Predictors of Treatment Resistance Across Different Clinical Subtypes of Depression: Comparison of Unipolar vs. Bipolar Cases

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Objective: Treatment-resistant depression (TRD) and treatment-resistant bipolar depression (TRBD) poses a significant clinical and societal burden, relying on different operational definitions and treatment approaches. The detection of clinical predictors of resistance is elusive, soliciting clinical subtyping of the depressive episodes, which represents the goal of the present study.

Methods: A hundred and thirty-one depressed outpatients underwent psychopathological evaluation using major rating tools, including the Hamilton Rating Scale for Depression, which served for subsequent principal component analysis, followed-up by cluster analysis, with the ultimate goal to fetch different clinical subtypes of depression.

Results: The cluster analysis identified two clinically interpretable, yet distinctive, groups among 53 bipolar (resistant cases = 15, or 28.3%) and 78 unipolar (resistant cases = 20, or 25.6%) patients. Among the MDD patients, cluster “1” included the following components: “Psychic symptoms, depressed mood, suicide, guilty, insomnia” and “genitourinary, gastrointestinal, weight loss, insight”. Altogether, with broadly defined “mixed features,” this latter cluster correctly predicted treatment outcome in 80.8% cases of MDD. The same “broadly-defined” mixed features of depression (namely, the standard Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition—DSM-5—specifier plus increased energy, psychomotor activity, irritability) correctly classified 71.7% of BD cases, either as TRBD or not.

Limitations: Small sample size and high rate of comorbidity.

Conclusions: Although relying on different operational criteria and treatment history, TRD and TRBD seem to be consistently predicted by broadly defined mixed features among different clinical subtypes of depression, either unipolar or bipolar cases. If replicated by upcoming studies to encompass also biological and neuropsychological measures, the present study may aid in precision medicine and informed pharmacotherapy.

Keywords: treatment-resistance, depression, bipolar disorder, mixed states, mixed features
INTRODUCTION

Almost half of the patients suffering from a major depressive episode (MDE) fail to achieve a response, despite sequential combination or augmentation treatment strategies, irrespective of the operational definition adopted for treatment-resistant depression (TRD) (1, 2). The rates of treatment-resistant bipolar depression (TRBD) within the course of bipolar disorder (BD) can even exceed those documented for major depressive disorder (MDD) and present a differential pattern of response to different medications, indeed (3). Both TRD (4) and TRBD (5, 6) pose a significant clinical and societal burden, soliciting the assessment of putative predictors using clinical, neuropsychological, neuroimaging, and genetic measures (7, 8). However, the general failure to find sensitive and specific predictors of treatment response in MDD and BD, either current- of future-state markers (9), is in part, due to the heterogeneity of these conditions, which range from biologically determined to event-dependent conditions (10).

The initial hype about digital phenotyping has been tempered by increasing awareness of the significant technical and analytical difficulties hindering translational change (11, 12) most likely due to differential neurobiology underpinning MDD (13, 14) and BD (15–17). To date, no single biological marker stood-out in selecting the best initial antidepressant treatment for a given individual, despite promising evidence coming from recent pharmacogenomics studies (18). Clinical risk stratification models for TRD, incorporating baseline sociodemographic and clinical features (19), preceded algorithm-based approaches proposed for TRBD (20). For MDD, a cluster of variables including marital status, insomnia, psychosocial impact, trauma, education, energy, disorder recurrence, comorbidity, race, and severity of current MDE resulted in a positive predictive value of TRD =.61 and a negative predictive value =.69, consistently across males and females and primary- vs. specialty care settings (19). Over the past decade, findings from the Group for the Study of Resistant Depression (GSRD), a multinational European research consortium, pointed toward strong effects of clinical variables on treatment outcome of MDD (21), as well as specific genetic signature (22). This is particularly relevant considering that, when considered separately, the potential predictors of TRD usually showed odd ratios (ORs) around 1.5, and thus, were not applicable as univocal hints in the clinical setting (23, 24).

Nonetheless, four potent clinical predictors of TRD emerged in a validation study that showed a collective predictive accuracy of 87%. These latter include symptom severity, suicidal risk, comorbid anxiety disorder, and the lifetime number of MDE episodes (25–27). Overall, symptom severity, suicidal risk, higher number of lifetime of MDEs, and comorbid anxiety disorder were consistently replicated as the most prominent risk factors for different stages of TRD in large-sampled studies (28).

Machine learning approaches may, however, further increase the detection of TRD (29, 30), as reinforced by the 2019 report by the GSRD study group for TRD (22).

Concerning BD, clinical predictors of “full clinical recovery” include outpatient treatment and more extended periods of lifetime mania (31). In contrast, higher baseline severity scores, presence of MDEs in the previous year, poor social functioning predict failure to achieve remission or recovery in BD (32). Among other clinical hallmarks, earlier (hypo-) manic or mixed recurrence, including sub-threshold manic symptoms and the proportion of days spent with an elevated mood in the preceding year, predict TRBD (33). The conceptualization of TRBD is more articulated than one of TRD, due to the differential natural and pharmacological course of BD and the controversial role of the antidepressants in BD (2). While drug resistance or worsening in MDD has been associated with mixed features and other bipolarity hints (34), relatively little is known about the impact of mixed features in bipolar depression and subsequence failure to respond. However, side-by-side comparisons of unipolar vs. bipolar MDEs relying on a relatively limited-range of retrospective data, suggesting that TDR represents a distinct psychopathological condition and not necessarily a prodromal state of BD (35).

