Sultans of Swing:

A Reappraisal of the Intertwined Association Between Affective Lability and Mood Reactivity in a Post Hoc Analysis of the BRIDGE-II-MIX Study

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ABSTRACT

Objective: This post hoc analysis of the BRIDGE-II-MIX study is aimed at evaluating affective lability (AL) as a possible clinical feature of mixed depression and assessing the relationship with atypical depressive features, particularly mood reactivity (MR).

Methods: In the BRIDGE-II-MIX multicenter, cross-sectional study, 2,811 individuals suffering from a major depressive episode (MDE; *DSM-IV-TR* criteria), in the context of bipolar I or II disorder (BD-I, BD-II, respectively) or major depressive disorder, were enrolled between June 2009 and July 2010. Patients with (MDE-AL, n = 694) and without (MDE-noAL, n = 1,883) AL and with (MDE-MR, n = 1,035) or without (MDE-noMR, n = 1,542) MR were compared through χ^2 test or Student *t* test. Stepwise backward logistic regression models, respectively testing AL and MR as the dependent variable, were performed to differentiate the 2 clinical constructs.

Results: AL was positively associated with BD-I ($P < .001$) and BD-II ($P < .001$), with *DSM-5* mixed (*DSM-5*-MXS) ($P < .001$) and atypical (*DSM-5*-AD) features ($P < .001$) and negatively associated with MDD ($P < .001$). In the logistic regression models, MR was the variable most significantly associated with AL and vice versa ($P < .001$ for both). AL was positively associated with severity of mania and *DSM-5*-MXS and negatively correlated with severity of depression, while MR was better predicted by atypical symptoms such as hyperphagia, hypersomnia, and leaden paralysis and correlated with both comorbid anxiety disorders and *DSM-5*-MXS.

Conclusions: Mixed and atypical depression may lie on the same continuum. MR and AL could represent the underlying matrix, bridging the gap between mixed and atypical depression.

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Affective lability (AL) is defined as the predisposition to rapidly reversible and marked shifts in affective states that are extremely sensitive to environmental events with intense behavioral responses.[1] According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), these abrupt switches are characterized by a few hours' duration and can represent a response to both pleasant and unpleasant events.[2,3]

Affective lability has been used as a synonym of mood lability and emotional lability in consideration of the fluctuation between different mood states (eg, anger, depression, anxiety, elation/hypomania, disgruntled mood) and difficulties in controlling the consequences of these oscillations.[4–7] Classically, AL was considered a trait feature of borderline personality disorder (BPD)[3] and attention-deficit/hyperactivity disorder (ADHD).[8,9] Nonetheless, AL has been considered a state symptom in mood disorders (mainly bipolar II disorder; BD-II) and in a percentage of patients with anxiety disorders and posttraumatic stress disorder (PTSD).[6,7,10–12]

The psychopathological construct of AL has been interpreted as a form of ultrarapid cycling.[13] In bipolar disorder, it was related to clinical features such as age at onset, Axis I comorbidities, and number of previous episodes.[11,14] It was also linked to impulse dyscontrol and suicidal behavior in BPD patients.[4] AL assumed a central role as a trait-like clinical feature in mixed episodes, especially in those with depressive polarity.[15–17] Moreover, it represented 1 of the 3 most frequent state features in mixed depression, together with agitation and irritability.[18]

Despite this crossover, AL was excluded from the *DSM-5* "with mixed features" specifier, possibly leaving many cases of mixed depression undiagnosed and subsequently inadequately treated.[19,20] On the contrary,

Clinical Points

- Although affective lability has been widely studied as a trait-like clinical symptom of affective disorders, its role as a mixed-state feature in depression still remains unclear.
- Affective lability represents a mixed feature that could help in targeting a tailored treatment strategy as it is positively correlated with the severity of mania, negatively correlated with the severity of depression, and strongly associated with mood reactivity and atypical depression.

in the *DSM-5*, mood reactivity (MR) represents a core criterion for depressive "atypical features" and is defined as a change of mood, but restrictively in response to positive stimuli.[3] Traditionally, atypical depression was associated with an affective temperamental dysregulation[21,22] as part of a common diathesis between depression, BD-II, and BPD.[23,24] The evidence that patients with depressive mixed states often display atypical features received wide support.[19,25–28]

Many experimental studies evaluated AL by means of a number of different assessment tools, with modest clinical agreement.[7,29] AL has been investigated in samples of patients with bipolar disorder and major depressive disorder (MDD) with major flaws in the study methodology, ie, not providing a clinical evaluation of comorbid BPD[30] and avoiding a differentiation between the clinical components of AL related to BPD and those associated with the specific affective disorders.[14] Finally, it has been poorly studied as a state clinical feature in large samples of patients in course of a major depressive episode (MDE). Indeed, several studies[5,10,11,14,30,31] focused on the evaluation of this clinical symptom during euthymic periods, with a poor understanding of the framing of AL as a trait or a symptom.[8]

As a consequence, this post hoc analysis of the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX study[19] was aimed at investigating the psychopathological role of AL in a sample of unipolar and bipolar depressed patients (excluding comorbidity with BPD) as a possible mixed symptom and a clinical correlate of atypical features in depression.

METHODS

Sample and Assessment

The general methodology of the BRIDGE-II-MIX study has been described in previous reports.[19,32–36] Briefly, the BRIDGE-II-MIX study was a multicenter, international, cross-sectional, diagnostic investigation conducted between June 2009 and July 2010 in 239 centers in 3 different continents. Hospital-based or community psychiatrists consecutively enrolled 10–20 eligible adult patients who were consulting them for a major depressive episode, diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*)[37] criteria.

Reasons for nonparticipation were precoded (refusal to participate, patient unable to complete the questionnaire, other).

Reasons for exclusion were represented by acute nonpsychiatric conditions or emergency events.

The full analysis population included 2,811 patients who gave their written informed consent to attend the investigation and provided complete data.

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment; http://www.wma.net). The Good Epidemiology Practice and the International Epidemiologic Association European Federation (http://ieaweb.org) Good Epidemiologic Practice (GEP)–IEA guidelines were followed for proper conduct of epidemiologic research, as were pertinent national legal and regulatory requirements. The protocol was authorized in each country by national and local ethics committees.

