Journal of Affective Disorders 229 (2018) 164–170

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Is recurrence in major depressive disorder related to bipolarity and mixed features? Results from the BRIDGE-II-Mix study

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ARTICLE INFO

Keywords:
Recurrence
Cyclicity
Major depressive disorder
Mixed features

ABSTRACT

Background: Current classifications separate Bipolar (BD) from Major Depressive Disorder (MDD) based on polarity rather than recurrence. We aimed to determine bipolar/mixed feature frequency in a large MDD multinational sample with (High-Rec) and without (Low-Rec) > 3 recurrences, comparing the two subsamples.
Methods: We measured frequency of bipolarity/hypomanic features during current depressive episodes (MDEs) in 2347 MDD patients from the BRIDGE-II-mix database, comparing High-Rec with Low-Rec. We used Bonferroni-corrected Student's *t*-test for continuous, and *chi*-squared test, for categorical variables. Logistic regression estimated the size of the association between clinical characteristics and High-Rec MDD.
Results: Compared to Low-Rec (n = 1084, 46.2%), High-Rec patients (n = 1263, 53.8%) were older, with earlier depressive onset, had more family history of BD, more atypical features, suicide attempts, hospitalisations, and treatment resistance and (hypo)manic switches when treated with antidepressants, higher comorbidity with borderline personality disorder, and more hypomanic symptoms during current MDE, resulting in higher rates of mixed depression according to both DSM-5 and research-based diagnostic (RBDC) criteria. Logistic regression showed age at first symptoms < 30 years, current MDE duration ≤ 1 month, hypomania/mania among first-degree relatives, past suicide attempts, treatment-resistance, antidepressant-induced swings, and atypical, mixed, or psychotic features during MDE to associate with High-Rec.
Limitations: Number of MDEs for defining recurrence was arbitrary; cross-sectionality did not allow assessment of conversion from MDD to BD.
Conclusions: High-Rec MDD differed from Low-Rec group for several clinical/epidemiological variables, including bipolar/mixed features. Bipolarity specifier and RBDC were more sensitive than DSM-5 criteria in detecting bipolar and mixed features in MDD.

1. Introduction

DSM-5 (American Psychiatric Association, 2013) separated Major Depressive (MDD) from Bipolar Disorders (BDs), allocating each condition an independent category. However, some patients with MDD may change diagnosis with time, developing (hypo)mania and converting to BDs (Kessing et al., 2017), while the opposite is nosographically impossible. Indeed, the diagnosis of a BD needs at least one hypomanic or manic episode in patient's history. This kind of dichotomy, essentially based on the polarity of the episodes, might result

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https://doi.org/10.1016/j.jad.2017.12.062
Received 10 July 2017; Received in revised form 28 November 2017; Accepted 31 December 2017
Available online 02 January 2018

in the neglect of other fundamental features of mood disorders such as recurrence, the core aspect in the original Kraepelinian definition of manic depressive illness.

There is a dearth of studies investigating the importance of recurrences on the course of MDD. Each new recurrence was found to increase probability of a new major depressive episode by 16% in a naturalistic study of MDD patients (Solomon et al., 2000). Many authors suggested the overall number of depressive episodes may be linked to the presence of a BD diathesis, regardless the occurrence of hypo/manic episodes (Andreasen et al., 1988; Benazzi, 2002; Ghaemi et al., 2002; Solomon et al., 2006; Goodwin and Jamison, 2007; Mitchell et al., 2008; Schaffer et al., 2010; Angst et al., 2011; Takeshima and Oka, 2013; Kessing et al., 2017). In this perspective, highly recurrent depression has shown some clinical characteristics that are nearer to BDs (Benazzi, 2002), like the similar tendency to develop hypomanic switches while on antidepressant drugs (Kupfer et al., 1988), and the presence of a BD family history (Akiskal and Benazzi, 2006). Scholars differ in their definition of highly recurrent MDD. Benazzi (2002) and the Danish group (Kessing et al., 1998) considered a cutoff of more than four major depressive episodes (MDE), while Ghaemi et al. (2002) suggested the presence of more than three MDE as one of the diagnostic criteria for bipolar spectrum disorders. Most studies identified predictors of further recurrences by comparing MDD patients with BD patients (Kessing et al., 1998; Benazzi, 2002) and only few studies focused on large MDD samples (Solomon et al., 2000, 2006; Mitchell et al., 2008). Moreover, while considering data on MDD and BD patients, diagnostic groups were infrequently matched by episode frequency (Benazzi, 2002).

