Predictors for Switch From Unipolar Major Depressive Disorder to Bipolar Disorder Type I or II: A 5-Year Prospective Study

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Objective: In this naturalistic study, we investigated the rate, time course, and predictors of a diagnostic switch from unipolar major depressive disorder (MDD) to bipolar disorder type I or II during a 5-year follow-up.

Method: The Vantaa Depression Study included at baseline 269 psychiatric outpatients (82.9%) and inpatients (17.1%) with DSM-IV MDD, diagnosed using structured and semi-structured interviews and followed up at 6 months, 18 months, and 5 years between February 1, 1997 and April 30, 2004. Information on 248 MDD patients (92.2%) was available for analyses of the risk of diagnostic switch. Cox proportional hazards models were used.

Results: Twenty-two subjects (8.9%) with previous unipolar MDD switched to bipolar disorder type II and 7 (2.8%) to type I. Median time for switch to bipolar type I was significantly shorter than to type II. In Cox proportional hazards analyses, severity of MDD (hazard ratio [HR] = 1.08, 95% CI = 1.00 to 1.15, p = .036), obsessive-compulsive disorder (OCD) (HR = 5.00, 95% CI = 2.04 to 12.5, p < .001), social phobia (HR = 2.33, 95% CI = 1.00 to 5.26, p = .050), and large number of cluster B personality disorder symptoms (HR = 1.10, 95% CI = 1.02 to 1.20, p = .022) predicted switch.

Conclusion: Among outpatients with MDD in secondary level psychiatric settings, diagnostic switch to bipolar disorder usually refers to type II rather than type I. The few switching to bipolar type I do so relatively early. Predictors for diagnostic switch include not only features of mood disorder, such as severity, but may also include some features of psychiatric comorbidity, such as concurrent social phobia, OCD, and symptoms of cluster B personality disorders.

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A proportion of patients who present with major depressive episode (MDE) will over time develop bipolar disorder. The challenge is predicting the group of patients who are more likely to do this, as the change in diagnosis has practical clinical consequences for both treatment and prognosis.

Several prospective studies have investigated the switch from unipolar major depressive disorder (MDD) to bipolar disorder.[1–6] According to these studies, bipolar disorders begin in about half of cases (51%–60%) with depression and in the other half (34%–79%) with mania. More specifically, bipolar type II begins more often with depression, while in bipolar type I, mania more often precedes depression.[7–12] Men have been reported to have more manic onsets.[13] The polarity of the initial mood disorder episode seems to predict the subsequent features of the clinical picture; subjects with depressive onset of illness have been considered to have more prolonged depressive episodes, more recurrences, and suicidal behavior.[9,14] Median time to first hypomanic or manic episode has been observed to be 5 to 8 years from the onset of first MDE.[8,15] In 2 major studies, the Zurich follow-up study and the National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS), 15.5% and 10.7% of subjects with unipolar MDD switched to bipolar disorder, 7.2% and 3.9% to type I, and 8.25% and 8.6% to type II, respectively.[1,2] Overall, studies that have investigated differences between switch rates to types I and II have found that they range from similar rates to up to 2.3-fold rates to type II and that switch occurs about twice as fast to type I as to type II.[1–4] The risk of diagnostic switch appears to

TAKE-HOME POINTS

- Switch from unipolar major depressive disorder to bipolar II disorder occurs more often than switch to type I.
- Predictors for diagnostic switch include features of mood disorder, such as severity of MDD, and psychiatric comorbidity, such as concurrent social phobia, obsessive-compulsive disorder, and cluster B personality disorder symptoms.

be largest during the first 5 years from age at onset or in childhood and early adulthood (typically 3%–5% per year) and thereafter being constant across the lifetime (about 1% per year). Every new MDE brings a new risk of mania.[1,7] The annual rate of subsequent diagnostic switch from type II to type I has been estimated to be about 2%.[1] Overall, the available literature provides a fairly consistent view of the rate of diagnostic switch, but some important methodological limitations exist.

Most previous studies are from inpatient cohorts,[1–6,16] while only a few studies have investigated bipolar switch among outpatients.[15,17] Studies showing the highest estimates of manic onset have used first hospitalization as the onset criterion. It is thus possible that depressive and hypomanic onsets have been underestimated, as they less frequently necessitate hospitalization.[7] The majority are also tertiary-care studies from major universities, which makes the epidemiologic generalizability of these findings more uncertain, especially regarding bipolar type II.[1,3–6,17] In addition, only a few studies have used life-chart methods,[2,3] possibly leading to onsets of bipolar II being missed due to lack of information on hypomanic episodes. Furthermore, despite psychiatric comorbidity in MDD and bipolar disorders being very common,[18] the predictive value of comorbidity for bipolar switch has been examined surprisingly little in prospective studies.