Data Collection

Information about sociodemographic variables, inpatient or outpatient status, history of psychiatric symptoms, and previous psychiatric hospitalizations were collected. Features of the MDE, bipolar symptoms, known risk factors for bipolar disorder, previous response to antidepressants, psychiatric comorbidity, and current treatment were also gathered. Functional status was determined with the Global Assessment Scale (GAS),[38] and illness severity was assessed using the Clinical Global Impressions scale for use in bipolar illness (CGI-BP).[39]

The primary objective of the BRIDGE-II-MIX study was to establish the frequency of depressive mixed states. After the publication of *DSM-5*, the frequency of depressive mixed states was retrospectively defined as (1) the proportion of patients fulfilling the *DSM-5* criteria for MDE with mixed features (*DSM-5*-MXS)[3] or (2) research-based diagnostic criteria for depressive mixed states (RBDC-MXS). RBDC-MXS are defined by the presence of MDE plus 3 of the following 14 hypomanic symptoms for at least 1 week: irritable mood, emotional/mood lability, distractibility, psychomotor agitation, impulsivity, verbal or physical aggression, racing thoughts, more talkative/pressure to keep talking, hyperactivity, increased energy, risky behavior, grandiosity, elation, and hypersexuality.

The aim of the present post hoc analysis of the BRIDGE-II-MIX study was to investigate the psychopathological construct of AL in unipolar and bipolar depression and its clinical correlates, assessing specific features of depressed patients with (MDE-AL) or without (MDE-noAL) affective lability. An operational clinical definition has been adopted, delineating AL as a state feature represented by marked and rapid shifts between different affective states in response to positive or negative environmental stimuli and with subsequent influences on behavior. In adapting a definition of AL to the BRIDGE-II-MIX study, the steering committee of the BRIDGE-II-MIX study decided to combine different previous classifications of AL[1,2,4,40] but not to consider it a trait symptom. In fact, AL was considered as a state feature

Table 1. Clinical Characteristics of 2,577 Patients: MDE-AL vs MDE-noAL Patients

Lifetime and Current Variables	MDE-AL (n = 694, 26.9%)	MDE-noAL (n = 1,883, 73.1%)	Statistic	
	n (%)	n (%)	OR (95% CI)	*P*
Sociodemographic characteristics				
Female	492 (70.9)	1,266 (67.2)	1.2 (0.98–1.46)	.085
Marital status				
Single	157 (22.6)	428 (22.7)	0.1 (0.81–1.23)	1.000
Married	384 (55.3)	985 (52.3)	1.1 (0.95–1.35)	.172
Divorced	94 (13.5)	289 (15.3)	0.9 (0.67–1.11)	.288
Widowed	57 (8.2)	177 (9.4)	0.9 (0.63–1.18)	.401
Diagnostic features				
DSM-IV-TR BD-I	102 (14.7)	141 (7.5)	2.1 (1.62–2.79)	< .001
DSM-IV-TR BD-II	68 (9.8)	89 (4.7)	2.2 (1.58–3.04)	< .001
DSM-IV-TR MDD	524 (75.5)	1,653 (87.8)	0.4 (0.34–0.54)	< .001
DSM-5-MXS	447 (64.4)	564 (30.0)	10.5 (7.10–15.49)	< .001
DSM-5-AD	78 (11.2)	86 (4.6)	2.7 (1.92–3.64)	< .001
Current comorbidity				
Anxiety disorder	237 (34.1)	446 (23.7)	1.7 (1.38–2.02)	< .001
Alcohol abuse	53 (7.6)	92 (4.9)	1.6 (1.13–2.28)	.010
Current symptoms				
Hypersomnia	143 (20.6)	275 (14.6)	1.5 (1.21–1.90)	< .001
Hyperphagia	126 (18.2)	234 (12.4)	1.6 (1.23–1.98)	< .001
Mood reactivity	455 (65.6)	580 (30.8)	4.3 (3.56–5.14)	< .001
Leaden paralysis	193 (27.8)	457 (24.3)	1.2 (0.99–1.46)	.074
Current psychiatric treatment				
Mood stabilizers	272 (39.2)	407 (21.6)	2.3 (1.94–2.82)	< .001
Antipsychotics	260 (37.5)	588 (31.2)	1.3 (1.10–1.58)	.003
Antidepressants	548 (79.0)	1,565 (83.1)	0.8 (0.61–0.95)	.018
	Mean (SD)	Mean (SD)	*t*	*P*
Age at first depressive episode, y	34.37 (12.368)	36.34 (12.634)	3.529	< .001
Severity of the condition				
Total number of previous mood episodes	5.17 (5.389)	4.36 (5.645)	−3.303	.001
Total number of lifetime suicide attempts	0.44 (2.102)	0.32 (0.860)	−1.537	.125
Severity of depression (CGI-BP)	4.40 (0.951)	4.52 (0.947)	2.868	.004
Severity of mania (CGI-BP)	1.69 (1.028)	1.13 (0.541)	−13.052	< .001

Abbreviations: AL = affective lability; BD = bipolar disorder; CGI-BP = Clinical Global Impressions Scale for use in bipolar illness; CI = confidence interval; *DSM-IV-TR* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; *DSM-5*-AD = major depressive episode with *DSM-5* atypical features; *DSM-5*-MXS = major depressive episode with *DSM-5* mixed features; MDD = major depressive disorder; MDE-AL = patients with a major depressive episode with affective lability; MDE-noAL = patients with a major depressive episode without affective lability; OR = odds ratio; SD = standard deviation.

of mixed depression, as highlighted in the Koukopoulos diagnostic criteria for mixed depression.[18,41]

The clinical implications of the association between AL and atypical features in depression, particularly MR, were also investigated. AL has been distinguished from MR, defined according to *DSM-5* as a variation of mood in depressed patients following only positive stimuli.[3]

The presence of mixed features was defined according to the *DSM-5* "with mixed features" specifier (*DSM-5*-MXS).

Patients diagnosed with BPD (n = 187) were excluded from the analysis in order not to bias the possible correlation between AL and mixed depression due to the trait-like characteristic of AL in BPD.[3,4,42] For the same reason,[7] patients presenting with ADHD comorbidity (n = 61) were excluded. The final total sample of the post hoc analysis was composed of 2,577 patients.

Statistical Analysis

Groups were compared using the χ^2 or the Student *t* test according to the types of variables. The bivariate analysis involved many tests of statistical significance, raising the problem of type I error. A Bonferroni-corrected threshold for statistical significance ($P \leq .003$) was then used.

