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Early clinical predictors and correlates of long-term morbidity in bipolar disorder

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ABSTRACT

Objectives: Identifying factors predictive of long-term morbidity should improve clinical planning limiting disability and mortality associated with bipolar disorder (BD).
Methods: We analyzed factors associated with total, depressive and mania-related long-term morbidity and their ratio D/M, as %-time ill between a first-lifetime major affective episode and last follow-up of 207 BD subjects. Bivariate comparisons were followed by multivariable linear regression modeling.
Results: Total % of months ill during follow-up was greater in 96 BD-II (40.2%) than 111 BD-I subjects (28.4%; $P = 0.001$). Time in depression averaged 26.1% in BD-II and 14.3% in BD-I, whereas mania-related morbidity was similar in both, averaging 13.9%. Their ratio D/M was 3.7-fold greater in BD-II than BD-I (5.74 vs. 1.96; $P < 0.0001$). Predictive factors independently associated with total %-time ill were: [a] BD-II diagnosis, [b] longer prodrome from antecedents to first affective episode, and [c] any psychiatric comorbidity. Associated with %-time depressed were: [a] BD-II diagnosis, [b] any antecedent psychiatric syndrome, [c] psychiatric comorbidity, and [d] agitated/psychotic depressive first affective episode. Associated with %-time in mania-like illness were: [a] fewer years ill and [b] (hypo)manic first affective episode. The long-term D/M morbidity ratio was associated with: [a] anxious temperament, [b] depressive first episode, and [c] BD-II diagnosis.
Conclusions: Long-term depressive greatly exceeded mania-like morbidity in BD patients. BD-II subjects spent 42% more time ill overall, with a 3.7-times greater D/M morbidity ratio, than BD-I. More time depressed was predicted by agitated/psychotic initial depressive episodes, psychiatric comorbidity, and BD-II diagnosis. Longer prodrome and any antecedent psychiatric syndrome were respectively associated with total and depressive morbidity.

1. Introduction

Major mood disorders are leading contributors to disease-burden due to their high prevalence and risks of recurrences, sustained morbidity, and mortality from suicide and comorbid medical illnesses [1]. Factors reported to be associated with morbidity and disability in mood disorders include symptomatic severity in acute episodes, more recurrences and hospitalizations, financial and legal problems, co-occurring anxiety disorders, and delay of or nonadherence to treatment [2–5]. Findings from a recent meta-analysis involving 25 studies indicated similarly high levels of long-term morbidity (44.4% [CI: 39.6–49.2] of months ill/time at risk, overall) in clinically treated bipolar disorder (BD-I, BD-II) and major depressive disorder (MDD) patients [1]. Notably, in BD subjects, 70%–80% of this unresolved morbidity was depressive (31% in BD-I, 36% in BD-II), whereas mania-like morbidity, averaged much less among BD-I (10%) and BD-II (6%) subjects [1].

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Given these high morbidity levels despite ongoing treatment, and especially depressive morbidity, the need to identify factors that can inform prognosis and predict future levels and types of morbidity is of great clinical importance. Encouraging findings arise from the strong predictive power of the type of initial affective episode in BD, notably for the predominant long-term polarity (excess of depressive or mania-like recurrences per year at risk). That is, depressive polarity was in large excess among patients presenting with an initial depressive, mixed (DSM-IV), or anxious episode, whereas an excess of mania-like recurrences was more likely to follow an initial manic, hypomanic, or psychotic episode both in type I and II BD subjects [6,7]. Other factors have been reported to be related to an initial depressive episode and to a later prevalent depressive polarity, and to predict a less favorable, long-term course. These include a predominant Depression-Mania-euthymic Interval (DMI) illness-course (contrasted to a Mania-Depression-Interval [MDI] course), a tendency toward a rapid cycling or continuous circular course, more use of antidepressants, more suicidal thoughts and actions, more mixed features, and a co-occurring personality disorder diagnosis [6,8].

Little has been reported about juvenile clinical features as predictors of the types and severity of future adult morbidity in BD, although it is recognized that adult mood disorders with a juvenile onset, generally are more severe and more recurrent than similar illnesses starting in adult years [9–13]. In particular, onset of BD in childhood or adolescence was associated with a greater number of future episodes, higher percent-time ill, higher risk of rapid cycling, more severe manic and depressive episodes [10,14], and greater rates of comorbid psychiatric disorders, especially anxiety and substance use disorders, as well as greater likelihood of suicide attempts and violent behavior [14].

