater agreement in diagnostic interviews was excellent.[14,17] In the third phase of both studies, the current symptomatology of the index episode was evaluated (Figure 1).[43–46]

Current comorbid psychiatric diagnoses were assigned during an acute phase of MDD or BD. However, in case of a manic or mixed episode severe enough to require hospitalization, this second diagnostic interview was conducted at the time the patient was discharged from the hospital, typically after about 3 weeks. The researcher made full DSM-IV Axis I diagnoses (SCID-I/P in JoBS, SCAN in VDS). Due to differences between the diagnostic tools, substance use disorders are comparable only concerning current alcohol dependence, which also influences the total Axis I comorbidity. The SCID-II for DSM-III-R[47] (VDS) or DSM-IV[48] (JoBS) personality disorders was used to assess all comorbid diagnoses on Axis II, which we modified for between-group analyses in 2 diagnoses. Antisocial personality disorder was adapted to DSM-IV criteria by deleting the items "irresponsible parenting" and "failure to sustain a monogamous relationship" and fusing 2 items exploring consistent responsibility from DSM-III (VDS). DSM-IV borderline personality

Figure 1. Lifetime and Current Comorbidity Among 191 Patients With DSM-IV Bipolar Disorder From the Jorvi Bipolar Study[a]



[a]All values shown as N(%).

disorder was changed to DSM-III-R by deleting the item "stress-related paranoid ideation." This affected the prevalences in BD versus MDD comparisons, leaving out no MDD patients with antisocial personality disorder but leaving out 8 BD patients with borderline personality disorder. Within the BD group, unmodified DSM-IV criteria were used in within-group analyses.

The 2 studies were made comparable with some minor modifications. Using the same forms, we gathered information on demographic characteristics, prior illness history, and preceding treatment. Age at illness onset was defined as onset of the first mood episode fulfilling DSM-IV criteria. The patients who declined to participate in the VDS did not differ significantly ($p > .05$) in age or gender from those who consented. In the JoBS, nonparticipants were older than participants.

Altogether, 191 BD and 269 MDD patients were included in the analyses. Females predominated in the MDD group (73.2%) and men in the bipolar I group (55.6%). Age at intake increased from bipolar II to MDD patients (median age: bipolar I, 38.0; bipolar II, 35.0; MDD, 40.0 years).

