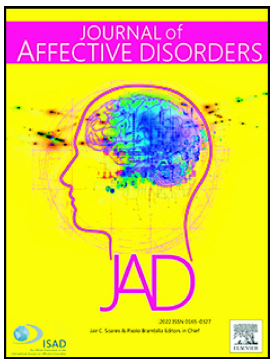

The progression trajectory of Bipolar Disorder: Results from the application of a staging model over a ten-year observation

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The progression trajectory of Bipolar Disorder:

results from the application of a staging model over a ten-year observation

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ABSTRACT

Background: Trying to better define Bipolar Disorder (BD) progression, different staging models have been conceptualized, each one emphasizing different aspects of illness. In a previous article we retrospectively applied the main staging models to a sample of 100 bipolar patients at four time points over a ten-year observation. In the present study, focusing on Kupka & Hillegers's model, we aimed to assess the transition of the same sample through the different stages of illness and to explore the potential role of clinical variables on the risk of progression.

Methods: Multistate Model using the mstate package in R and Markov model with stratified hazards were used for statistical analysis.

Results: A high hazard of transition from stage 2 to 3 emerged, with a probability of staying in stage 2 decreasing to 14% after 3 years. BD II and depressive predominant polarity were significantly associated with transition from stage 1 to 2, whereas the number of lifetime episodes > 3 and the elevated predominant polarity with transition from stage 3 to 4.

Conclusion: Our results corroborated the evidence on BD progression and contributed to outline its trajectory over time. Further effort may help to define a standardized staging approach towards ever increasing tailored interventions.

Key words: bipolar disorder; clinical staging; staging model; multi-state model; disease progression; retrospective study.

1. Introduction

The longitudinal course of Bipolar Disorder (BD) is likely to be related to an active process of neuroprogression, associated with neuroimaging and molecular changes, and clinically reflected by enhanced risk of facing new affective episodes, reduced chances of recovery from them, along with increased cognitive and functional decline (Berk et al., 2014; Muneer, 2016; Kapczinski et al., 2017; Serafini et al., 2021).

Neuroimaging studies in BD support the neuroprogressive hypothesis, showing specific structural and functional alterations during the course of illness (Serafini et al., 2021). Moreover, research on biomarkers, including Brain-Derived Neurotrophic Factor (BDNF) and inflammatory cytokines, strengthen the notion of a progressive disorder model, since reduced BDNF levels have been found during manic and depressive episodes, potentially linked to gene expression downregulation (Kauer-Sant'Anna et al., 2008; D'Addario et al., 2012). In addition, the relationship between inflammation and BD depends on the disease stage and phase (Rosenblat & McIntyre, 2016).

Several clinical factors may influence illness trajectory, including the number of episodes and hospitalizations, the presence of medical and psychiatric comorbid conditions, the occurrence of stressful life events, and the familiality for psychiatric disorders (Post, 2020). A longer duration of illness entails more pronounced changes at either a clinical and a neuropathological level, which may lead to treatment refractoriness and neuropsychological deficits (Berk et al., 2011). Furthermore, compiling evidence endorses the role of incomplete recovery in the interepisodic phases as well as the persistence of cognitive deficits during euthymia in significantly affecting BD outcome (Tsapekos et al., 2021).

Trying to better define such progression, over the last decades several authors conceptualized different staging models for BD, each one emphasizing different aspects of illness (McGorry et al., 2006; Berk et al., 2007; Kapczinski et al., 2009; Kupka & Hillegers, 2012; Duffy, 2014). A comprehensive description of the existing staging approaches was provided in a previous article from our group (Macellaro et al., 2023).

The integration of staging models in clinical practice was aimed to promote prevention for at-risk subjects, timely intervention strategies for newly diagnosed individuals, and to tailor treatment options according to the stage of illness (Berk et al., 2014). Nevertheless, only scant evidence is available on their applicability in longitudinal data sets (van der Markt et al., 2019; van der Markt et al., 2020; de la Fuente-Tomàs et al, 2020; Macellaro et al., 2023).

In this regard, Van der Markt and coworkers first tested in 2019 the applicability of a BD staging model: they applied Kupka & Hillegers's model (Kupka & Hillegers, 2012) to a sample of 99 outpatients, collecting retrospectively life chart data with monthly evaluations and covering a time frame of five years since the onset of first mood symptoms (Van der Markt et al., 2019). Their findings supported a general BD progression to more advanced stages, with certain covariates (e.g., biphasic mood episodes at onset, male gender) potentially influencing the transition rate (Van der Markt et al., 2019). Authors from the same group also cross-sectionally assessed the clinical utility of Berk's and Kapczinski's staging models in a sample of 1396 BD type 1 (BD I) patients: for both of them, age at onset, treatment resistance and episode acceleration changed concordantly with stages (van der Markt et al., 2020).

In 2020, de la Fuente-Tomàs and colleagues developed a k-means clustering model based on clinical characteristics, functioning, cognition, general health, and health-related quality of life. They included 224 patients at baseline, of whom 129 reached 3-year-follow-up: almost half of the sample remained at the same stage, a quarter progressed and another quarter regressed one stage. Moreover, the progression through stages was associated with a significant worsening of all life domains (de la Fuente-Tomàs et al., 2020).

In a previous article from our group (Macellaro et al., 2023), we applied the main BD staging models available in literature to a sample of Italian bipolar patients mainly referred to outpatient services of Luigi Sacco Hospital in Milan, at four time points over a ten-year retrospective observation. We also assessed potential associations and/or interactions between the mean stage values and the clinical variables over time. A pattern of stage worsening emerged for each model, with a significant increase at every time point from the furthest assessment. Greater stage increases were reported in patients with lower educational level, age at first elevated episode ≤ 35 years, duration of illness ≤ 25 years, and duration of untreated illness (DUI) ≤ 5 years. Lower stage values were associated with BD type 2 (BD II), no psychiatric hospitalization, depressive onset and predominant polarity, ≤ 3 lifetime episodes, age at first mood stabilizer > 40 years, duration of illness ≤ 25 years, and engaged/employed status. Higher stage values were related to lower age at first elevated episode and mood stabilizing treatment instead (Macellaro et al., 2023).

In the present study, authors opted to focus on Kupka & Hillegers's staging model (Table 1), owing to its favourable ratio between the number of classes and the transitions previously observed. The aim was to assess the transition of the sample through the different stages of illness and to explore the potential role of clinical variables on the risk of illness progression.