According to previous research, subjects who are more liable to diagnostic switch are younger and have an earlier age at onset of MDD, more preceding stress, more severe depressions with psychotic or atypical symptoms, more lifetime suicide attempts, more previous MDEs, and a positive bipolar family history.[4–6,15–17,19–23] When differentiating between bipolar disorder subtypes, type I has been predicted by male gender,[1] psychotic symptoms,[1–3] severity and acuteness of symptoms,[1,2] and positive family history[3] and type II has been predicted by female gender,[24] young age,[3] early[2,3,25] or later[1] age at onset, chronicity of index episode,[3] shorter well intervals,[2] atypical or mixed depressive symptoms,[25] and mood lability.[2,26]

Psychiatric comorbidity is very common in both MDD and bipolar disorders. We have previously investigated differences in Axis I and II comorbidity between bipolar I and II disorders and unipolar MDD.[18] Unipolar subjects had more Axis I comorbidity, specifically anxiety disorders and cluster A and C disorders, while bipolar subjects had more cluster B personality disorders. Bipolar I and II disorders were similar in current overall comorbidity, but this was strongly associated with the current illness phase. Bipolar subjects have in other studies been observed to have twice as many comorbid panic disorders, obsessive-compulsive disorder (OCD), social phobia, and substance use disorders as unipolar subjects.[27,28] However, few prospective studies have investigated the role of psychiatric comorbidity in predicting diagnostic switch. A recent study found borderline personality disorder more often than schizotypal, avoidant, or obsessive-compulsive personality disorder to be associated with new onsets of bipolar disorder.[29] However, an overall view of Axis I and II disorders in predicting switch is still missing.

In this naturalistic study, our aim was to investigate the rate, time course, and risk factors for a diagnostic change from unipolar MDD to bipolar disorder during a 5-year follow-up. We hypothesized that higher severity of depression, presence of psychotic and atypical features, lower age at onset, greater number of prior MDEs, current psychiatric comorbidity, and especially symptoms of cluster B personality disorders would be significant predictors.

METHOD

The Vantaa Depression Study is a collaborative depression research project between the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki, Finland, and the Department of Psychiatry of the Peijas Medical Care District (PMCD), Vantaa, Finland. Its background and methodology have been described previously.[30–32]

Screening and Baseline Evaluation

In the first phase of the study, 806 psychiatric subjects were screened for the presence of depressive symptoms during an 18-month period starting on February 1, 1997. The study continued until April 30, 2004. Of the 703 eligible subjects, 542 (77%) agreed to participate and gave their written informed consent.[32] In the second phase, a researcher using the World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (SCAN)

2.0[33] interviewed these consenting patients, 269 of whom were subsequently diagnosed as having DSM-IV MDD and included in the study. At baseline, 82.9% of the subjects were outpatients and 17.1% were inpatients. The baseline interviewers received all relevant training from a World Health Organization–certified training center; this training was supervised by the last author. Diagnostic reliability was investigated by using 20 videotaped diagnostic interviews; the κ coefficient for MDD was 0.86 (95% CI = 0.58 to 1.0), with a 95% observed agreement rate. The Structured Clinical Interview for DSM-III-R personality disorders (SCID-II) was used to assess diagnoses on Axis II.[34] The baseline measurements included the 17-item Hamilton Rating Scale for Depression (HAM-D),[35] 21-item Beck Depression Inventory (BDI),[36] Beck Anxiety Inventory,[37] Beck Hopelessness Scale,[38] Scale for Suicidal Ideation,[39] Social and Occupational Functioning Assessment Scale of DSM-IV,[40] Social Adjustment Scale Self-Report,[41] Interview for Recent Life Events,[42] Interview Measure of Social Relationships,[43] Perceived Social Support Scale-Revised,[44] and Eysenck Personality Inventory.[45] In addition, number of chronic medical disorders (Axis III) was investigated with a checklist. The comorbidities were current with a time frame of 1 month.