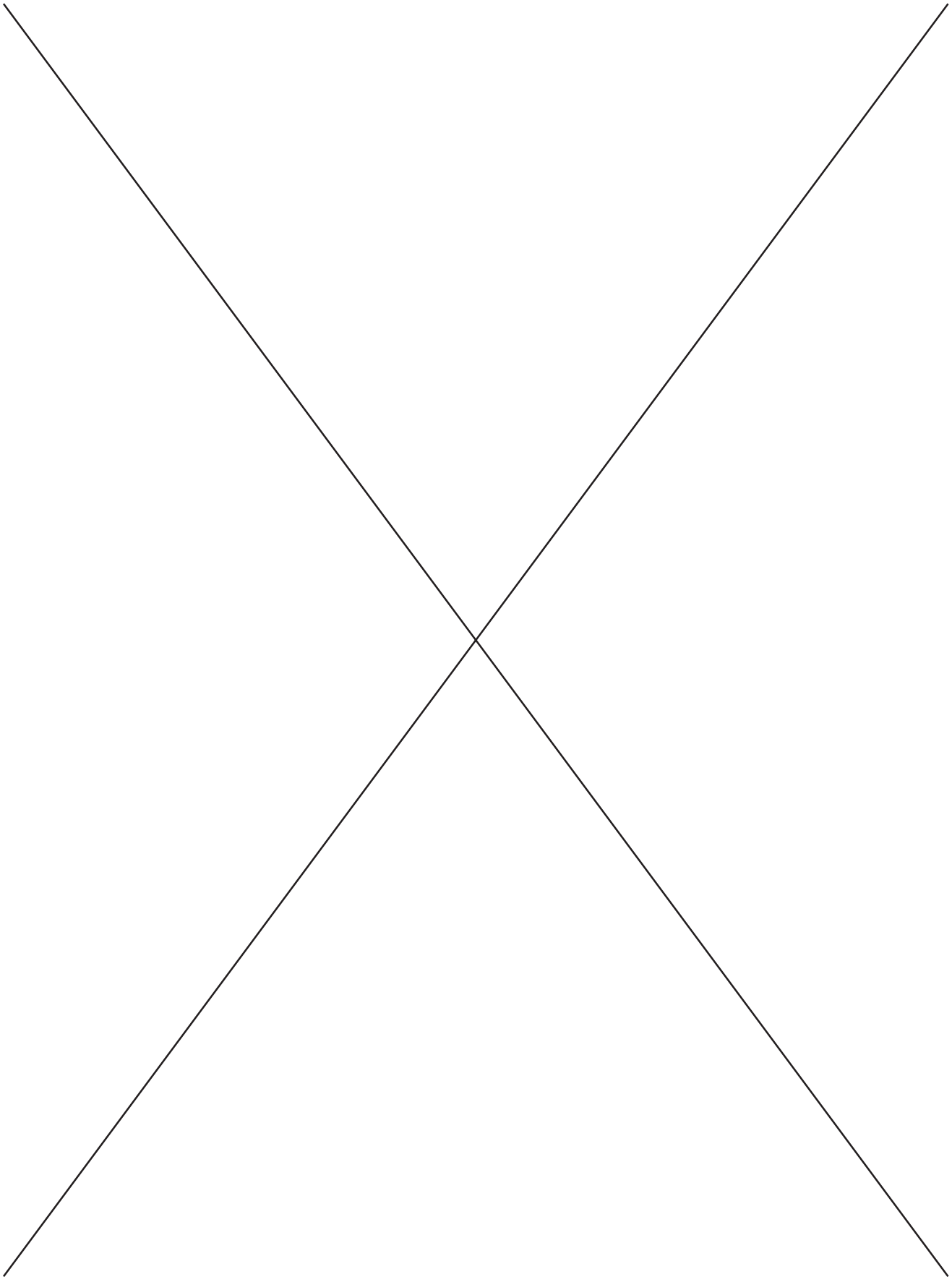
Statistics

Univariate analyses were conducted to examine between-group differences in comorbidity comparing (1) bipolar I, bipolar II, and MDD, (2) BD and MDD, and (3) bipolar I and bipolar II, as well as the associations between comorbidity and demographic and clinical variables. The Student t test, the Pearson χ^2 and Fisher exact tests, the Mann-Whitney U test, the 1-way analysis of variance (ANOVA), and the Kruskall-Wallis test were used when appropriate. For descriptive purposes, in the tables we present all p values significant at the $p < .05$ level, irrespective of the high number of statistical tests. The hypotheses proper are tested by using multinomial regression models. A multinomial regression model was created, classifying the dependent variable of major diagnosis into 3 categories: MDD, bipolar I, and bipolar II. The predetermined independent variables comprised gender, age at intake, professional education, and income; Beck Depression Inventory, Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$), or current phase; any anxiety disorder, any somatoform disorder, any eating disorder, alcohol dependence, and cluster A, B, and C personality disorders. Variables that were not significantly associated with the independent variable were omitted from the final model, in which the Beck Depression Inventory was forced into the model to adjust for the effect of current illness phase. In a secondary analysis, we also evaluated the effect of other aspects of severity (psychotic symptoms, treatment setting, Social and Occupational Functioning Assessment Scale of DSM-IV [SOFAS] score, and marital status) on comorbidity. The Statistical Package for the Social Sciences (SPSS) software, version 11.0,[49] was used.