A stepwise backward logistic regression model was used to identify the association between AL and 14 significant variables (*DSM-5*-MXS, BD-II diagnosis, MDD diagnosis, depression "with atypical features" according to *DSM-5* [*DSM-5*-AD], severity of mania, severity of depression, age at first depressive episode, number of previous affective episodes, comorbid anxiety disorder, hyperphagia, hypersomnia, mood reactivity, treatment with mood stabilizers, and treatment with antipsychotics). Bipolar I disorder (BD-I) was excluded from the model because it violated the assumption of multicollinearity. Subsequently, a stepwise logistic regression model was performed to differentiate AL from MR, testing the correlations between MR and the same clinical variables included in the previous model, plus leaden paralysis. *DSM-5*-AD diagnosis was excluded from the model because it violated the assumption of multicollinearity. Finally, 2 further stepwise logistic regression models were performed to assess the associations between AL or MR and the 14 RBDC-MXS hypomanic symptoms.

Table 2. Clinical Characteristics of 2,577 Patients: MDE-MR vs MDE-noMR Patients

Lifetime and Current Variables	MDE-MR (n = 1,035, 40.2%)	MDE-noMR (n = 1,542, 59.8%)	Statistic	
	n (%)	n (%)	OR (95% CI)	*P*
Sociodemographic characteristics				
Female	739 (71.4)	1,019 (66.1)	1.3 (1.08–1.52)	.005
Marital status				
Single	240 (23.2)	345 (22.4)	1.1 (0.87–1.26)	.672
Married	559 (54.0)	810 (52.5)	1.1 (0.90–1.24)	.501
Divorced	138 (13.3)	245 (15.9)	0.8 (0.65–1.02)	.082
Widowed	97 (9.4)	137 (8.9)	1.1 (0.81–1.39)	.730
Diagnostic features				
DSM-IV-TR BD-I	117 (11.3)	126 (8.2)	1.4 (1.10–1.87)	.009
DSM-IV-TR BD-II	71 (6.9)	86 (5.6)	1.3 (0.90–1.73)	.211
DSM-IV-TR MDD	847 (81.8)	1,330 (86.3)	0.7 (0.58–0.89)	.003
DSM-5-MXS	517 (50.0)	494 (32.0)	3.6 (2.54–5.19)	< .001
DSM-5-AD	164 (15.8)	0 (0)	,,,	< .001
Current comorbidity				
Anxiety disorder	340 (32.9)	343 (22.2)	1.7 (1.43–2.04)	< .001
Alcohol abuse	67 (6.5)	78 (5.1)	1.2 (0.93–1.82)	.150
Current symptoms				
Hypersomnia	213 (20.6)	205 (13.3)	1.7 (1.37–2.09)	< .001
Hyperphagia	183 (17.7)	177 (11.5)	1.7 (1.32–2.07)	< .001
Affective lability	455 (44.0)	239 (15.5)	4.3 (3.56–5.14)	< .001
Leaden paralysis	318 (30.7)	332 (21.5)	1.6 (1.35–1.93)	< .001
Current psychiatric treatment				
Mood stabilizers	325 (31.4)	354 (23.0)	1.5 (1.29–1.83)	< .001
Antipsychotics	362 (35.0)	486 (31.5)	1.2 (0.99–1.38)	.074
Antidepressants	834 (80.6)	1,279 (82.9)	0.9 (0.70–1.05)	.139
	Mean (SD)	Mean (SD)	*t*	*P*
Age at first depressive episode, y	35.06 (12.628)	36.31 (12.545)	2.465	.014
Severity of the condition				
Total number of previous mood episodes	4.86 (6.577)	4.39 (4.804)	−1.980	.048
Total number of lifetime suicide attempts	0.38 (1.803)	0.33 (0.845)	−1.060	.289
Severity of depression (CGI-BP)	4.45 (0.942)	4.51 (0.955)	1.441	.150
Severity of mania (CGI-BP)	1.41 (0.855)	1.18 (0.643)	−6.815	< .001

Abbreviations: BD = bipolar disorder; CGI-BP = Clinical Global Impressions Scale for use in bipolar illness; CI = confidence interval; *DSM-IV-TR* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; *DSM-5*-AD = major depressive episode with *DSM-5* atypical features; *DSM-5*-MXS = major depressive episode with *DSM-5* mixed features; MDD = major depressive disorder; MDE-MR = patients with a major depressive episode with mood reactivity; MDE-noMR = patients with a major depressive episode without mood reactivity; MR = mood reactivity; OR = odds ratio; SD = standard deviation.
Symbol: … = not applicable.

The stepwise modeling procedure started with the full model and consisted of eliminating, for each step, the least statistically significant variable from the model and recomputing the revised model, until all remaining variables were at $P < .1$. Odds ratios (OR) with 95% confidence intervals were assessed for observed associations. All tolerance values in the regression analyses were > 0.2 and all variance inflation factors were < 2.0, expressing that multicollinearity was not a source of bias in the regression models. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, version 23.0, IBM Corp, Armonk, New York). All *P* values were 2-tailed, and statistical significance was set at $P < .05$.