Follow-Up

After baseline assessments, subjects were investigated at 6 and 18 months with a life-chart methodology and the scales mentioned above. Of the 269 subjects with current MDD initially included in the study, 229 participated in the 6-month follow-up and 207 in the 18-month follow-up. By 18 months, the diagnoses of 13 subjects (6.2%) had switched to bipolar disorder.[31]

Of the original cohort, 182 subjects participated in the 5-year follow-up interviews. These were performed individually by 2 interviewers (K.H. and I.H.), and all available medical and psychiatric records were used to complement the interview data. The average duration of an interview was 2 to 3 hours, and the interviews were conducted in psychiatric outpatient units. After baseline assessments, the subjects were prospectively followed up with a life chart, and BDI was rated monthly until 6 months; the outcome of MDD and comorbid disorders was then investigated at 6 and 18 months by repeated SCAN 2.0 and SCID-II interviews. In the 5-year follow-up interviews, we used SCID-I (for DSM-IV-TR)[46] instead of SCAN 2.0. All observer and self-report scales were included at follow-up assessments. In addition, information on family history was gathered.

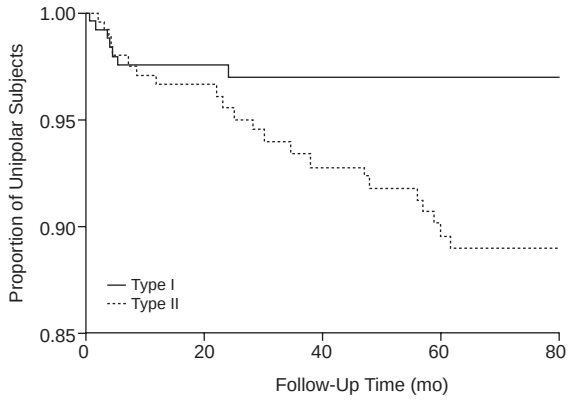
The diagnoses and timing of different mood disorders and episodes were based on these structured interviews and patient records—a graphic life chart was created after reviewing with the subject all information from the follow-up period. The life chart was based on DSM-IV criteria and definitions. Besides using symptom ratings and visiting attending personnel, we also inquired about change points in the psychopathologic states by using probes related to important life events in order to improve the accuracy of the assessment. Our life-chart method was similar, but not identical, to the Longitudinal Interval Follow-Up Evaluation methodology used in the NIMH CDS, developed by Keller et al.[47] Time after the first baseline interview was divided into 4 periods: (1) full remission (none of the 9 MDE criteria symptoms), (2) partial remission (1–4 of the 9 symptoms), (3) MDE (5 or more of the 9 symptoms), and (4) hypomanic, mixed, or manic period. Diagnostic switch to bipolar disorder was defined to occur at the onset of the first lifetime hypomanic, mixed, or manic episode.

Information on 248 of 269 subjects (92.2%) was included in the analyses of the risk of diagnostic switch from unipolar MDD to bipolar disorder. At the 5-year follow-up, 16 subjects were diagnosed with bipolar disorder, 1 with schizophrenia, and 2 with schizoaffective disorder. Ten subjects had died; 1 of them had had bipolar disorder. The median (SD) follow-up time was 64.0 (24.4) months from baseline. Compared with participants, those dropping out from all follow-up interviews (N = 21) were at baseline younger (mean age, 32.6 vs. 40.2 years; $Z = -3.62$; $p = .001$), had a lower age at onset (mean age, 26.5 vs. 32.3 years; $Z = -2.75$; $p = .011$), had more comorbid psychiatric disorders (mean, 3.9 vs. 3.0 disorders; $Z = 2.15$; $p = .032$), had more cases of dysthymia (33.3% vs. 10.1%, $\chi^2 = 9.99$, df = 1, $p = .006$) and social phobia (38.1% vs. 18.1%, $\chi^2 = 4.87$, df = 1, $p = .042$), and were more often not married or cohabiting (81.0% vs. 47.2%, $\chi^2 = 8.83$, df = 1, $p = .003$).

Statistical Methods

We used Kaplan-Meier survival curves to estimate the probability of a diagnostic switch from unipolar MDD to bipolar disorder during the 5-year follow-up. Cox proportional hazards models were used for univariate and multivariate analyses to predict hazard to diagnostic switch. In these analyses, censored data included subjects who left the study before any follow-up interview. All available information on the subjects was used for analyses, and all analyses were controlled for age and gender. Subjects who became bipolar were compared with unipolar subjects by using the χ^2 statistic with Yates continuity correction or Fisher exact test when the expected cell count was less than 5 in the 2×2 table. In comparisons of continuous variables, the 2-sample t test was used for normal distribution and the Mann-Whitney and Kruskal-Wallis tests for nonnormal variables. Univariate logistic regression models were used for analysis of the differences in sociodemographic and clinical characteristics of subjects. An α level of .05 (2-tailed) was used. The baseline predictors represented different domains of risk factors, e.g., sociodemographic features, clinical features of MDD,