Consistent and concordant findings have linked early onset of mood disorder to less favorable long-term outcomes, but details of relationships between early onset or longer delay of diagnosis and appropriate treatment, and particular aspects of future morbidity remain uncertain or inconsistent in BD. For example, whether longer delay of diagnosis and treatment yields a less favorable long-term outcome is debated. Such a relationship is clinically plausible [15], but the specific question of whether early history exerts a dominant influence on future response to treatment seems increasingly unlikely in both BD [16–20] and MDD [21].

Given the limited information about early factors associated with long-term morbidity in adult BD, the present study aimed to identify demographic, family history, and antecedent juvenile or early adult clinical features associated with time in overall and polarity-specific morbidity in a sample of adult BD subjects observed prospectively and systematically over several years.

2. Methods

Historical and prospective data obtained during clinical assessment and treatment were extracted from detailed, semi-structured clinical records of adult outpatients diagnosed with BD, evaluated and treated for many years by the same mood disorder expert, the late Athanasios Koukopoulos, M.D., at the Lucio Bini Mood Disorder Center which he had founded in Rome. At clinic intake, participants provided written, informed consent for potential research analysis and anonymous reporting of clinical findings in aggregate form, in accord with Italian ethical requirements. Two investigators (GS and LDC) selected patients' records in random order among those of subjects with a final DSM-IV-TR diagnosis of BD (type I or II). Study subjects were drawn at alphabetically from a total of approximately 1000 bipolar patients evaluated and followed by Dr. Koukopoulos for at least one year. Records had to include details of family history, past history, features of current and previous illness including comorbid syndromes (anxiety, eating, or substance abuse disorders) based on at least one year of repeated, systematic assessments and observation at the study center. Only records with required information were selected (leading to the exclusion of 5.0% of records with missing required information).

Dr. Athanasios Koukopoulos systematically followed and treated all study subjects for several years before this study was designed. His diagnoses following DSM-IV-TR criteria were later confirmed for this study by direct examination (the majority were confirmed based on live clinical reassessments and some from chart reviews) by one other senior research psychiatrist at the study center (Dr. Gabriele Sani or Prof. Paolo Girardi) using the Structured Clinical Interview for DSM-IV-TR-Patient Edition (SCID-I/P).

If diagnoses were not consistent, more data were gathered and diagnostic assessment was continued until final consensus was reached or the potential participant was excluded. To maximize reliability, each chart was reviewed independently by two investigators (LDC and AEK) and required data were extracted from clinical records and summarized in structured research forms by the two investigators, working to consensus with a third investigator (GS).

2.1. Subject assessment

Historical and prospective information was collected in semi-structured assessments used at Lucio Bini Mood Disorder Center since 1974 with mood disorder patients at first evaluations and during long-term follow-up. Assessments are based on DSM criteria and on detailed clinical evaluation (not on simple yes/no answers to structured questions). Wording of questions posed could be changed to improve understanding, and evaluations were routinely supplemented with information from family members or close friends during at least one visit, as well as by all available medical documentation. Data collected about education, employment, past, social and family history were entered into preprinted medical record forms. Affective temperaments were evaluated clinically, following criteria described by Akiskal & Mallya [22].

Current and historical assessments included retrospective evaluation of juvenile psychiatric symptoms, syndromes, or behavioral abnormalities, with approximate ages at their appearance, as well as estimates of their intensity and approximate duration. In addition, details of the history of BD prior to entering the study center were recorded routinely, including the type of first episode, number and types of subsequent affective episodes, treatments, hospitalizations, levels of impairment, and information about suicidal behaviors.

2.2. Long-term follow-up

During follow-up at the study center, participants were assessed at 1–12 week intervals, as required clinically, with semi-structured interviews routinely supplemented with standardized ratings of for depressive (21-item Hamilton Depression Rating Scale [HDRS-21]) [23] and (hypo)manic features (Young Mania Rating Scale [YMRS]) [24]. During follow-up the number, type (polarity and subtype), duration and severity of major affective episodes were recorded in life-charts used at the center since 1980 [25], as well as information about treatments, psychiatric hospitalizations, and the occurrence, timing, methods and circumstances of lifetime suicidal or self-injurious behaviors. Mania-related morbidity included manic, hypomania and mixed episodes (DSM-IV-TR) with and without psychosis whereas depressive morbidity included simple depression as well as

depression with psychosis, agitation, or dysphoric-mixed features as described by Koukopoulos [26] during the years at risk.

2.3. Time at risk

Time at risk following initial expression of overt syndromal illness was calculated from the start of a first-lifetime major affective episode to the last observation at the study center. Systematically, retrospectively and prospectively collected clinical assessment data included in records and life-charts allowed quarterly estimates of episode counts and durations, and estimates of the percentage of months of mania-related illness, depression, and all affective illness during the total time at risk, to support life-charting.