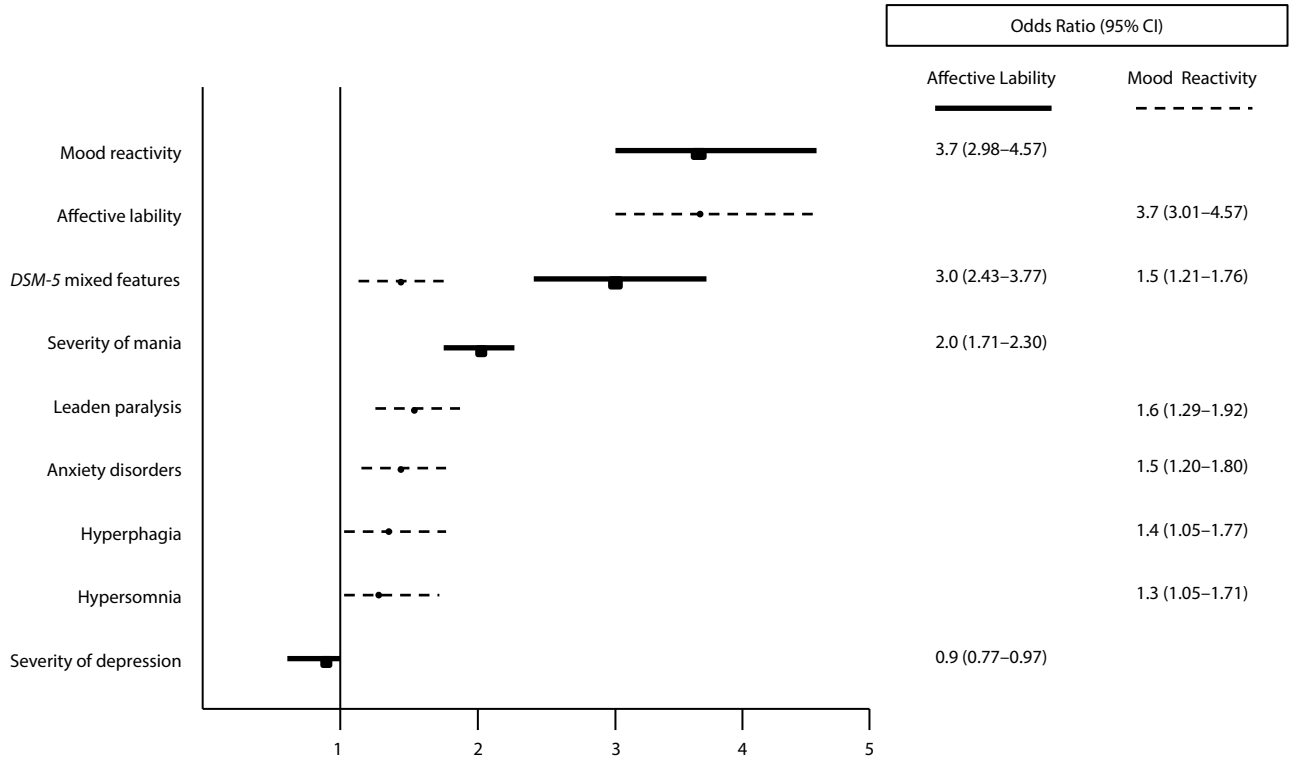
RESULTS

Diagnostic and Clinical Correlates of Affective Lability

Of 2,577 patients with MDE, 694 (26.9%) presented with AL (MDE-AL group). The presence of AL was positively associated with BD-I (OR = 2.1; 95% CI, 1.62–2.79) and BD-II (OR = 2.2; 95% CI, 1.58–3.04) and negatively associated with the diagnosis of MDD (OR = 0.4; 95% CI, 0.34–0.54). The high relative percentage of MDD diagnosis and the low relative percentages of BD-I and BD-II diagnoses in the MDE-AL group depended on the diagnostic distribution of MDD, BD-I, and BD-II in the total sample size (84.5%, 9.4% and 6.1%, respectively). In addition, the MDE-AL group, compared with the MDE-noAL group, was more frequently diagnosed with *DSM-5*-MXS (OR = 10.5; 95% CI, 7.10–15.49) and *DSM-5*-AD (OR = 2.7; 95% CI, 1.92–3.64) (Table 1; bivariate analyses of MR are shown in Table 2).

Patients in the MDE-AL group (vs MDE-noAL group) showed higher prevalence of atypical features such as hypersomnia (20.6% vs 14.6%, $\chi^2 = 13.000$), hyperphagia (18.2% vs 12.4%, $\chi^2 = 13.375$), and MR (65.6% vs 30.8%, $\chi^2 = 253.509$), but not leaden paralysis (27.8% vs 24.3%, $\chi^2 = 3.184$) (Table 1).

Figure 1. Logistic Regression: Significant Clinical Variables Associated With Affective Lability and Mood Reactivity



Abbreviation: CI = confidence interval.

A total of 164 (6.4%) patients were diagnosed with *DSM-5*-AD. Of these, 103 (62.8%) patients also presented *DSM-5*-MXS.

Lifetime Psychiatric History and Severity of the Clinical Presentation of Patients in the MDE-AL Group

The MDE-AL group differed significantly from the MDE-noAL group regarding mean ± SD age at onset of first depressive episode (34.37 ± 12.368 vs 36.34 ± 12.634, $t = 3.529$, $P < .001$) and total number of previous mood episodes (5.17 ± 5.389 vs 4.36 ± 5.645, $t = -3.303$, $P = .001$) (Table 1).

Patients in the MDE-AL group presented higher severity of mania (1.69 ± 1.028 vs 1.13 ± 0.541, $t = -13.052$, $P < .001$) evaluated with the CGI-BP and a lower severity of depression (4.40 ± 0.951 vs 4.52 ± 0.947, $t = 2.868$, $P = .004$) compared with those in the MDE-noAL group (Table 1).

Clinical Variables Associated With Affective Lability and Mood Reactivity

After performing a stepwise backward multiple logistic regression modeling procedure ($\chi^2_5 = 546.632$, $P < .001$) using AL as the dependent variable, the model explained between 20.6% (Cox and Snell R^2) and 30.3% (Nagelkerke R^2) of the variance. Statistical significance persisted for the presence of mixed features according to *DSM-5* (OR = 3.0; 95% CI, 2.43–3.77), severity of mania (OR = 2.0; 95% CI, 1.71–2.30), and MR (OR = 3.7; 95% CI, 2.98–4.57), which were positively associated with AL, and severity of depression (OR = 0.9; 95% CI, 0.77–0.97), which showed a negative correlation with AL. The variables most significantly associated with AL were MR and *DSM-5*-MXS (Figure 1 and Table 3).

To test the differences between AL and MR, a second stepwise backward logistic regression was performed, using MR as the dependent variable. The model ($\chi^2_7 = 317.795$, $P < .001$) explained between 12.6% (Cox and Snell R^2) and 17% (Nagelkerke R^2) of the variance. Variables significantly associated with MR were the presence of mixed features according to *DSM-5* (OR = 1.5; 95% CI, 1.21–1.76), AL (OR = 3.7; 95% CI, 3.01–4.57), leaden paralysis (OR = 1.6; 95% CI, 1.29–1.92), hyperphagia (OR = 1.4; 95% CI, 1.05–1.77), hypersomnia (OR = 1.3; 95% CI, 1.05–1.71), and comorbidity with anxiety disorders (OR = 1.5; 95% CI, 1.20–1.80). The strongest correlation with MR was presented by AL. All the variables were positively correlated (Figure 1 and Table 3).

The RBDC-MXS symptoms significantly associated with AL or MR are shown in Supplementary Table 1. Irritable mood, racing thoughts, more talkative/pressure to keep talking, distractibility, and impulsivity were directly significantly associated with both AL and MR. Elation was directly significantly associated with AL, while risky behavior was inversely associated with MR.

