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Research paper

Bipolar disorder predicted shorter and borderline personality disorder symptoms longer time to remission – A prospective cohort study of major depressive patients

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ABSTRACT

Background: Major depressive episodes (MDEs) of major depressive (MDD) or bipolar disorders (BD) are frequently complicated by features of borderline personality disorder (BPD). Mixed features are a hallmark of BD and affective lability of BPD, and both may markedly influence illness course. However, direct comparisons of outcome of depression in MDD, BD, and BPD are scarce.

Methods: In a cohort study based on stratified sampling, we diagnosed psychiatric MDE patients with SCID-I/P and SCID-II interviews and examined mixed symptoms using the Mix-MDE scale and borderline symptoms using the Borderline Personality Disorder Severity Index. During a six-month prospective follow-up, the MDE patients with MDD (n = 39), BD (n = 33), or BPD (n = 23) completed biweekly online assessments. Using life chart methodology, we divided the follow-up period into qualitatively different mood state periods. We investigated durations of mood episodes, times to first full symptomatic remission, and their predictors.

Results: Remission rates were similar in MDD, MDE/BD, and MDE/BPD patients. MDE/BD patients experienced more numerous and shorter distinct mood state periods during follow-up than the others. MDE/BD was associated with shorter (HR = 2.44, 95 % CI = 1.27–4.67) and dimensionally assessed BPD severity with longer time to first remission (HR = 0.95, 95 % CI = 0.91–1.00).

Limitations: Moderate sample size and follow-up duration.

Conclusions: Course of illness over six months differs between the three depressive groups. Bipolar depressive patients have the most alternating course and the shortest time to first period of remission. Dimensionally assessed severity of BPD may predict longer time to remission from depression.

1. Introduction

Major depressive disorder (MDD) as defined by the Diagnostic and Statistical Manual, 5th edition (DSM-5, American Psychiatric Association, 2013), is a heterogeneous entity in many ways, including prognosis. The course of MDD can vary from spontaneous achievement of long-term remission to treatment-resistant chronic MDD. The reported prognosis varies markedly according to setting: general population, primary care, psychiatric care, or hospital. According to a systematic review, the vast majority of subjects (70–85 %) with MDD achieve at least temporary recovery, although there is significant heterogeneity across studies (Steinert et al., 2014). The risk of later recurrence is also variable, largely depending on the duration of follow-up and the setting, with many population-based studies showing recurrence rates around 40–50 % (Eaton et al., 2008; Mattisson et al., 2007) and increasing rates with longer follow-up times. In a previous Finnish primary care sample with a 5-year follow-up, recurrences were experienced by every third participant (Riihimäki et al., 2014). In psychiatric care, the risk of later recurrence has generally been greater, with rates in the 40–70 % range (Holma et al., 2008; Kanai et al., 2003), and worse outcomes seen in

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older studies and in in-patient settings. Even in these psychiatric cohorts, however, failure to achieve temporary remission seems rare (Holma et al., 2008; Kanai et al., 2003). Offering additional treatment options to primary non-responders is beneficial, with a majority eventually responding (Gaynes et al., 2009). Still, among patients who suffer from chronic or highly recurrent depression, remission is achieved only by a minority even after extensive treatment (Trivedi et al., 2006). Early identification of patients with less favourable prognosis could allow offering more tailored treatment based on their specific needs, and interventions targeted at modifiable risk factors might lessen the burden of depression on patients and society.

An enduring problem in the field is the lack of consistently applied definitions and terminology for such central concepts as remission, recovery, recurrence, and relapse, despite long-standing efforts to establish them (Frank et al., 1991; Rush et al., 2006). The DSM-5 definition of remission as a period of 2 months or more with at most two symptoms, which must be mild, has clarified the issue somewhat, but not always been consistently applied. One specific reason for the difficulties in reaching a full terminological consensus may be the lack of an empirical basis for unambiguous temporal cut-off points between the concepts of remission and recovery (de Zwart et al., 2019). Nevertheless, achieving a full symptomatic remission of non-trivial length is seen as a key step towards long-term recovery (Judd et al., 2000; Rush et al., 2006).

In addition to MDD, major depressive episodes (MDEs) also occur in bipolar disorder (BD). In fact, BD patients spend a much larger portion of time in depressed state than in manic or hypomanic states (Kupka et al., 2007). MDE in bipolar disorder (MDE/BD) is often difficult to treat (Post et al., 2003), and in patients with BD remission from depressive episodes is slower and less certain than from episodes of manic polarity (Solomon et al., 2010). Remission in the context of BD should take into account both affective polarities; one proposed definition of remission is a period of one week or more without depressive or manic symptoms, whereas a period of 12 weeks or more would be described as sustained remission (Hirschfeld et al., 2007). While the majority of BD patients do achieve remission after an acute episode, it is often partial, and the course of the illness is most often best characterized as relapsing-remitting (Pallaskorpi et al., 2015).