2. Methods

2.1. Sample and stage assignment

A detailed description of the sample was provided in a previous article from our group (Macellaro et al., 2023). Herein we summarized the main steps of the recruitment and stage assignment process: after approval by the local Ethics Committee and giving written informed consent, 100 patients with a DSM-IV-TR (APA, 2000) diagnosis of BD (53 BD I, 47 BD II) and age > 18 years were recruited from January to June 2020 at Luigi Sacco Hospital in Milan, mainly from 2nd level outpatient services and secondarily from inpatient unit. Among inclusion criteria there were also a clinical history of at least 10 years of psychiatric follow-up, the availability of monthly to quarterly psychiatric assessments as well as of complete clinical information in medical records. Some of the socio-demographic and clinical variables have been dichotomized in order to be more suitable for the longitudinal analyses. The clinical stage was retrospectively assessed according to Kupka & Hillegers's model at six time points (time of recruitment, 1, 2, 5, 7 and 10 years before inclusion): nonetheless, to cluster most of the variations around a limited number of time points, minimize the potential erratic change of patterns, and lead to more precise estimates, only four of them were considered: T0 (2010, 10 years before recruitment), T1 (2015, 5 years before recruitment), T2 (2018, 2 years before recruitment), and T3 (2020, time of recruitment). Furthermore, the five sub-stages of the model were recoded into their main classes by pooling together the three subclasses of stages 1 and 3, the four subclasses of stage 2 and the two subclasses of stage 4.

2.2. Statistical analyses

Given that patients can enter the study in all stages, possible transitions were from stage 1 to stage 2 and 3, from stage 2 to 3 and from stage 3 to 4. Backward transitions were not considered as only one emerged at the considered times.Therefore, the multistate model, fitted using the mstate package in R (de Wreede et al., 2010; de Wreede et al., 2011; Putter et al., 2007), included four possible states. Estimates from a Markov clock-forward model and a semi-Markov clock-reset model with stratified hazards over the transitions for each covariate under study and adjusted by gender and age were calculated. In the clock-forward model, given the present state and the event history, the transition only depends on the present state. In the clock-reset model, the time-scale in the current state depends on the length of stay in the current state. The following covariates were considered among those found to be

significantly associated with stage variations (increase/decrease) in the previous study (Macellaro et al., 2023): BD type, duration of illness, DUI, number of lifetime episodes, predominant polarity, age at first elevated episode, and polarity of first episode. No multivariable regression model was fitted considering the limited number of transitions. Transition probabilities were calculated according to the Markov model. The Markov property was tested using the approach proposed by Titman & Putter (Titman & Putter, 2022) and implemented in the MarkovTest function of the mstate package in the open source R language. To estimate transition probabilities in non-Markov models, the non-parametric landmark Aalen-Johansen method was used (Putter & Spitoni, 2018).

3. Results

Socio-demographic and clinical data of the total sample are reported in detail in the previous manuscript (Macellaro et al., 2023) and briefly summarized in Table 2.

Considering stage transitions, 11 patients who were already in stage 4 at baseline have been excluded. Only one patient in stage 3 at baseline, after a transition to stage 4, made a transition back to stage 3 and then again to stage 4: hence, the back-transition was ignored. One patient starting in stage 0 was considered as starting in stage 1. Out of 15 patients starting in stage 1, 8 made a transition to stage 2 and 7 to stage 3. Fourteen patients were recruited in stage 2 for a total of 22 patients going through this stage; out of 22, 17 patients made a transition to stage 3. Fifty-nine patients started in stage 3, for a total of 83 patients overpassing stage 3. Out of 83 patients in stage 3, 25 entered stage 4.

Figure 1 shows the cumulative hazard for the possible transitions across stages: it is worth noting the high hazard of transition from stage 2 to stage 3 over the ten-year observation.

Figure 2, left panel, illustrates the probability of remaining in stage 1 without making any transition and of moving from stage 1 to stages 2 and 3. Similarly the central and right panels report the probability of transitions starting from stage 2 and 3, respectively. It is worth underlining that the probability of staying in stage 1 diminishes to 60% after 3 years (CI: 44%-83%), and furtherly to 33% at 5 years (CI: 19%-57%), reaching 7% after 8 years (CI: 3%-17%). For stage 2, the probability of staying in stage 2 decreases to 14% after 3 years (CI: 9%-23%), to 3% after 5 years (CI: 1%-7%), and to 2% after 10 years (CI: 1%-6%). As regards stage 3, the probability of staying in stage 3 gradually declines to 65% after 10 years (CI: 56%-77%).

Table 3 reports the estimate of the transition probabilities through all the stages at different time points (3, 5, 8, and 10 years), together with the 95% CI. It is critical to note that, in relation to transition from

stage 1 to 2, the probability ranges from 20% to 32% over 10 years, whereas from stage 1 to 3, the rate more than doubles after 5 years and still raises to almost 60% at 8 and 10 years. Dissimilarly, when examining stage 2, the probability of moving to stage 3 is extremely high already after 3 years (86%) and still show elevated rates at the end of the observation (75%).

Considering the global test of the Markov property, there was evidence of refusing the null hypothesis for all transitions except for the transition from stage 2 to 3. The transition probabilities from stage 1 and stage 2 were also estimated using the landmark Aalen-Johansen estimator, while it was not possible to obtain the estimates from stage 3. The pattern of transition probabilities was similar to the one obtained with the Markov model especially for stage 1 transitions.

As regards the role of covariates on transition rates, Table 4 reports the clock-forward and clock-reset model results that were very similar. No significant associations were reported for the following clinical variables: duration of illness (p=0.5), DUI (p=0.3), age at first elevated episode (p=0.7), and polarity of first episode (p=0.6).

When considering BD type, a significant association emerged instead (p=0.03), with the transition from stage 1 to 2 regarding only BD II patients. No difference was found for the remaining transitions, for which, however, BD I patients were more frequently represented.

As regards predominant polarity, all patients making a transition from stage 1 to 2 have a depressive predominant polarity. No differences were reported for transition from stage 1 to 3 and from stage 2 to 3, whereas elevated predominant polarity was found to be significantly associated with the transition from stage 3 to 4 (HR=3.4; 95% CI: 1.5-7.7; p<0.01).

In relation to the number of lifetime episodes (p=0.09), almost all patients (except one) with more than 3 lifetime episodes started from stage 3. Therefore, the only estimable transition is the one from stage 3 to 4, that turned out to be significantly associated with such clinical variable (HR=2.5; 95% CI: 1.1-5.7; p=0.03).

With respect to the polarity of first episode, although there was no evidence of association, it is noteworthy that only patients with elevated polarity of first episode (i.e., hypo/mania), made the transition from stage 1 (i.e., a positive family history for BD, with non-specific symptoms, as irritability, or depressive episode(s)), to 2.