2.4. Clinical antecedents

Antecedent events considered were psychopathological symptoms, altered or abnormal behaviors, or non-affective syndromes identified as occurring prior to a first major affective episode – all retrospectively assessed [27]. Juvenile antecedent symptoms and signs (not DSM-syndromes) included clinical features occurring during childhood (ages 1–12) or adolescence (ages 13–18 years) with estimated duration, intensity, and with single or recurrent pattern sustained over several juvenile years that were not severe enough to satisfy DSM-IV-TR criteria for a psychiatric disorder [27].

2.5. Antecedent non-affective syndromes

We also considered antecedent non-affective syndromes meeting DSM-IV-TR diagnostic criteria occurring before a first major affective episode such as anxiety disorders (panic disorder, generalized anxiety disorder, obsessive compulsive disorder, or phobia), eating disorders (anorexia or bulimia nervosa), and substance abuse or dependence disorders.

2.6. Analyses

Data analyses were made by a co-investigator (RJB) held independent of data-collection and clinical assessments. Reported averages are means with standard deviation (± SD) or 95% confidence interval (CI). We analyzed factors associated with morbidity as the percentage of months of total, depressive (D), and mania-related (M) affective illness during the time at risk, as well as the D/M ratio. These outcomes were analyzed in preliminary bivariate analyses (Anova) with t-scores for continuous variables or contingency tables [χ^2] for categorical measures, followed by stepwise, multivariable, linear regression modeling to provide slope functions (β with CI) and corresponding t-scores for association with factors of interest. Analyses used commercial statistical software (Stata.13®; StataCorp, College Station, TX) using data spreadsheets based on Excel (Microsoft Corp., Redmond, WA) and Statview.5® (SAS Institute; Cary, NC).

3. Results

3.1. Subjects

The study sample included a total of 207 consenting, randomly selected, adults diagnosed with DSM-IV-TR bipolar disorder (BD), type I (n = 111) or II (n = 96), enrolled at the study center at adult ages averaging 42.2 ± 15.4 years; 62.0% were women. All participants were followed at clinically determined intervals of 1–12 weeks, assessed repeatedly, and treated by Dr. Koukopoulos for an average of 7.45 ± 8.03 years.

3.2. Morbidity in mood disorder subjects

During the time at risk (from the first affective episode to the last visit at the center), we assessed estimates of total, mania-related, and depressive morbidity, estimated as percentage of months during an average of 18.9 ± 12.9 years. Time at risk was similar between diagnostic groups (Table 1). Total morbidity represented 33.9 ± 25.5% of time at risk among all BD subjects, based on the presence of major affective episodes. This measure was significantly higher among BD-II (40.2 ± 27.1%) than BD-I subjects (28.4 ± 22.9%; Table 1).

Depressive morbidity included simple major depressive episodes and episodes with mixed, agitated, or psychotic features, all of which accounted for 19.8 ± 19.1% of time at risk, or a majority (58.4%) of the 33.9% of time estimated for total morbidity. Depressive morbidity was 1.9-times greater among BD-II (26.1 ± 19.7%) than BD-I subjects (14.3 ± 16.8% of time; Table 1). Mania-related morbidity (hypomanic, manic, and mixed episodes with or without psychosis) averaged 14.0 ± 15.3% of time at risk among BD subjects and did not differ significantly between BD-I and -II cases (13.9 ± 13.9% vs. 14.2 ± 17.0%; Table 1). The ratio of % of time in depressive/mania-related morbidity (D/M) was 3.67 ± 6.93 for all BD subjects, and 2.9-times greater in BD-II than BD-I subjects (5.74 ± 8.74 vs. 1.96 ± 4.39; Table 1).

3.3. Factors associated with total morbidity

Total morbidity was associated with fewer years at risk, but probably as an artifact of "dilution" of non-chronic morbidity (as %-time ill) with longer exposure time. Total morbidity was 1.4-times greater in BD-II than BD-I subjects (40.2% vs. 28.4%; Table 1). Additional factors associated in preliminary bivariate analyses included the following: longer prodromal latency from first antecedent (symptoms or non-affective syndromes) to first major affective episode, shorter delay of mood-stabilizer treatment, more hospitalizations/year, co-occurrence of other psychiatric disorders, the occurrence of any psychiatric syndrome prior to a first episode of depression or mania, older age at first major affective episode, presenting initially in hypomania or severe (agitated-mixed or psychotic) depression, a childhood history of insomnia, and family history of anxiety (Table 2a). Several of these measures co-vary

Table 1
Morbidity in 207 bipolar disorder subjects.

