Aggressiveness in depression: A neglected symptom possibly associated to bipolarity and mixed features

Running title: aggressiveness in mixed depression

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Abstract

Objective: To evaluate aggressiveness during a major depressive episode (MDE) and its relationship with bipolar disorder (BD) in a post-hoc analysis of the BRIDGE-II-MIX study.

Method: A total of 2,811 individuals were enrolled in this multicenter cross-sectional study. MDE patients with (MDE-A, n=399) and without aggressiveness (MDE-N, n=2,412) were compared through Chi-square test or Student's t-test. A stepwise backward logistic regression model was performed.

Results: MDE-A group was more frequently associated with BD (p<0.001) whilst aggressiveness was negatively correlated with unipolar depression (p<0.001). At the logistic regression aggressiveness was associated with: the age at first depressive episode (p<0.001); the severity of mania (p=0.03); the diagnosis of BD (p=0.001); comorbid borderline personality disorder (BPD) (p<0.001) but not substance abuse (p=0.63); no current psychiatric treatment (p<0.001); psychotic symptoms (p=0.007); the marked social/occupational impairment (p=0.002). The variable most significantly associated with aggressiveness was the presence of DSM-5 mixed features (p<0.001, OR=3.815). After the exclusion of BPD, the variable of lifetime suicide attempts became significant (p=0.013, OR=1.405).

Conclusion: Aggressiveness seems to be significantly associated with bipolar spectrum disorders, independently from BPD and substance abuse. Aggressiveness should be considered as a diagnostic criterion for the mixed features specifier and a target of tailored treatment strategy.

Keys words: aggressiveness, bipolar disorder, DSM-5 mixed features specifier, major depressive episode

Significant outcomes

- In this post-hoc analysis of the BRIDGE-II-MIX study, the presence of aggressive behaviors was mainly related with socio-demographic and clinical characteristics associated with bipolarity.

- The most relevant clinical variable associated with aggressiveness during a major depressive episode was the presence of mixed features.

- The identification of aggressive behaviors could be the target of a tailored treatment strategy in this subgroup of bipolar disorder patients.

Limitations

- There is a possible bias due to the fact that the psychiatrists involved in the study were those with a particular interest in bipolar disorder.

- This is a post-hoc analysis of the BRIDGE-II-Mix study, whose primary aim was not aggressiveness.

- The retrospective assessment of aggressiveness avoided to explain causality and could possibly lead to self-report bias

Introduction

Aggressiveness is defined as an overt behavior involving intent to inflict noxious stimulation or to behave destructively towards another organism or object (1). In psychiatry, it is a behavioral or motor response associated with intent to do harm and it may be self-directed (2).

Several psychiatric disorders, including mood disorders, have been associated with increased rates of aggressiveness and violent behaviors (3). Particularly, bipolar disorder (BD) patients presented increased risk for aggressive behaviors (4,5). Indeed, aggressiveness has assumed particular importance as a core feature of manic and mixed states (6), independently from psychosis (7), and often emerging as a correlate of comorbid substance abuse and suicidality (8).

In comparison with subjects with no-BD, but suffering from other psychiatric disorders, and healthy controls, BD patients showed in previous studies increased self-reported verbal and physical aggressiveness, particularly during acute episodes and independently from BD subtypes, severity and polarity of the current episode, psychotic symptoms and current pharmacological treatments (4,9). In addition, manic patients showed the highest odds ratio for aggressive incidents among psychiatric inpatients (10).

As for trait characteristics of depressive episodes, it has been found that BD-I and BD-II depressed patients had more life-time aggressiveness/hostility than unipolar depressed patients (11).

Previous studies have shown that comorbidity with other disorders, namely substance and alcohol abuse and borderline personality disorder (BPD), increased the risk of aggressiveness in BD patients (12,13).

Several factor analyses described the clinical context of aggressiveness in mania. Aggressiveness was associated with paranoia and irritability, loading on the same factor ("irritable aggressiveness") (14). In another factor analysis, aggressiveness loaded on the same factor as irritability, uncooperativeness, impatience and lack of insight, suggesting the existence of a distinct subtype of mania defined as "aggressive" (7). In a more recent study, the factor analysis revealed 5 factors, and one of them was termed ''Dysphoria', with positive significant loading for hostility, uncooperativeness, and suspiciousness, representing one of the two classical aspects of manic states (15). In this context, aggressiveness could represent a core feature of manic and mixed episodes of BD, and might be a persistent trait in the sense of appearing in the same patients across repeated episodes.

