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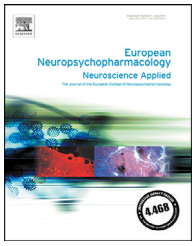

Patterns of response to antidepressants in major depressive disorder: Drug resistance or worsening of depression are associated with a bipolar diathesis

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Abstract
Resistance and worsening of depression in response to antidepressants (ADs) are major clinical challenges. In a large international sample of patients with major depressive disorder (MDD), we aim to explore the possible associations between different patterns of response to ADs and bipolarity. A total of 2811 individuals with a major depressive episode (MDE) were enrolled in the BRIDGE-II-MIX study. This post-hoc analysis included only 1329 (47%) patients suffering from MDD. Patients with (TRD-MDD, $n = 404$) and without (NTRD-MDD, $n = 925$) history of resistance to AD treatment and with ($n = 184$) and without ($n = 1145$) previous AD-induced irritability and mood lability (AIM) were compared using Chi-square, t-Student's test and logistic regression models. TRD-MDD patients resulted significantly associated with higher rates of AIM, psychotic features, history of suicide attempts, emotional lability and impulsivity, comorbid borderline personality disorder and polipharmacological treatment, compared to NTRD-MDD group. In comparison to NAIM-MDD patients, subjects in the AIM-MDD group showed significantly higher rates of first-degree family history for BD, previous TRD, atypical features, mixed features, psychiatric comorbidities, lifetime suicide attempts and lower age at first psychiatric symptoms. In addition, patients with AIM presented more often almost all the hypomanic symptoms evaluated in this study. Among these latter symptoms, logistic regressions showed that distractibility, impulsivity and hypersexuality were significantly associated with AIM-MDD. In conclusion, in MDD patients, a lifetime history of resistance and/or irritability/mood lability in response to ADs was associated with the presence of mixed features and a possible underlying bipolar diathesis.

1. Introduction

The pattern of clinical response to antidepressants (ADs) has been addressed by many, due to the widespread use of such treatments in patients with a major depressive episode (MDE) (Baldessarini et al., 2007). Factors associated with the lack of effect of ADs and their negative impact in patients with bipolar depression have been debated (Pacchiarotti et al., 2013a). Nevertheless, the effectiveness and safety of AD treatment in unipolar depression remain open issues. The challenge in addressing these questions lies mainly in the clinical and etiopathogenetic heterogeneity of depressive episodes, the misdiagnosis problems and the unclear difference between unipolar and bipolar depression in patterns of response to ADs (Vázquez et al., 2011).

Patients have been considered suffering from treatment resistant depression (TRD) when consecutive treatment with at least two substances of different pharmacological classes, used for a sufficient length of time at an adequate dose, fail to induce a clinically meaningful effect (inadequate response) (Committee for Medicinal Products for Human Use (CHMP), 2013).

Resistance to AD treatment is generally more frequent in bipolar than in unipolar depression, with non-response rates being up to 54% in bipolar disorder (BD) (Ghaemi et al., 2004) and 30%—40% in major depressive disorder (MDD) (Vázquez et al., 2011). Previous studies outlined that AD-treatment resistance during a MDE might be related to an unrecognized BD diagnosis or an underlying bipolar diathesis (Pacchiarotti et al., 2013a; Rihmer et al., 2013).

In addition to non-response to ADs, some patients with unipolar or bipolar depression may even experience worsening symptoms during AD treatment, including mood switches and subthreshold mixed features (Harada et al., 2014). In a study conducted on BD patients, a triad of dysphoria, irritability and middle insomnia was described as a potential complication of long-term AD treatment (El-Mallakh and Karippot, 2005). Such response has been termed "antidepressant-associated chronic irritable dysphoria" and may be more likely to occur in BD patients treated with an AD that reported a lifetime history of AD-related mood switching (El-Mallakh et al., 2008). In addition, the iatrogenic onset of (mixed) agitated depression has been described in individuals recently prescribed with AD treatment (Sani et al., 2014).

The worsening of depression with AD-monotherapy was also hypothesized to be correlated with suicidal behavior in specific subgroups of patients (Rihmer and Gonda, 2011). This could entail a psychopathological substrate that might reside in an agitated and mentally overstimulated state arising from an hypothetical underlying bipolarity (Rihmer et al., 2013; Zaninotto et al., 2015). Despite interesting proposals, the question of whether the worsening of depression with ADs, including emergence/worsening of irritability or agitation, might be considered as a form of treatment resistance, or whether it may be related to bipolar diathesis, remains unsettled.