In addition to pure depressive or (hypo)manic states, BD patients may also experience episodes with features of both affective polarities, which is recognized by DSM-5 in the form of the mixed feature episode specifier (American Psychiatric Association, 2013). Interestingly, manic or hypomanic symptoms have also been described in a significant portion of depressive patients without BD (McIntyre et al., 2015; Socada et al., 2021), and have been linked to a greater total burden of illness (Corponi et al., 2020). We have previously developed the Mix-MDE, an instrument for retrospectively quantifying (hypo)manic features during an MDE (Socada et al., 2021), the prognostic relevance of which in the context of MDE is accordingly of interest. As this is a dimensional instrument, it differs from the (categorical) DSM-5 definition of mixed features, and could potentially achieve a more nuanced evaluation of this phenomenon.

Borderline personality disorder (BPD) involves significant affective lability and carries a substantial risk for depression, with 96 % of BPD patients experiencing a mood disorder, most commonly major depression, during their lifetime (Zanarini et al., 1998). The presence of BPD in MDE patients is related to a higher risk of having a persisting form of depression (Skodol et al., 2011), less favourable treatment response (Ceresa et al., 2021), longer time to remission (Grilo et al., 2005), and significant risk of suicidal thoughts and acts (Soderholm et al., 2020). In the DSM-5, personality disorders (PDs) are diagnosed categorically, but the distribution of BPD in the population seems continuous and unimodal, and a dimensional assessment may be useful in many situations (Trull et al., 2010). For instance, dimensional BPD measures correlate with such clinically central phenomena as suicidal ideation and action (Soderholm et al., 2020; Yen et al., 2009) and general risk of other psychopathology (Gluschkoff et al., 2021). BPD symptomatology generally improves over time (Gunderson et al., 2011), which further increases the value of dimensional assessment. The relationship between dimensionally assessed borderline symptoms and course of depressive illness is currently unclear.

BD and BPD are not mutually exclusive entities; indeed, there is a significant risk of comorbid BD in BPD patients and vice versa (Zimmerman and Morgan, 2013). If one accepts hypomanic episodes of shorter duration than required by the DSM-5 as indicative of a bipolar spectrum disorder, comorbidity between these categories is even more common (Perugi et al., 2013). There is also specific symptomatic overlap between BPD and (hypo)mania, namely irritability and impulsivity/increased high-risk behaviour. This may in part explain the high prevalence of (hypo)manic symptoms among MDE patients with BPD (Socada et al., 2021). There is, however, a lack of studies prospectively comparing the presence of (hypo)manic symptoms over time during the recovery process from MDE between MDD, MDE/BD, and MDE/BPD patients. Such studies could help to clarify diagnostic boundaries of these disorders and elucidate potential differences in the prognosis of MDE.

Regarding the risk factors for a poorer prognosis in depression, a recent meta-analysis identified a strong correlation between depression severity and a poorer long-term prognosis in MDD patients; additional risk factors were duration of depressive and anxious symptomatology, comorbid panic disorder, and a history of pharmacological treatment (Buckman et al., 2021). Severity of anxiety symptoms has also previously been noted to correlate negatively with achievement of remission in treatment trials (Saveanu et al., 2015). In a previous Finnish 18-month prospective cohort study of psychiatric care MDD in- and outpatients, severity of depressive symptoms and psychiatric comorbid diagnoses were the main predictors of an unfavourable course of illness (Melartin et al., 2004). The centrality of comorbidity and depression severity as risk factors for poor prognosis has further been confirmed in a model based on the large NESARC epidemiological sample, whereas seeking treatment was associated with a better outcome (Hoertel et al., 2017). Substance use disorders (SUDs), such as alcohol use disorder (AUD), are frequent comorbidities. Interestingly, AUD has correlated with faster initial recovery times but a worse long-term prognosis in terms of time spent depressed in MDD patients (M. Holma et al., 2020).