Features	Diagnostic groups (% or mean ± SD)			P-value (statistic)
	A. BD-I (n = 111)	B. BD-II (n = 96)	C. All BD (n = 207)	A vs. B
At risk (years)	18.9 ± 10.9	19.5 ± 13.0	18.4 ± 12.9	0.20 (1.29)
Total % time ill	28.4 ± 22.9	40.2 ± 27.1	33.9 ± 25.5	0.003 (2.95)
Mania % time ill	13.9 ± 13.9	14.2 ± 17.0	14.0 ± 15.3	0.87 (0.17)
Depression % time ill	14.3 ± 16.8	26.1 ± 19.7	19.8 ± 19.1	0.02 (2.38)
Depression/Mania (D/M) ratio[a]	1.96 ± 4.39	5.74 ± 8.74	3.67 ± 6.93	< 0.0001 (4.01)

[a] Computed as mean of individual ratios.

Table 2a
Factors associated with total %-time ill in 207 bipolar disorder subjects.

Factors	% of time of ill (±SD) or β [95% CI]	*t*-score	*P*-value
Years at risk[a]	−0.936 [−1.21 to −0.67]	6.83	< 0.0001
Years from first major affective episode to mood-stabilizer treatment	−0.686 [−1.05 to −0.325]	3.74	0.0002
Bipolar types		3.42	0.001
Type I	28.4 ± 22.9		
Type II	40.2 ± 27.1		
Years from first antecedent to first major affective episode	0.533 [0.217–0.850]	3.32	0.001
Hospitalizations/year	13.6 [4.93–22.2]	3.10	0.002
Psychiatric comorbidity		2.71	0.007
Present	41.1 ± 26.2		
Absent	30.8 ± 24.7		
Antecedent syndromes		2.37	0.02
Any	38.7 ± 26.2		
None	30.3 ± 24.5		
Age at first major affective episode[a]	0.372 [0.041–0.703]	2.22	0.03
First affective episode type		1.71	0.04
Hypomania	42.3 ± 23.1		
Agitated/psychotic depression	39.6 ± 29.7		
Simple depression	30.5 ± 23.2		
Mania/mixed	29.9 ± 26.3		
Insomnia at age < 12		2.11	0.04
Present	51.3 ± 22.5		
Absent	33.1 ± 25.4		
Family history of anxiety		2.09	0.04
Present	39.8 ± 26.0		
Absent	31.6 ± 25.1		

[a] Years at risk produces an artifactual increase in apparent %-time ill in non-chronic illness, and confounds age at first major affective episode and probably hospitalization rate.

Table 2b
Multivariable linear regression model: factors associated with total %-time ill.

Factors	β [95% CI]	*t*-score	*P*-value
Bipolar II > I diagnosis	10.4 [3.76–17.1]	3.08	0.002
Longer from first antecedent to first major affective episode	2.22 [1.32–7.07]	2.87	0.004
Psychiatric comorbidity	9.88 [2.67–17.1]	2.70	0.007

Other factors not significantly associated with %-time ill included: sex; substance misuse; any comorbid medical disorder; family history of major affective disorder or suicide; suicide attempted and number of suicide attempts/years at risk; psychiatric hospitalization; juvenile symptoms (anxiety, depressive, heightened emotionality, mood swings, low self-esteem, phobia, withdrawn-asocial); as well as age at first antecedent or first major affective episode; total number of antecedents/years at risk; years from first antecedent to first mood-stabilizer treatment; multivariable model excludes years at risk from first episode, which has a strong "diluting" effect on morbidity expressed as % of time/year, we also excluded hospitalizations/year as probably confounded by both time at risk and by illness severity.

with illness severity. Moreover, some measures are time-dependent and may be influenced artifactually by total time ill (notably age at first affective episode), whereas other time-dependent measures remained significant after adjusting for years of illness. Of note, total morbidity was not correlated with suicide attempt ever (%time ill in suicide attempters 33.2 ± 25.8 versus non-attempters 35.6 ± 24.9; $t = 0.59$, $P = 0.57$) and with number of suicide attempts/years at risk (β = 0.132 [−2.13 to 139]; $t = 1.91$, $P = 0.06$).

Multivariable linear regression modeling found three factors to be significantly and independently associated with total percent-time ill, ranking by significance: [a] diagnosis of BD-II, [b] longer prodromal latency from first antecedent to a first major affective episode; [c] comorbid psychiatric disorder (Table 2b).