To our knowledge, no studies evaluated the clinical correlates of resistance to AD treatment in a large sample of patients with a MDE and its possible association with AD-related symptoms or bipolar diathesis. The aim of the present post-hoc analysis of the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX study is to compare clinical features of patients with and without atypical responses to ADs within a large international sample of individuals suffering from MDD.

2. Methods

2.1. Sample and assessment

The general methodology of the BRIDGE-II-MIX study has been previously described (Perugi et al., 2015). The BRIDGE-II-MIX study was a multicentre, international, cross-sectional, non-interventional study conducted between June 2009 and July 2010 in 239 centres in Bulgaria, Egypt, Morocco, Netherlands, Portugal, Russia, Spain and Turkey. The number of investigators per country ranged from 62 in Spain to 18 in Egypt.

Patients included were adults aged 18 or older, with a primary diagnosis of MDE according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV edition, text revision (DSM-IV-TR) (American Psychiatric Association., 2000). The exclusion criteria were the patient's refusal to participate, the patient's inability to complete the self-questionnaire and the presence of an acute non-psychiatric condition.

A total of 2811 participants gave their written informed consent and provided complete data. Demographic features were generally similar across countries.

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 (IEA) European Federation guidelines for proper conduct of epidemiologic research. National and local ethics committees authorized the protocol in each country.

2.2. Data collection

In a single consultation the participating psychiatrists completed a case report form for each patient, incorporating inclusion criteria, socio-demographic variables, in- or out- patient status, history of psychiatric symptoms (mood symptoms, post-partum depression, suicide attempts) and previous psychiatric hospitalizations. Features of the current MDE, including bipolar symptoms listed in the DSM IV-TR diagnostic criteria for BD, known risk factors for BD (e.g. family history of BD, post-partum depression), previous response to ADs, psychiatric comorbidity, current treatment (ADs, mood-stabilizers intended as lithium and/or anticonvulsants, antipsychotics, benzodiazepines, ECT) were assessed. Illness severity was evaluated using the Clinical Global Impression-Bipolar Version (CGI-BP) (Spearing et al., 1997) and functional status was determined by the Global Assessment of Functioning (GAF) (Endicott et al., 1976). For a better detection of BD patients, criteria for bipolarity proposed by Angst et al. (2013) were also used. These criteria attribute a diagnosis of bipolarity in patients who experienced an episode of elevated or 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: (i) unequivocal and observable change in functioning uncharacteristic of the person's usual behaviour, (ii) marked impairment in social or occupational functioning observable by others or (iii) requiring hospitalisation or outpatient treatment. No minimum duration was required and no exclusion criteria were applied.

The duration of the evaluation was variable, depending on clinical needs, and was not recorded. Thus, information about its duration is not available. The evaluation packet was explicitly structured to use skills that fully trained psychiatrists would have and routinely apply in conducting an initial evaluation of an acutely ill patient. Clinicians had access to patient's clinical records during the consultation. No rating scales requiring calibration with a standard were incorporated. Raters were instructed to follow their usual practice, as training might have altered these practices and been seen as a biasing factor.

The main 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 (a) the proportion of patients fulfilling the DSM-5 criteria for MDE with mixed features (DSM-5-MXS) (American Psychiatric Association., 2013), or (b) research-based diagnostic criteria for depressive mixed states (RBDC-MXS) (Perugi et al., 2015). RBDC-MXS were defined by the presence of MDE plus 3 out of the following 14 hypomanic symptoms (distractibility, elation, emotional/mood lability, grandiosity, hyperactivity, hyper-sexuality, impulsivity, increased energy, irritable mood, more talkative/pressure to keep talking, psychomotor agitation, racing thoughts, risky behaviour, verbal or physical aggression) for at least one week. The presence of mixed symptoms for at least one week was established by means of both self-report and psychiatrist's clinical impression during the evaluation. RBDC-MXS were described as a priori, operational criteria for assessing mixed features during a MDE. No validity and reliability studies are provided. Despite this, it has to be noted that data about the validity of such set of symptoms in diagnosing depressive mixed states has been provided by previous research (Perugi et al., 2015). RBDC-MXS have been reported to assess depressive mixed states with a high sensitivity in comparison with two other possible definitions of mixed states (DSM-5 and DSM-5 Subtreshold), representing valid evidence-based criteria.