Identifying risk factors for not achieving remission in MDE can be of clinical value, if it is helpful in targeting treatments based on patients' relevant characteristics and specific needs. However, studies directly comparing the course of illness and prognostic determinants of MDEs in MDD, BD, and BPD are lacking. Therefore, our aim was to characterize prospectively the course of illness and factors influencing it in a cohort of MDE patients divided into MDE/MDD, MDE/BD, and MDE/BPD subcohorts. This paper also investigates predictors for time to remission, which is relevant for both longer term prognosis and patient-level illness burden. Based on the above literature, our hypotheses were: a) Remission from depression is achieved more quickly in BD than in MDD; b) BPD severity is associated with achieving remission more slowly; c) significant differences exist between MDE/MDD, MDE/BD, and MDE/BPD patients in number and duration of qualitatively different mood state periods during MDE and recovery from MDE, with BD patients experiencing the highest number of periods (of shortest duration) and MDD patients the fewest; and d) mixed features of the MDE at baseline (assessed with Mix-MDE) are positively correlated with the number of distinct periods during follow-up.

2. Methods

2.1. Study design

This is a prospective naturalistic cohort study of treatment-seeking MDE patients referred to specialized psychiatric (secondary level) care in Helsinki, Finland. The study was conducted according to the tenets of the Declaration of Helsinki (2013). Written informed consent was

obtained from each participant.

The research protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District, and a research permit was granted by the City of Helsinki.

2.2. Recruitment and subcohort assignment

Our recruitment process (including detailed inclusion and exclusion criteria) has been described in detail elsewhere (Socada et al., 2021); essentially we applied stratified recruitment process in order to recruit a sufficient number of patients of male and female sex into each of our three subcohorts: MDE/MDD, MDE/BD, and MDE/BPD.

Inclusion criteria for the study comprised fulfilling MDE criteria, and a Montgomery-Åsberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979) score of 15 or higher. Exclusion criteria comprised SUD with ongoing use, psychotic illness, and current psychotic symptoms. The patients were assigned to subcohorts according to the following criteria: a) MDE/MDD subcohort: MDD, no diagnosis of BPD or BD; b) MDE/BD subcohort: diagnosis of BD; c) MDE/BPD subcohort: diagnosis of BPD.

Patients meeting the criteria for both BD and BPD were sorted into the MDE/BD subcohort if they had BD type I, otherwise into the MDE/BD or MDE/BPD subcohort according to principal clinical presentation. Unclear cases were discussed by the research team (J.L.S., J.E., E.I., and J.J.S.), and final subcohort assignment made by consensus.

Out of 1655 potential referrals, 124 patients (83 females, 41 males) met the inclusion criteria and gave their informed consent to participate. Of these, 50 (29 females, 21 males) were classified into the MDE/MDD, 43 (31/12) into the MDE/BD, and 31 (23/8) into the MDE/BPD subcohorts. Baseline findings have been reported in more detail previously (Socada et al., 2021). Briefly, no significant differences emerged between the subcohorts in gender, age, or depression severity as measured by the MADRS, whereas significant differences were present in the BPDSI and Mix-MDE scores, which were lower in the MDE/MDD cohorts than in the others. In the original cohort of 124 patients, 6 patients (14 %) of the MDE/BD subcohort had comorbid BPD and, in the MDE/BPD subcohort, 8 patients (25 %) had comorbid type II BD. Of the 96 patients who completed the lifechart, 2/33 (6,1 %) in the MDE/BD cohort had comorbid BPD, and 6/24 (25 %) in the MDE/BPD subcohort had comorbid BD.

2.3. Interviews and rating scales

The patients were assessed at baseline by J.L.S. and J.J.S. with diagnostic interviews such as the structured clinical interview for DSM i.e. SCID I and II (First et al., 1997; First and Spitzer, 2002), updated to include DSM-5 criteria; the inter-rater reliability was excellent (Cohen's κ 1.00 for MDD, 0.90 for BD, 1.00 for type I BD and 0.89 for BPD).

We assessed the severity of depressive symptoms with the Montgomery-Åsberg Depression Rating Scale or MADRS (Montgomery and Asberg, 1979), presence of (hypo)manic symptoms during the index MDE dimensionally with the Mix-MDE (Socada et al., 2021), severity of BPD features/symptoms with the Borderline Personality Disorder Severity Index or BPDSI (Arntz et al., 2003), severity of anxiety symptoms with the overall anxiety severity and impairment scale OASIS (Campbell-Sills et al., 2009), and alcohol use with the Alcohol Use Disorders Identification Test AUDIT (Saunders et al., 1993).

2.4. Follow-up

After initial assessment, the patients were prospectively followed for a period of 6 months with a biweekly online questionnaire: the Personal Health Questionnaire 9 [PHQ-9 (Kroenke et al., 2001)], with added questions regarding the DSM-5 core symptoms of hypomania or mania, i.e. elevated/irritable mood and/or increased activity or energy. After this follow-up period, the patients were met for follow-up interviews. Each patient who completed the study was assessed in person on at least six different, often multi-hour, appointments.. 94 patients completed at least one PHQ-9. The mean number of online questionnaires completed per responder was 8.62 (SD 2.73).