3.4. Factors associated with depressive morbidity

Again, shorter exposure led to greater proportions of time depressed, and BD-II subjects spent 1.8-fold more time depressed than BD-I cases, based on preliminary bivariate analyses (Table 3a). Other factors preliminarily associated with %-time depressed included: presence of any psychiatric comorbid condition, hospitalization rate, initial agitated/psychotic depression or hypomania more than mania, an antecedent non-affective syndrome before the first major affective episode (especially an anxiety disorder), depressive polarity of first major affective episode, longer prodromal latency from initial antecedent and a first-lifetime major affective episode, a rapidly or continuously cycling or erratic illness-course, and shorter latency from first major affective episode to start of mood-stabilizer treatment (Table 3a). Again, some of these time-related factors co-vary with illness severity in general, and others appeared to be artifactually influenced by total exposure time, and became nonsignificant when adjusted for years ill, including hospitalizations/year, and time from first episode to treatment. As total morbidity, also depressive morbidity was not correlated with suicide attempt ever ($t = 0.90$, $P = 0.37$) and with number of suicide attempts/years at risk ($t = 1.43$, $P = 0.16$).

Multivariable linear regression modeling indicated that four factors remained significantly and independently associated with long-term percent-time depressed, ranking by significance as: [a] BD-II > BD-I diagnosis; [b] having an antecedent non-affective syndrome before the first major affective episode, [c] having a psychiatric comorbidity and [d] history of an agitated or psychotic depressive first episode (Table 3b).

3.5. Factors associated with mania-related morbidity

The expected "dilution" effect of longer exposure time was found again. There was no difference in time spent in mania or hypomania, long-term, among BD-I and BD-II subjects. Additional

Table 3a
Factors associated with %-time depressed in 207 bipolar disorder subjects.

Factors	% Time Ill (±SD) or β [95% CI]	*t*-score	*P*-value
Bipolar type		4.63	< 0.0001
Type I	14.3 ± 16.8		
Type II	26.1 ± 19.7		
Years at risk	−0.482 [−0.695 to 0.269]	4.45	< 0.0001
Psychiatric comorbidity		3.71	< 0.0001
Present	27.1 ± 22.9		
Absent	16.7 ± 16.3		
Hospitalizations/years at risk	9.57 [4.35–14.8]	3.62	< 0.0001
First affective episode type		2.76	< 0.0001
Agitated/psychotic depression	29.6 ± 27.0		
Hypomania	23.6 ± 17.7		
Simple depression	20.3 ± 16.6		
Mania/mixed	11.6 ± 14.7		
Antecedent psychiatric disorders		3.23	0.002
Present	24.7 ± 22.0		
Absent	16.2 ± 15.7		
Antecedent anxiety disorder		2.63	0.009
Present	26.0 ± 22.9		
Absent	17.9 ± 22.9		
Depressive polarity at first major affective episode	6.72 [1.56–11.9]	2.57	0.01
Years first antecedent to first major affective episode	0.310 [0.068–0.546]	2.54	0.01
Predominant course-type		1.70	0.02
Continuously or rapidly cycling	26.9 ± 19.3		
Irregular	22.6 ± 21.5		
DMI	19.6 ± 22.3		
Seasonal	19.2 ± 16.5		
MDI	13.0 ± 12.7		
Years from first major affective episode to mood-stabilizer treatment	−0.281 [−0.555 to −0.007]	2.03	0.04

Table 3b
Multivariable linear regression model: factors associated with %-time depressed.

Factors	β [95% CI]	*t*-score	*P*-value
Bipolar II > I diagnosis	11.2 [6.40–16.0]	4.61	< 0.0001
Any antecedent psychiatric syndrome before first major affective episode	6.90 [1.83–11.9]	2.69	0.008
Any psychiatric comorbidity	7.18 [1.69–12.7]	2.58	0.01
First episode: agitated or psychotic major depression	8.23 [1.52–14.9]	2.42	0.02

Multivariable model excludes years at risk from first episode, which has a strong "diluting" effect on morbidity expressed as %-of time ill/year, as well as latency to first mood-stabilizer treatment, and also excludes hospitalizations/year as probably confounded by both time at risk and by illness severity. Other factors not significantly related to %-time depressed included: sex; substance misuse; any comorbid medical disorder; family history of major affective disorder or suicide; attempted suicide and number of suicide attempts/years at risk; ever psychiatrically hospitalized, juvenile symptoms (anxiety, depressive, heightened emotionality, insomnia, mood swings, low self-esteem, phobia, withdrawn-asocial); number of antecedents/years at risk; age at first antecedent and at first major affective episode.

Table 4a
Factors associated with %-time in manic, hypomanic, or mixed episodes among 207 bipolar disorder subjects.