4. Discussion

In the present study, we retrospectively assessed the transition of a sample of 100 bipolar patients over a 10-year observation, at four time points, according to the model proposed by Kupka and Hillegers, exploring the potential role of clinical variables on the risk of illness progression.

Taken as a whole, our findings furtherly corroborate the existing evidence on the chronic and recurrent nature of the disorder, but also strengthen the notion of illness worsening to more advanced stages (Kessing & Andersen, 2016).

For instance, a pattern of progression has been confirmed in our sample over the ten-year observation. In presence of increased risk (i.e., 1st degree relative with BD) and non-specific psychiatric symptoms/bipolar-specific prodromal symptoms or depressive episodes, the associated probability of not facing BD onset is 60% after 3 years, and furtherly halves at 5 years, reaching 7% after 8 years. Once BD diagnosis has been formulated, the associated probability of not presenting mood recurrences even more rapidly decreases from 100% to 14% after 3 years, to 3% after 5 years, and to 2% after 10 years.

Correspondingly, when examining the transition probabilities, an extremely high hazard of transition from stage 2 (i.e., after a first episode qualifying for BD) to 3 (i.e., recurrence of any mood episode) has been documented over the whole observation period (75-86%). In case of non-specific symptoms or depressive episodes, the probability of moving to stage 2 and 3 are comparable after 3 years, but then the first (i.e., 1 > 2) slowly raises to one third after 10 years, whereas the latter (i.e., 1 > 3) more than doubles already after 5 years and reach 60% after 8 and 10 years. It has to be acknowledged that our sample may not fully represent the broader population of individuals with BD, given that those who have achieved remission and are no longer in treatment were not considered. This selection bias might indeed lead to an overestimation of the transition rates across stages.

Overall, these findings are in line with recent data by van der Markt and coauthors: according to them, five years after BD onset (stage 2), 72% of the sample reached stage 3 and 21% stage 4 (i.e., persisting unremitting illness) (van der Markt et al., 2019).

Taken as a whole, these data shed light on the crucial importance of early detection and close monitoring of non-specific, depressive or prodromal bipolar symptoms, especially in at-risk subpopulations (e.g., in case of positive family history for BD) (Del Favero et al., 2021). This may have a remarkable impact on illness course and outcome, by means of timely intevention prior to and at onset, through pharmacological and non-pharmacological strategies (i.e., on social, familial, or environmental stressors, psychoeducation) as well as prevention or delay of mood recurrences, with the purpose of lengthening time spent in stage 1 and 2. It may be also determining in terms of immediate

treatment of relapses, recurrences, and persisting subsyndromal symptoms in order to shorten their duration, extend inter-episodic phases, promote patients' fuctioning and minimize the impact on essential domains of daily life.

In this perspective, the authors investigated potential associations between certain clinical variables and the different transition intensities: BD II and depressive predominant polarity were found to be significantly associated with transition from stage 1 to 2, whereas the number of lifetime episodes > 3 and the elevated predominant polarity with transition from stage 3 to 4.

More in detail, when considering BD subtype, only patients with a BD II diagnosis at the last observation made the transition from stage 1 to 2 during the study period: this may be explained considering that BD II patients are more likely to face a depressive onset compared with BD I patients (Buoli et al., 2021; Tondo et al., 2022). Although without statistical significance, BD I patients were more frequently represented in remaining transitions, somehow consistently with data showing that BD I patients are usually burdened by higher hospitalization rates and more severe cognitive impairment (Altamura et al., 2018; Cotrena et al., 2020), despite the existing controversy regarding cognitive deficits in BD, as some studies have not found significant differences between BD I and II (Ancin et al., 2013).

Furthemore, an association emerged for predominant polarity, since all patients transiting from stage 1 to 2 had depressive predominant polarity. It is well documented that BD II patients usually show a depressive predominant polarity, related to multiple recurrent depressive episodes interspersed by less frequent hypomanic episodes (Baldessarini et al., 2012a; Tondo et al., 2022), with a longitudinal ratio of depressive to hypomanic episodes over time of about 3:1 (Kupka et al., 2007). Thus, BD II phenotype is characterized by the predominance of depression, which, although less striking than mania, could represent the problematic aspect of the disorder (Drancourt et al., 2013).

Conversely, the elevated predominant polarity was found to be significantly associated with the transition from stage 3 to 4: along with the higher prevalence of BD I found in the transitions across these stages, these data are in line with the association between BD I and elevated predominant polarity, well-documented in literature (Baldessarini et al., 2012b). Moreover, the manic predominant polarity type has been associated with an earlier age of onset, higher number of hospitalizations, more frequent psychotic symptoms, rapid cycling, and cognitive impairment (Martinez-Aran et al., 2004; Carvalho et al., 2014; Popovic et al., 2014; Colom et al., 2015; Sanchez-Morla et al., 2018), all factors that may be involved in progression to advanced phases of illness. Moreover, the presence of psychotic symptoms in BD is associated with a more severe and complex disease trajectory, influencing the

progression of the disorder through various pathways including earlier onset, increased episode frequency, and greater functional impairment (Dell'Osso et al., 2017). However to date there are no studies evaluating the impact of psychotic symptoms on stage progression in BD.

The transition from stage 3 to 4 was found to be significantly associated also with the number of lifetime episodes > 3, in line with the notion that a higher frequency of mood episodes is related to increased risk of recurrences, duration and severity of episodes, lower threshold for developing mood phases and reduced treatment response, potentially leading to advanced stages (Kessing & Andersen, 2016; Passos et al., 2016).

It is worth mentioning the lack of significant associations between transition rates and DUI, duration of illness, age at onset, and polarity of first episode, although several contributions suggest the role of duration of illness (Cardoso et al., 2015), age and polarity of first episode on the course of illness (Tundo et al., 2015; Cremaschi et al., 2017), as well as underline the negative long-term effect of DUI in terms of increased rates of suicidal behaviour, hospitalization, and depressive/hypomanic episodes (Buoli et al., 2021). Our data seem to be more consistent with recent evidence suggesting that poor functioning in BD could be the result of multiple affective relapses, rather than a direct effect of DUI (Fico et al., 2021).

To the best of our knowledge, this is the longest retrospective application of a clinical staging model for BD to a sample of 100 patients, including the assessment of the transition through the different stages of illness.

However, findings of the present study should be cautiously interpreted due to some limitations. First, due to the naturalistic and retrospective design of the study, our estimates of stage transition probabilities may be higher than what would be observed in a prospectively followed cohort from the general population. Secondly, although a 10-year observation is the longest one performed in research on staging models, it still represents a limited time of assessment. In addition, since enrolled patients were referred to a 2nd level specialist clinic, they could overall suffer from a more severe disorder and be influenced by the therapeutic setting. Another relevant limitation potentially affecting the findings is that treatments administered over the 10 years were not retrievable, thus being excluded from the analyses. Considered together, the above-mentioned issues, along with the relatively small sample size, may hamper the generalizability of results.