In order to explore the possible influence of recurrence in a large sample of MDD patients evaluated for the naturalistic BRIDGE-II-Mix study (Perugi et al., 2015a, 2015b; Popovic et al., 2015), we adopted a cut-off of more than three MDE. The primary objective of this study was to determine the frequency of a number of predefined bipolar features in MDD patients with (High-Rec) and without (Low-Rec) more than three recurrences. The secondary objective was to compare the rates of mixed features during current depressive episodes in High-Rec and Low-Rec patients.

2. Materials and methods

The BRIDGE-II-MIX study, which is different from and does not overlap with the BRIDGE study (Angst et al., 2011), was a multinational (involving eight countries in three continents, i.e., Egypt and Morocco for Africa, Bulgaria, the Netherlands, Portugal, and Spain for Europe, and Russia and Turkey for both Asia and Europe), naturalistic (non-interventional), cross-sectional diagnostic effort conducted in 239 hospital-based or community centres by one psychiatrist in each centre with each centre reflecting the common psychiatric healthcare practices of each country. It had the objective to provide a reliable frequency estimate of mixed states in a large international sample of patients with major depressive episode (MDE). From June 2009 to July 2010, each centre enrolled for three consecutive months 10–20 consecutive adult patients (aged ≥ 18 years) who sought help for a DSM-IV-TR MDE in three-month periods. The original study focused on mixed feature prevalence and definition in patients with MDE and analysed data of 2811 patients with MDE, independently from whether they were diagnosed with major depressive disorder (MDD) or BD. From the 239 psychiatrists involved in the study, 237 returned their site questionnaire. The number of investigators per country ranged from 62 in Spain to 18 in Egypt. Practice settings were primary care (26%), community mental health services (23%), or hospital based (48%). The location of the practice was almost entirely urban. The mean proportion of patients who were hospitalised for the full sample was 26.0%. Demographic features were generally similar across countries. In this study we focus only on those 2347 patients diagnosed with MDD. This is a post hoc analysis of the original dataset.

Psychiatric comorbidities were established through DSM-IV-TR–based checklists focusing on alcohol/substance abuse/addiction, panic disorder, obsessive-compulsive disorder, social phobia, generalised anxiety disorder, eating disorders, borderline personality disorder, and attention deficit/hyperactivity disorder (ADHD). Patients presenting with an acute nonpsychiatric condition/emergency were excluded.

The study was conducted according to the Declaration of Human Rights, as adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequently amended by the 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; (http://www.wma.net); the Good Epidemiology Practice and the International Epidemiologic Association (IEA) European Federation Guidelines (http://ieaweb.org) were followed. Written, informed consent was obtained from each patient. In each country, the protocol was approved by local ethical committees.

2.1. Data collection

Participating psychiatrists completed the same case report form in all centres, consisting in meeting inclusion criteria (DSM-IV-TR MDE) and collecting sociodemographic data, like age, gender, and marital status, and clinical data, like inpatient/outpatient status, history of psychiatric symptoms (mood changes, postpartum depression, and suicide attempts), and previous psychiatric hospitalisations. Noted were all features of the current depressive episode, including bipolar symptoms listed in the DSM-IV-TR diagnostic criteria for BD (American Psychiatric Association, 2000), known risk factors for BD, previous response to antidepressants, including reactions, psychiatric comorbidity, and current treatment, while global functioning was assessed through the Global Assessment of Functioning (GAF) scale (Endicott et al., 1976). The primary objective of the entire Bridge-II project was to establish in a mood disorder cohort the frequency of *depressive mixed states*, which was defined as the proportion of patients meeting: (1) *DSM-5* criteria for MDE with mixed features and (2) research-based diagnostic criteria (RBDC) (Angst et al., 2011). DSM-5 criteria require the presence for at least a week of an MDE and at least 3 of the following (nonoverlapping) hypomanic symptoms: (1) elevated, expansive mood, (2) inflated self-esteem or grandiosity, (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or impression of racing thoughts, (5) increase in energy or goal-directed activity, (6) increased or excessive involvement in activities with a high potential for untoward consequences, and (7) decreased need for sleep. Since data collection took place before publication of the DSM- 5, we applied its criteria retrospectively, based on case report forms.