The lack of response to two appropriate trials of different classes of ADs, indicating clinical TRD, was retrospectively assessed. An operational clinical definition of lifetime AD-related worsening or activation syndrome was used, evaluating the presence of both irritability and mood lability in response to AD treatments (AD-induced Irritability and Mood lability, AIM). Irritability was delineated as a proneness to persistent anger, frustration or annoyance, with a tendency to respond to minor trigger events with angry outbursts, blaming others, and a sense of frustration. These pattern could be accompanied by the feeling that one's emotional responses are unjustified or disproportionate to the immediate source, but difficult to control (Barata et al., 2016). Mood lability was operationally defined as a state feature represented by marked and rapid fluctuations between different mood states in response to positive or negative environmental stimuli, with difficulties in controlling their consequences (Broome et al., 2015). The case report form used during the recruitment assessed the presence of borderline personality disorder (BPD) characteristics, labelled as trait characteristics in order not to bias the evaluation of mixed symptoms and AIM, which were evaluated as state characteristics.

From the whole sample of MDE patients, those diagnosed with BD according to DSM-IV-TR criteria ($n = 464$) were excluded from the post-hoc analysis in consideration of the aim of the study. Patients at their first MDE were also removed ($n = 646$) from the present analysis due to the possibility of a subsequent bipolar course. On the basis of the evidence that AD-induced hypomania/mania can now be included in the rubric of BD (American Psychiatric Association., 2013), patients with positive history of switching in course of AD treatment ($n = 372$) were excluded. The adjunctive diagnosis of BPD and attention deficit hyperactivity disorder (ADHD) in MDD patients is not as represented as among bipolar subjects and, as a consequence, we decided not to exclude these two comorbidities from the present analysis.

The final sample of this post-hoc analysis was composed of 1329 depressive patients, with a diagnosis of MDD and at least one MDE in the past.

2.3. Statistical analysis

Groups were compared using the Chi-square or the Student's *t*-test. We did not test for irritability and mood lability in the AIM subgroup, in order to not bias using variables yet included in the definition of AIM. The bivariate analyses involved many tests of statistical

significance, raising the problem of type I error. Hence, a Bonferroni-corrected threshold for statistical significance was used.

A stepwise backward logistic regression model was used to identify the association between TRD and 9 significant variables chosen from the bivariate analysis (age, AIM, CGI-BP scores for severity of depression, current treatment with antipsychotics, current treatment with more than 3 drugs, GAF score, mood stabilizers or benzodiazepines, the presence of lifetime suicide attempts). Two further stepwise logistic regression model were performed in order to assess: (a) the predictors of AIM within clinical and course characteristics significantly associated with AIM in the bivariate analysis and (b) the predictors of AIM within the RBDC-MXS symptoms significantly associated in the bivariate analyses (distractibility, emotional/mood lability, hyperactivity, hypersexuality, impulsivity, increased energy, irritable mood, psychomotor agitation, racing thoughts, verbal or physical aggression). The stepwise modelling procedure started with the full model and consisted in eliminating, for each step, the least statistically significant variable from the model and re-computing the revised model, until all remaining variables were at $p < 0.1$. Statistical significance was set at $p < 0.05$ and Odds Ratios (OR) with 95% confidence intervals for significant independent variables were assessed for observed associations and reported. All tolerance values in the regression analyses were >0.2 and all variance inflation factors were <2, expressing that multicollinearity was not a source of bias in the regression models. Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA). All p values were two-tailed and statistical significance was set at $p < 0.05$.

3. Results

The percentage of patients recruited in each country ranged from 5.6% in Spain to 37.0% in Russia (Bulgaria 12.1%; Egypt 9.0%; Marocco 8.2%; Netherlands 7.5%; Portugal 10.6%; Turkey 9.9%). The mean proportion of patients who were hospitalized for the full sample was 29.6%. No statistically significant difference among different countries was observed in rates of mixed states, TRD and AIM.

(a) Comparison between patients with (TRD-MDD) and without (NTRD-MDD) treatment resistant depression

TRD-MDD patients presented older age at the moment of evaluation compared to NTRD-patients (respectively, 48.3 vs 45.4 years), as well as higher rates of AIM (22.8% vs 9.9%), psychotic features (9.7% vs 5.9%), history of suicide attempts (31.2% vs 18.5%), and duration of current MDE less than 1 month (29.5% vs 36.1%) (Table 1). In addition, patients in the TRD group showed lower GAF (47.7 vs52.5) and higher CGI-BP (4.6 vs 4.4) scores compared to subjects in the NTRD group.

According to both DSM-5 and RBDC diagnostic criteria, the rates of mixed features did not differ between the two groups while, among current hypomanic symptoms, emotional lability and impulsivity were found to be more frequent in TRD-MDD group compared to NTRD-MDD group (respectively, 27.5% vs 21.6% and 13.9% vs 9.7%).

TRD-MDD and NTR-MDD patients present similar rates of BD family history, current atypical features, age at first psychiatric symptoms and diagnosis of bipolarity according to Angst criteria (Angst et al., 2013). When considering psychiatric comorbidities, the two groups differed solely on the presence of a greater prevalence of BPD in the TRD-MDD patients (6,4%) compared to NTRD subjects (3,8%).