Figure 1. Survival Curves of Time to Diagnostic Switch From Unipolar Depression to Bipolar Disorder Types I and II in the Vantaa Depression Study, 5-Year Follow-Up



symptom and functional ability scales, Axis I and II comorbid disorders, number of Axis III disorders, MDD subtype features, and various psychosocial and personality factors. We chose predictors to our model on the basis of our hypothesis as well as clinical and univariate significance. We chose in our final model to treat personality disorder clusters as dimensional, continuous variables on the basis of the number of symptoms in SCID-II interviews. The Statistical Package for Social Sciences (SPSS), version 14.0 (SPSS Inc., Chicago, Ill.), was used.

Table 1. Sociodemographic and Clinical Characteristics of Subjects Who Switched From Unipolar Depression to Bipolar Disorder (N = 29) Versus Unipolar Subjects (N = 219) in the Vantaa Depression Study, 5-Year Follow-Up[a]

Predictor at Entry	OR	95% CI	p
Age	0.98	0.94 to 1.01	.175
Female gender	1.40	0.54 to 3.64	.487
Employed	0.61	0.27 to 1.37	.233
Professional education	1.14	0.51 to 2.52	.748
Income	0.59	0.25 to 1.39	.226
Married or cohabiting	0.73	0.33 to 1.59	.423
Outpatient status	0.73	0.33 to 1.59	.423
Age at onset	0.81	0.66 to 0.99	.041
Number of previous MDEs	1.06	0.88 to 1.29	.519
MDE duration prior to entry	0.88	0.76 to 1.01	.060
Melancholic	1.47	0.67 to 3.25	.338
Psychotic	2.90	0.96 to 8.85	.060
HAM-D	1.10	1.02 to 1.17	.008
Beck Depression Inventory	1.04	0.99 to 1.08	.144
Beck Anxiety Inventory	1.03	1.00 to 1.07	.087
SOFAS	0.99	0.96 to 1.03	.752
Beck Hopelessness Scale	0.99	0.91 to 1.07	.759
Scale for Suicidal Ideation	0.98	0.93 to 1.03	.440
Size of social network	0.97	0.86 to 1.09	.612
PSSS-R	1.00	0.97 to 1.04	.883
Negative life events[b]	1.10	0.99 to 1.21	.067
Neuroticism[c]	1.08	0.96 to 1.21	.192
Extroversion[c]	0.98	0.90 to 1.07	.599

[a]Logistic regression models; all analyses controlled for age and gender and time at risk.
[b]Interview for Recent Life Events: objective measure of negative impact of adverse life events.
[c]Eysenck Personality Inventory: for dimensions of neuroticism and extroversion.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MDE = major depressive episode, PSSS-R = Perceived Social Support Scale-Revised, SOFAS = Social and Occupational Functioning Assessment Scale.

RESULTS

During the 5-year follow-up period 29 subjects (11.7%) with previous unipolar MDD switched to bipolar disorder type I or II. Diagnostic change to bipolar disorder type II compared with type I was 3 times more common: 22 (8.9%) versus 7 (2.8%) subjects, respectively. Thus, the annual incidence of switch was 2.8% (95% CI = 1.86 to 4.04): 0.68% for type I (95% CI = 0.27 to 1.40) and 2.14% for type II (95% CI = 1.34 to 3.23). Four of 7 bipolar disorder type I patients had mixed episodes. The median (SD) time to first hypomanic or manic episode was 22.0 (13.0) months from baseline: to manic, 4.2 (0.5) months and to hypomanic, 25.0 (4.7) months ($\chi^2 = 10.7$, df = 1, p = .001) (Figure 1). The median (SD) time from age at onset to diagnostic switch was 7.7 (1.9) years: to bipolar disorder type I, 2.8 (0.6) years and to type II, 7.7 (2.7) years. Three of the followed-up patients experienced substance-induced hypomanic or manic episodes.

Characteristics

The sociodemographic characteristics of unipolar MDD subjects and bipolar subjects were not significantly different (Table 1). No differences in family history of mood disorders were found. All bipolar disorder type I subjects were female, but this was not statistically significant because of the small number of subjects in this subgroup. The clinical characteristics differed in some respects: bipolar subjects were more often psychotic, had a younger age at onset, and had more severe MDD at baseline (Table 1); especially bipolar disorder type I subjects suffered more at baseline from psychotic symptoms compared with bipolar disorder type II and unipolar subjects (42.9% vs. 9.1% and 6.8%, $\chi^2 = 11.9$, df = 2, p = .003). Somewhat surprisingly, none of the bipolar subjects had atypical MDD at baseline ($\chi^2 = 3.20$, df = 1, p = .086).