RBDC were met when a MDE plus three of 14 hypomanic symptoms (i.e., irritable mood, emotional/mood lability, distractibility, psychomotor agitation, impulsiveness, verbal/physical aggression, racing thoughts, more talkative/speech pressure, hyperactivity, increased energy, risky behaviour, grandiosity, elation, and hypersexuality) co-occurred for at least one week. Revised BD-I specifier included manic episodes with the DSM-5 additional A criterion increased activity/energy without any exclusion criteria, while the revised BD-II specifier included 1–3 days hypomanic episodes (Angst et al., 2013).

Patients meeting DSM-IV-TR criteria for BD were excluded for the purpose of the current study, leaving a sample of patients with MDD. To this sample we applied the bipolarity specifier proposed by Angst et al. (2011, 2013). This “bipolarity” specifier attributes a diagnosis of “BD” to patients who experienced an episode of elevated mood or an episode of irritable mood or an episode of increased activity with at least 3 of the symptoms listed under Criterion B of the DSM-IV-TR, associated with at least 1 of the 3 following consequences: (1) unequivocal and observable change in functioning uncharacteristic of the person's usual behaviour, (2) marked impairment in social or occupational functioning observable by others, or (3) requiring hospitalisation or outpatient treatment. This specifier may apply to several subthreshold cases,

Table 1
Sociodemographic and clinical characteristics of the MDD sample subdivided according to number of lifetime episodes (> 3, N = 1263, High-Rec; ≤ 3, N = 1084, Low-Rec). *P*-values are shown with the Bonferroni-related cut-off, i.e., 0.0015.

	> 3 episodes (High-Rec)	≤ 3episodes (Low-Rec)	*t*-Test or *chi*-square	*p*	OR (CI)
Age, mean (SD)	47.6 (13.5)	40.4 (13.4)	0.207	< .0001	
Age of onset, mean (SD)	31.8 (12.4)	35.3 (13.5)	11.01	< .0001	
Gender, Female N (%)	933 (73.9)	704 (64.9)	22.03	< .0001	1.526 1.279–1.822)
Family history, N (%)					
First-degree family history of BD	211 (16.9)	97 (9.1)	30.49	< .0001	2.035 1.576–2.628)
Course characteristics, N (%)					
Age 1st depressive diagnosis, mean in years (SD)	35.0 (12.2)	37.0 (13.1)	7.76	< .0001	
Psychotic features	104 (8.2)	71 (6.5)	2.40	ns	1.280 0.936–1.751)
First MDE < 30 years	669 (53.0)	475 (43.8)	19.55	< .0001	1.444 1.227–1.700)
Atypical features	106 (8.4)	46 (4.2)	16.58	< .0001	2.067 1.448–2.951)
Current episode duration < 1 month	645 (51.1)	324 (29.9)	111.39	< .0001	3.001 2.283–4.541)
History of suicide attempts	356 (28.2)	146 (13.5)	75.16	< .0001	2.522 2.038–3.121)
Number of suicide attempts, mean (SD)	8.11 (6.79)	3.13 (0.49)	1.01	< .0001	
Memory disturbance	840 (66.5)	617 (56.9)	22.79	< .0001	1.503 1.271–1.777)
Number of hospitalisations, mean (SD)	2.6 (4.2)	.301 (0.8)	574.63	< .0001	
Duration current depressive episode, mean (SD)	77.9 (94.9)	122.8 (153.3)	106.34	< .0001	
GAF, mean (SD)	49.7 (12.7)	52.7 (12.6)	2.73	< .0001	
Number of mood episodes, mean (SD)	7.3 (7.1)	1.4 (.6)	446.74	< .0001	
Lifetime comorbidity, N (%)					
OCD	78 (6.2)	38 (3.5)	8.93	ns	1.816 1.222–2.701)
Eating disorder	81 (6.5)	59 (5.5)	1.02	ns	1.195.846–1.689)
ADHD	39 (3.1)	14 (1.3)	8.44	ns	2.425 1.309–4.491)
Anxiety disorder	354 (28.0)	308 (28.4)	0.04	ns	0.981 0.819–1.175)
Alcohol/substance use disorder	111 (8.8)	87 (8.0)	0.44	ns	1.104.824–1.480)
Borderline personality disorder	90 (7.1)	38 (3.5)	14.83	< .0001	2.112 1.432–3.114)
Previous treatments, n (%)					
Antidepressants	1130 (89.5)	824 (76.0)	75.75	< .0001	2.681 2.136–3.365)
Antipsychotic agents	471 (37.3)	253 (23.3)	53.24	< .0001	1.953 1.630–2.341)
Mood stabilisers	407 (32.2)	125 (11.5)	142.50	< .0001	3.648 2.926–4.548)
ECT	20 (1.6)	13 (1.2)	0.62	ns	1.326 0.656–2.677)
BDZ	649 (51.4)	445 (41.1)	25.03	< .0001	1.518 1.289–1.788)
> 3 drugs	493 (39.0)	212 (19.6)	105.3	< .0001	2.634 2.182–3.178)
Past reactions to antidepressants, n (%)					
(Hypo)manic switches or Mood lability	315 (24.9)	75 (6.9)	136.74	< .0001	4.470 3.423–5.838)
Treatment resistance	494 (39.1)	165 (15.2)	164.89	< .0001	3.578 2.928–4.373)