Despite these previous findings, aggressiveness is not currently considered as a DSM diagnostic criterion of mania and consequently is not included in the DSM-5 mixed features in both bipolar and unipolar depressive episodes (16). In fact, only irritable mood represents a major defining characteristic of manic episodes since the first edition of DSM (17) and across the different revisions of the manual up to the last DSM-5. The DSM-5 fails to include the most common symptoms of mixity, including anxiety, agitation, and irritability as criteria for mixed features (18,19).

Few studies between those mentioned above evaluated possible clinical correlates of aggressiveness during a major depressive episode (MDE) across mood disorders. These studies were conducted on small samples of patients or derived only from one psychiatric center.

Aims of the study

The aim of the present post-hoc analysis was to assess the relationship between BD diagnosis or features and the presence of aggressive behaviors during a major depressive episode. We explored the possible clinical and treatment implications of this association.

Material and methods

Sample and assessment

This study is a post-hoc analysis of the BRIDGE-II-Mix study. The general methodology of the BRIDGE-II-MIX study was described in detail in previous reports (20–23). The BRIDGE-II-Mix study was a multicenter, international, non-interventional, cross-sectional study. It was conducted between June 2009 and July 2010 in 239 centers in Bulgaria, Egypt, Morocco, the Netherlands, Portugal, Russia, Spain, and Turkey where hospital-based or community psychiatrists were expected to enroll consecutively 10-20 eligible adult patients aged 18 or older consulting for a MDE according to the Diagnostic and Statistical Manual of Mental Disorders-IV edition (DSM-IV) criteria during a three month recruitment period.

The selection of the different centers in each country would reflect the psychiatric healthcare provision and the patient care typical of the country's practice and regional diversity. Each center collected anonymous screening logs of the patients. Reasons for nonparticipation were pre-coded (refusal to participate, patient unable to complete the questionnaire, and other). Patients presenting with an acute non-psychiatric condition/emergency were excluded.

From the 239 psychiatrists involved in the study, 237 returned their site questionnaire. A total of 2,811 patients agreed to participate and provided complete

data, representing the full analysis population. Demographic features were generally similar across countries.

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment; http://www.wma.net) and the Good Epidemiology Practice and the International Epidemiologic Association (IEA) European Federation (http://ieaweb.org). Good Epidemiologic Practice (GEP)–IEA Guidelines were followed for proper conduct of epidemiologic research, as well as pertinent national, legal and regulatory requirements. Written informed consent was obtained from each patient. In each country, the protocol was approved by the local ethics committee.

Data collection

For each patient, the psychiatrists completed a case report, incorporating inclusion criteria, socio-demographic variables (age, gender, marital status), inpatient or outpatient status, history of psychiatric symptoms (mood symptoms, postpartum depression, suicide attempts), and previous psychiatric hospitalizations. Features of the MDE, including bipolar symptoms listed in the DSM-IV-TR (24) diagnostic criteria for BD, known risk factors for BD (e.g., family history of BD and postpartum depression), previous response to antidepressants, psychiatric comorbidity, current treatment were recorded. The functional status was determined by the investigator using the Global Assessment of Functioning (GAF) (25) and the global illness severity was assessed through the Clinical Global Impression-Bipolar Version (CGI-BP) (26).

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. 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 primary objective of the BRIDGE-II-Mix study was to establish the frequency of depressive mixed states by analyzing all the relevant symptoms of either pole. The frequency of depressive mixed states was post hoc defined as (i) the proportion of patients fulfilling the DSM-5 criteria for MDE with mixed features (DSM-5-MXS) (16), or (ii) research-based diagnostic criteria for depressive mixed states (RBDC-MXS). RBDC-MXS are defined by the presence of MDE plus three of the following 14 hypomanic symptoms for at least a week: irritable mood, emotional/mood lability, distractibility, psychomotor agitation, impulsivity, aggression (verbal or physical), racing thoughts, more talkative/pressure to keep talking, hyperactivity, increased energy, risky behavior, grandiosity, elation and hypersexuality. The proportion of patients fulfilling the criteria for BD according to the DSM-IV-TR and bipolarity specifier proposed by Angst et al. (27,28) was also identified.

The objective of the present analysis of the BRIDGE-II-Mix study data was to assess the specific features of patients with (MDE-A) or without (MDE-N) aggressiveness.