5. Conclusion

In summary, our results corroborated the existing evidence on the progressive nature of BD, including the one previously reported from our group, and contributed to better define its trajectory over time. Bipolar subtype, predominant polarity, and number of lifetime episodes were found to be significantly associated with transition across stages. Although the heterogeneity intrinsic to BD may limit the clinical use of staging models and their ability to guide its prognosis and treatment is still to be determined, further research effort on their longitudinal application may point to the definition of a standardized system, hopefully implementing data on illness progression over time and thus allowing ever increasing early and tailored interventions. Prospective studies are warranted in order to provide more accurate estimates and validate the present findings.

Tables

Table 1. Staging model by Kupka & Hillegers.

STAGE 0	↑ risk (as defined by a 1st degree relative with BD‡); no psychiatric symptoms
STAGE 1	**Non-specific psychiatric symptoms or depressive episode(s)**
1A	↑ risk and non-specific psychiatric symptoms, no history of depressive episode(s)
1B	↑ risk and bipolar-specific prodromal symptoms, no history of depressive episode(s)
1C	↑ risk, with a first MDE†
1D	↑ risk, with recurrent MDEs†
STAGE 2	**1st episode that qualifies for diagnosis of BD**
2A	1st manic episode (BD‡ I diagnosis) without previous history of depressive episode(s) and without depression immediately preceding or following 1st manic episode
2B	1st hypomanic (BD‡ II diagnosis) or manic episode (dx BD‡ I) without previous history of depressive episode(s) but with depression immediately preceding or following 1st (hypo)manic episode
2C	1st hypomanic (BD‡ I diagnosis) or manic episode (dx BD‡ I) with previous history of depressive episode(s), with or without depression immediately preceding or following 1st (hypo)manic
2D	1st depression after hypomanic episode (BD‡ II diagnosis)
STAGE 3	**Recurrence of any depressive, hypomanic, or manic/mixed episode**
3A	Recurrence of subsyndromal depressive or manic symptoms after the diagnosis of BD‡
3B	Recurrent BD‡ (recurrence of any depressive, hypomanic, or manic/mixed episode) and with full symptomatic and functional recovery between episodes
3C	Recurrent BD‡ (recurrence of any depressive, hypomanic, or manic/mixed episode), with subsyndromal symptoms and/or impaired functioning between episodes
STAGE 4	**Persistent unremitting illness; chronic (> 2 years) depressive, manic or mixed episodes, including rapid cycling**
4A	Chronic depressive, manic or mixed episode(s), without symptomatic and functional recovery for 2 years
4B	Rapid cycling (≥ 4 mood episodes/year), without symptomatic and functional recovery for 2 years

Legend: ↑: increased; †MDE: Major Depressive Episode; ‡BD: Bipolar Disorder.

Table 2. Main socio-demographic and clinical data of the total sample.

	Total Sample
N (%)	100
Age (years, mean±SD[†])	58.27±10.22
Gender, female (%)	57
Ethnicity, caucasian (%)	99
Recruitment service (%)	
2nd level specialist outpatient service	39
Other outpatient service	57
Psychiatric ward	4
Family history (%)	
Positive	64
For mood disorders	44
BD[‡] (%)	
I	53
II	47
Age at onset (years, mean±SD[†])	30.91±12.44
Onset < 18 years (%)	24
Stress event at onset (%)	62
Duration of illness (years, mean±SD[†])	27.62±12.35
DUI[§] (years, mean±SD[†])	4.22±0.70
Age at first episode (years, mean±SD[†])	
Depressive	33.78±12.47
Elevated	36.33±13.41
Polarity of first episode (%)	
Manic	17
Hypomanic	5
Depressive	61
Manic with mixed features	1
Hypomanic with mixed features	2
Depressive with mixed features	8
Depressive with psychotic features	6
Number of lifetime episodes (%)	
1-3	6
4-5	20
6-10	47
> 10	27

	Total sample
Polarity of last episode (%)	
Manic	11
Hypomanic	17
Depressive	49
Manic with mixed features	3
Hypomanic with mixed features	3
Depressive with mixed features	10
Depressive with psychotic features	7
Predominant polarity (%)	
Manic	20
Hypomanic	5
Depressive	50
Manic with mixed features	6
Hypomanic with mixed features	2
Depressive with mixed features	14
Depressive with psychotic features	3
Lifetime mixed episodes (%)	65
Lifetime rapid cycling (%)	20
Age at first mood stabilizer treatment (years, mean±SD[†])	39.32±12.58
Lifetime suicide attempts (%)	25
Lifetime psychiatric hospitalizations (%)	
None	38
1	20
2	22
≥ 3	20
Pharmacotherapy at recruitment (%)	
Lithium	24
Antiepileptics	51
Antidepressants	52
First generation antipsychotics	9
Second/third generation antipsychotics	61
Complex pharmacotherapy (> 3)	12

Legend: [†]SD=standard deviation; [‡]BD= bipolar disorder; [§]DUI=duration of untreated illness.

Table 3. Estimates of the transition probabilities through all the stages at different time points.

From	To	3 years	5 years
1	2	20% (95% CI: 9%-46%)	17% (95% CI: 6%-47%)
1	3	20% (95% CI: 9%-46%)	46% (95% CI: 29%-73%)
2	3	86% (95% CI: 76%-97%)	83% (95% CI: 73%-94%)
3	4	12% (95% CI: 6%-23%)	26% (95% CI: 18%-38%)

From	To	8 years	10 years
1	2	25% (95% CI: 11%-57%)	32% (95% CI: 16%-63%)
1	3	61% (95% CI: 44%-86%)	59% (95% CI: 42%-84%)
2	3	77% (95% CI: 67%-89%)	75% (95% CI: 64%-87%)
3	4	32% (95% CI: 24%-44%)	35% (95% CI: 26%-46%)

Legend: CI=confidence interval.

Table 4. Associations of covariates with transition rates in clock-forward and clock-reset regression models.