Bipolar type II subjects had a significantly higher mean (SD) number of MDEs before the diagnostic switch than type I subjects, i.e., 4.7 (2.7) versus 2.1 (0.7) episodes, (t = –3.77, df = 24, p = .001). Bipolar subjects had significantly more comorbid psychiatric disorders, over 2 times more social phobia, 5 times more OCD, and 2 times more alcohol dependence than unipolar subjects (Table 2). Bipolar disorder type I subjects compared with type II and unipolar MDD subjects had more alcohol dependence (57.1% vs. 13.6% and 11.9%, $\chi^2 = 12.0$, df = 2, p = .002), phobic anxiety disorders (85.7% vs. 45.5%

Table 2. Comorbid Disorders Among Subjects Who Switched From Unipolar Depression to Bipolar Disorder (N = 29) Versus Unipolar Subjects (N = 219) in the Vantaa Depression Study, 5-Year Follow-Up[a]

Predictor at Entry	OR	95% CI	p
Axis I comorbidity	2.43	0.89 to 6.67	.084
Dysthymia	1.20	0.33 to 4.39	.781
Anxiety disorders	1.76	0.77 to 4.08	.182
Phobic/nonphobic	1.99	0.91 to 4.37	.087
Panic disorder	1.71	0.67 to 4.33	.262
With agoraphobia	2.54	0.75 to 8.55	.132
Without agoraphobia	1.07	0.30 to 3.85	.921
Agoraphobia without panic	0.88	0.25 to 3.16	.850
Specific phobia	1.07	0.44 to 2.58	.879
Social phobia	2.87	1.22 to 6.76	.016
Obsessive-compulsive disorder	6.80	2.31 to 20.0	< .001
Generalized anxiety disorder	0.73	0.21 to 2.57	.622
Alcohol use disorders	1.61	0.67 to 3.91	.290
Dependence	2.52	0.94 to 6.71	.066
Abuse	0.62	0.14 to 2.79	.529
Axis II comorbidity			
Personality disorders	1.23	0.56 to 2.71	.609
Cluster A	1.57	0.62 to 4.00	.344
Cluster B	1.21	0.42 to 3.48	.725
Cluster C	1.60	0.72 to 3.56	.253
No. of cluster A symptoms	1.18	1.02 to 1.37	.022
No. of cluster B symptoms	1.23	1.11 to 1.36	< .001
No. of cluster C symptoms	1.10	1.01 to 1.20	.026
No. of psychiatric disorders	1.32	1.08 to 1.62	.007
Axis III comorbidity			
No. of current somatic diseases	0.58	0.30 to 1.14	.112
No. of all Axis I–III disorders	1.16	0.97 to 1.38	.116

[a]Logistic regression models; all analyses controlled for age and gender and time at risk.

Table 3. Significant Baseline Univariate Predictors for Switch From Unipolar Depression to Bipolar Disorder in the Vantaa Depression Study, 5-Year Follow-Up[a]

Predictor at Entry	Hazard Ratio	95% CI	p
HAM-D	1.10	1.03 to 1.16	.003
No. of anxiety disorder symptoms	1.09	1.04 to 1.15	< .001
No. of phobic disorder symptoms	1.10	1.03 to 1.19	.007
Social phobia	2.78	1.27 to 5.88	.010
Obsessive-compulsive disorder	5.88	2.50 to 14.3	< .001
Alcohol dependence	2.94	1.23 to 7.14	.014
Psychotic major depressive disorder	3.33	1.25 to 9.09	.016
No. of psychiatric disorders	1.30	1.08 to 1.56	.004
No. of cluster A personality disorder symptoms	1.16	1.03 to 1.32	.015
No. of cluster B personality disorder symptoms	1.19	1.10 to 1.28	< .001
No. of cluster C personality disorder symptoms	1.09	1.01 to 1.16	.025
Negative life events[b]	1.10	1.00 to 1.19	.048

[a]Cox proportional hazards models; all analyses controlled for age and gender.
[b]Interview for Recent Life Events: objective measure of negative impact of adverse life events.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Table 4. Baseline Multivariate Predictors for Switch Time From Unipolar Depression to Bipolar Disorder in the Vantaa Depression Study, 5-Year Follow-Up[a]