Patients with a history of TRD were more frequently treated with mood stabilizers, antipsychotics, benzodiazepines and polypharmacotherapy (more than 3 drugs) in comparison to NTRD patients.

In the multivariate logistic regression analysis, the clinical features significantly associated with a previous history of TRD were higher age, lifetime suicide attempts, AIM, lower GAF, use of mood stabilizers, antipsychotics and benzodiazepines (Table 2).

(b) Comparison between patients with (AIM-MDD) and without (NAIM-MDD) antidepressant-induced irritability and mood lability

Compared to NAIM-MDD group, subjects in the AIM-MDD group showed significantly lower age at first psychiatric symptoms (respectively, 33.5 vs 31.3 years) and higher prevalence of psychiatric symptoms before 30 years of age (47.6% vs 56.5%) (Table 3). Similarly, AIM-MDD patients showed higher rates of first-degree family history of BD (20.9% vs 9.8%), TRD (50% vs 27.2%), atypical features (11.4% vs 5.4%), duration of the current episode less than 1 month (41.3% vs 32.9%), and lifetime suicide attempts (29.3% vs 21.2%) in comparison to NAIM-MDD subjects.

According to both DSM-5 (9.2% vs 2.6%) and RBDC (48.9% vs 17.9%) diagnostic criteria, mixed features were more common in the AIM-MDD group compared to NAIM-MDD group. In addition, AIM-MDD patients have more often met the criteria for bipolarity and presented more frequently all the evaluated hypomanic symptoms except for grandiosity, in comparison to patients without AIM (39.7% vs 19%).

No differences were found between the two groups regarding the prevalence of psychotic features, GAF and CGI-BP scores. ADHD, alcohol-substance use disorders, BPD, eating disorders and panic disorder were significantly more often diagnosed in AIM-MDD group compared to NAIM-MDD group.

Patients in the AIM-MDD group were more often treated compared to NAIM-MDD patients with mood-stabilizers (respectively, 38% vs 15.1%), antipsychotics (37.5% vs 29.1%), benzodiazepines (61.4% vs 47.7%), and polipharmacotherapy (47.3% vs 27.2%).

In the multivariate logistic regression model, the clinical features significantly associated with AIM-MDD were BD family history, TRD, a diagnosis of bipolarity, panic disorder, treatment with mood-stabilizers and benzodiazepines (Table 4a). On the other hand, the hypomanic/manic symptoms significantly associated with AIM-MDD were distractibility, impulsivity and hypersexuality (Table 4b).

4. Discussion

In this post-hoc analysis of the BRIDGE-II-MIX study, nearly 1 out of 3 patients (30.4%) diagnosed with MDD presented a previous history of resistance to AD treatment. Similar rates of non-response to ADs have been reported (Vázquez et al., 2011).

The presence of impulsivity and emotional lability during the current MDE was associated with a history of TRD. Both these symptoms are included among the RDBC criteria of mixed features. In our study, a clear correlation between TRD and MDE with mixed features, according to both DSM-5 and RBDC diagnostic criteria, has not been found. However,

Table 1 Clinical features in 1329 depressed patients with Major Depressive Disorder (MDD): comparison among patients with (TRD-MDD) and without (NTRD-MDD) resistance to AD treatment.