		Clock-forward			Clock-reset				
Variable	From - to	HR	95% CI	p-value	HR	95% CI	p-value	BD type=1	BD type=2
BD Type	1 → 2	Inf	[0.00;Inf]	0.99	Inf	[0.00;Inf]	0.99	0/4	8/11
	1 → 3	0.23	[0.05;1.08]	0.06	0.23	[0.05;1.08]	0.06	4/4	3/11
	2 → 3	0.75	[0.19;2.95]	0.68 0.03	0.72	[0.19;2.72]	0.62 0.02	3/3	14/19
	3 → 4	0.47	[0.20;1.10]	0.08	0.47	[0.20;1.08]	0.08	17/42	8/41
Age		1.01	[0.99;1.04]	0.30	1.01	[0.99;1.04]	0.31		
Sex		0.89	[0.52;1.54]	0.69	0.88	[0.51;1.52]	0.65	Age first≤35	Age first>35
Age at first elevated episode	1 → 2	2.66	[0.30;23.79]	0.38	2.66	[0.30;23.88]	0.38	2/5	6/10
	1 → 3	0.59	[0.12;2.91]	0.52	0.59	[0.12;2.93]	0.52	3/5	4/10
	2 → 3	0.74	[0.18;3.06]	0.68 0.71	0.79	[0.19;3.29]	0.74 0.71	4/4	14/18
	3 → 4	1.31	[0.58;2.94]	0.52	1.34	[0.59;3.03]	0.49	11/39	14/44
Age		1.01	[0.98;1.04]	0.51	1.01	[0.98;1.04]	0.54		
Sex		0.90	[0.52;1.56]	0.71	0.88	[0.51;1.53]	0.66	Dur <27	Dur ≥27
Duration of illness	1 → 2	1.97	[0.18;21.85]	0.58	1.97	[0.18;21.92]	0.58	7/12	1/3
	1 → 3	7.86	[0.71;87.39]	0.09	7.89	[0.71;87.68]	0.09	5/12	2/3
	2 → 3	1.15	[0.32;4.07]	0.83 0.46	1.75	[0.47;6.53]	0.41 0.38	14/19	3/3
	3 → 4	0.81	[0.37;1.80]	0.61	0.82	[0.37;1.82]	0.63	12/41	13/42
Age		1.01	[0.98;1.03]	0.47	1.01	[0.98;1.03]	0.55		
Sex		0.88	[0.51;1.50]	0.63	0.89	[0.52;1.53]	0.67	DUI≤5	DUI>5
DUI	1 → 2	1.33	[0.14;12.29]	0.80	1.34	[0.15;12.39]	0.79	7/12	1/3
	1 → 3	3.64	[0.59;22.68]	0.17	3.68	[0.59;22.90]	0.16	5/12	2/3
	2 → 3	1.03	[0.37;2.85]	0.96 0.29	1.41	[0.52;3.82]	0.50 0.21	10/15	7/7
	3 → 4	0.47	[0.20;1.10]	0.08	0.45	[0.19;1.05]	0.07	17/45	8/38
Age		1.01	[0.99;1.03]	0.43	1.01	[0.98;1.03]	0.50		
Sex		0.87	[0.51;1.50]	0.62	0.85	[0.50;1.46]	0.56	Mania	Other
Polarity of first episode	1 → 2	inf	[0.00;Inf]	0.99	Inf	[0.00;Inf]	0.99	0/1	8/14
	1 → 3	0.15	[0.01;1.76]	0.13	0.15	[0.01;1.75]	0.13	1/1	6/14
	2 → 3	0.87	[0.23;3.33]	0.84 0.58	0.82	[0.22;3.06]	0.77 0.54	3/3	14/19
	3 → 4	0.70	[0.30;1.64]	0.41	0.67	[0.29;1.56]	0.35	8/20	17/63
Age		1.01	[0.99;1.03]	0.45	1.01	[0.99;1.03]	0.45		
Sex		0.90	[0.52;1.56]	0.70	0.89	[0.51;1.54]	0.67	Mania	Other
Predominant	1 → 2	0.00	[0.00;Inf]	0.99	0.00	[0.00;Inf]	0.99	8/13	0/2
	1 → 3	1.34	[0.23;7.70]	0.74 0.01	1.32	[0.23;7.61]	0.75 0.01	5/13	2/2

Polarity	2 → 3	1.12	[0.14;8.80]	0.91		1.18	[0.15;9.14]	0.88		16/21	1/1
	3 → 4	3.44	[1.54;7.69]	0.00		3.61	[1.64;7.97]	0.00		11/58	14/25
Age		1.01	[0.99;1.04]	0.40		1.01	[0.98;1.04]	0.41			
Sex		0.87	[0.50;1.50]	0.61		0.85	[0.49;1.46]	0.56		<3	>3
Number of lifetimes episodes	1 → 2	NA	[NA;NA]	NA		NA	[NA;NA]	NA		8/15	0/0
	1 → 3	NA	[NA;NA]	NA		NA	[NA;NA]	NA		7/15	0/0
	2 → 3	0.49	[0.06;3.90]	0.50	0.09	0.59	[0.07;4.74]	0.62	0.10	16/21	1/1
	3 → 4	2.50	[1.09;5.73]	0.03		2.47	[1.09;5.61]	0.03		15/64	10/19
Age		1.01	[0.98;1.03]	0.60		1.01	[0.98;1.03]	0.61			
Sex		0.80	[0.47;1.38]	0.43		0.80	[0.47;1.38]	0.43			

Legend: NA=not applicable; DUI=duration of untreated illness; BD= bipolar disorder; In case of perfect separation, i.e. when the variable perfectly discriminates between those making transitions and those not, the HR is either 0 or Inf and the 95% CI has Inf in the upper limit.

Figures

Figure 1. Cumulative hazard for the possible transitions across stages.