An operational clinical definition of aggressiveness has been used, defined by the presence of at least one of the following behaviors during the index MDE: 1. Physical Aggressiveness (PHY): a. ever threatened or b. hit people, or c. got into fights more than most people or d. become so mad to have broken things; 2. Verbal Aggressiveness (VER): a. to argue a lot with other people, or b. to can't help getting into arguments when people disagree, or c. to get very angry for no good reason with troubles in self-controlling.

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Statistical analysis

The Chi-square test was used for comparison between groups for categorical variables and Student's t-test for continuous variables. The bivariate analysis involved many tests of statistical significance, raising the problem of type I errors. For this reason, we corrected for multiple comparisons and utilized a Bonferroni-corrected threshold for statistical significance, including in the logistic regression only those clinically sound variables under this threshold of 0.004. A stepwise backward logistic regression model was then used to identify the association between aggressiveness and 10 significant variables (BD diagnosis, DSM-5-MXS, severity of mania, comorbid BPD, comorbid substance abuse, lifetime suicide attempts, psychotic features, marked impairment in functioning, no psychiatric treatment, age at first depressive episode). The presence of mixed features in this post-hoc analysis was defined according to the DSM-5 mixed specifier (DSM-5-MXS). The stepwise modeling procedure started with the full model and consisted, for each step, in eliminating the least statistically significant variable from the model and re-computing the revised model, until all remaining variables were at $p<0.1$. Odds ratios with 95% confidence intervals were used for observed associations. All tolerance values in the regression analyses were > 0.2 and all variance inflation factors were < 2, thereby indicating that multicollinearity was not a source of bias in the regression models (29). 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 $p<0.05$.

Results

Clinical features: MDE-A patients versus MDE-N patients

From a total sample of 2,811 patients, 399 (14.2%) presented verbal or physical aggressiveness (MDE-A group) during the index MDE. The socio-demographic and clinical features are reported in **Table 1**.

Patients in the MDE-A group were diagnosed more frequently with BD (<0.001), in particular BD-I (<0.001) but not BD-II (0.997), than those in the MDE-N group (see **Table 1**). The presence of aggressiveness was negatively associated with the diagnosis of unipolar depression (p<0.001). MDE-A group more frequently presented DSM-5-MXS than MDE-N group (p<0.001).

Patients in the MDE-A group showed higher rates of comorbid disorders compared to those in the MDE-N group such as: BPD (p<0.001), anxiety disorder (p<0.001), eating disorders (p=0.003) and attention-deficit hyperactivity disorder (ADHD) (p=0.011).

Patients in the MDE-A reported more frequently a current substance abuse (p=0.003) but not a current alcohol abuse (p=0.086) than those in the MDE-N group (see **Table 1**). In both cases the alcohol or substance abuse was not in the context of dependence of alcohol (67.2% versus 61%, p=0.022) or substance (66.9% versus 61.4%, p=0.04) dependence. Patients in the MDE-A group more frequently reported recurrent alcohol- (2.8% versus 0.8%, p=0.002) and substance-related (2% versus 0.2%, p<0.001) legal problems compared to patients in the MDE-N group.

Functioning and severity of patients in the MDE-A group
The severity of depression (p=0.044), mania (p<0.001) and overall BD (p<0.001) were significantly higher in the MDE-A group compared with the MDE-N group. The GAF score was significantly lower in the MDE-A group than in the MDE-N group (p=0.015) (see **Table 1**).

Patients in the MDE-A group presented with more marked impairment in social/occupational functioning (49.6% versus 24%, p<0.001) than patients in the MDE-N group.

The presence of psychotic symptoms was more represented in the MDE-A group than in the MDE-N group (15.5% versus 7%, p<0.001).

Lifetime psychiatric history characteristics of patients in the MDE-A group

Age at first psychiatric symptoms (p<0.001) and age at first depressive episode (p<0.001) was significantly lower in patients in the MDE-A group (see **Table 1**).

The total number of mood episodes was significantly higher in patients in the MDE-A group (p=0.006).

The presence of previous suicide attempts (31.6% versus 20.8%, p<0.001) was more frequently reported in the MDE-A group.

Patients in the MDE-A group more frequently had a family member requiring treatment (32.1% versus 18.8%, p<0.001) or a first degree relative with BD (22.1% versus 14.2%, p<0.001) than those in the MDE-N group.

Current psychiatric treatment

Patients in the MDE-A group were more frequently without any psychiatric treatment than those in the MDE-N group (p=0.004) (see **Table 1**).

MDE-A patients were more frequently under treatment with antipsychotics (p=0.044), mood stabilizers (p<0.001) or electroconvulsive treatment (ECT) (p<0.001) than patients in the MDE-N group.