RESULTS

Sociodemographic and Clinical Characteristics

The diagnostic groups differed in terms of sex distribution (female bipolar I vs. bipolar II vs. MDD: 44.4% vs. 60.4% vs. 73.2%; $\chi^2 = 25.6$, df = 2, $p < .001$), level of education (university: 22.2%, 10.9%, and 6.7%, respectively; $\chi^2 = 20.9$, df = 8, p = .007), and work status ($\chi^2 = 61.1$, df = 12, $p < .001$), with differences particularly in disability pension (32.2%, 14.9%, 4.9%) and unemployment (12.2%, 12.9%, 21.6%). In addition, age at illness onset (median: 21.2, 21.2, 29.3 years; $\chi^2 = 45.1$, df = 2, $p < .001$) and total number of episodes (median: 5, 4, 2; $\chi^2 = 93.0$, df = 2, $p < .001$) differed significantly. Half (22/47, 46.8%) of depressive bipolar I patients were currently inpatients, compared with 1 in 4 bipolar II (15/59,



25.4%) and 1 in 5 MDD (46/269, 17.1%) ($\chi^2 = 38.0$, df = 2, $p < .001$) patients, and the proportions were similar in the total sample. Bipolar I had twice-as-often current psychotic symptoms (22.2% vs. 10.9% vs. 8.2%; $\chi^2 = 13.1$, df = 2, p = .001); the proportions were similar when only depressed patients were included. No major differences were detected in symptom status of depressive bipolar I, bipolar II, and MDD in Beck Depression Inventory (mean ± SD: 26.7 ± 9.3 vs. 25.7 ± 9.7 vs. 27.7 ± 8.6, NS) and Beck Anxiety Inventory scores (22.6 ± 12.5 vs. 23.4 ± 11.5 vs. 22.4 ± 10.7, NS); the means of HAM-D_{17} differed slightly (21.9 ± 5.6 vs. 20.1 ± 7.5 vs. 19.3 ± 6.2; F = 3.5, df = 2, p = .032).

Bipolar Disorder Versus Major Depressive Disorder Comorbidity

Nearly all comorbid disorders had a slightly different distribution in BD versus MDD patients. To exclude the possibility that the differences were due to type of disorder or current illness phase of BD, the analyses were made 3 times: (1) with total BD, (2) with types I and II separated, and (3) with only depressive BD patients included; the statistical significance of the differences remained mostly the same (Table 2). In univariate analyses, MDD had significantly more current comorbid Axis I disorders (69.1% vs. 57.1%), anxiety disorders, and cluster A and C personality disorders. Bipolar disorder had more eating disorders, somatoform disorders, and cluster B personality disorders. More MDD patients had phobic anxiety disorders (bipolar I vs. bipolar II vs. MDD: 20.0% vs. 26.7% vs. 37.9%, respectively; $\chi^2 = 11.6$, df = 2, p = .003), also when comparing only depressive MDD and BD patients. In depressive MDD patients, phobic disorders were correlated to cluster B (Pearson correlation MDD, 0.14, $p < .05$) and cluster C (Pearson correlation MDD, 0.21, $p < .01$) personality disorders (RR, 3.2 and 1.4, respectively), but not in depressive BD patients.

In nominal regression models with the main categories of comorbidity (Table 3), after adjusting for level of depression, gender, and age, the differences in anxiety disorder, eating disorder, and personality clusters A and B remained significant. The other aspects of severity had no effect on the results and were omitted from the final model.

Comorbidity in Bipolar Disorder

The overall current (Table 2 and Figure 1) and lifetime (Figure 1) comorbidity in BD was high. In BD overall, 69.8% had a current comorbid disorder (unmodified proportions, see Method): on Axis I, 60.2% (bipolar I, 54.4%; bipolar II, 65.3%), and on Axis II, 42.9% (42.2% and 43.6%, respectively). Anxiety disorders were currently present in 44.5%, substance use disorders in 19.9%, and eating disorders in 7.9% of BD patients. Bipolar II had more anxiety disorders, posttraumatic stress disorder, and binge eating. In a logistic regression model with bipolar I and II, after adjusting for gender, age, and Beck Depression Inventory, no significant differences emerged. In substance use disorders, current prevalences were one third of lifetime prevalences, but in anxiety disorders, current and lifetime rates were rather consistent.