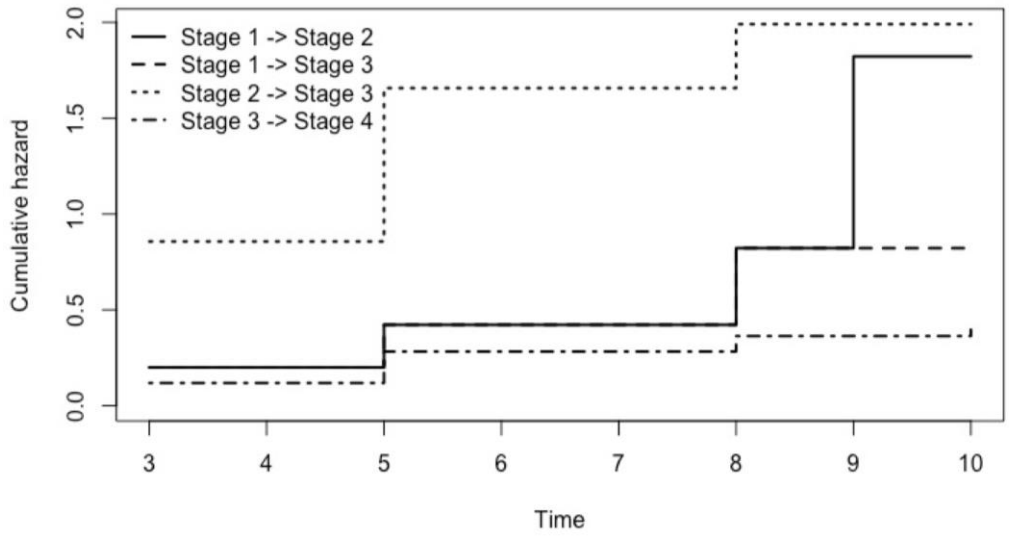
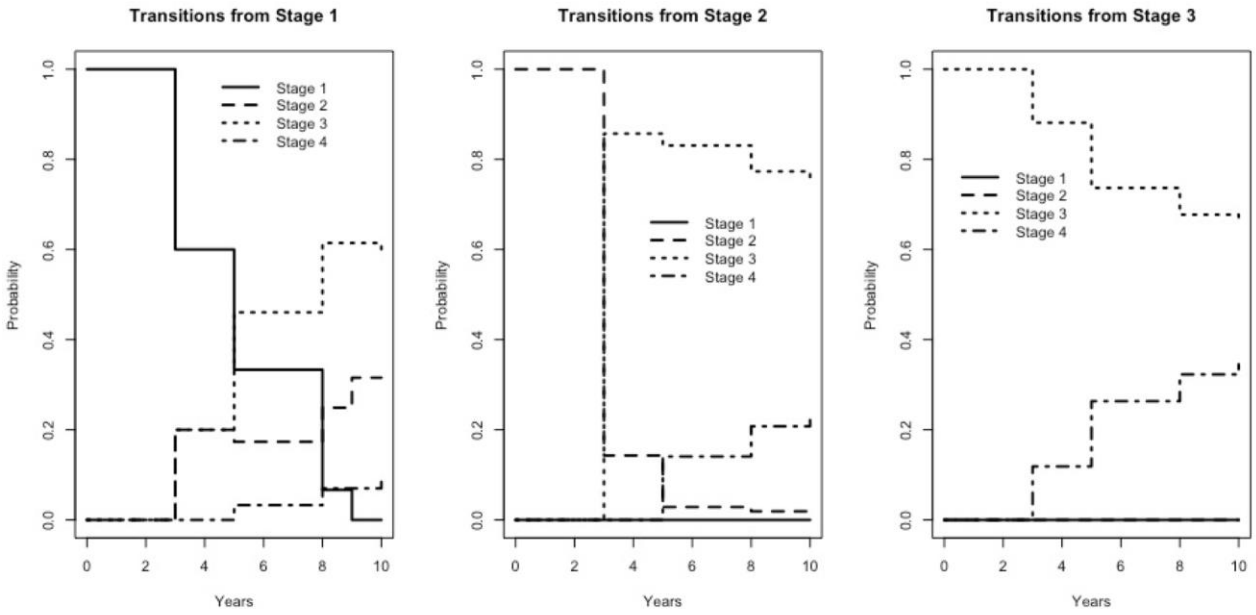


Figure 2. Probability of transitions starting from stage 1, 2 and 3.



References

Altamura, A.C., Buoli, M., Cesana, B., Dell'Osso, B., Tacchini, G., Albert, U., Fagiolini, A., de Bartolomeis, A., Maina, G., Sacchetti, E., 2018. Socio-demographic and clinical characterization of patients with Bipolar Disorder I vs II: a Nationwide Italian Study. Eur. Arch. Psychiatry Clin. Neurosci. 268(2), 169–177. https://doi.org/10.1007/s00406-017-0791-0

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders. Washington D.C, 4th ed. Text Revised.

Ancín, I., Cabranes, J. A., Santos, J. L., Sánchez-Morla, E., & Barabash, A. (2013). Executive deficits: a continuum schizophrenia-bipolar disorder or specific to schizophrenia?. Journal of psychiatric research, 47(11), 1564–1571. https://doi.org/10.1016/j.jpsychires.2013.07.008

Baldessarini, R.J., Tondo, L., Vazquez, G.H., Undurraga, J., Bolzani, L., Yildiz, A., Khalsa, H.M., Lai, M., Lepri, B., Lolich, M., Maffei, P.M., Salvatore, P., Faedda, G.L., Vieta, E., Tohen, M., 2012a. Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. World psychiatry 11(1), 40–46. https://doi.org/10.1016/j.wpsyc.2012.01.006

Baldessarini, R.J., Undurraga, J., Vázquez, G.H., Tondo, L., Salvatore, P., Ha, K., Khalsa, H.M., Lepri, B., Ha, T.H., Chang, J.S., Tohen, M., Vieta, E., 2012b. Predominant recurrence polarity among 928 adult international bipolar I disorder patients. Acta psychiatr. Scand. 125(4), 293–302. https://doi.org/10.1111/j.1600-0447.2011.01818.x

Berk, M., Conus, P., Lucas, N., Hallam, K., Malhi, G.S., Dodd, S., Yatham, L.N., Yung, A., McGorry, P., 2007. Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disord. 9(7), 671–678. https://doi.org/10.1111/j.1399-5618.2007.00484.x

Berk, M., Kapczinski, F., Andreazza, A.C., Dean, O.M., Giorlando, F., Maes, M., Yücel, M., Gama, C.S., Dodd, S., Dean, B., Magalhães, P.V., Amminger, P., McGorry, P., Malhi, G.S., 2011. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 35(3), 804–817. https://doi.org/10.1016/j.neubiorev.2010.10.001

Berk, M., Berk, L., Dodd, S., Cotton, S., Macneil, C., Daglas, R., Conus, P., Bechdolf, A., Moylan, S., Malhi, G.S., 2014. Stage managing bipolar disorder. Bipolar Disord. 16(5), 471–477. https://doi.org/10.1111/bdi.12099

Buoli, M., Cesana, B.M., Fagiolini, A., Albert, U., Maina, G., de Bartolomeis, A., Pompili, M., Bondi, E., Steardo, L.Jr, Amore, M., Bellomo, A., Bertolino, A., Di Nicola, M., Di Sciascio, G., Fiorillo, A., Rocca, P., Sacchetti, E., Sani, G., Siracusano, A., Di Lorenzo, G., Tortorella, A., Altamura, A.C., Dell'Osso, B., ISBD Italian Chapter Epidemiologic Group, 2021. Which factors delay treatment in bipolar disorder? A nationwide study focussed on duration of untreated illness. Early Interv. Psychiatry 15(5), 1136–1145. https://doi.org/10.1111/eip.13051