Factors	% Time Ill (±SD) or β [95% CI]	*t*-score	*P*-value
Years of follow-up	−0.461 [−0.629 to −0.292]	5.40	< 0.0001
First affective episode polarity		3.95	< 0.0001
[Hypo]manic	18.3 ± 18.3		
Depressive	10.2 ± 10.8		
Hospitalizations/years at risk	9.57 [4.35–14.8]	3.62	< 0.0001
Years from first major episode to mood-stabilizer treatment	−0.420 [−0.640 to −0.200]	3.77	0.0002
Years from first antecedent to first major affective episode	0.230 [0.037–0.422]	2.35	0.02

factors associated preliminarily with more time in mania-like morbidity included: a manic or hypomanic first-lifetime major affective episode (1.8-fold more time in later mania-like illness than depression), more hospitalizations/year, years from first major affective episode to start of mood-stabilizer treatment, and prodromal time from first antecedent to first major affective episode (Table 4a). Factors that became nonsignificant when co-varied with total exposure years included: prodromal years from antecedent to first major affective episode, and years from first major affective episode to start of mood-stabilizer treatment.

By multivariable linear regression modeling, two factors remained independently associated with long-term mania-related morbidity: [a] fewer years ill, and [b] a mania-like first major affective episode (Table 4b).

3.6. Factors associated with ratio of time in depression/mania (D/M)

The ratio of depressive to mania-related morbidity (D/M) was not associated with total years of illness. However, the ratio was 2.9-times greater among BD-II than BD-I subjects (Tables 1 and 5a), paralleling the excess of depressive morbidity among BD-II cases (Tables 1 and 3a). Several other factors also were significantly associated with a higher D/M ratio based on bivariate analyses. In addition to BD-II diagnosis, these included: depressive polarity at first-lifetime major affective episode, a predominant DMI vs. MDI

Table 4b
Multivariable linear regression model for factors associated with percent-time in mania-like illness.

Factors	β [95% CI]	*t*-score	*P*-value
Fewer years ill	2.54 [1.76–4.52]	4.50	< 0.0001
First-lifetime episode [hypo]manic	5.54 [1.48–9.60]	2.69	0.008

Multivariate modeling excluded hospitalization rate as closely related to illness severity itself. Factors not significantly related to %-time in mania-like illness include: diagnosis (type I vs. II); sex; substance misuse; any comorbid psychiatric or medical disorder; family history of major affective or anxiety disorder or suicide; attempted suicide and number of suicide attempts/years at risk; ever psychiatrically hospitalized; juvenile psychiatric symptoms (anxiety, depressive, heightened emotionality, insomnia, mood swings, low self-esteem, phobia, withdrawn-asocial) or syndromes; number of antecedents/years at risk; age at first antecedent or at first major affective episode; years from first antecedent to first mood-stabilizer treatment; and course-type.

Table 5a
Factors associated with ratio (D/M) of %-time in depressive/mania-like illness among 207 bipolar disorder subjects.

Factors	D/M (± SD) or β [95% CI]	*t*-score	*P*-value
Polarity of first major affective episode		4.44	< 0.0001
Depressive	5.67 ± 9.01		
[Hypo]manic	1.53 ± 2.19		
Course-type		4.02	< 0.0001
Depression-Mania-Interval (DMI)	7.28 ± 11.0		
Mania-Depression-Interval (MDI)	1.37 ± 1.87		
Bipolar disorder type		4.01	< 0.0001
Type I	1.96 ± 4.39		
Type II	5.72 ± 8.66		
First affective episode type		2.74	< 0.0001
Agitated/psychotic depression	7.14 ± 10.1		
Simple major depression	5.10 ± 8.47		
Hypomania	2.28 ± 2.97		
Mania/mixed	1.05 ± 1.32		
Years from first major affective episode to first mood-stabilizer treatment	0.182 [0.085–0.280]	3.70	0.0003
Temperament		2.52	0.0004
Anxious	10.8 ± 15.6		
Cyclo- or hyperthymic	3.26 ± 5.59		
Irritable	1.51 ± 1.35		
Dysthymic	1.05 ± 0.82		
Years from first antecedent to first mood-stabilizer treatment	0.082 [0.012–0.153]	2.29	0.02
Antecedent anxiety disorder		2.07	0.04
Present	5.49 ± 8.94		
Absent	3.12 ± 6.17		
Older at first mood-stabilizer treatment	0.077 [0.002–0.152]	2.03	0.04

Table 5b
Multivariable linear regression model of factors associated with D/M morbidity ratio.