Patients in the MDE-A group were less frequently prescribed with antidepressants (ADs) than those in the MDE-N group (<0.001); however, in those

taking ADs, an AD-induced hypomania/mania during the current MDE was more frequently observed in the MDE-A group than in the MDE-N group (23.1% versus 15.9%, p<0.001).

Clinical variables associated with aggressiveness

After performing a stepwise backward multivariate modeling procedure ($\chi^2(8)$=300.695, p<0.001), the model explained between 10.6% (COX and Snell R Square) and 18.9 % (Nagelkerke R Square) of the variance and statistical significance persisted for: age at first depressive episode (p<0.001), negatively correlated with aggressiveness; severity of mania (p=0.031); diagnosis of BD (p=0.001); comorbidity with BPD (p<0.001) but not with substance abuse (p=0.633); absence of current psychiatric treatments (p<0.001); presence of psychotic symptoms (p=0.007); marked impairment in social/occupational functioning (p=0.002) that were positively correlated with aggressiveness. DSM.5-MXS was the variable most significantly associated with aggressiveness (p<0.001, OR=3.8) (see **Figure 1**).

In order to control for the possible bias of impulsivity-mediated components influencing the association between bipolarity and aggressive behaviors, we performed a second stepwise backward multivariate modeling procedure ($\chi^2(8)$=275.677, p<0.001), excluding the variable of BPD comorbidity. The model explained between 9.7% (COX and Snell R Square) and 17.4% (Nagelkerke R Square) of the variance. DSM-5-MXS still remained the highest significant association with aggressiveness (p<0.001, OR=3.9). Also, the association with BD diagnosis still remained significant (p=0.002, OR=1.6) whilst the presence of lifetime suicide attempts became significant at the logistic regression (p=0.013, OR=1.4) (see **Figure 2**).

Discussion

In this multinational sample of 2,811 patients with MDE, a prevalence of aggressive behaviors of 14.2% was found. The detected prevalence is slightly higher than that found in previous large epidemiological studies (30).

Almost one in four BD patients in our study presented physical or verbal aggressiveness during a MDE. This is in line with the results of previous findings supporting the quite frequent association between aggressiveness and BD (11,30–32).

In general, the presence of aggressiveness during a MDE was associated with a higher severity of manic and depressive episodes. This emerged from both psychometric and clinical assessment, and included higher rates of psychiatric comorbidities, more affective episodes, higher frequencies of lack of psychiatric treatment, greater impairment in global social/occupational functioning, more frequent psychotic symptoms and higher rates of previous suicide attempts. Similar findings were reported in previous studies (13,23,33), showing that the presence of aggressive behaviors had a significant impact on the clinical outcome of the BD illness, with major implications in terms of management and treatment strategies.

Several findings from the present study seem to support that the presence of aggressive behaviors in the MDE-A group was associated with bipolarity. First, significantly higher frequencies of BD diagnosis were found in depressed patients with aggressiveness, whilst a diagnosis of unipolar depression was negatively correlated with aggressive behaviors. This is consistent with previous reports of a higher association between aggressiveness and BD depression compared to unipolar depression (11). The MDE-A group showed higher rates of family history for BD as well as younger age at the first depressive episode, which represent the most relevant clinical indicators of

unrecognized bipolarity in depressed patients (27,34–36).

Interestingly, the presence of mixed features during the current MDE was significantly more common in MDE-A patients compared with depressed patients without aggressive behaviors. This is in line with current views on the spectrum of mixed states (37). Hence, several reports showed that the presence of mixed features during a MDE might be considered as a clinical indicator of bipolarity (38–40). The higher rates of mixed features in our depressed patients with aggressive behaviors seem to further support the inclusion of aggressiveness in the BD rubric and within the pool of mixed features during a MDE. This is in accord with the results of a previous study which found that the dimension "Feel angry", as assessed by the Multiple Visual Analog Scales of Bipolarity (MVAS-BP) was the second most frequent (49,5%) bipolar dimension among the mixed depressive patients (41).

As for psychiatric treatment, in the present sample, MDE-A patients had lower rates of AD use compared with patients without aggressiveness. Nevertheless, the MDE-A patients treated with ADs showed significantly higher rates of AD-induced mania/hypomania compared with patients without aggressiveness, which represents another strong indicator of bipolarity (20,21,27,34,35,37,42–45).