Table 3. Stepwise Backward Multiple Logistic Regression Model of Clinical Variables Associated With AL or MR in Patients With a MDE

	MDE-AL vs MDE-noAL[a]			MDE-MR vs MDE-noMR[b]		
Variables in the equation	Wald	OR (95% CI)	*P*	Wald	OR (95% CI)	*P*
Affective lability	…	…	…	151.708	3.7 (3.01–4.57)	<.001
Anxiety disorders	3.109	1.2 (0.98–1.56)	.078	14.247	1.5 (1.20–1.80)	<.001
DSM-5-MXS	97.237	3.0 (2.43–3.77)	<.001	15.325	1.5 (1.21–1.76)	<.001
Hyperphagia	…	…	…	5.585	1.4 (1.05–1.77)	.018
Hypersomnia	…	…	…	5.545	1.3 (1.05–1.71)	.019
Leaden paralysis	…	…	…	20.011	1.6 (1.29–1.92)	<.001
Mood reactivity	144.213	3.7 (2.98–4.57)	<.001	…	…	…
Severity of depression	6.315	0.9 (0.77–0.97)	.012	3.316	0.9 (0.83–1.01)	.069
Severity of mania	83.139	2.0 (1.71–2.30)	<.001	…	…	…

[a] $\chi^2_5 = 546.632$, $P < .001$; variables not in the equation: bipolar II disorder, major depressive disorder, depression with atypical features, age at first depressive episode, number of previous affective episodes, hyperphagia, hypersomnia, treatment with mood stabilizers, treatment with antipsychotics.
[b] $\chi^2_7 = 317.795$, $P < .001$; variables not in the equation: bipolar II disorder, major depressive disorder, age at first depressive episode, number of previous affective episodes, severity of mania, treatment with mood stabilizers, treatment with antipsychotics.
Abbreviations: AL = affective lability, CI = confidence interval, *DSM-5*-MXS = major depressive episode with *DSM-5* mixed features, MDE = major depressive episode, MDE-AL = patients with a major depressive episode with affective lability, MDE-noAL = patients with a major depressive episode without affective lability, MDE-MR = patients with a major depressive episode with mood reactivity, MDE-noMR = patients with a major depressive episode without mood reactivity, MR = mood reactivity, OR = odds ratio.
Symbol: … = not calculated.

DISCUSSION

In this BRIDGE-II-MIX post hoc analysis, AL was a common clinical state feature, assessed in 1 of every 4 patients presenting with a MDE, similar to previous studies.[43] AL was a clinical feature associated with BD-I and BD-II, as already reported in clinical[5,11] and neuropathology studies.[44] Despite being a common symptom in MDD, AL in the present sample was inversely correlated with unipolar depression when compared with bipolar disorder. This does not mean that AL represents a bipolar symptom, but that this symptom could act as a possible bridge between unipolar depression and BD,[5] within the concept of a mood spectrum.[45,46]

More than half the patients reporting AL were diagnosed with a mixed features specifier, in line with literature.[18] Traditionally, AL in a depressive mixed episode was considered as a risk factor of shifting between MDD and BD.[23,47] Several findings from the present study seem to support that the presence of AL during a MDE was associated with mixicity. We detected a 3-fold increased association between AL and mixed features (Figure 1). AL was positively associated with severity of co-occurring hypomanic and manic symptoms during a MDE, while it was negatively associated with the severity of depression , as found in previous research.[43] Patients in the MDE-AL group were more frequently treated with antipsychotic and mood stabilizers and less frequently treated with antidepressants than patients in the MDE-noAL group, in accordance with the recent guidelines on mixed depression.[48,49]

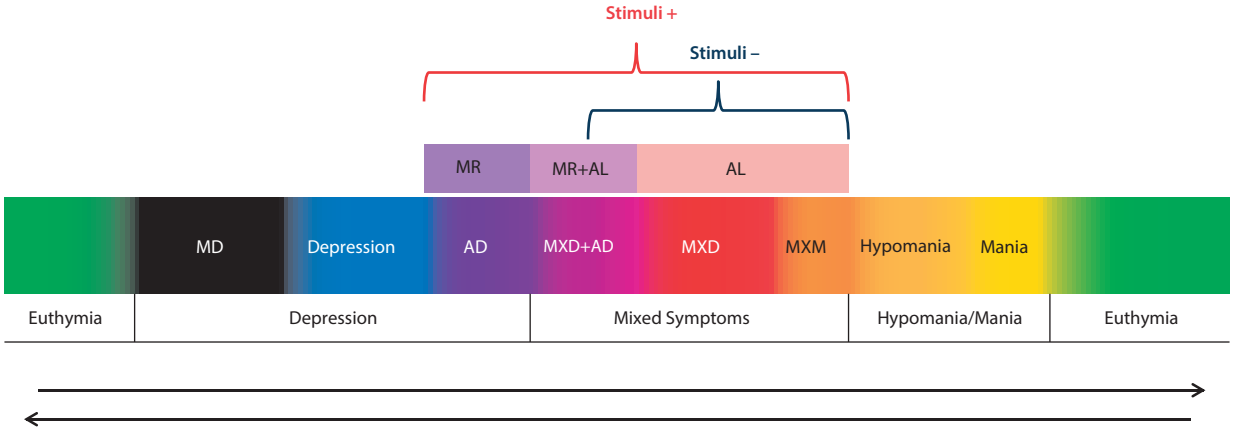
Another finding claiming the "mixed" identity of AL was the association with a more severe clinical condition, evaluated through indirect measures of psychopathology, such as a higher total number of previous mood episodes and an earlier age at first depressive episode. Indeed, AL was found to independently predict worse outcomes in BD.[16,50–56]

In terms of outcomes, AL hinders the modulation of mood oscillations with consequent behavioral responses. In the present study, AL correlated with dysregulated behaviors such as alcohol abuse, as in previous findings.[14] A possible association with suicidal attempts was not reported in this study. Previous findings are conflicting, with some studies[31,57] reporting that AL does not increase the risk of suicidal behavior and others[30,58] underlining that the risk of suicidal ideation increases with the level of AL.