Factors	β [95% CI]	*t*-score	*P*-value
Anxious temperament	7.25 [3.78–10.7]	4.13	< 0.0001
Depressive polarity of first major affective episode	3.41 [1.44–5.39]	3.42	0.001
Bipolar II > I diagnosis	2.35 [0.36–4.35]	2.33	0.02

Other factors not significantly related to D/M included: sex; any substance misuse; any comorbid medical or psychiatric disorder; family history for major affective or anxiety disorder or suicide; prior suicide attempt or number of attempts/years at risk; psychiatric hospitalization or number of admissions/years at risk; years at risk (from first episode to present); juvenile symptoms (depressive, mood swings, anxiety, heightened emotionality, low self-esteem, phobia, insomnia, withdrawn-asocial), juvenile eating or substance abuse disorders, number of antecedents/years at risk; and latency from first antecedent to first major affective episode.

course-pattern, initial depression with agitation or psychotic features, latency from first major affective episode to mood-stabilizer treatment, anxious temperament, years from first antecedent and initial mood-stabilizer treatment, anxiety disorder before first major mood episode, and being older at initial treatment with a mood-stabilizer (Table 5a).

In multivariable linear regression modeling, three factors remained associated independently with a higher D/M ratio. By statistical significance, they ranked as: [a] anxious temperament; [b] depressive polarity of first major affective episode, and [c] BD-II diagnosis (Table 5b).

4. Discussion

Total morbidity observed in the present clinically treated study sample of 207 BD patients accounted for 34% of time at risk. This level of clinically treated morbidity was somewhat lower than comparable levels averaging 43.5% in BD subjects reported in a recent review of morbidity in clinically treated major affective disorder subjects [1]. The discrepancy probably reflects characteristics of patients sampled and in their treatment, but also a much longer duration of exposure in the present study (18 years), compared to the average of 9.4 years from previous studies [1]. Longer exposure was found in the present study to be a major factor leading to lower proportions of time ill in the typically intermittent disorders considered, as noted previously [1,18,28]. In the present data, proportions of total, depressive and manic time ill all declined highly significantly with longer exposure (Tables 2a, 3a, 4a). This tendency does not seem consistent with the view that major affective disorders may worsen and show an acceleration of recurrences over time [6,29]. Instead, we propose that prolonged observation (denominator) tends to "dilute" intermittent morbidity by including increasing amounts of time in more or less euthymic states ("temporal dilution" artifact). This concern led to

excluding total time ill from the present multivariable modeling (Tables 2b, 3b, 4b).

In addition, association of higher %-time ill with the rate of psychiatric hospitalizations/years at risk but not with hospitalization at any time (Table 2a), suggests that this measure, too, was influenced by overall time at risk. Other time-related measures also may be influenced artifactually by total exposure time, including the prodromal latency from initial antecedents to the first major affective episode, and the latency from first episode to initial mood-stabilizer treatment (Table 2a). Perhaps counter-intuitively, the latency to treatment was negatively associated with %-time ill (shorter delay of treatment, worse long-term morbidity), probably owing to earlier intervention for more severe illness including acute mania. These preliminary associations with long-term morbidity/time were no longer significantly associated after adjusting for total exposure time.

We also propose that an unexpected, selective, inverse relationship of younger age at first major affective episode predicting less long-term morbidity (Table 2a) is a further manifestation of the effect of diluting intermittent morbidity with longer time at risk. This interpretation is supported by a very strong inverse relationship between onset-age and duration of illness from onset to the end of follow-up, and loss of significant association of onset-age with long-term morbidity/time with adjustment for total exposure time. It is important to clarify that the apparent association of shorter overall exposure time with more intense morbidity/time is to be contrasted to consistent findings that juvenile onset of major mood disorders usually is followed by an unfavorable later illness-course [9–13].

Another notable finding is that BD-II subjects had 1.42-fold higher levels of overall morbidity than BD-I cases; 64.9% of this unsolved morbidity was depressive in BD-II subjects and 50.4% in BD-I (Table 1), compared to more than 70% reported previously [1]. It also followed that the ratio of D/M morbidity was 2.9-times greater in BD-II than BD-I subjects (Table 1). These findings add to growing impressions that BD-II is a more severe illness than sometimes is supposed, including rates of suicidal behavior that are similar to those in BD-I patients [28].

The polarity and type of first major affective episode strongly predicted a predominance of the same polarity during follow-up, consistent with previous findings with other samples [6,7]. A new finding is that a first-lifetime agitated, mixed or psychotic depressive episode was strongly associated with both high levels of long-term depressive morbidity ($29.7 \pm 27.0\%$) and prevalent depressive polarity ($D/M = 7.14 \pm 10.1$) in BD subjects. Contrarily, manic polarity at the first major affective episode in BD was associated with a high percentage of later time in mania-like morbidity ($18.3 \pm 18.3\%$) as well as a much less time in depression than among subjects who started with depression (D/M ratio = 1.05 ± 0.82 vs. 7.14 ± 10.1, respectively). It should also be noted that the D/M ratio based on %-time ill is slightly greater than that calculated by dividing the number of depressive/manic episodes per year [7] – probably reflecting the typically shorter duration of manic than depressive episodes.