Predictor at Entry	Hazard Ratio	95% CI	p
Severity of unipolar MDD (HAM-D)	1.08	1.00 to 1.15	.036
Obsessive-compulsive disorder	5.00	2.04 to 12.5	< .001
Social phobia	2.33	1.00 to 5.26	.050
Large no. of cluster B personality disorder symptoms	1.10	1.02 to 1.20	.022

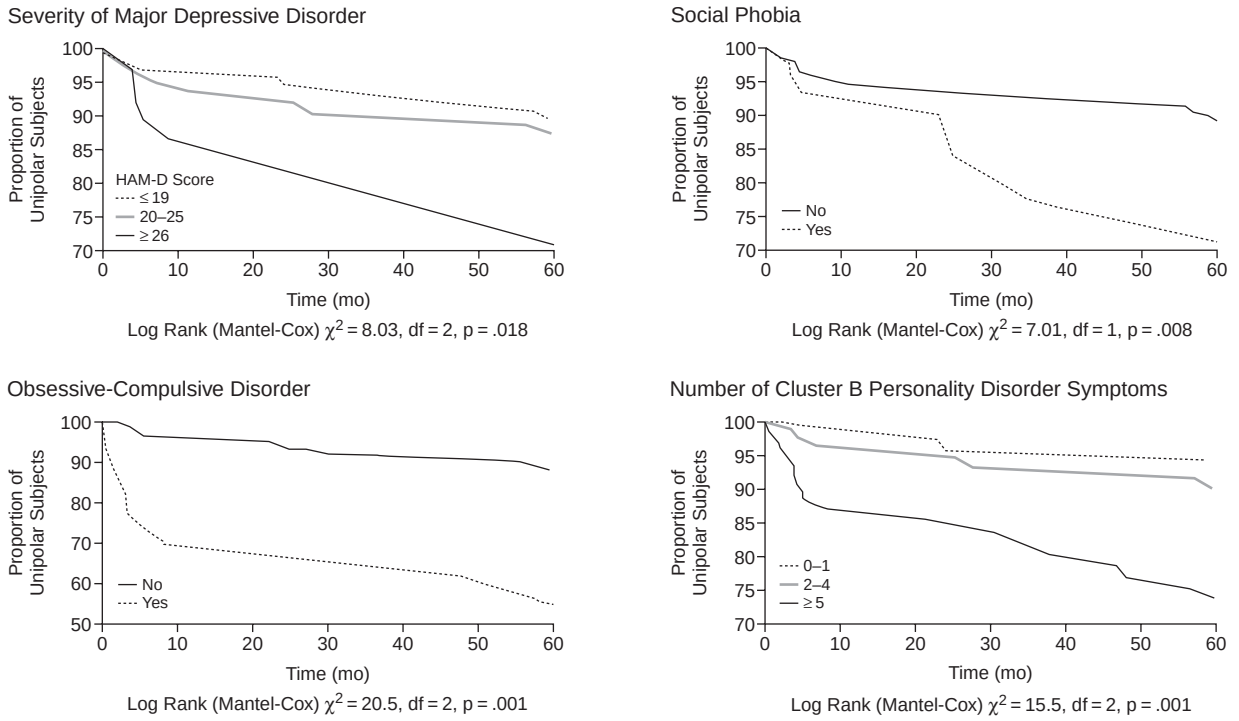
[a]Cox proportional hazards models; all analyses controlled for age and gender.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder.

and 37.4%, $\chi^2 = 6.97$, df = 2, p = .031), panic disorder with agoraphobia (28.6% vs. 9.1% and 5.5%, $\chi^2 = 6.27$, df = 2, p = .043), and OCD (28.6% vs. 22.7% and 4.6%, $\chi^2 = 15.6$, df = 2, p < .001). Bipolar type II subjects had significantly more social phobia than the other 2 groups (36.4% vs. 28.6% and 16.0%, $\chi^2 = 6.12$, df = 2, p = .047). Patients who switched to bipolar disorder received antidepressant treatment for a significantly longer time than patients who remained unipolar (t = –2.21, df = 246, p = .028). However, the difference lost significance after we adjusted for number of MDE recurrences, indicating that these patients were proportionally more ill during their follow-up. Bipolar and unipolar patients received maintenance antidepressant treatment at similar proportions of time.