There were 29 patients (23.4 % of the 124) who did not participate in the follow-up SCID at 6 months, of these 11 belonged to the MDD (8 females, 3 males), 10 (6 females, 4 males) to the BD, and 8 (7 females, and 1 male) to the BPD subcohort. There were no significant differences between dropouts and non-dropouts in subcohort assignment ($p = 0.921$), sex ($p = 0.648$), baseline MADRS score ($p = 0.927$), duration of MDE ($p = 0.2459$), or baseline OASIS score ($p = 0.4951$); the baseline AUDIT score was 9.59 (SD 7.33) among dropouts and 6.75 (SD 5.90) among non-dropouts ($p = 0.064$).

2.5. Life charts and mood states

We made a life chart documenting mood state periods during the follow-up period based on: a) baseline interviews and measures, b) the prospective online modified PHQ-9 questionnaires, c) clinical follow-up data from patients' charts, and d) clinical follow-up interviews. Clinical treatment and follow-up intensity and chart data varied. Life charts were constructed collaboratively with the patients, but the researchers made the final classification decisions. If information from available sources indicated possible manic or mixed symptoms, the period in question was investigated more thoroughly using clinical interview practices. If significant doubt remained regarding possible symptoms, we rated down. The interviewers were not blind to the clinical diagnoses of the patients. For patients who were unavailable for follow-up interviews but had not withdrawn their consent, life charts were constructed by a researcher (J.L.S. or J.J.S.) based on all available information. If the information was sparse, the patient was treated as a dropout. Any unclear cases were discussed by the research team, and decisions made by consensus.

In the life chart, the whole follow-up period was divided into *mood state periods*, with a switch from one period to the next being triggered by a change in affective symptom intensity on the depressive axis, the manic axis, or both axes. Depressive mood intensity was rated from 0 to 2, with 0 signifying no or minimal depressive symptoms, 1 signifying subsyndromal depressive symptomatology, and 2 signifying symptoms meeting the symptomatic (but not necessarily durational) MDE criteria in DSM-5. Manic symptom intensity was rated from 0 to 3, with 0 signifying no or minimal symptoms of manic polarity, 1 signifying symptomatically subsyndromal hypomanic symptoms, 2 signifying DSM-5 symptomatic (but not necessarily durational) hypomania, and 3 signifying symptomatic mania. Consequently, each period was classified into one of 12 potential mood states. For example, a period with pure (i.e., non-mixed) MDE symptoms filling DSM symptomatic (but not necessarily durational) criteria would be rated as (2, 0), whereas a period of hypomanic symptom intensity with subsyndromal depressive features would be rated as a (1, 2), and a full absence of manic and depressive symptoms would be rated as (0, 0). To maximize retention of information, the minimum episode duration required was 1 day (24 h), whereas conversely, the whole follow-up period could potentially consist of a single period in a mood state of unremitting depression.

For each patient, we measured the time (in days) from inclusion in the study until first period of remission, which was defined as a period with no or minimal depressive symptoms, no or subsyndromal hypomanic symptoms, and a duration of 14 days or more.

2.6. Statistical analysis

A database was assembled in SQLite (https://www.sqlite.org/index.html) and the data were analysed with R version 4.0.3 (https://www.r-project.org/), using the tidyverse, survival, and survminer packages. For significance testing, we used two-sided *t*-tests, and *F*- and χ^2-tests, as appropriate. For investigating episode numbers, we used Poisson regression models, and for time to remission, Kaplan-Meier survival

curves and Cox proportional hazards modelling.

3. Results

3.1. Clinical outcome

Table 1 reports descriptive statistics and the clinical outcome of the whole cohort and subcohorts at the end of the study. Since there were patients with both BPD and BD in two of the cohorts, we also examined how these diagnoses affected DSM-5 remission from MDE regardless of subcohort assignment. At follow-up, 32 (57.1 %) of 56 non-BD patients, and 22 (56.1 %) of 39 BD patients were in remission from depression, with no significant difference between these groups ($p = 1$). For the non-BPD versus BPD patients, these numbers were 40 of 70 (57.1 %) and 14 of 25 (56 %), respectively, with no evidence of a significant difference ($p = 1$).