In addition, juvenile factors also were associated with subsequent adult levels and types of morbidity in BD. A non-affective syndrome, particularly an anxiety disorder, before the first major affective episode was associated with greater total and depressive morbidity and a predominance of depression over mania, based on bivariate analyses (Tables 3a, 5a). These associations are consistent with previous findings that BD subjects presenting first with an anxiety disorder have a higher D/M ratio than subjects with other types of onset [7]. Moreover, an anxious temperament was highly significantly and independently associated with prevalent depressive polarity, with D/M ratios 7- to 10-times higher than with other temperament types (Table 5). That is, anxious temperament and juvenile anxiety symptoms and syndromes predicted higher levels of later depressive morbidity.

Predominant course-patterns also were significantly associated with the prevalent polarity type, although their prospective, predictive value is very limited. Subjects presenting with a chronic illness-course were manic for 40% of time at risk compared to the 14% of time in all BD subjects, whereas subjects with a rapid cycling or continuous circular course presented the highest levels of depressive morbidity (27%) compared to 19% in the total BD sample. Moreover, rapid cycling was associated more with depressive (26.9 [CI: 19.8–34.0]%) than manic morbidity (15.0 [10.3–19.7] %-time ill). In addition, those with a predominant DMI episode-sequence were much more likely to present initially in depression and to have predominant depressive polarity, as reported previously [7].

Antecedent syndromes, as well as co-occurring psychiatric disorders, and especially anxiety and eating disorders, were strongly associated with total and depressive morbidity in BD subjects (Tables 2a, 3a) and with prevalent depressive polarity (Table 5a). These relationships are not surprising as BD patients with Axis I comorbidity usually present greater illness severity and proportion of time ill, as well as responding less favorably to mood-stabilizing treatment [30–34]. Overuse of antidepressants as anti-anxiety treatments for such comorbid BD patients may risk worsening and destabilizing effects [35].

Factors associated with long-term %-time ill, surprisingly, were found to be dissimilar to factors predicting diagnostic outcomes and suicide attempts, based on developmental psychopathology occurring during very early ages. Whereas family history of affective disorders or suicide, temperamental characteristics, and juvenile symptoms appear to have some value in predicting diagnosis (BD vs. MDD) and later suicidal behaviors [27,36], these same factors had little value for predicting the type and intensity of future, long-term morbidity in mood disorder patients in the present findings (Tables 2–5). Importantly however, early characteristics of syndromal mood disorders did predict later morbidity. These included the polarity of first-lifetime episodes, initial complex versus simple depression, early anxiety features, and later comorbidity with non-affective psychiatric disorders. We propose that diagnosis and suicidal behaviors have roots in very early and even congenital factors, whereas prognosis of types and intensities of morbidity probably reflect factors that include experiential and environmental events as well as effects of treatment.

4.1. Limitations

This study was limited mainly by retrospective identification of early, predictive events, sometimes occurring years prior to entry into the study site in adulthood, followed by long-term, prospective follow-up, during which other correlates of morbidity were identified. All these factors may have been influenced by a recall bias. However, since the comparisons were between diagnostic groups, the possible bias may have been equally distributed among the groups.

5. Conclusions

In summary, we found that the total %-time ill was greater among BD-II (40.2%) than BD-I subjects (28.4%). Mania-related morbidity averaged 14.0% of follow-up time in both types I and II BD, whereas the prevalence of depressive morbidity was much greater, and consequently the ratio of time in depression/mania-like illness (D/M) was nearly three-times greater in BD-II than BD-I subjects. Predictive factors associated with total %-time ill were:

[a] BD-II diagnosis, [b] longer prodromal latency from first symptoms to first major affective episodes, and [c] comorbid psychiatric disorders. Associated with %-time depressed were: [a] BP-II diagnosis, [b] antecedent non-affective psychiatric syndromes, [c] psychiatric comorbidity, and [d] agitated or psychotic depressive first episode. Associated with %-time in mania-like illness were: [a] shorter overall years at risk, and [b] a mania-like first affective episode. The ratio D/M was greater with: [a] anxious temperament, [b] depressive first episode, and [c] BD-II diagnosis. These findings support the impression that important dimensions of later morbidity can be predicted by factors identified early in the course of BD, including features present before or during a first major affective episode. Such predictive relationships should have clinical value in helping to identify and guide treatment needs early in the course of BD.

Disclosure of interest

The authors declare that they have no competing interest.

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