Predictors

The probability and time to diagnostic switch from unipolar MDD to bipolar disorder were predicted by many univariate variables (Table 3). However, after removing all nonsignificant factors, in multivariate Cox proportional hazards analyses, severity of MDD, OCD, social phobia, and a large number of cluster B personality disorder symptoms predicted switch to bipolar disorder type I or II most significantly (Table 4). Figure 2 shows how baseline severity of MDD, OCD, social phobia, and number of cluster B personality disorder symptoms affect the survival time and proportions of remaining unipolar MDD subjects. Within cluster B personality disorders, the numbers of narcissistic and antisocial symptoms were the strongest predictors (hazard ratio [HR] = 0.72, 95% CI = 0.57 to 0.90, p = .003, and HR = 0.47, 95% CI = 0.30 to 0.74, p = .001, respectively). Different cluster B items predicted switch in only univariate analyses: of borderline items, affective instability as a trend (OR = 2.14, 95% CI = 0.90 to 5.05, p = .084); of narcissistic items, sensitivity to criticism (OR = 2.62, 95% CI = 1.10 to 6.25, p = .030), interpersonal exploitation (OR = 3.75, 95% CI = 0.89 to 15.8, p = .072), daydreaming (OR = 3.04, 95% CI = 0.95 to 9.80, p = .062), and attention seeking (OR = 3.83, 95% CI = 1.18 to 12.5, p = .025); of antisocial items, running away as child (OR = 2.74, 95% CI = 0.88 to 8.47, p = .081), unemployment despite available work (OR = 14.1, 95% CI = 1.16 to 166, p = .038),

Figure 2. Survival Curves of Time to Diagnostic Switch From Unipolar Depression to Bipolar Disorder in the Vantaa Depression Study, 5-Year Follow-Up



Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

and aggressive behavior (OR = 15.2, 95% CI = 1.56 to 142, p = .019). In multivariate analyses, of different cluster B items, only attention seeking remained significant as a trend (OR = 2.57, 95% CI = 0.93 to 7.14, p = .069).

DISCUSSION

Within a 5-year period, in our secondary care cohort comprising mainly psychiatric outpatients, 29 subjects (11.7%) with previous unipolar MDD switched to bipolar disorder. The majority (three fourths) switched to type II. The switch to type I usually occurred much faster than to type II when estimated from both age at onset and baseline. In multivariate Cox proportional hazards analyses, severity of MDD, OCD, social phobia, and number of cluster B personality disorder symptoms independently predicted diagnostic switch to bipolar disorder.

Our study has some major strengths. It comprises a representative cohort of psychiatric outpatients and inpatients with MDD in a medium-large Finnish city; two thirds of all depressed subjects in the city of Vantaa are estimated to be treated in the PMCD.[48] The study is from the modern era in terms of the use of DSM-IV diagnoses and definitions and structured interviews. Furthermore, we used a detailed life chart, which probably made our assessment of switch more sensitive, particularly regarding type II bipolar disorder, than studies using merely hospitalization as an endpoint. Unlike previous studies, our study was able to investigate the role of different Axis I and II comorbid disorders as predictors for the risk of diagnostic switch. In addition, temperamental and psychosocial factors were evaluated; structured and semistructured measures, both objective and subjective, were used. Only 21 subjects (7.8%) dropped out from all follow-up interviews; the Cox proportional hazards model enabled analyses of information on subjects remaining in the study for different lengths of time.

However, some limitations should also be noted. The follow-up period of 5 years is only moderately long for investigation of a phenomenon that may occur even after decades of follow-up.[1,16] Despite our large cohort of depressed patients, the number of bipolar patients was modest, and particularly the small number of bipolar type I patients (N = 7) was insufficient for differentiation of predictors for both bipolar types. Moreover, it is possible that during baseline interviews subjects may have failed to recall previous mood elevations, although this was carefully investigated. While we had full access to patient records, a long follow-up interval (3.5 years between the last 2 interviews) may have affected the temporal accuracy of information and recall of especially hypomanic episodes. As we strictly followed DSM-IV criteria, we did not investigate

episodes, such as depressive mixed state,[25] that are not included in the DSM-IV. Due to the DSM-IV's 4-day limit on criteria for hypomanic episodes, the number of bipolar type II patients may be an underestimate. In addition, we gathered information on family history only from the 5-year follow-up, not earlier interviews, and on all who switched. Thus, we were unable to reliably investigate the predictive value of bipolar family on bipolar switch. Finally, due to higher severity and more recurrences, patients who switched to bipolar disorder received antidepressant treatment for a significantly longer period of time than those who remained unipolar. However, when diagnosing bipolar disorders, we followed the DSM-IV and excluded episodes coinciding with recent onset or increase in dose of an antidepressant.