3.2. Mood states during follow-up

The mean number of distinct mood state periods during the follow-up period was 5.75 (SD4.13, range 1–25, with a positively skewed distribution), and the mean duration was 60.9 (SD 48.6, range 1–228) days. Subcohortwise, the mean period number and lengths were 4.49 (SD 3.15) periods of 69.2 (SD 45.0) days for the MDD, 8.03 (SD 5.01) periods of 40.30 (SD 31.12) days in the BD, and 4.67 (2.79) periods of 75.6 (SD 64.0) days in the BPD subcohort, with no significant differences (ANOVA $p = 0.532$ for period number and $p = 0.939$ for duration). There were significant ($p = 0.002$) differences in mean period number between females (mean 6.51, SD 4.55 episodes) and males (4.19, SD 2.42).

Comparing diagnostic groups (as opposed to subcohorts), BD patients had a mean of 7.62 (SD 4.94) different periods of 48.7 (SD 47.7) days and non-BD patients 4.47 (SD 2.89) periods of 69.2 (SD 47.8) days; these differences were significant ($p < 0.001$ for number, $p = 0.0427$ for duration). BPD patients had a mean of 5.04 (SD 3.24) periods with a length of 72.0 (SD 62.8) days, non-BPD patients 6.01 (SD 4.41) episodes of 56.7 (SD 41.9) days; these differences were non-significant ($p = 0.2422$ for number, $p = 0.2586$ for duration). A Poisson regression model for the number of periods during follow-up offset by individual follow-up duration is reported in Table 2. In an alternative model that included otherwise identical variables but excluded the BD diagnosis status (in order to reduce redundancy with the Mix-MDE score), the Mix-MDE score was a significant ($p < 0.001$) predictor of episode number with a RR of 1.450 (95 % CI 1.011–1.032) after controlling for sex and BPDSI scores. In other explored models, we found no evidence of a relationship between age or MADRS score and period number, thus, they were not included in our final model.

For each period type, we calculated the relative amount of time (expressed as portion of the whole follow-up period) spent in that state during the whole follow-up period for each patient. The results for the whole cohort and for subcohorts are presented in Table 3. There were also highly significant differences between non-BD and BD patients (that is, when the whole cohort was divided by BD diagnostic status instead of subcohortwise) in the relative amount of time they spent in states with no manic symptoms (non-BD patients 98.7 % of the follow-up period, SD 6.49 %; BD patients 83.5 %, SD 20.1 %; $p < 0.001$), subthreshold hypomanic symptoms (non-BD 1.02 %, SD 4.72 %; BD 8.93 %, SD 12.6 %; $p < 0.001$), and symptoms of hypomanic intensity (non-BD 0.310 %, SD 1.98 %; BD 7.44 % SD 10.3 %; $p < 0.001$).

3.3. Time to first period of remission

Kaplan-Meier survival curves of time to first period of remission (for exact definition, see the Methods section above) by cohort are presented in Fig. 1. Survival curves for patients grouped by BD diagnostic status (i.e., BD vs. non-BD patients) are presented in Fig. 2. No significant differences were observed in time to first period of remission between BPD and non-BPD patients ($p = 0.21$) or between females and males ($p = 0.39$).

We analysed the contribution of different potential factors affecting time to first period of remission with Cox proportional hazards models. Our model, including sex, age, MADRS at baseline, diagnosis of BD, BPDSI at baseline, and AUDIT score, is presented in Table 4. We further explored the validity of this model for all patients without a BPD diagnosis ($n = 71$), which is reported in the same table. Factors explored but not included in our final model since they did not significantly affect time to first period of remission included Mix-MDE, duration of depressive episode at baseline, age at onset of first depressive episode, and OASIS score.

To explore dose-response effects of BPD symptom severity on time to first period of remission, we split the cohort into quintiles according to BPDSI score. There were significant differences between these quintiles in their times to first period of remission (ANOVA F 7.816, df 1, $p = 0.006$), mean times to first period of remission and SD (in days) being 132 (84.7) in the first, 146 (64.1) in the second, 167 (87.2) in the third, 156 (67.6) in the fourth, and 200 (49.4) in the fifth quintile.

4. Discussion

In this prospective follow-up cohort study of psychiatric outpatients with major depressive episodes, we found that BD, but not BPD, was associated with a shorter time to first remission (with a length of 14 days or more) and a more variable course of illness, with more periods of different mood states of shorter mean duration than in unipolar depression. These findings remained robust when controlling for other variables. Baseline severity of depression and dimensionally measured BPD features were associated with longer time to first period of remission, whereas the opposite was the case for a diagnosis of BD and a higher AUDIT score.

Hypomanic features of the MDEs preceding recruitment, dimensionally measured at baseline with the Mix-MDE (previously described in Socada et al., 2021), predicted a more variable course of affective

Table 1
Clinical outcome at follow-up interview.