	TRD-MDD $n = 404$ (30.4%)	NTRD-MDD $n = 925$ (69.6%)	χ^2/t	p
Female Gender	294 (72.8%)	670 (72.4%)	0.004	0.951
Age, years - mean (SD)	48.31 (13.791)	45.42 (13.857)	−3.415	0.001**
BD first-Degree Family History	51 (12.8%)	98 (10.8%)	0.881	0.348
AIM	92 (22.8%)	92 (9.9%)	37.714	<0.001**
Atypical Features	27 (6.7%)	56 (6.1%)	0.098	0.754
Psychotic Features	39 (9.7%)	55 (5.9%)	5.330	0.021*
Duration current episode <1 month	119 (29.5%)	334 (36.1%)	5.247	0.022*
Age at first psychiatric symptom - mean (SD)	33.09 (12.637)	33.27 (13.139)	0.231	0.817
First symptoms <30 years	193 (47.8%)	456 (49.3%)	0.204	0.651
Lifetime Suicide attempts	126 (31.2%)	171 (18.5%)	25.415	<0.001**
DSM-5-MXS	18 (4.5%)	29 (3.1%)	1.076	0.300
RBDC-MXS	98 (24.3%)	197 (21.3%)	1.260	0.262
Bipolar specifier	92 (22.8%)	199 (21.5%)	0.192	0.661
CGI-Severity of depression - mean (SD)	4.65 (0.970)	4.44 (0.893)	−3.955	<0.001**
GAF - mean (SD)	47.71 (11.874)	52.47 (12.561)	6.415	<0.001**
Hypomanic/manic symptoms				
Aggression	42 (10.4%)	117 (12.6%)	1.149	0.284
Distractibility	79 (19.6%)	164 (17.7%)	0.510	0.475
Elation	11 (2.7%)	25 (2.7%)	0.000	1.000
Emotional lability	111 (27.5%)	200 (21.6%)	5.054	0.025*
Grandiosity	7 (1.7%)	23 (2.5%)	0.423	0.516
Hyperactivity	22 (5.4%)	31 (3.4%)	2.697	0.101
Hypersexuality	8 (2%)	17 (1.8%)	0.000	1.000
Impulsivity	56 (13.9%)	90 (9.7%)	4.495	0.034*
Increased energy	19 (4.7%)	24 (2.6%)	3.347	0.067
Irritable mood	108 (26.7%)	236 (25.5%)	0.159	0.690
Pressure to speech	33 (8.2%)	55 (5.9%)	1.901	0.168
Psychomotor Agitation	49 (12.1%)	109 (11.8%)	0.007	0.931
Racing thoughts	33 (8.2%)	68 (7.4%)	0.164	0.686
Risky behaviour	23 (5.7%)	38 (4.1%)	1.271	0.260
Psychiatric Comorbidities				
ADHD	10 (2.5%)	20 (2.2%)	0.019	0.889
Alcohol-substance use disorders	36 (8.9%)	66 (7.1%)	1.013	0.314
BPD	26 (6.4%)	35 (3.8%)	3.930	0.047*
Eating disorders	21 (5.3%)	42 (4.6%)	0.150	0.698
Obsessive-compulsive disorder	16 (4%)	48 (5.2%)	0.676	0.411
Anxiety disorders	109 (27%)	245 (26.5%)	0.014	0.905
Panic disorder	37 (9.2%)	88 (9.5%)	0.010	0.920
Social phobia	25 (6.2%)	58 (6.3%)	0.000	1.000
Current Pharmacological Treatment				
Mood-stabilizers	108 (26.7%)	135 (14.6%)	26.921	<0.001**
Antipsychotics	161 (39.9%)	241 (26.1%)	24.721	<0.001**
Benzodiazepines	233 (57.7%)	426 (46.1%)	14.725	<0.001**
ECT	8 (2.0%)	14 (1.5%)	0.144	0.704
More than 3 drugs	171 (42.3%)	228 (24.6%)	40.990	<0.001**

Notes: ADHD=Attention Deficit Hyperactivity Disorder; AIM=Antidepressant-induced Irritability and Mood lability; BD=Bipolar Disorder; BPD: Borderline personality disoders; CGI=Clinical Global Impression; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-5-MXS=MDE with Mixed Features according to DSM-5; ECT=Electroconvulsive Therapy; GAF=Global Assessment of Functioning; MDE=Major Depressive Episode; RBDC=Research-Based Diagnostic Criteria; RBDC-MXS=Depressive Mixed State according to RBDC.

* $p < 0,05$.

** $p < 0.00119$ (0.05/42).

Table 2 Multiple logistic regression of clinical features on the presence of treatment resistance in subjects with Major Depressive Disorder (MDD).

Variables in equation	Wald	p	OR (95% CI)
Age	10.944	0.001	1.015 (1.006-1.025)
AIM	24.374	<0.001	2.364 (1.680-3.326)
Antipsychotics	9.713	0.002	1.529 (1.171-1.997)
Benzodiazepines	4.951	0.026	1.331 (1.035-1.712)
GAF	14.995	<0.001	0.979 (0.969-0.990)
Lifetime suicide attempts	8.669	0.003	1.553 (1.159-2.082)
Mood stabilizers	11.927	0.001	1.739 (1.270-2.380)

Variables not in equation: CGI-severity of depression; more than 3 drugs.
Wald: 126.662; **df**: 7; $p < 0.001$.
Notes: AIM=Antidepressant-induced Irritability and Mood lability; GAF=Global Assessment of Functioning.

the occurrence of hypomanic symptoms in patients with TRD seems to confirm the link between this group of patients and bipolarity (Benazzi, 2010; Rihmer et al., 2013; Sharma et al., 2005). In TRD patients, the severity of the MDE and the presence of subthreshold mixed symptoms could explain the high prescription rates of mood stabilizers, antipsychotics and polypharmacotherapy (Stahl, 2017).