In the present study, MR was the variable most significantly associated with AL, and vice versa. The association did not violate the assumption of independence, thus it is unlikely to consider the 2 clinical features as 2 overlapping symptoms. Different factors predicted AL and MR. The construct of AL was positively associated to severity of mania, while MR was predicted by atypical symptoms such as hyperphagia, hypersomnia, and leaden paralysis. This last finding is not surprising in consideration of the diagnostic criteria of the new "atypical features specifier" for depression, namely MR plus 2 or more atypical symptoms.[3] Furthermore, there were few differences in the RBDC-MXS symptoms that predicted AL or MR. Despite few common clinical symptoms associated with both AL and MR (irritable mood, racing thoughts, more talkative/pressure to keep talking, distractibility, and impulsivity), AL was positively associated with elation. On the contrary, the presence of risky behavior was negatively associated with MR.

Mixed depression was seen to correlate with atypical features. In a French national study,[16] severe clinical profiles displayed by patients with mixed depression included the presence of atypical features, and MDE with atypical features was significantly correlated with more depressive mixed states in an Italian study.[25] Almost 50% of patients with atypical depression presented more than 2 hypomanic symptoms.[59] The presence of a depressive mixed state

Figure 2. Affective Spectrum Revised[a]



[a]The figure refers to the dimensions of depression to hypomania/mania.
Abbreviations: AD = atypical depression, AL = affective lability, MD = melancholic depression, MR = mood reactivity, MXD = mixed depression, MXM = mixed mania.
Symbols: + = positive stimuli, – = negative stimuli.

was found to be the strongest bipolar diagnostic validator predicting atypical depression.[60] Finally, mixed depression overlapped with atypical depression.[26] As a consequence, our findings underlined that the polythetic diagnostic criteria of the new "atypical features specifier" for depression might not be completely reliable and valid because they do not take into consideration the longitudinal course of depression, particularly the association with other clinical features such as bipolarity, mixed depression, and the co-occurrence of anxious symptoms, deemed crucial in the diagnosis of atypical depression.[61] The different *DSM* definitions of atypical depression were based on the response to monoamine oxidase inhibitors and emerged by a pattern of linked symptoms followed by studies pursuing diagnostic validity with little research support.[61] In particular, the mandatory criterion of reactive mood may not be completely discriminatory, as it was seen to be significantly associated to other atypical symptoms in BD-II but not in unipolar depression.[25] As a consequence, a reformulation of atypical depression within a dimensional framework in the context of both unipolar and bipolar depression, including certain expressions of anxiety and considering the longitudinal association and stability of atypical symptoms, that represents real psychopathological symptoms and not only adaptive homeostatic responses should be pursued in future research.[61]

The notion of mood tone has been extended through a dimensional approach to the construct of emotional reactivity, considering not only the tone, but also the intensity and reactivity of mood.[43] A cluster analysis revealed 2 types of depression characterized by hypo- or hyperreactivity. Hyporeactivity identified the inhibited typical depression with loss of pleasure, anhedonia, and emotional anesthesia. Emotional hyperreactivity distinguished depressive states with prominent affective symptoms, identifying mixed depression. Emotional hyperreactivity was not restricted to positive stimuli and might affect all emotions, causing emotional pain.[25]

In the hypothetical assumption of a continuum between mood symptoms, Akiskal and Benazzi[60] disclosed that atypical depression could link unipolar depression and BD-II. Benazzi[26] challenged the unipolar-bipolar dichotomy, indicating that mixed depression could bridge the gap between the 2 affective disorders, on the basis of the correlation between intradepressive hypomanic symptoms and depressive symptoms. In other studies,[53,62] Benazzi showed that intradepressive hypomanic symptoms did not present a bimodal distribution, reinforcing the continuity between BD-II and MDD depressions. Unipolar MDD patients that converted to BD-II were robustly distinguished from those who remained unipolar on the basis of AL, with AL intruding into, and possibly being accentuated during, depressive episodes, leading to a braided mixed weaving of trait and state.[23]

As a consequence, the findings of this study suggest that mixed depression and atypical depression lie on the same continuum from unipolar melancholic depression to BD-I manic episodes. The underpinning matrix might be the emotional hyperreactivity experienced by the patient. The difference between the 2 types of depression was represented by the presence of swings due to negative actual or perceived stimuli within the construct of AL.[43] Indeed, MR and AL are strongly associated in terms of reaction to positive stimuli but are differentiated by the response to negative stressors (see Figure 2).

The main strengths of the BRIDGE-II-MIX study include the large sample size and the multicenter international nature of the design.

The first limitation is the widely varying rates of hospitalized patients across countries, which reflected locally driven policies. A second limitation is that the participating centers were not randomly selected, comprising psychiatrists selected because of their particular interest in bipolar spectrum disorders. Also, the definitions of AL and MR relied only on retrospectively coded criteria and selected

variables already collected in the dataset, rather than ad hoc variables fetched using validated ratings, which might introduce a measurement bias, especially considering that the operational definitions of AL and MR adopted were clinical. Another limitation is that atypical depression was not an a priori–defined primary outcome. The evaluators did not assess the presence of long-standing interpersonal rejection sensitivity; consequently, the investigators established retrospectively a diagnosis of *DSM-5*-AD that could be underestimated due to the presence of only 3 of the 4 symptoms defining criterion B of the *DSM-5*.

For these reasons, additional analyses correlating AL with mixed and atypical features should be undertaken in longitudinal prospective studies, addressing potential confounders.

In conclusion, affective lability seems to represent a simple discriminatory criterion for identifying depressive states with mixed features and should be included in the rubric of mixed features of major depressive episode. The role of affective lability as a mixed symptom in mixed mania could be extrapolated, but the authors suggest conducting further research on this specific topic. The intertwined association between affective lability and mood reactivity might bridge the gap between mixed and atypical depression, in the construct of a unique continuum between mood states. A better understanding of the presence of mixed and atypical features is needed to advocate the therapeutic research on 2 neglected areas and tailoring specific focused treatment strategies.