Subcohort	MDE/MDD			MDE/BD			MDE/BPD			Total			Statistical significance
	n	%/mean	SD	n	%/mean	SD	n	%/mean	SD	n	%/mean	SD	
Total	39			33			23			95			
Female	21	53.85		25	75.76		16	69.57		62	65.26		$p = 0.1331$
Male	18	46.15		8	24.24		7	30.43		33	34.74		
Age		31.41	10.29		32.92	9.69		27.98	7.10		31.11	9.49	$p = 0.255$
Remission from MDE[a]	22	56.41		20	60.61		12	52.17		54	56.84		$p = 0.8196$
MADRS		15.69	9.53		13.67	11.98		16.91	7.20		15.28	9.97	$p = 0.781$
Mix-MDE		2.92	2.98		10.64	9.20		9.17	8.00		7.12	7.75	$p < 0.001$
YMRS		0.64	1.18		2.85	5.01		2.13	2.85		1.77	3.46	$p = 0.049$

Note: Statistical testing with χ^2 - tests and analysis of variance.
[a] Did not meet DSM-5 MDE criteria at the follow-up interview.

Table 2
Poisson regression table for number of distinct mood state periods during follow up.

	Controlled (multiple regression)					Uncontrolled (simple regression)				
	RR	CI		z-Value	Significance	RR	CI		z-Value	Significance
		2.50 %	97.50 %				2.50 %	97.50 %		
(Intercept)	0.027	0.021	0.034	−31.129	<0.0001					
Sex (male, ref: female)	0.694	0.568	0.844	−3.67	0.0003	0.643	0.528	0.779	−4.448	<0.0001
Bipolar disorder	1.45	1.2	1.752	3.854	0.0001	1.725	1.46	2.039	6.403	<0.0001
Mix-MDE (per point)	1.011	0.999	1.023	1.905	0.0567	1.022	1.012	1.032	4.287	<0.0001
BPDSI (per point)	0.988	0.987	0.998	−2.353	0.0186	0.991	0.982	1.001	−1.757	0.0788

Note: Model null deviance: 203.13 on 94 degrees of freedom.
Residual deviance: 148.12 on 90 degrees of freedom.
AIC: 483.72.

Table 3
Discrete affective episodes during follow-up, for whole sample and by subcohorts.

Manic polarity	Depressive polarity: Subcohort	2 (meeting MDE symptomatic criteria)		1 (partial symptomatic remission)		0 (full symptomatic remission)		All depressive severities (all episodes of this manic severity)	
		Relative duration	Sd	Relative duration	Sd	Relative duration	Sd	Relative duration	Sd
0	All	0.423	0.294	0.321	0.259	0.18	0.243	0.925	0.156
No manic symptoms	MDE/MDD	0.472	0.286	0.357	0.233	0.166	0.23	0.996	0.0263
	MDE/BD	0.355	0.29	0.22	0.227	0.266	0.277	0.845	0.17
	MDE/BPD	0.435	0.306	0.4	0.304	0.0844	0.175	0.92	0.204
	p	0.795		0.851		0.704		0.665	
1	All	0.0197	0.0124	0.0156	0.0388	0.00707	0.0252	0.0423	0.096
Subthreshold manic symptoms	MDE/MDD	0.0198	0.0124	0.00223	0.0139	0	0	0.00421	0.0263
	MDE/BD	0.0321	0.0668	0.03	0.0444	0.0206	0.0399	0.0826	0.113
	MDE/BPD	0.0313	0.0848	0.0175	0.0505	0	0	0.0489	0.12
	p	0.348		0.629		1		0.616	
2	All	0.00402	0.0161	0.0159	0.0502	0.0122	0.0448	0.0321	0.0755
Hypomanic symptoms	MDE/MDD	0	0	0	0	0	0	0	0
	MDE/BD	0.0077	0.216	0.0275	0.0521	0.0354	0.0714	0.0706	0.0945
	MDE/BPD	0.00549	0.0194	0.0256	0.0769	0	0	0.0311	0.0851
	p	0.513		0.372		1		0.71	
3	All	0	0	0.000672	0.00658	0	0	0.000672	0.00658
Manic symptoms	MDE/MDD	0	0	0	0	0	0	0	0
	MDE/BD	0	0	0.00196	0.0112	0	0	0.00196	0.0112
	MDE/BPD	0	0	0	0	0	0	0	0
	p	–		1		–		1	
All manic severities (all episodes of this depressive severity)	All	0.447	0.3	0.353	0.253	0.199	0.263		
	MDE/MDD	0.475	0.288	0.359	0.231	0.166	0.23		
	MDE/BD	0.395	0.31	0.279	0.239	0.322	0.305		
	MDE/BPD	0.472	0.31	0.444	0.281	0.0844	0.175		
	p	0.977		0.656		0.781			

Note: p-values signify p for analysis of variance comparing subcohorts.