The high prevalence of lifetime suicide attempts in patients with TRD suggests an increased risk for suicidal behaviours lifetime (Rihmer et al., 2013). Unfortunately, from our data we cannot know if suicide attempts occurred during periods of TRD and/or were associated to specific administered treatments. Anyway, the obsevation indicates that people with MDD reporting previous TRD could represent a target population for a treatment strategy tailored to suicide prevention.

Notably, a significant association was found between a history of TRD and previous AIM, that persisted in the logistic regression model. A significant overlap between TRD and AIM was identified, as one out five participants with TRD reported also a previous worsening of depressive symptoms with AD treatment. Interestingly, most of previous studies evaluated only the correlations between TRD and hypomanic/manic switches, without considering the link between TRD and the worsening of depressive symptoms in response to ADs (Dudek et al., 2010).

Several variables related to bipolarity (first degree family history of BD, early onset of first psychiatric symptoms, atypical features, history of suicide attempts) (Angst et al., 2012; Serretti et al., 2013) were significantly associated with AIM, strongly indicating the presence of a bipolar diathesis within this subgroup.

The AIM group also showed higher frequencies of comorbid panic disorder, ADHD and BPD. The high rates of psychiatric comorbidities could be viewed as an element linked to bipolarity, in a complex relationship which considers comorbidity and partial symptoms overlap. Anxiety disorders appear to be a prominent aspect of mixed states and consequently, of bipolarity (Swann et al., 2009). In addition, panic attacks are not uncommon among individuals with BD and 'soft' bipolar conditions, often characterizing the onset of the illness (Nabavi et al., 2015). The comorbidity between ADHD and BD has been frequently reported and seems to be associated with more severe symptoms, worse course of illness, and worse outcome of both conditions (Nierenberg et al., 2005; Tamam et al., 2008).

The presence of overlapping clinical features between ADHD, BPD and BD is a relevant and broadly-discussed issue (Brus et al., 2014). In the present study, data collection included the evaluation of BPD features, such as impulsivity and affective lability. BPD has been conceptualized as belonging to the broad clinical bipolar spectrum, with overlapping psychopathology and temperamental underpinnings between the two disorders (Perugi et al., 2011). Such features have to be considered as trait characteristics in BPD, while the evaluation of these variables among the RBDC-MXS have been evaluated as state characteristics. It also has to be noted that ADHD presents as well affective lability as a trait characteristic (Marwaha et al., 2014). Although suicide attempts are common in several mental disorders, the presence of para-suicidal self-harm was noted to increase the sensitivity of a BPD diagnosis, differentiating it from BD (Ghaemi, 2016). On the contrary, current research shows an increasing prevalence of "non-suicidal self-injury" behaviours and their association with a wide range of psychaitric disorders including MDD and BD. Therefore, the discriminatory power of NSSI in differentiating between BPD and BD may require re-evaluation (Hayes et al., 2016).

Among the 12 hypomanic symptoms evaluated, 11 were associated with a history of AIM, in particular impulsivity, distractibility and hypersexuality. According to Koukopoulos et al. (2007), a MDE that rapidly worsens after starting AD treatment should be considered prone to the development of mixed features, suggesting a close relationship with bipolarity. Our results are in line with previous reports underlying the importance of the association of "subthreshold" manic symptoms in patients with a diagnosis of MDD and suicide attempt. Among hypomanic/manic symptoms, irritability and psychomotor agitation were the strongest predictors of suicide attempt (Balázs et al., 2006).

The relationship between suicidal behaviours, different patterns of response to ADs and symtoms related to mixed features during a MDE (anxiety, inner tension, psychomotor hyperactivity) has been highlighted in previous studies (Rihmer and Gonda, 2011). In the present post-hoc analysis, people with a past history of AIM showed significantly higher rates of lifetime suicide attempts. Several studies provided supporting evidence for the role of mixed features during depression in increasing the risk of suicide attempts (Pacchiarotti et al., 2013b). Indeed, the worsening of depression could play a fundamental role in the development of suicidal behaviour in a vulnerable population of

Table 3 Clinical features in 1329 depressed patients with Major Depressive Disorder (MDD): comparison among patients with (AIM) and without (NAIM) Antidepressant-induced Irritability and Mood lability.