Cardoso, T., Bauer, I.E., Meyer, T.D., Kapczinski, F., Soares, J.C., 2015. Neuroprogression and Cognitive Functioning in Bipolar Disorder: A Systematic Review. Curr. Psychiatry Rep. 17(9), 75. https://doi.org/10.1007/s11920-015-0605-x

Carvalho, A.F., McIntyre, R.S., Dimelis, D., Gonda, X., Berk, M., Nunes-Neto, P.R., Cha, D.S., Hyphantis, T.N., Angst, J., Fountoulakis, K.N., 2014. Predominant polarity as a course specifier for bipolar disorder: a systematic review. J. Affect. Disord. 163, 56–64. https://doi.org/10.1016/j.jad.2014.03.035

Colom, F., Vieta, E., Suppes, T., 2015. Predominant polarity in bipolar disorders: refining or redefining diagnosis? Acta Psychiatr. Scand. 132(5): 324–326. https://doi.org/10.1111/acps.12503

Cotrena, C., Damiani Branco, L., Ponsoni, A., Samamé, C., Milman Shansis, F., Paz Fonseca, R., 2020. Executive functions and memory in bipolar disorders I and II: new insights from meta-analytic results. Acta Psychiatr. Scand. 141(2), 110–130. https://doi.org/10.1111/acps.13121

Cremaschi, L., Dell'Osso, B., Vismara, M., Dobrea, C., Buoli, M., Ketter, T. A., Altamura, A. C., 2017. Onset polarity in bipolar disorder: A strong association between first depressive episode and suicide attempts. J. Affect. Disord. 209, 182–187. https://doi.org/10.1016/j.jad.2016.11.043

D'Addario, C., Dell'Osso, B., Palazzo, M. C., Benatti, B., Lietti, L., Cattaneo, E., Galimberti, D., Fenoglio, C., Cortini, F., Scarpini, E., Arosio, B., Di Francesco, A., Di Benedetto, M., Romualdi, P., Candeletti, S., Mari, D., Bergamaschini, L., Bresolin, N., Maccarrone, M., & Altamura, A. C. (2012). Selective DNA methylation of BDNF promoter in bipolar disorder: differences among patients with BDI and BDII. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 37(7), 1647–1655. https://doi.org/10.1038/npp.2012.10

de la Fuente-Tomás, L., Sierra, P., Sanchez-Autet, M., Arranz, B., García-Blanco, A., Safont, G., García-Portilla, M.P., 2020. A clinical staging model for bipolar disorder: longitudinal approach. Transl. Psychiatry 10(1), 45. https://doi.org/10.1038/s41398-020-0718-9

Del Favero, E., Montemagni, C., Bozzatello, P., Brasso, C., Riccardi, C., Rocca, P., 2021. The Management of Prodromal Symptoms of Bipolar Disorder: Available Options and Future Perspectives. Medicina (Kaunas) 57(6), 545. https://doi.org/10.3390/medicina57060545

Dell'Osso, B., Camuri, G., Cremaschi, L., Dobrea, C., Buoli, M., Ketter, T. A., & Altamura, A. C. (2017). Lifetime presence of psychotic symptoms in bipolar disorder is associated with less favorable socio-demographic and certain clinical features. Comprehensive psychiatry, 76, 169–176. https://doi.org/10.1016/j.comppsych.2017.04.005

de Wreede, L.C., Fiocco, M., Putter, H., 2010. The {mstate} Package for Estimation and Prediction in Non- and Semi-Parametric Multi-State and Competing Risks Models. Comput. Methods Programs Biomed. 99(3), 261–274. https://doi.org/10.1016/j.cmpb.2010.01.001

de Wreede, L.C., Fiocco, M., Putter, H., 2011. mstate: An R Package for the Analysis of Competing Risks and Multi-State Models. J. Stat. Softw. 38(7), 1-30. https://www.jstatsoft.org/v38/i07/

Drancourt, N., Etain, B., Lajnef, M., Henry, C., Raust, A., Cochet, B., Mathieu, F., Gard, S., Mbailara, K., Zanouy, L., Kahn, J.P., Cohen, R.F., Wajsbrot-Elgrabli, O., Leboyer, M., Scott, J., Bellivier, F., 2013. Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. Acta psychiatrica Scandinavica 127(2), 136–144. https://doi.org/10.1111/j.1600-0447.2012.01917.x

Duffy, A., 2014. Toward a comprehensive clinical staging model for bipolar disorder: integrating the evidence. Can. J. Psychiatry 59 (12), 659–666. https://doi.org/10.1177/070674371405901208.

Fico, G., Anmella, G., Gomez-Ramiro, M., de Miquel, C., Hidalgo-Mazzei, D., Manchia, M., Alda, M., Gonzalez-Pinto, A., Carvalho, A. F., Vieta, E., Murru, A., 2021. Duration of untreated illness and bipolar disorder: time for a new definition? Results from a cross-sectional study. J. Affect. Disord. 294, 513–520. https://doi.org/10.1016/j.jad.2021.07.062

Kapczinski, F., Dias, V.V., Kauer-Sant'Anna, M., Frey, B.N., Grassi-Oliveira, R., Colom, F., Berk, M., 2009. Clinical implications of a staging model for bipolar disorders. Expert. Rev. Neurother. 9 (7), 957–966. https://doi.org/10.1586/ern.09.31.

Kapczinski, N.S., Mwangi, B., Cassidy, R.M., Librenza-Garcia, D., Bermudez, M.B., Kauer-Sant'anna, M., Kapczinski, F., Passos, I.C., 2017. Neuroprogression and illness trajectories in bipolar disorder. Expert. Rev. Neurother. 17(3), 277–285. https://doi.org/10.1080/14737175.2017.1240615

Kauer-Sant'Anna, M., Kapczinski, F., Andreazza, A. C., Bond, D. J., Lam, R. W., Young, L. T., & Yatham, L. N. (2009). Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. The international journal of neuropsychopharmacology, 12(4), 447–458. https://doi.org/10.1017/S1461145708009310

Kessing, L.V., Andersen, P.K., 2016. Evidence for clinical progression of unipolar and bipolar disorders. Acta Psychiatr. Scand. 135(1), 51–64. https://doi.org/10.1111/acps.12667

Kupka, R.W., Altshuler, L.L., Nolen, W.A., Suppes, T., Luckenbaugh, D.A., Leverich, G.S., Frye, M.A., Keck, P.E.Jr., McElroy, S.L., Grunze, H., Post, R.M., 2007. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disord. 9(5), 531–535. https://doi.org/10.1111/j.1399-5618.2007.00467.x.