Abbreviations: ADHD, attention deficit/hyperactivity disorder; BD, bipolar disorder; BDZ, benzodiazepines; CI, confidence interval; ECT, electroconvulsive therapy; GAF, Global Assessment of Functioning scale; High-Rec, high recurrence group; Low-Rec, low recurrence group; MDD, major depressive disorder; MDE, major depressive episode; OCD, obsessive-compulsive disorder; OR, odds ratio; SD, standard deviation.

which do meet neither full range of DSM/ICD symptom requirements nor duration criteria, thus overcoming the classical unipolar/bipolar dichotomy. This specifier requires no minimum duration and no exclusion of cases induced by drug treatment, recreational drug consumption or medical disease.

2.2. Statistical analysis

Comparisons between the two sample groups, MDD patients with less than or equal to 3 lifetime episodes (Low-Rec) *vs*. MDD patients with more than 3 lifetime episodes (High-Rec), were assessed by using independent samples Student's *t*-test for continuous variables and Chi-squared test for categorical variables. *P*-values, as well as odds ratios (OR) with 95% confidence intervals (CIs), were used for observed group differences. The analysis involved many tests of statistical significance, raising the potential of obtaining false-positive results (type I error). Consequently, we corrected for multiple comparisons, by employing a Bonferroni-corrected threshold for statistical significance, and divided the critical *p*-value (α) by the number of comparisons being made. In our study, 32 hypotheses were tested, thus the new critical *p*-value was $\alpha/32 = 0.0015$. The statistical power of the study was then calculated based on this modified *p*-value.

Logistic regression was then used to calculate OR with 95% CI, so to estimate the size of the association between High-Rec and 8 *a priori* selected variables known to be associated with BD (Angst et al., 2011; Perugi et al., 2015a). These variables were age at first symptoms < 30 years, duration of current depressive episode ≤ 1 month, current atypical, mixed, or psychotic depressive symptoms, current psychiatric comorbidities, history of suicide attempts, antidepressant treatment-resistance, antidepressants induced mania/hypomania or mood lability, and hypomania/mania among first degree relatives. MDD "predictors" for High-Rec were regarded as potential confounders and considered actual confounders if their distributions were substantially different in the two samples, regardless of statistical significance. The cutoff for statistical significance for logistic regression was set at $p < 0.05$. All analyses were two-sided. When reporting logistic regression results, $p < 0.05$ was considered as indicative of an association with High-Rec MDD, whereas $p \geq 0.05$ as indicative of no association with High-Rec MDD. Due consideration was given to associations at the edge of significance.

All analyses were performed by using the statistical software SPSS Statistics for Macintosh, Version 20.0 (IBM Corp., Armonk, NY, USA).