	AIM-MDD $n = 184$ (13.8%)	NAIM-MDD $n = 1145$ (86.2%)	χ^2/t	p
Female gender	138 (75%)	826 (72.1%)	0.515	0.473
Age, years - mean (SD)	45.16 (13.318)	46.45 (13.981)	1.208	0.228
BD first-Degree Family History	38 (20.9%)	111 (9.8%)	17.821	<0.001**
TRD	92 (50%)	312 (27.2%)	37.714	<0.001**
Atypical features	21 (11.4%)	62 (5.4%)	8.743	0.003*
Psychotic features	18 (9.8%)	76 (6.6%)	1.931	0.165
Duration current episode <1 month	76 (41.3%)	377 (32.9%)	4.587	0.032*
Age at first psychiatric symptoms - mean (SD)	31.30 (11.804)	33.52 (13.143)	2.324	0.021*
First symptoms <30 years	104 (56.5%)	545 (47.6%)	4.701	0.030*
Lifetime Suicide attempts	54 (29.3%)	243 (21.2%)	5.572	0.018*
DSM-5-MXS	17 (9.2%)	30 (2.6%)	18.465	<0.001**
RBDC-MXS	90 (48.9%)	205 (17.9%)	86.478	<0.001**
Bipolar specifier	73 (39.7%)	218 (19%)	38.271	<0.001**
CGI- Severity of depression - mean (SD)	4.53 (1.078)	4.50 (0.896)	−0.376	0.708
GAF - mean (SD)	50.25 (12.891)	51.16 (12.492)	0.904	0.366
Hypomanic/manic symptoms				
Aggression	36 (19.6%)	123 (10.7%)	10.893	0.001**
Distractibility	61 (33.2%)	182 (15.9%)	30.452	<0.001**
Elation	11 (6.0%)	25 (2.2%)	7.282	0.007*
Grandiosity	6 (3.3%)	24 (2.1%)	0.518	0.472
Hyperactivity	18 (9.8%)	35 (3.1%)	17.014	<0.001**
Hypersexuality	11 (6.0%)	14 (1.2%)	16.933	<0.001**
Impulsivity	49 (26.6%)	97 (8.5%)	51.614	<0.001**
Increased energy	15 (8.2%)	28 (2.4%)	14.718	<0.001**
Pressure to speech	21 (11.4%)	67 (5.9%)	7.056	0.008*
Psychomotor Agitation	36 (19.6%)	122 (10.7%)	11.179	0.001**
Racing thoughts	29 (15.8%)	72 (6.3%)	18.930	<0.001**
Risky behaviour	16 (8.7%)	45 (3.9%)	7.169	0.007*
Psychiatric Comorbidities				
ADHD	10 (5.5%)	20 (1.8%)	8.230	0.004*
Alcohol-substance use disorders	23 (12.5%)	79 (6.9%)	6.249	0.012
BPD	18 (9.8%)	43 (3.8%)	11.810	0.001**
Eating disorders	15 (8.2%)	48 (4.2%)	4.712	0.030*
Obsessive-compulsive disorder	9 (4.9%)	55 (4.8%)	0.000	1.000
Anxiety disorders	59 (32.1%)	295 (25.8%)	2.906	0.088
Panic disorder	31 (16.9%)	94 (8.2%)	13.033	<0.001**
Social phobia	16 (8.7%)	67 (5.9%)	1.706	0.192
Current Pharmacological Treatment				
Mood-stabilizers	70 (38%)	173 (15.1%)	54.282	<0.001**
Antipsychotics	69 (37.5%)	333 (29.1%)	4.932	0.026*
Benzodiazepines	113 (61.4%)	546 (47.7%)	11.407	0.001**
ECT	1 (0.5%)	21 (1.8%)	0.926	0.336
More than 3 drugs	87 (47.3%)	312 (27.2%)	29.338	<0.001**

Notes: ADHD=Attention Deficit Hyperactivity Disorder; BD=Bipolar Disorder; BPD=Borderline Personality Disorder; CGI=Clinical Global Impression; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-5-MXS=MDE with Mixed Features according to DSM-5; ECT=Electroconvulsive Therapy; GAF=Global Assessment of Functioning; MDE=Major Depressive Episode; RBDC=Research-Based Diagnostic Criteria; RBDC-MXS=Depressive Mixed State according to RBDC; TRD=Treatment resistant depression.

* $p < 0.05$.

** $p < 0.00125$ (0.05/40).

individuals, both when associated to AD treatment and as a clinical feature *per se* (Rihmer and Gonda, 2011).

The possible implications of resistance and/or irritability/mood lability in response to ADs have not widely been investigated in unipolar depression. It would be hypothesized that different responses to AD-treatment could lie in a continuum going from optimal response to the occurrence of hypomanic/manic switches, with TRD and worsening of depression considered as intermediate steps (Rihmer and Gonda, 2011). According to the findings of the present study, TRD and AIM may represent two different aspects of the same phenomenon, at least in a significant proportion

Table 4a Multiple logistic regression of clinical features on the presence of Antidepressant-induced Irritability and Mood lability (AIM) in subjects with Major Depressive Disorder (MDD).