Our overall switch rate, 2.8% annually, is slightly higher than in previous studies in which the rate has been 1% to 2%.[1–4] The switch rate to type I is somewhat low (0.7% per year); this may be due to our study cohort comprising predominantly outpatients and not patients from a tertiary care setting. The majority of diagnostic switches in our study were to bipolar type II; as our annual rate of switch to bipolar II (2.14%) is higher than in previous studies (0.5%–1.8%),[1–4] we may have been more sensitive in its detection. The median time from baseline to first manic episode was 6 times shorter than to hypomanic episode and from age at onset, about 3 times faster. Previous reports have described about 2 times faster switch rates to manic episodes then to hypomanic episodes.[1–4] Bipolar type I patients have been reported in new episodes to have more manic episodes than type II patients have hypomanic episodes.[7,49] The median overall time to diagnostic switch from age at onset, 7.7 years, is consistent with earlier findings of 5 to 8 years.[7,8,15] Overall, our results suggest that among outpatients presenting with MDE, a switch to bipolar II disorder is more likely than a switch to bipolar I.

A diagnostic switch from unipolar MDD to bipolar disorder was associated with many clinical features, i.e., baseline severity of MDD, a variety of comorbid disorders, psychotic symptoms, and negative life events. The number of previous episodes was not associated with switch, although this has in many previous studies[6,16,19,20,22] predicted diagnostic switch. It is, however, important to determine which of the predictors are confounded by other factors and which appear as independent predictors. In the multivariate Cox proportional hazards analyses, severity of MDD, OCD, social phobia, and high number of cluster B personality disorder symptoms were found to be the most significant independent predictors. Regarding the role of severity, our findings are consistent with the results from the Zurich Follow-Up Study and CDS, in which severity of MDD predicted especially the switch to bipolar disorder type I.[1,2] Severity of MDD was also correlated with existence of psychotic symptoms, which has, in several studies, predicted switch.[3–5,15] All our patients with mania were women, a result that is in accord with the known gender differences in bipolar disorder. Among men, manic episodes tend to emerge at an earlier stage of illness and with clinically more acute symptoms. Men are also likely to be diagnosed with bipolar disorder at a younger age than women, and, thus, have not entered our study cohort as unipolars.[7,50]

Comorbid psychiatric disorders are very common in both MDD and bipolar disorders. However, whether different comorbid disorders might differentially predict switch has been systematically investigated little. According to our study, both Axis I and II disorders are important. Bipolar subjects have been found to have twice as much social phobia as unipolar MDD subjects.[28] In an Italian study, lifetime social phobia was associated with an earlier age at onset of bipolar disorder.[51] In the same study, OCD was found, contrary to our results, to delay the onset of bipolarity. In our previous article,[30] social phobia was significantly associated with MDE recurrences, which may be related to the switch to bipolar disorder being frequently associated with a higher number of previous MDEs.[6,16,19,22] Investigating the temporal relationship between anxiety disorders and (hypo)mania in bipolar subjects, Perugi et al.[52] found social phobia and OCD to chronologically precede hypomanic episodes. Nevertheless, to our knowledge, none of these earlier studies have found social phobia or OCD to also predict the diagnostic switch to bipolar disorder among patients with MDD.

In our analyses, we chose to investigate personality disorders as dimensional variables based on the number of different cluster or individual personality disorder symptoms, as this approach is more consistent with current views on personality disorders. We found the number of cluster B personality disorder symptoms to significantly predict the diagnostic switch. Within cluster B, the number of antisocial personality symptoms was the strongest predictor in multivariate analyses, while the number of histrionic, narcissistic, and borderline personality symptoms predicted switch in only univariate analyses. In CDS, Akiskal et al.[2] investigated predictors for switch to bipolar disorder type II and reported temperamental and mood instabilities with minor antisocial acts and social anxiety to be significant. Benazzi[53] revealed cyclothymic and borderline personality temperaments to be more common in subjects with bipolar disorder type II than in subjects with unipolar MDD and found affect instability to be especially associated with type II. None of these studies have found an association between these features and bipolar disorder type I. In our study, switch to both bipolar disorder types was associated with the number of cluster B symptoms, but, taking into account the small number of subjects with type I, these results must be interpreted with caution.

In conclusion, in our study of community-treated secondary-care psychiatric patients, the overall switch rate from unipolar MDD to bipolar disorder (mostly to type II) was slightly higher than in previous studies. The switch to bipolar disorder type I usually occurred early, whereas the switch to type II took place more gradually over time. In addition to previously known predictors, severity of MDD, comorbid social phobia, OCD, and cluster B features warrant further research as potential predictors of diagnostic switch. These risk factors should be taken into account in clinical practice, as the change in diagnosis has practical clinical consequences for treatment and prognosis.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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