The comorbidity in BD was distributed according to current illness phase (Table 4). Manic and hypomanic patients had the lowest prevalences in all main categories of disorders, and mixed and depressive mixed patients combined the highest, with prevalences of total comorbidity of 56.8% and 82.9%, respectively. One fifth of manic/hypomanic patients had an anxiety disorder. This proportion was 2-fold in depressive and 3-fold in mixed patients. In mania, the prevalence of Axis II comorbidity seemed to be 20% lower, composed mainly of cluster B personality disorders. Borderline personality disorder was equally present in mixed/depressive mixed and depressive episodes (29.3% vs. 31.1%, NS).

Axis I Versus Axis II Comorbidity in Bipolar Disorder

Axis I and II comorbidity in BD clustered in several ways (Figure 1). Patients with any Axis II disorder had significantly more alcohol dependence (lifetime: 48.8% vs. 32.1%, $\chi^2 = 5.5$, p = .020), anxiety disorders (lifetime: 64.6% vs. 45.0%, $\chi^2 = 7.3$, p = .007; current: 56.1% vs. 35.8%, $\chi^2 = 7.8$, p = .005), and eating disorders (current: 14.6% vs. 2.8%, $\chi^2 = 9.1$, p = .003). Patients with cluster A personality disorder had more eating disorders (current: 21.1% vs. 6.4%, $\chi^2 = 5.1$, p = .024); patients with cluster B had more anxiety (lifetime: 66.7% vs. 48.2%, $\chi^2 = 5.3$, p = .021; current: 53.3% vs. 38.7%, $\chi^2 = 6.6$, p = .010), substance use (lifetime: 66.7% vs. 44.5%, $\chi^2 = 7.6$, p = .006), and eating disorders (current: 18.5% vs. 3.6%, $\chi^2 = 11.8$, p = .001); and patients with cluster C had more anxiety (lifetime: 70.5% vs. 48.3%, $\chi^2 = 6.7$, p = .010; current: 61.4% vs. 39.5%, $\chi^2 = 6.6$, p = .010) and eating disorders (current: 48.2% vs. 15.9%, $\chi^2 = 5.1$, p = .024). Specifically, several comorbid disorders were more prevalent in patients with borderline personality disorder. In a multinomial regression model with borderline personality disorder as a dependent variable, after adjusting for gender and age, substance use disorders (Wald 9.8, df = 1, p = .002, OR 3.4 [95% CI = 1.6 to 7.4]) and anxiety disorders (Wald 4.3, df = 1, p = .038, OR 2.2 [95% CI = 1.0 to 4.7]) during lifetime and cluster A personality disorder (Wald 14.3, df = 1, $p < .001$, OR 9.4 [95% CI = 2.9 to 30.2]) remained significant.

DISCUSSION

We found patterns of psychiatric comorbidity of BD and MDD to differ somewhat qualitatively. Major depressive disorder patients had more current Axis I disorders, specifically anxiety disorders, and more cluster A

Table 2. Current DSM-IV Axis I and II Comorbidity in 269 MDD Patients in the Vantaa Depression Study and 191 Bipolar Patients and 106 Bipolar Currently Depressive Patients in the Jorvi Bipolar Study