Variables in equation	Wald	*p*	OR (95% CI)
BD first-Degree Family History	6.144	0.013	1.754 (1.125-2.735)
TRD	25.836	<0.001	2.406 (1.715-3.375)
Bipolar specifier	16.176	<0.001	2.100 (1.463-3. 014)
Panic disorder	7.286	0.007	1.926 (1.197-3.101)
Mood-stabilizers	22.363	<0.001	2.423 (1.679-3.496)
Benzodiazepines	4.863	0.027	1.464 (1.043-2.055)

Variables not in equation: BPD; DSM-5-MXS; more than 3 drugs.
Wald: 114.217; **df**: 6; $p < 0.001$.
Notes: BD=Bipolar Disorder; BPD=Borderline Personality Disorder; DSM-5-MXS= mixed features according to DSM-5; TRD=Treatment Resistant Depression.

Table 4b Multiple logistic regression of hypomanic/manic symptoms on the presence of Antidepressant-induced Irritability and Mood lability (AIM) in subjects with Major Depressive Disorder (MDD).

Variables in equation	Wald	*p*-value	OR (95% CI)
Distractibility	11.828	0.001	1.927 (1.326-2.799)
Impulsivity	22.586	<0.001	2.805(1.833-4.293)
Hypersexuality	4.486	0.034	2.541(1.072-6.025)

Variables not in equation: aggression; hyperactivity; increased energy; psychomotor agitation; racing thoughts.
Wald: 58.419; **df**: 3; $p < 0.001$.

of patients, as shown by the correlation of both responses with suicide attempts and some mixed features. Nonetheless, non-response and worsening of depression following AD treatment may lie on a gradient, where AIM resulted more related to the presence of mixed symptoms.

The main strengths of the BRIDGE-II-MIX study included the large sample size, as well as the wide range of care settings. Furthermore, the presence of few exclusionary criteria might have increased the generalizability of the findings. A major limitation of the present study concerns the retrospective nature of the information about patterns of previous response to ADs. Previous history of TRD and AIM were assessed by the clinician during the consultation with possible subjectivity and recall bias, even if the patient's clinical documentation was always available. The retrospective nature of AIM evaluation made it difficult to provide information about the possibility of co-occurrence of alcohol/substance abuse during AD treatment or AD withdrawal symptoms. As for symptom duration, no criteria have been established for the definition of AIM, mainly in consideration of the fact that previous definitions of atypical responses to ADs did not report standardized duration criteria (El-Mallakh et al., 2008; Harada et al., 2014; Koukopoulos et al., 2007; Takeshima and Oka, 2013). Another limitation was the non-random selection of the participating centres, which might have led to a bias through the inclusion of psychiatrists with a particular interest in bipolar spectrum disorders. This may be seen, however, as a positive point, in the sense that some expertise is needed to detect past hypomania in MDE patients. Furthermore, in the current study, information about the type of prescribed ADs, possible combined treatments, dosages and duration of treatment, along with starting doses and tapering strategies were not available. The relationship between patterns of previous response to ADs and mixed features should be controlled for these potential confounding factors in future longitudinal prospective studies, using external validators.

In conclusion, it is likely that different responses to ADs represent a heterogeneous framework, underpinning different clinical pictures and probably different pathogenic mechanisms. A careful evaluation of previous atypical responses to AD treatment, such as development of irritability, agitation or mood lability, other than hypomanic/manic switches, could be of huge importance. Identifying people with unipolar depression and a history of AD treatment resistance or AD-induced irritability/mood lability might address specific treatment strategies, such as avoiding ADs monotherapy and considering medications such as mood stabilizers and atypical antipsychotics as potential alternative strategies. This clinical approach could be useful to differentiate between depression subtypes, empowering the diagnostic process and helping in personalized therapeutic strategies.

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Conflict of interest

Prof. Angst, Dr. Mainardi, Dr. Barbuti, Dr. Menculini declare no conflict of interest and report no financial or other relationship relevant to the subject of this article.

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CRediT authorship contribution statement

Giulio Perugi: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing - review & editing. **Isabella Pacchiarotti:** Writing - original draft, Writing - review & editing. **Cecilia Mainardi:** Writing - original draft, Writing - review & editing. **Norma Verdolini:** Writing - original draft, Writing - review & editing. **Giulia Menculini:** Writing - original draft, Writing - review & editing. **Margherita Barbuti:** Writing - original draft, Writing - review & editing. **Jules Angst:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **Jean-Michel Azorin:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **Sergey Mosolov:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **Allan H. Young:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **Eduard Vieta:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing.

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