3. Results

Patients in the High-Rec group were more likely to be women, older, have had an earlier depressive onset than patients in the Low-Rec group, and to have more BD diagnosed in their relatives (Table 1). With respect to Low-Rec, High-Rec patients were more likely to have been diagnosed with MDD earlier, to have had their first MDE at a lower age than 30 years, to have more atypical features, to be more positive for a history of suicide attempts, to have more past suicide attempts, more hospitalisations, more global functioning impairment, and have a briefer duration of their current depressive episode and be more likely

Table 2
RBDC (hypomanic) symptom distribution comparison between the High-Rec sample, with > 3 lifetime episodes (N = 1263) and the Low-Rec sample, with ≤ 3 lifetime episodes (N = 1084).

	> 3 episodes N (%)	≤ 3 episodes N (%)	*chi*-square	*p*	OR (CI)
Irritable mood	389 (30.8)	307 (28.3)	1.72	ns	1.126 0.943–1.346)
Emotional/mood lability	366 (29.0)	248 (22.9)	11.24	= .001	1.375 1.141–1.658)
Distractibility	304 (24.1)	200 (18.5)	10.92	= .001	1.401 1.147–1.712)
Psychomotor agitation	190 (15.0)	139 (12.8)	2.39	ns	1.204 0.951–1.524)
Impulsiveness	192 (15.2)	87 (8.0)	28.68	< .0001	2.054 1.572–2.685)
Aggression (verbal or physical)	171 (13.5)	132 (12.2)	.963	ns	1.129 0.886–1.440)
Racing thoughts	153 (12.1)	80 (7.4)	14.62	< .0001	1.730 1.303–2.297)
More talkative/pressure to keep talking	159 (12.6)	65 (6.0)	29.37	< .0001	2.258 1.671–3.050)
Hyperactivity	92 (7.3)	35 (3.2)	18.74	< .0001	2.355 1.581–3.506)
Increased energy	109 (8.6)	42 (3.9)	21.91	< .0001	2.343 1.626–3.378)
Risky behaviour	98 (7.8)	43 (4.0)	14.86	< .0001	2.036 1.409–2.943)
Grandiosity	53 (4.2)	17 (1.6)	13.92	< .0001	2.749 1.582–4.777)
Euphoria	63 (5.0)	23 (2.1)	13.58	< .0001	2.422 1.492–3.932)
Hypersexuality	36 (2.9)	17 (1.6)	4.34	= .037	1.842 1.028–3.298)

Abbreviations: CI, confidence interval; High-Rec, high recurrence group; Low-Rec, low recurrence group; OR, odds ratio; RBDC, research-based diagnostic criteria (Angst et al., 2011, 2013).

Table 3
Comparison of the distribution between the sample with > 3 lifetime episodes (High-Rec, N = 1263) and that with ≤ 3 lifetime episodes (Low-Rec, N = 1084) of RBDC bipolar disorder specifiers and mixed depression according to the DSM-5 and to the RBDC criteria.

	> 3 episodes N (%)	≤3 episodes N (%)	*chi*-square (df = 1)	*p*	OR (CI)
Bipolar disorder specifier	524 (41.5)	182 (16.8)	169.19	< .0001	3.514 2.893–4.269)
Bipolar I disorder	304 (24.1)	71 (6.5)	133.37	< .0001	4.523 3.442–5.943)
Bipolar II disorder	220 (17.4)	111 (10.2)	24.82	< .0001	1.849 1.448–2.361)
Depressive mixed state					
DSM-5 criteria	100 (7.9)	31 (2.9)	28.32	< .0001	2.921 1.936–4.407)
RBDC mixed depression	363 (28.7)	228 (21.0)	18.4	< .0001	1.514 1.252–1.832)

Abbreviations: CI, confidence interval; df, degrees of freedom; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; High-Rec, high recurrence group; Low-Rec, low recurrence group; OR, odds ratio; RBDC, research-based diagnostic criteria (Angst et al., 2011, 2013).

to have a current major depressive episode of less than one month (Table 1). They also had more borderline personality disorder comorbidity, whereas other comorbidities did not differ between High-Rec and Low-Rec. In particular, they did not differ for psychotic features(p = 0.121), lifetime comorbid eating disorders (p = 0.312), anxiety disorders (p = 0.836), alcohol and/or substance use disorder (p = 0.507), with borderline *p*-values (after the Bonferroni correction, *p* = 0.0015) for OCD (*p* = 0.003) and ADHD (*p* = 0.004). Regarding their previous treatments, High-Rec patients had used more antidepressant, antipsychotic, mood stabilizing drugs and anxiolytic drugs and more than three drugs per individual than the Low-Rec group. The two groups of patients did not differ for electroconvulsive therapy, in terms of mean number of sessions (p = 0.431). The two groups differed also for their reactions to antidepressant drug treatment, in that patients in the High-Rec group had more manic- or hypomanic switches and antidepressant resistance (defined as non-response to at least two courses of different classes of antidepressants administered for adequate periods and at adequate doses (Souery et al., 1999)) than Low-Rec patients (Table 1).