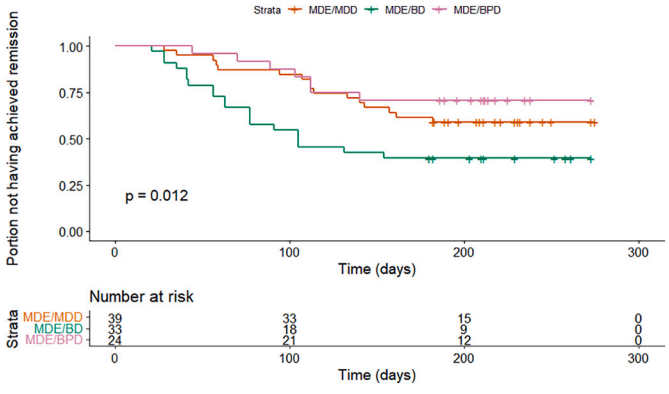

Fig. 1. Time to first full remission by subcohort.

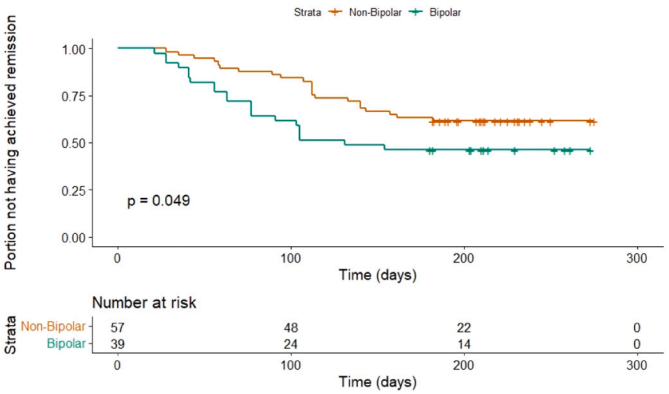

Fig. 2. Time to first full remission by bipolar diagnostic status.

symptomatology, which, however, did not remain significant when controlling for a diagnosis of BD. Periods with (hypo)manic symptoms were expectedly significantly more common in BD patients than in others.

Comparing subcohorts and diagnostic groups (BD vs. non-BD and

Table 4
Cox proportional hazards regression model of factors associated with time to first full remission.

	Whole sample (n = 95)							Sample excluding patients with a BPD diagnosis (n = 71)						
	Estimate	SE	HR	CI		Z statistic	p	Estimate	SE	HR	CI		Z statistic	p
				2.50 %	97.50 %						2.50 %	97.50 %		
Age (years)	−0.0257	0.0171	0.9746	0.9424	1.0078	−1.5034	0.13275	−0.0162	0.01881	0.9839	0.9483	1.0209	−0.862	0.38869
Sex (male)	0.3144	0.3283	1.3694	0.7196	2.6061	0.9577	0.33821	0.47304	0.38842	1.6049	0.7496	3.436	1.21786	0.22328
MADRS (score)	−0.0957	0.0352	0.9087	0.8482	0.9736	−2.7193	0.00654	−0.0883	0.0405	0.9155	0.8456	0.9911	−2.1812	0.02917
Bipolar diagnosis	0.9675	0.3364	2.6314	1.3609	5.0882	2.87587	0.00403	1.06301	0.38237	2.8951	1.3683	6.1254	2.78008	0.00543
BPDSI (score)	−0.0519	0.0229	0.9494	0.9087	0.993	−2.2667	0.02341	−0.0626	0.03583	0.9393	0.8756	1.0076	−1.7475	0.08055
AUDIT (score)	0.0683	0.0276	1.0707	1.0144	1.1302	2.47732	0.01324	0.05089	0.03301	1.0522	0.9863	1.1225	1.54138	0.12322

Note 1: HR = exp(coef).
Note 2: Whole sample concordance = 0.744 (se = 0.037), likelihood ratio test = 36.64 on 6 df, p = 2e−06; sample excluding BPD patients concordance = 0.73 (se = 0.044), likelihood ratio test = 27.58 on 6 df, p = 1e−04.

BPD vs. non-BPD), a two week or longer period of remission at some point of the follow-up was as likely in all groups.