	Bipolar I (N = 90)		Bipolar II (N = 101)		Total Bipolar (N = 191)		Depressive Bipolar (N = 106)		MDD (N = 269)		Significance					
											Bipolar I vs Bipolar II vs MDD[a]		BD vs MDD[b]		Depressive BD vs MDD[c]	
Diagnosis	N	%	N	%	N	%	N	%	N	%	χ^2	p	χ^2	p	χ^2	p
Any comorbid Axis I diagnosis	46	51.1	63	62.4	109	57.1	59	55.7	186	69.1	9.7	.008	8.3	.004	6.1	.013
Dysthymia	5	5.6	5	5.0	10	5.2	6	5.7	32	11.9	6.0	.05	6.0	.015		–
Any anxiety disorder	32	35.6	53	52.5	85	44.5	47	44.3	152	56.5	11.9	.003	6.4	.011	4.5	.034
Panic disorder	17	18.9	29	28.7	46	24.1	27	25.5	45	16.7	6.7	.035	3.8	.051	3.7	.053
Agoraphobia without panic	3	3.3	1	1.0	4	2.1	1	0.9	31	11.5	14.5	.001	14.1	< .001	10.9	< .001
Social phobia	13	14.4	21	20.8	34	17.8	19	17.9	53	19.7		–		–		–
Simple phobia	5	5.6	10	9.9	15	7.9	9	8.5	68	25.3	23.5	< .001	23.0	< .001	13.1	< .001
OCD	3	3.3	1	1.0	4	2.1	4	3.8	18	6.7		–	5.2	.023		–
GAD	12	13.3	17	16.8	29	15.2	17	16.0	37	13.8		–		–		–
PTSD	5	5.6	15	14.9	20	10.5	12	11.3	2	0.7	32.2	< .001	23.2	< .001	23.7	< .001
Eating disorder	4	4.4	11	10.9	15	7.9	10	9.4	2	0.7	21.4	< .001	15.9	< .001	18.5	< .001
Any somatoform disorder	3	3.3	6	5.9	10	5.2	5	4.7	0	0	14.6	.001	14.4	< .001	12.9	< .001
Alcohol dependence	15	16.7	12	11.9	27	14.1	13	12.3	38	14.1		–		–		–
Any comorbid Axis II diagnosis	38	42.2	40	39.6	78	40.8	45	42.5	117	43.5		–		–		–
Cluster A	10	11.1	9	8.9	19	9.9	12	11.3	51	19.0	7.2	.03	7.0	.008		–
Paranoid	9	10.0	9	8.9	18	9.4	11	10.4	47	17.5	6.0	.05	6.0	.015		–
Schizoid	1	1.1	0	0	1	0.5	1	0.9	5	1.9		–		–		–
Schizotypal	1	1.1	0	0	1	0.5	1	0.9	0	0		–		–		–
Cluster B	27	30.0	20	19.8	47	24.6	29	27.4	39	14.5	10.8	.005	7.5	.006	8.5	.004
Antisocial	4	4.4	2	2.0	6	3.1	5	4.7	4	1.5		–		–		–
Histrionic	1	1.1	1	1.0	2	1.0	1	0.9	5	1.9		–		–		–
Borderline	23	25.6	19	18.8	42	22.0	27	25.5	32	11.9	10.0	.007	8.4	.004	10.6	.001
Narcissistic	3	3.3	0	0	3	1.6	1	0.9	4	1.5		–		–		–
Cluster C	18	20.0	26	25.7	44	23.0	22	20.8	85	31.6		–	4.6	.032	4.4	.036
Obsessive-compulsive	11	12.2	12	11.9	23	12.0	11	10.4	17	6.3		–		–		–
Dependent	5	5.6	3	3.0	8	4.2	3	2.8	18	6.7		–	10.1	.002		–
Avoidant	8	8.9	15	14.9	23	12.0	14	13.2	64	23.8	1.2	.004		–	5.2	.023
No comorbid disorder	31	34.4	27	26.7	58	30.4	32	30.2	56	20.8	7.0	.030	5.5	.019	3.7	–

[a]df = 2, [b]df = 1, [c]df = 1.
Symbol:– = not significant.
Abbreviations: BD = bipolar disorder, GAD = generalized anxiety disorder, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.