Of the 14 symptoms listed in the RBDC (hypomanic) criteria, patients in the High- Rec group had more symptoms than Low-Rec patients in 11 of these, i.e., emotional/mood lability, distractibility, impulsiveness, racing thoughts, talkativeness/pressure to keep talking, hyperactivity, increased energy, risky behaviour, grandiosity, euphoria, and hypersexuality (Table 2).

High-Rec patients had more occurrences of RBDC BD specifiers and mixed depression according to the DSM-5 and RBDC criteria, in particular overall BD RBDC specifiers, bipolar I disorder RBDC specifiers, and bipolar II disorder RBDC specifiers, and also DSM-5 depressive mixed state specifiers and RBDC mixed depression criteria than Low-Rec patients (Table 3).

In logistic regression, most variables were found to significantly predict a diagnosis of High-Rec MDD. When we estimated ORs and their respective CIs, age of first symptoms < 30 years (*p* = 0.004), duration of current depressive episode ≤ 1 month (*p* = 0.028), current atypical, mixed, or psychotic depressive symptoms (*p* = 0.005), history of suicide attempts (*p* = 0.024), antidepressant treatment resistance (*p* = 0.012), previous response of mania/hypomania or mood lability to antidepressants (*p* = 0.015), and hypomania/mania among first degree relatives 2.09 (*p* = 0.032) showed significantly higher occurrence in High-Rec than in Low-Rec. The only variable not associated with a diagnosis of High-Rec MDD was current psychiatric comorbidities (*p* = 0.101) (Table 4).

4. Discussion

In our large sample of 2347 patients diagnosed with MDD, we found subjects with more than 3 episodes (High-Rec) to differ from subjects with 1, 2 or 3 episodes (Low-Rec) for numerous sociodemographic and clinical characteristics. Independently from the diagnostic system adopted, High-Rec more frequently displayed bipolar/mixed features than Low-Rec. Notably in our sample, RBDC specifier showed significantly higher sensitivity in identifying bipolarity and mixed features than the DSM-5 criteria and mixed features specifier. These results are quite strong, as they resisted Bonferroni correction. As hypothesised, High-Rec were found to meet RBDC and DSM-5 mixed features more often than Low- Rec, to have more BD-In their family history, more hypomanic symptoms during MDE and suicidality, and more hypomanic switches and mood lability with antidepressants than Low-Rec. This result may be explained considering that RBDC criteria are wider

Table 4
Predictive factors for a diagnosis of MDD characterised by more than 3 lifetime episodes (High-Rec).

Variables	Odds Ratio [95% CI]	*p*-value
Age of first symptoms < 30 years	5.02 [1.20–7.10]	**0.004**
Duration of current depressive episode ≤ 1 month	2.28 [1.12–3.65]	**0.027**
Current atypical, mixed, or psychotic depressive symptoms	4.96 [1.01–7.99]	**0.005**
Current psychiatric comorbidities	1.76 [1.17–2.82]	0.101
History of suicide attempts	2.35 [1.07–5.19]	**0.024**
Antidepressant treatment resistance	3.15 [1.02–6.71]	**0.012**
Previous response of mania/hypomania or mood lability to antidepressants	3.10 [1.19–5.22]	**0.015**
Hypomania/mania among first degree relatives	2.09 [1.16–6.01]	**0.032**

Abbreviations: CI, confidence intervals; High-Rec, high recurrence group. Significant results in **bold**.

and more inclusive than those of the corresponding DSM-5 specifiers. Our data point to the heterogeneity of MDD and to the importance of considering recurrence as an important clue as to the treatment to adopt, as antidepressant treatment may expose highly recurrent patients to more clinical risks than less recurrent ones. The fact that High-Rec patients were more likely to have a current major depressive episode lasting less than one month and had a briefer mean duration of their current MDE with respect to Low-Rec patients can be viewed as indicating that patients with more episodes were more sensitised to the reemergence of their depressive symptoms and sought help earlier than did people with less MDEs in their history. This may be taken as a hypothesis to test, although other interpretations are possible, like conditioning and kindling.