In general, depending on the subcohort, the patients spent around 40–50 % of the follow-up period in a state fulfilling MDE criteria, 20–40 % in partial remission, and 10–30 % in full symptomatic remission. A depressive state with subthreshold hypomanic symptoms was more common in the BD subcohort than in the others, which was also true for all hypomanic states and all subthreshold hypomanic states. However, even low-grade manic symptoms were experienced by under 10 % of patients in the BD subcohort, and pure hypomania and mania were rarer still. Although a diagnosis of BD was accordingly associated with a significant proclivity towards hypomanic features, our results are in line with earlier studies reporting that BD patients spend significantly more time depressed than manic or hypomanic (Pallaskorpi et al., 2015; Tondo et al., 2017). We used prospective methods with biweekly assessments of core manic symptoms (in addition to depressive symptomatology) and multiple sources of illness course information, but mobile monitoring by smartphone apps, actigraphy, or ecological momentary assessments or methods might potentially have a higher sensitivity in detecting low-grade mixed mood states (De Crescenzo et al., 2017).

The finding of a more affectively variable course of illness, i.e., a higher number of distinct mood state periods, in BD patients than in other patients is perhaps not unexpected; we especially looked for symptoms of elevated mood, which are by diagnostic definition a feature of BD, but not MDD. Still, it is interesting to note that more severe BPD symptomatology was associated with a lower number of discrete periods as well as a longer remission latency, even though affective instability is a core diagnostic feature of BPD itself. When the cohort was divided into quintiles according to BPD feature severity, there was an approximately one-month difference in time to first period of remission between the first and third and between the third and fifth quintiles, with longer times seen in patients with more severe BPD symptoms. Thus, in MDE patients, BPD feature severity may be a useful prognostic marker, specifically in the context of remission latency. Additionally, this finding may support the notion that a propensity towards mood swings in the short term (minutes–hours) can often be reliably separated from a tendency to experience more long-lasting affective states (days–months) of depressed, elevated, or irritable quality (Bassett et al., 2017).

Interestingly, our results support the previously reported notion that alcohol abuse may be paradoxically associated with a better short-term prognosis in MDE patients (Holma et al., 2020). Our finding may be partially related to the requirement of remission from AUD at the point of inclusion in our study – achieving sobriety is related to improvement in depressive symptomatology in AUD patients. In the longer term, prognosis of depression seems worse in patients with severe and/or current AUD (Boschloo et al., 2012; Holma et al., 2020).

Strengths of this study include representative samples of subjects with disorders prevalent in psychiatric settings, the prospective and multimodal assessment of affective states (including biweekly online follow-up), high baseline inter-rater reliability, and the comparison of these three clinically and theoretically central patient groups within a single study design and methodology. The patients were also evaluated thoroughly, as they met with researchers for six multi-hour appointments in addition to online and clinical follow-up. Limitations include the relatively limited sample size and short follow-up time precluding investigation of depressive recurrence, the biweekly screening of hypomanic symptoms being limited to online assessment of core symptoms only, the lack of even more intensive (i.e., weekly or daily) follow-up, lack of diagnostic blinding during life chart creation, and the varying treatment schedules of the subjects. Since the MADRS does not assess the depressive symptoms of hypersomnia and increased appetite, the use of a MADRS score of ≥15 as an inclusion criterion might have influenced subject selection. When interpreting our medium-term findings of time to first remission, it is important to note that this refers to a shorter (≥14 days) period of remission than the minimum of two months as defined in

the DSM-5.

In conclusion, in this prospective 6-month cohort study of MDE patients in psychiatric care, there were differences between patient groups in how quickly a period of remission was reached; compared with unipolar depression, the time was shorter in depression in BD, but longer in patients with comorbid BPD. Switches from depression to full hypomanic or manic states seem uncommon in a 6-month time frame among (mostly type II) BD patients in outpatient care. As BPD was not associated with a quickly relapsing-remitting course of depression, nor with states with simultaneous depressive and (hypo)manic symptoms, but rather, a longer time to remission from depressive symptoms, it may, at least in the context of depression, perhaps best be understood as a sign of more severe psychopathology overall. Dimensional assessment of BPD features appears to be related to longer times to remission from depression symptoms and could therefore be useful in future prognostic studies of major depression.

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CRediT authorship contribution statement

The study was designed by authors JJS, JLS, JE (supervisor) and EI (supervisor). Patients were recruited and interviewed by JJS and JLS, who were also responsible for data management. JJS researched earlier literature (with guidance provided by EI), conducted the statistical analyses, and composed all drafts.TR acted as statistical consultant and provided expert guidance in conducting all analyses. All authors were actively involved in commenting on and revising the manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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