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REFERENCES

1. Siever LJ, Davis KL. A psychobiological perspective on the personality disorders. *Am J Psychiatry*. 1991;148(12):1647–1658.
2. Thompson RJ, Berenbaum H, Bredemeier K. Cross-sectional and longitudinal relations between affective instability and depression. *J Affect Disord*. 2011;130(1–2):53–59.
3. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
4. Links PS, Boggild A, Sarin N. Modeling the relationship between affective lability, impulsivity, and suicidal behavior in patients with borderline personality disorder. *J Psychiatr Pract*. 2000;6(5):247–255.
5. Benazzi F, Akiskal HS. A downscaled practical measure of mood lability as a screening tool for bipolar II. *J Affect Disord*. 2005;84(2–3):225–232.
6. Bowen RC, Wang Y, Balbuena L, et al. The relationship between mood instability and depression: implications for studying and treating depression. *Med Hypotheses*. 2013;81(3):459–462.
7. Broome MR, Saunders KEA, Harrison PJ, et al. Mood instability: significance, definition and measurement. *Br J Psychiatry*. 2015;207(4):283–285.
8. Marwaha S, He Z, Broome M, et al. How is affective instability defined and measured? a systematic review. *Psychol Med*. 2014;44(9):1793–1808.
9. Skirrow C, McLoughlin G, Kuntsi J, et al. Behavioral, neurocognitive and treatment overlap between attention-deficit/hyperactivity disorder and mood instability. *Expert Rev Neurother*. 2009;9(4):489–503.
10. Benazzi F. Inter-episode mood lability in mood disorders: residual symptom or natural course of illness? *Psychiatry Clin Neurosci*. 2004;58(5):480–486.
11. Henry C, Van den Bulke D, Bellivier F, et al. Affective lability and affect intensity as core dimensions of bipolar disorders during

euthymic period. *Psychiatry Res*. 2008;159(1–2):1–6.
12. Patel R, Lloyd T, Jackson R, et al. Mood instability is a common feature of mental health disorders and is associated with poor clinical outcomes. *BMJ Open*. 2015;5(5):e007504.
13. Mackinnon DF, Pies R. Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. *Bipolar Disord*. 2006;8(1):1–14.
14. Lagerberg TV, Aminoff SR, Aas M, et al. Alcohol use disorders are associated with increased affective lability in bipolar disorder. *J Affect Disord*. 2017;208:316–324.
15. Benazzi F. Impact of temperamental mood lability on depressive mixed state. *Psychopathology*. 2006;39(1):19–24.
16. Azorin J-M, Kaladjian A, Adida M, et al. Self-assessment and characteristics of mixed depression in the French national EPIDEP study. *J Affect Disord*. 2012;143(1-3):109–117.
17. Solé E, Garriga M, Valentí M, et al. Mixed features in bipolar disorder. *CNS Spectr*. 2017;22(2):134–140.
18. Sani G, Vöhringer PA, Napoletano F, et al. Koukopoulos' diagnostic criteria for mixed depression: a validation study. *J Affect Disord*. 2014;164:14–18.
19. Perugi G, Angst J, Azorin J-M, et al; BRIDGE-II-Mix Study Group. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J Clin Psychiatry*. 2015;76(3):e351–e358.
20. Vieta E. DSM-5.1. *Acta Psychiatr Scand*. 2016;134(3):187–188.
21. Akiskal HS, Chen SE, Davis GC, et al. Borderline: an adjective in search of a noun. *J Clin Psychiatry*. 1985;46(2):41–48.
22. Perugi G, Fornaro M, Akiskal HS. Are atypical depression, borderline personality disorder and bipolar II disorder overlapping manifestations of a common cyclothymic diathesis? *World Psychiatry*. 2011;10(1):45–51.
23. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from 'unipolar' to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry*. 1995;52(2):114–123.
24. Perugi G, Toni C, Travierso MC, et al. The role of cyclothymia in atypical depression: toward a data-based reconceptualization of the borderline-bipolar II connection. *J Affect Disord*. 2003;73(1–2):87–98.
25. Benazzi F. Should mood reactivity be included in the *DSM-IV* atypical features specifier? *Eur Arch Psychiatry Clin Neurosci*. 2002;252(3):135–140.
26. Benazzi F. Intra-episode hypomanic symptoms during major depression and their correlates. *Psychiatry Clin Neurosci*. 2004;58(3):289–294.
27. Verdolini N, Dean J, Elisei S, et al. Bipolar disorder: the importance of clinical assessment in identifying prognostic factors—an audit. Part 2: mixed state features and rapid cycling. *Psychiatr Danub*. 2014;26(suppl 1):301–308.
28. Grande I, Berk M, Birmaher B, et al. Bipolar disorder. *Lancet*. 2016;387(10027):1561–1572.
29. Solhan MB, Trull TJ, Jahng S, et al. Clinical assessment of affective instability: comparing EMA indices, questionnaire reports, and retrospective recall. *Psychol Assess*. 2009;21(3):425–436.
30. Ducasse D, Jaussent I, Guillaume S, et al; FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) Collaborators. Affect lability predicts occurrence of suicidal ideation in bipolar patients: a two-year prospective study. *Acta Psychiatr Scand*. 2017;135(5):460–469.
31. Parmentier C, Etain B, Yon L, et al. Clinical and dimensional characteristics of euthymic bipolar patients with or without suicidal behavior. *Eur Psychiatry*. 2012;27(8):570–576.
32. Verdolini N, Perugi G, Samalin L, et al; BRIDGE-II-MIX Study Group. Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features. *Acta Psychiatr Scand*. 2017;136(4):362–372.
33. Popovic D, Vieta E, Azorin J-M, et al. Suicide attempts in major depressive episode: evidence from the BRIDGE-II-MIX study. *Bipolar Disord*. 2015;17(7):795–803.
34. Perugi G, Angst J, Azorin J-M, et al; the BRIDGE-II-MIX Study Group. Relationships between mixed features and borderline personality disorder in 2811 patients with major depressive episode. *Acta Psychiatr Scand*. 2016;133(2):133–143.
35. Siporin S. Lighting the darkness of addiction: can phototherapy enhance contingency-management-based treatment of substance-related and addictive disorders? *J Addict Nurs*. 2014;25(4):197–203.
36. Barbuti M, Pacchiarotti I, Vieta E, et al; BRIDGE-II-MIX Study Group. Antidepressant-induced hypomania/mania in patients with major depression: evidence from the BRIDGE-II-MIX study. *J Affect Disord*. 2017;219:187–192.
37. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
38. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry*. 1976;33(6):766–771.
39. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997;73(3):159–171.
40. Harvey PD, Greenberg BR, Serper MR. The Affective Lability Scales: development, reliability, and validity. *J Clin Psychol*. 1989;45(5):786–793.
41. Sani G, Vöhringer PA, Barroilhet SA, et al. The Koukopoulos Mixed Depression Rating Scale (KMDRS): an International Mood Network (IMN) validation study of a new mixed mood rating scale. *J Affect Disord*. 2018;232:9–16.
42. Tragesser SL, Robinson RJ. The role of affective instability and UPPS impulsivity in borderline personality disorder features. *J Pers Disord*. 2009;23(4):370–383.
43. Henry C, M'Baïlara K, Poinsot R, et al. Evidence for two types of bipolar depression using a dimensional approach. *Psychother Psychosom*. 2007;76(6):325–331.
44. Lee P-S, Chen Y-S, Hsieh J-C, et al. Distinct neuronal oscillatory responses between patients with bipolar and unipolar disorders: a magnetoencephalographic study. *J Affect Disord*. 2010;123(1–3):270–275.
45. Cassano GB, Rucci P, Frank E, et al. The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. *Am J Psychiatry*. 2004;161(7):1264–1269.
46. Akiskal HS, Benazzi F. The *DSM-IV* and *ICD-10* categories of recurrent [major] depressive and bipolar II disorders: evidence that they lie on a dimensional spectrum. *J Affect Disord*. 2006;92(1):45–54.
47. Benazzi F. The relationship of major depressive disorder to bipolar disorder: continuous or discontinuous? *Curr Psychiatry Rep*. 2005;7(6):462–470.
48. Stahl SM, Morrissette DA, Faedda G, et al. Guidelines for the recognition and management of mixed depression. *CNS Spectr*. 2017;22(2):203–219.
49. Grunze H, Vieta E, Goodwin GM, et al; Members of the WFSBP Task Force on Bipolar Affective Disorders Working on this topic. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry*. 2018;19(1):2–58.
50. Strejilevich SA, Martino DJ, Murru A, et al. Mood instability and functional recovery in bipolar disorders. *Acta Psychiatr Scand*. 2013;128(3):194–202.
51. Verdolini N, Agius M, Quartesan R, et al. Mixed States: a "new" nosographic entity. *Psychiatr Danub*. 2014;26(suppl 1):103–111.
52. Cassidy F, Carroll BJ. The clinical epidemiology of pure and mixed manic episodes. *Bipolar Disord*. 2001;3(1):35–40.
53. Benazzi F. Reviewing the diagnostic validity and utility of mixed depression (depressive mixed states). *Eur Psychiatry*. 2008;23(1):40–48.
54. Goldberg JF, Perlis RH, Bowden CL, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry*. 2009;166(2):173–181.
55. González-Pinto A, Barbeito S, Alonso M, et al. Poor long-term prognosis in mixed bipolar patients: 10-year outcomes in the Vitoria prospective naturalistic study in Spain. *J Clin Psychiatry*. 2011;72(5):671–676.
56. Valentí M, Pacchiarotti I, Rosa AR, et al. Bipolar mixed episodes and antidepressants: a cohort study of bipolar I disorder patients. *Bipolar Disord*. 2011;13(2):145–154.
57. Olié E, Seyller M, Beziat S, et al. Clinical and neuropsychological characteristics of euthymic bipolar patients having a history of severe suicide attempt. *Acta Psychiatr Scand*. 2015;131(2):129–138.
58. Aas M, Henry C, Bellivier F, et al. Affective lability mediates the association between childhood trauma and suicide attempts, mixed episodes and co-morbid anxiety disorders in bipolar disorders. *Psychol Med*. 2017;47(5):902–912.
59. Benazzi F. Atypical depression with hypomanic symptoms. *J Affect Disord*. 2001;65(2):179–183.
60. Akiskal HS, Benazzi F. Atypical depression: a variant of bipolar II or a bridge between unipolar and bipolar II? *J Affect Disord*. 2005;84(2–3):209–217.
61. Parker G, Roy K, Mitchell P, et al. Atypical depression: a reappraisal. *Am J Psychiatry*. 2002;159(9):1470–1479.
62. Benazzi F. A continuity between bipolar II depression and major depressive disorder? *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30(6):1043–1050.