Consistent with Benazzi (2002), who used a much smaller sample, we found High- Rec to be older than Low-Rec and also to have an earlier onset, more familial occurrence of BD and more atypical features during MDE. Furthermore, similarly to Benazzi (2002), we did not find the two groups to differ for the presence of psychotic features. Comorbidity with Borderline Personality Disorder resulted more common in our High- Rec than in Low-Rec patients, while other comorbidities did not differ significantly between the two groups (only two showed “trends” toward significance; in fact, OCD and ADHD were significantly higher in High-Rec without the Bonferroni correction). It is important for clinicians to assess MDD patients for the presence of borderline personality disorder, as this comorbidity was previously found to share some features with our High- Rec sample, like early age at onset, highly recurrent course, mood switch while on antidepressants, high occurrence of family history for BD and of DSM-5 mixed features, and treatment-resistance (Perugi et al., 2015b).

Splitting the MDD population into High-Rec and Low-Rec is not merely an academic concept; it might identify cases of greater proneness to convert to BD, thus having possible clinical and therapeutic implications. In fact, long-term antidepressant treatment has been shown to be associated with the conversion from MDD to BD (Baldessarini et al., 2013; Dudek et al., 2013). Despite most patients with MDD remain so after one or two years, about 15% of them converto to BD after one year and more than 20% after an additional year of follow-up (Kim et al., 2011). Mixed features and subsyndromal hypomanic symptoms during MDE were also found to be linked to conversion from MDD to BD (Zimmermann et al., 2009; Dudek et al., 2010; Fiedorowicz et al., 2011; Faedda et al., 2015); in our study, eleven out of fourteen hypomanic symptoms explored during MDE were found to be significantly associated with High-Rec. Another study found lower age at onset to predict conversion from MDD to BD-I, and positive family history for BD to be associated with conversion from MDD to BD-II, which both match our data (Angst et al., 2005). Converters from MDD to BD had also higher numbers of hospitalisation and more treatment-resistance as our High-Rec sample (Li et al., 2012; Dudek et al., 2013). Furthermore, having more than three depressive episodes was associated with higher conversion rates (Dudek et al., 2013). Like in our sample, several studies found early onset of depression to be related to conversion from MDD to BD (Dudek et al., 2013; Takeshima and Oka, 2013; Tondo et al., 2014).

As in our first BRIDGE-II reports on MDEs (Perugi et al., 2015a) and borderline personality disorder (Perugi et al., 2015b), RBDC was able to identify more bipolar/mixed features than DSM-5 in the MDD subsample (Table 3). This points to the need to adopt RBDC in evaluating patients with mood disorders, especially with MDD, and to distinguish them according to their total past mood episodes, so to better characterise their bipolar risk and treat them accordingly.

In our sample we found a prominent use of antipsychotics, justified by the frequency of occurrence of psychotic and anxiety symptoms, benzodiazepine antianxiety agents, justified by the occurrence of anxiety symptoms which are core symptoms of mood disorders, and mood stabilisers, justified by treatment-resistance and the need to protect MDD patients from suicide risk. In fact, lithium is the only drug that showed anti-suicidal properties independently from diagnosis (Baldessarini et al., 2006).

Among the predefined bipolar features, logistic regression showed age at first symptoms < 30 years, duration of current depressive episode ≤ 1 month, hypomania/mania among first degree relatives, history of suicide attempts, past history of antidepressant treatment-resistance and antidepressant induced mania/hypomania, and atypical, mixed, or psychotic features during the current depressive episode were associated with High- Rec. This finding is consistent with a study on polygenic loading of BD spectrum in MDD patients that identified characteristics like early onset, suicide attempt, recurrent and atypical depression, subclinical mania, subclinical psychosis, and severity (Wiste et al., 2014). The idea that in the MDD population there might be hidden a bipolar-prone population is an old-one and dates back to Kraepelin (1913), but more recently, Goodwin and Jamison (1990, 2007), Akiskal and Pinto (1999), and Akiskal and Benazzi (2006) refreshed it by putting forth more data and by reconsidering current classifications and enlarging diagnostic boundaries.