Kupka, R.W., Hillegers, M.H., 2012. Stagering en profilering bij bipolaire stoornissen [Staging and profiling in bipolar disorders]. Tijdschr. Psychiatr. 54(11), 949–956.

Macellaro, M., Girone, N., Cremaschi, L., Bosi, M., Cesana, B.M., Ambrogi, F., Caricasole, V., Giorgetti, F., Ketter, T.A., Dell'Osso, B., 2023. Staging models applied in a sample of patients with bipolar disorder: Results from a retrospective cohort study. J. Affect. Disord. 323, 452–460. https://doi.org/10.1016/j.jad.2022.11.081

Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., Benabarre, A., Goikolea, J.M., Comes, M., Salamero, M., 2004. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am. J. Psychiatry 161(2), 262–270. https://doi.org/10.1176/appi.ajp.161.2.262

McGorry, P.D., Hickie, I.B., Yung, A.R., Pantelis, C., Jackson, H.J., 2006. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Australian N. Z. J. Psychiatry 40(8), 616–622. https://doi.org/10.1080/j.1440-1614.2006.01860.x

Muneer, A., 2016. The Neurobiology of Bipolar Disorder: An Integrated Approach. Chonnam Med. J. 52(1), 18–37. https://doi.org/10.4068/cmj.2016.52.1.18

Passos, I.C., Mwangi, B., Vieta, E., Berk, M., Kapczinski, F., 2016. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr. Scand. 134(2), 91–103. https://doi.org/10.1111/acps.12581

Popovic, D., Torrent, C., Goikolea, J.M., Cruz, N., Sánchez-Moreno, J., González-Pinto, A., Vieta, E., 2014. Clinical implications of predominant polarity and the polarity index in bipolar disorder: a naturalistic study. Acta Psychiatr. Scand. 129(5), 366–374. https://doi.org/10.1111/acps.12179

Post, R.M., 2020. How to prevent the malignant progression of bipolar disorder. Braz. J. Psychiatry 42(5), 552–557. https://doi.org/10.1590/1516-4446-2020-0874

Putter, H., Fiocco, M., Geskus, R.B., 2007. Tutorial in biostatistics: competing risks and multi-state models. Stat. Med. 26(11), 2389–2430. https://doi.org/10.1002/sim.2712

Putter, H., Spitoni, C., 2018 Non-parametric estimation of transition probabilities in non-Markov multi-state models: The landmark Aalen-Johansen estimator. Stat Methods Med Res. 27(7):2081-2092. https://doi: 10.1177/0962280216674497

Rosenblat, J. D., & McIntyre, R. S. (2016). Bipolar Disorder and Inflammation. The Psychiatric clinics of North America, 39(1), 125–137. https://doi.org/10.1016/j.psc.2015.09.006

Sánchez-Morla, E. M., López-Villarreal, A., Jiménez-López, E., Aparicio, A. I., Martínez-Vizcaíno, V., Roberto, R. J., Vieta, E., & Santos, J. L. (2019). Impact of number of episodes on neurocognitive trajectory in bipolar disorder patients: a 5-year follow-up study. Psychological medicine, 49(8), 1299–1307. https://doi.org/10.1017/S0033291718001885

Serafini, G., Pardini, M., Monacelli, F., Orso, B., Girtler, N., Brugnolo, A., Amore, M., Nobili, F., Team On Dementia Of The Irccs Ospedale Policlinico San Martino, D.M., 2021. Neuroprogression as an Illness Trajectory in Bipolar Disorder: A Selective Review of the Current Literature. Brain Sci. 11(2), 276. https://doi.org/10.3390/brainsci11020276

Titman, A.C., Putter, H., 2022 General tests of the Markov property in multi-state models , Biostatistics, 23(2), 380–396, https://doi: 10.1093/biostatistics/kxaa030

Tondo, L., Miola, A., Pinna, M., Contu, M., Baldessarini, R.J., 2022. Differences between bipolar disorder types 1 and 2 support the DSM two-syndrome concept. Int. J. Bipolar Disord. 10(1), 21. https://doi.org/10.1186/s40345-022-00268-2

Tsapekos, D., Strawbridge, R., Cella, M., Wykes, T., Young, A.H., 2021. Cognitive impairment in euthymic patients with bipolar disorder: Prevalence estimation and model selection for predictors of cognitive performance. J. Affect. Disord. 294, 497–504. https://doi.org/10.1016/j.jad.2021.07.036

Tundo, A., Musetti, L., Benedetti, A., Berti, B., Massimetti, G., Dell'Osso, L., 2015. Onset polarity and illness course in bipolar I and II disorders: The predictive role of broadly defined mixed states. Compr. Psychiatry 63, 15–21. https://doi.org/10.1016/j.comppsych.2015.07.018

van der Markt, A., Klumpers, U.M., Draisma, S., Dols, A., Nolen, W.A., Post, R.M., Altshuler, L.L., Frye, M.A., Grunze, H., Keck, P.E.Jr., McElroy, S.L., Suppes, T., Beekman, A.T., Kupka, R.W., 2019. Testing a clinical staging model for bipolar disorder using longitudinal life chart data. Bipolar Disord. 21(3), 228–234. https://doi.org/10.1111/bdi.12727

van der Markt, A., Klumpers, U.M.H., Dols, A., Draisma, S., Boks, M.P., van Bergen, A., Ophoff, R.A., Beekman, A.T.F., Kupka, R.W., 2020. Exploring the clinical utility of two staging models for bipolar disorder. Bipolar Disord. 22(1), 38–45. https://doi.org/10.1111/bdi.12825

Declaration of interest

In the last three years, Prof. Dell'Osso has received lecture honoraria and grants from Angelini, Lundbeck, Janssen, Pfizer, Otzuka, Neuraxpharm, and Livanova. The other authors have no conflicts to declare.

CRediT authorship contribution statement

Laura Cremaschi, Monica Macellaro, Monica Bosi, Bernardo Dell'Osso: psychiatrists (conceptualization, methodology, investigation, writing); Nicolaja Girone: clinical psychologist (conceptualization, methodology, investigation, writing); Federico Ambrogi and Bruno Mario Cesana: statisticians (formal analyses, writing).

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Highlights

- We retrospectively applied Kupka & Hillegers's model to a sample of 100 bipolar patients at 4 time-points over 10 years
- We assessed the transition across stages and the role of clinical variables on the risk of progression
- A high hazard of transition from stage 2 to 3 emerged, with a probability of staying in stage 2 decreasing to 14% after 3 years
- BD II and depressive predominant polarity were significantly associated with transition from stage 1 to 2, whereas the number of lifetime episodes > 3 and the elevated predominant polarity with transition from stage 3 to 4