Table 3. Multinomial Regression Model for Current Axis I Comorbidity in 269 Major Depressive Disorder (MDD) Patients in the Vantaa Depression Study and 191 Bipolar Patients in the Jorvi Bipolar Study

	MDD[a]	Bipolar II				Bipolar I			
Variable	OR	OR	95% CI	Wald χ^2	p	OR	95% CI	Wald χ^2	p
Sociodemographic characteristics									
Age	1.0	0.98	0.96 to 1.0	4.0	.05	1.0	0.98 to 1.0	0.04	.85
Sex	1.0	2.0	1.2 to 3.4	6.8	.009	3.3	1.9 to 5.7	17.6	< .001
Clinical status									
Beck Depression Inventory	1.0	0.96	0.93 to 0.98	10.9	.001	0.94	0.91 to 0.95	20.1	< .001
Axis I									
Any anxiety disorder	1.0	0.90	0.54 to 1.5	0.18	.67	0.54	0.31 to 0.95	4.5	.03
Any eating disorder	1.0	30.9	5.8 to 163.7	16.3	< .001	21.4	3.2 to 140.9	10.1	.001
Axis II									
Cluster A	1.0	0.28	0.12 to 0.65	8.7	.003	0.26	0.11 to 0.63	9.1	.003
Cluster B	1.0	2.3	1.1 to 4.6	5.2	.02	6.1	3.0 to 12.4	25.5	< .001

[a]Reference category.

Table 4. Effect of Current Phase on Current DSM-IV Axis I and II Comorbidity in 191 Bipolar Patients in the Jorvi Bipolar Study

	Depressive (N = 106)		Manic or Hypomanic (N = 44)		Mixed or Depressive Mixed (N = 41)		Significance[a]	
DSM-IV Diagnosis	N	%	N	%	N	%	Pearson χ^2	p
Any comorbid Axis I diagnosis	63	59.4	20	45.5	30	73.2	6.8	.034
Any anxiety disorder	47	44.3	10	22.7	28	68.3	17.8	< .001
Panic disorder	27	25.5	4	9.1	15	36.6	9.0	.011
Social phobia	19	17.9	3	6.8	12	29.3	7.3	.026
Any eating disorder	10	9.4	1	2.3	4	9.8		–
Any somatoform disorder	5	4.7	2	4.5	3	7.3		–
Any substance use disorder	19	17.9	10	22.7	9	22.0		–
Any comorbid Axis II diagnosis	50	47.2	14	31.8	19	46.3		–
Cluster A	12	11.3	3	6.8	4	9.8		–
Cluster B	35	33.0	7	15.9	12	29.3		–
Cluster C	22	20.8	10	22.7	12	29.3		–
No comorbid Axis I or II disorder	30	28.3	19	43.2	7	17.1	7.1	.029

[a]df = 2.
Symbol: – = not significant.

personality disorders. In contrast, bipolar patients had more cluster B personality disorders. Bipolar I and II patients were quite similar in comorbidity, the latter being in a slightly intermediate position in terms of total Axis I (but not Axis II) comorbidity. Among bipolar patients, the prevalence of psychiatric comorbidity was strongly associated with the current illness phase.

This is, to our knowledge, a unique clinical study because we were able to compare 3 diagnostic groups (bipolar I, bipolar II, and MDD) in terms of DSM-IV Axis I and II psychiatric comorbidity. A major strength of the study was also that it involved a large pooled sample (N = 460) of MDD and BD patients who effectively represented psychiatric patients of districts that provide free-of-charge, secondary-care psychiatric services in community mental health centers. The representativeness of both patient samples was assured by screening all eligible patients of the catchment area,[40,50] uncovering many patients previously undiagnosed. All patients were systematically diagnosed using a semi-structured interview completed with several informants in case of uncertainty, and inter-rater reliability of the mood disorder diagnoses was assessed and found to be excellent, although the reliability of the comorbid diagnoses remains unknown. The current symptom status was carefully evaluated, and its effect on comorbidity was explored cross-sectionally.