As expected, when considering comorbid psychiatric diagnoses, we found that MDE-A patients had higher rates of psychiatric comorbidity, indicating a more severe and difficult-to-treat condition. In particular, the comorbidity with BPD and substance abuse were significantly more reported in depressed patients with aggressiveness. Previous studies found that the presence of comorbid BPD could have an independent predictive value in determining trait aggressiveness in patients with BD (13). It has been supposed that the link between BD, BPD, substance abuse and aggressiveness involves the role of impulsivity (13,46), indicating that aggressive

behaviors could be more associated with impulsive-related comorbidities than with bipolar illness itself. Nonetheless, in order to control for the possible bias of impulsivity-mediated components influencing the association between bipolarity and aggressive behaviors, we excluded the variable of BPD comorbidity from the second stepwise multivariate modeling procedure (the variable substance abuse yet resulted to not be significantly correlated with aggressiveness in the first logistic regression). Interestingly, the significance persisted for all the variables considered in the first modeling, with DSM-5 mixed features becoming the most significant variable associated with aggressiveness.

Surprisingly, the presence of lifetime suicide attempts became significant at the logistic regression, when BPD comorbidity was excluded in the second model (see **Figure 2**). These results support our hypothesis that aggressiveness could be associated with bipolarity *per se*, independently from comorbid disorders such as BPD and substance abuse.

The role of aggressiveness in suicidal behaviors has been investigated in several studies. Oquendo and colleagues (47) found higher lifetime aggressiveness in BD patients with a history of suicide attempts compared with BD non-attempters. The same authors (48) reported that aggressive traits besides other clinical factors contribute to predict future suicidal behaviors both in depressed BD and MDD individuals. Moreover, impulsivity was found to be a reliable predictor of suicide risk in BD and MDD patients not as a single trait but only in association with aggressiveness (33,49,50). In this context, aggressiveness could be seen as a part of the construct associated with suicidal behaviors in depressed BD and MDD patients. Furthermore, in our study the presence of DSM-5 mixed features was the variable most significantly associated with aggressiveness. Previous studies found that the presence of DSM-5

mixed features at the index episode was probably the most important risk factor for suicidality (37,51) and partly contributed to the increased risk of suicide observed in BD-II compared to unipolar depression (52).

Regarding treatment considerations, recent guidelines recommend the need for the early detection of aggressive behaviors in mood disorders (53–55). In our sample, the MDE-A group presented higher rates of psychotic symptoms and more severe mania, together with higher rates of no current pharmacological treatment. Furthermore, the MDE-A group showed higher rates of AD-induced hypomania/mania. Several reports suggest that a prompt therapeutic strategy should be considered to prevent aggressiveness in those patients with higher risk factors, such as severe manic, psychotic symptoms and lifetime history of self-aggressive behaviors (56,57). Taken together, these results claim for the need of an "anti-aggressive" treatment strategy in this subgroup of BD patients. Moreover, AD monotherapy should be avoided and a combination treatment with mood stabilizers and/or antipsychotics should be considered (58).

The main strengths of the BRIDGE-II-Mix study include the large sample size, and the wide range of care settings, both hospital and community, from eight countries across three continents. Furthermore, narrow exclusion criteria increase the generalizability of the findings. The first limitation is the widely varying rates of hospitalized patients across countries, ranging from 1.0% to 57.8%, which reflect economically driven policies on the use of hospitalization-based treatment. A second limitation is that the participating centers were not randomly selected, which may 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. Indeed, in the present study aggressiveness in the MDE-A group was assessed retrospectively with high subjectivity of the original rating performed by trained psychiatrists (59). This means that the definition of aggressiveness relies just on retrospectively coded criteria and selected variables already collected in the dataset, rather than ad-hoc variables fetched using validated ratings. This may introduce a measurement bias, especially considering that the operational definition of aggressiveness adopted is a clinical one.

Moreover, there is a need for additional correlation analyses regarding the relationship between aggressiveness and mixed features, controlling for potential confounders to be included in future longitudinal prospective studies using external validators.

In conclusion, aggressiveness might not only be state-related but also a trait component of bipolarity and a diagnostic indicator of mixicity in patients with MDE. Moreover, the association of aggressiveness and the presence of mixed features in depressed patients could represent an indicator of increased risk for suicidal behaviors. Taken together, these results might have important implications in terms of the reconsideration of aggressiveness for diagnostic criteria for the mixed features specifier. Finally, the detection of aggressiveness in MDEs could help in establishing a therapeutic strategy aimed at reducing aggressiveness and preventing suicidal tendencies in the perspective of a personalized pharmacological treatment for this subtype of patients.

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