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Supplementary Material

Article Title: Sultans of Swing: A Reappraisal of the Intertwined Association Between Affective Lability and Mood Reactivity in a Post Hoc Analysis of the BRIDGE-II-MIX Study

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List of Supplementary Material for the article

1. Table 1 Stepwise Backward Multiple Logistic Regression Model of RBDC-MXS Hypo/manic Symptoms Associated With AL or MR

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Supplementary Table 1 *Stepwise backward multiple logistic regression model of RBDC-MXS hypo/manic symptoms associated with AL or MR*

	MDE-AL vs MDE-noAL*			MDE-MR vs MDE-noMR†		
Variables in the Equation	**Wald**	**OR (95% CI)**	***P***	**Wald**	**OR (95% CI)**	***P***
Irritable mood	187.978	5.36 (4.21-6.81)	< .001	15.341	1.50 (1.23-1.84)	< .001
Racing thoughts	16.279	2.08 (1.46-2.97)	< .001	6.203	1.48 (1.09-2.02)	.013
More talkative/pressure to keep talking	22.884	2.49 (1.71-3.61)	< .001	10.694	1.74 (1.25-2.43)	.001
Distractibility	82.459	3.13 (2.45-4.00)	< .001	12.382	1.48 (1.19-1.85)	< .001
Increased energy	-	-	-	2.805	1.44 (1.44-0.94)	.094
Impulsivity	16.314	2.02 (1.44-2.85)	< .001	12.655	1.72 (1.27-2.31)	< .001
Risky behavior	3.220	0.65 (0.40-1.04)	.073	8.153	0.55 (0.37-0.83)	.004
Grandiosity	2.958	1.78 (0.92-3.43)	.085	-	-	-
Elation	18.572	3.97 (2.12-7.43)	< .001	-	-	-
Verbal or physical aggression	3.800	0.72 (0.52-1.00)	.051	-	-	-

AL=affective lability; **MDE**=major depressive episode; **MDE-AL**=patients with a major depressive episode with affective lability; **MDE-noAL**=patients with a major depressive episode without affective lability; **MDE-MR**=patients with a major depressive episode with mood reactivity; **MDE-noMR**=patients with a major depressive episode without mood reactivity; **MR=**mood reactivity; **RBDC-MXS**=research-based diagnostic criteria for depressive mixed states.

*Chi-square=869.808; df=5; $P < .001$; variables not in the equation: psychomotor agitation, hyperactivity, increased energy, hyper-sexuality.

†Chi-square=178.965; df=7; $P < .001$; variables not in the equation: psychomotor agitation, verbal or physical aggression, hyperactivity, grandiosity, elation, hyper-sexuality