Some methodological issues need to be addressed. First, screening patients and also including previously clinically undiagnosed BD patients (38.7% of the BD cohort) makes the cohort more representative and may explain some differences in the profile of comorbidity when compared to other studies. Second, since we compare 2 cohorts with separate catchment areas, confirming that the differences found in comorbidity between BD and MDD patients are not due to confounding dissimilarities in their other characteristics or in the 2 treatment organizations is essential. However, adjustment for sociodemographic factors in the regression models had little influence on the findings, and we conclude that it is unlikely that the referral patterns or thresholds for treatment in psychiatric care vary markedly in these 2 neighboring areas. The overall similarity of symptom scores between unipolar[14] and bipolar[17] patients further supports the validity of the comparison. While disorders related to sub-

stances other than alcohol have become more prevalent between the screening for the 2 studies in Finland, substance use disorders overall, as reported also in other European countries,[4,22,24,25] were still less frequent than reported in American BD cohorts.[3,10,11,15,21,23,26] Third, the 2 diagnostic interviews, SCAN[40] and SCID,[41] both generate DSM-IV Axis I diagnoses. However, minor differences between them could slightly affect the prevalences of some single diagnostic groups. In BD-MDD comparisons, some criteria modifications to assure comparability on Axis II were necessary because of the different versions of the SCID-II[47,48] used. We included in total Axis I comorbidity current alcohol dependence instead of total substance use disorders, and modifications lowered total Axis II comorbidity and the prevalence of borderline personality disorder in BD by 2% to 3%. Fourth, a current illness phase of patients affects comorbidity ratings; for example, patients often deny symptoms while in a manic state,[19] and depression and anxiety seem to be related.[6] Rating was, however, done deliberately in both groups to investigate the persistence of comorbid disorders in follow-up. Furthermore, patients were met twice, and comorbid disorders were assessed in a later subacute phase. We also compared depressive BD and MDD patients, and in the regression models, we adjusted for current illness phase. We emphasize that the diagnoses of personality disorder were based on multiple sources of information and a longitudinal view of patients' functioning during euthymic phases, not on current behavior. For example, borderline personality disorder shares affective lability with BD, possibly reflecting similarities in temperamental profile,[51–53] but this may be differentiated from mood disorders by impulsivity and aggressiveness between mood episodes.[51,54] We diagnosed comorbid borderline personality disorder in BD strictly according to DSM-IV criteria; thus, impulsivity and affect lability had to be present during the interepisodic time. Despite our best efforts, we cannot, however, totally exclude the possibility that the current state might have colored our perception of personality. Compared with studies of strictly euthymic patients,[13,24–30] the overall level of Axis II comorbidity here was intermediate. Overall, our design was constructed as closely as possible to the situation in which a clinician meets mood disorder patients during the acute phase. Fifth, a methodological difficulty resulted from overlapping time periods of an index episode and the SCID definition of a current disorder being present during the last month. Finally, multiple testing for descriptive purposes might result in spurious differences regarding single disorders. Thus, a multinomial regression model, based on our hypotheses, including only the main diagnostic categories, and adjusting for confounding factors, constitutes our main findings.

Both unipolar and bipolar mood disorders appear to be highly comorbid, and their profiles of comorbidity are somewhat different. Overall, a current Axis I comorbidity was more prevalent in MDD than BD (69% vs. 57%). In our MDD cohort, the prevalences were convergent with those previously reported, with the prevalence of personality disorder being somewhat lower and that of alcohol disorders being higher than the weighted means of prevalences reported earlier.[14] In the BD cohort, the prevalence of any comorbidity on Axis I was relatively high,[3,11] and on Axis II (42.9%) intermediate compared with clinical studies of euthymic-phase patients.[13,24–30] To the best of our knowledge, this is the largest clinical study reporting differences in anxiety and the first to examine differences in alcohol dependence and eating disorders between BD and MDD. In line with previous literature, MDD patients had more anxiety disorders,[36,37] but BD patients had more panic disorders.[33,38] Panic disorder and posttraumatic stress disorder were especially prevalent in bipolar II. The similarity of prevalences of alcohol dependence was unexpected.[1,10,32,35] However, for methodological reasons, we were unable to exclude a possible difference in abuse. Although the magnitude of comorbidity in Axis I disorders is clearly influenced by the current illness phase, when comparing only depressive BD and MDD, the differences in comorbidity remained consistent in quality and quantity. Current illness phase and gender were controlled for in our final analyses.