Petra Zimmermann and colleagues (2009) identified a MDD subpopulation with increased subsyndromal bipolar symptoms and family history of BD that were more likely to convert to BD, thus questioning the diagnostic appropriateness of current practices and pointing to the heterogeneity of what we currently call MDD. These authors did not investigate recurrence of depression as a factor in conversion proneness, but Goodwin and Jamison (1990, 2007) promoted the view that recurrence rather than polarity may explain the heterogeneity of MDD and its belonging to the manic-depressive illness spectrum. Results from our study, along with other studies, which identified recurrence as a key factor in conversion from MDD to BD (Dudek et al., 2010, 2013; Takeshima and Oka, 2013; Tondo et al., 2014; Kessing et al., 2017), provide further support to this view. This has an important therapeutic implication, since the finding that antidepressants used in bipolar disorder do not increase switch rates (Sachs et al., 2007) in fact focused on just two antidepressants, so it is still controversial, while focusing on recurrence rates and treating patients according to the ISBD guidelines (Pacchiarotti et al., 2013) could represent a change in clinical practice that could improve patient management. Another way of approaching this concept is staging. Staging has been used in many medical and psychiatric conditions, including schizophrenia (McGorry, 2007) and bipolar disorder (Kapczinski et al., 2014; Vieta, 2015), and is now being introduced in depression (Guidi et al., 2017). To some extent, our findings can also be conceptualised as emerging from a comparison between “early stage” versus “late stage” patients, but ideally a longitudinal design would have shed more light into this approach. The idea that mixed features, suicidality, and treatment response may be markers of late-stage depression is worth pursuing.

4.1. Limitations

The main limitation of this study was that the choice of the more than three MDEs cut-off criterion we adopted to define recurrence was literature-based, rather than obtained through the use of ROC (receiver operator characteristic). Furthermore, its cross-sectional nature prevents us from being able to assess conversion from MDD to BD. Moreover, clinical variables and treatment response were collected retrospectively, hence are susceptible to recall bias. However, our study has also remarkable strengths, represented by the large sample and the use of a MDD only population.

Further research is needed focusing on recurrence rather than on polarity; other than clinical, genetic, neuroimaging, neuropsychological, neurobiological, and treatment response data are required to better characterise this issue. Our results are consistent with the existence of heterogeneous populations in the conundrum termed MDD.

5. Conclusions

This study met both primary and secondary objectives, i.e., it determined frequency of bipolar features in High-Rec and Low-Rec MDD patients and compared the rates of mixed features in such patients. It aimed to identify a reliable clinical pattern in affective patients that would be based on recurrence, rather than on polarity; this would allow clinicians to adopt therapeutic strategies that would avoid transition from MDD to BD. For example, the use of antidepressants alone, without concomitantly using mood stabilisers, would unnecessarily expose people who have some BD risk to factors that would increase such risk. Presence of family history of BD, untoward reactions to antidepressants, irritability or resistance, suicidality, RBDC (hypo)manic symptoms and switch, and early onset characterise a different subset of recurrent MDD patients with greater severity and poorer outcome and should alert clinicians to adopt specific treatment strategies and precautions. Summarising, our data are consistent with highly recurrent MDD being related to bipolarity/mixed features and prompt us to take into consideration recurrence in treating patients.

Acknowledgments

We gratefully acknowledge the contribution of the Librarians of the School of Medicine and Psychology of Sapienza University, Ms. Mimma Ariano, Ms. Felicia Proietti, Ms. Ales Casciaro, Ms. Teresa Prioreschi, and Ms. Susanna Rospo for rendering precious bibliographical material accessible, as well as our Secretary Lucilla Martinelli for her assistance during the writing of this manuscript.

Role of funding sources

The sponsor of this study (Sanofi-Aventis) was involved in the study design, conduct, monitoring, and preparation of the final database, but not in the content of this report. All investigators recruited received fees from the sponsor in recognition of their patecipation in the study on a per patient basis. The corrisponding Author had full access to all the data and had final responsibility for data analisys, preparation of the report, and the decision to sumit for pubblication.

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