As we hypothesized, the 3 clusters on Axis II appeared differently distributed between MDD and BD. Unlike previous reports on inpatients, in which MDD had more Axis II comorbidity,[39,55] we found no significant differences in total prevalences of Axis II disorder. However, we found more borderline personality disorder among BD than MDD patients, which is in accordance with 1 outpatient[56] but no inpatient studies.[27,39,55] Furthermore, among BD patients, borderline personality disorder was associated with substance use disorders, anxiety disorders, and cluster A personality disorders. Also, BD patients seemed to have eating disorders more often than those with MDD. In contrast, phobic anxiety disorders were associated with cluster B and C personality disorders only among MDD patients. Overall, the findings are convergent with the idea that the temperamental profile underlying clusters of personality disorders might be more concentrated on cluster B in BD but be broader in MDD. including more cluster C and cluster A. Some shared temperamental features[51,52,57–59] might explain differences between MDD and BD as well as comorbid and non-comorbid mood disorders, but they were not assessed in this study. Alternatively, mental disorders may be classified into clusters of internalizing or externalizing disorders, both of which may share their own pool of susceptibility genes.[60] The comorbid disorders related to BD may include more externalizing disorders than those of MDD, particularly in the hypomanic or manic phases. Whether this is more a permanent trait-like characteristic of the patient, or a phenomenon related to the illness phases, needs to be investi-

gated in longitudinal studies. Finally, in line with a previous report,[22] we found no evidence for the theory that increasing any aspect of severity would markedly increase overall comorbidity.

Despite somewhat different clinical pictures, bipolar I and II did not differ significantly in terms of comorbidity profile.[3,4,21,23] This was true regarding even anxiety disorders, a finding that is supported by many [3,4,21] but not all comparative studies.[22,23] In contrast, the current index phase of BD strongly affected the comorbidity, with Axis I prevalences being highest in patients with a current mixed or depressive mixed episode and lowest in patients with a manic/hypomanic episode.[19] More specifically, only one fifth of manic/hypomanic patients had an anxiety disorder, whereas among patients with depressive and mixed phases, the corresponding proportions were 2-fold and 3-fold, respectively. It is currently not clear to what extent comorbid Axis I disorders are longitudinally connected to the phases of bipolar illness or whether they have a course of their own. Although anxiety disorders were associated with depressive or mixed phases, the ratio of current versus lifetime comorbidity still seemed high. Thus, as also reported earlier,[15] anxiety disorders seemed rather chronic, whereas the prevalences of distinct and total substance use disorders were currently only one third of lifetime prevalences, suggesting a more episodic nature. It is also noteworthy that, among BD patients,[3,7,11,15] some comorbid disorders cluster together with patterns similar to those in MDD.[14] Only a few patients had, for instance, current alcohol use disorder alone, whereas anxiety disorders were the most common as a single disorder. Axis I and II disorders also frequently coexisted. The remarkable cross-sectional and longitudinal complexity of not only the mood disorder per se, but also the concurrent disorders, is a major challenge for a clinician. More longitudinal information is needed on whether the same patients have the same profile of comorbidity when euthymic, whether a comorbidity profile affects the type and course of the current phase, and whether there are differences in stability of comorbid disorders in follow-up.

In conclusion, patterns of psychiatric comorbidity of BD and MDD are likely to differ somewhat qualitatively, and, among BD patients, the prevalence of psychiatric comorbidity is strongly related to the current illness phase. Overall, MDD patients are more likely to have more anxiety disorders and cluster A personality disorders, and BD patients are more likely to have more cluster B personality disorders. Bipolar I and II patients appear to differ little, but bipolar II patients may be in an intermediate position in terms of Axis I comorbidity.

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