The aim of the present exploratory-hypothesis generating study is to assess multiple clinical predictors of treatment resistance comparing unipolar vs. bipolar patients across different clinical subtypes of current MDE. To the best of our knowledge, the present data-driven study is the first of its kind to a side-by-side comparison of a range of putative clinical predictors of treatment resistance across different clinical subtypes of depression, either unipolar or bipolar major depression.

METHODS

Participants

A hundred and thirty-one outpatients, both sexes, 18–65 years old, consecutively enrolled in a non-interventional study at a tertiary care unit of the Department of Psychiatry of the Federico II University of Naples, Italy, between May 3, 2017, and June 17, 2019. All patients met the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) (36) criteria for a current MDE, either in the course of MDD or BD. Six experienced psychiatrists (MF, AF, SN, AA, ABl, PM) made the clinical diagnoses. Eligible patients signed a valid written informed consent after the study procedures had fully explained by the appointed principal investigator (MF). The protocol of the study was approved by the local I.R.B. on May 2nd, 2017, according to the 1964 Declaration of Helsinki and its subsequent amendments (37). Exclusion criteria were the lack of valid informed consent, untreated thyroid disease, schizophrenia, severe brain syndrome, or other organic conditions, potentially hampering the validity of the consent.

Evaluation Procedure and Operational Definitions

The participating outpatients were rated according to the Hamilton Rating Scale for Depression, 17-item version scale (HAM-D-17) (38), Young Mania Rating Scale (YMRS) (39), and Temperament Evaluation of Memphis, Pisa, Paris, and San
Diego, 110-item version (TEMPS-110) (40). The following clinical variables were recorded: age, sex, duration of the untreated illness (DUI), family history for header MDD or BD, lifetime suicidal behavior, significant psychiatric and medical comorbidities, and essential current and lifetime psychiatric treatment. The DUI was defined as the “time interval between the first lifetime onset of symptoms of depression, not necessarily reaching the diagnostic threshold set by the DSM-5: at least five symptoms of depression, and the first adequate treatment” (41). TRD was defined as “failure of two or more consecutive trials with antidepressants” (2). TRBD was defined as a lack of response to treatment to at least two previously established treatments for bipolar depression (e.g., olanzapine/fluoxetine combination, brexiprazole, cariprazine, quetiapine, aripiprazole). TRBD could, however, have been exposed to at least one mood stabilizer drug plus an antidepressant as in case of the previous failure to “adequate” trials for acute bipolar depression, especially whenever such therapy had been started elsewhere before seeking our consultation or in the presence of significant comorbidities (e.g., anxiety or obsessive–compulsive disorders).

Finally, the mixed features of the current MDE reflected the DSM-5 specifier. Besides, the “overlapping” symptoms otherwise excluded by the DSM-5 for a DSM-5-defined MDE with mixed features, i.e., “irritability,” “distractibility,” “impulsivity,” “mood lability,” and “psychomotor agitation,” were nonetheless recorded given their clinical relevance (42).

Statistical Analysis
The statistical analysis was performed using IBM™ SPSS™ Statistics™ v.25.0.0 for Windows™ (43), adopting alpha.05, two-tailed. Non-parametric distributions were transformed as necessary. The interrater reliability for the analysis using Cohen’s k statistics was ascertained for consistency issues. Descriptive statistics followed by principal component analysis (PCA) and by two-step cluster analysis were carried-out for MDD and BD patients, separately. Patients recorded as TRD or TRBD were considered as “cases”; those without a history of treatment resistance were deemed as “controls.” Oblique rotation solution (Promax) was performed by calculating the coefficient for each pair of variables, and multi-collinearity was excluded; coefficient ≤.3 were suppressed. We assumed the conservative loadings >.3 to be significant. The Kaiser–Meyer–Olkin measure of sampling adequacy resulted in.65, indicating an acceptable sample size, with Bartlett’s test of sphericity scoring lower than.05. To determine the component number, we considered only eigenvalues > 1. For readers’ convenience, an eigenvalue of 1 would explain as much variance as the one explained by a single variable.

In plain, the PCA aimed to extract the psychopathological components captured by the HAM-D scale, while the cluster analysis carried aimed at discriminate the cases at study based on the PCA-fetched components. The generated clusters of depressions were compared against each other using descriptive statistics and binary logistic regression analysis.

RESULTS
Demographic and Clinical Variables Across Different Clinical Subtypes of Depression
A summary of the essential clinical and demographic features of the included sample has been reported in Table 1. Essential current and lifetime pharmacological history are presented in Table 2, while Table 3 provides the core rating tools and predominant affective temperament. Among other clinical variables, mixed, anxious, and psychotic features of current MDE were statistically more frequent among BD patients compared to the MDD counterpart.

Principal Component and Cluster Analysis Statistics
PCA was performed on the items of the HAM-D-17 to characterize the sample at the report better, discriminating between unipolar and bipolar cases of depression. Two-step cluster analysis of cases based on the three components generated by the PCA led to two clinically interpretable clusters, both in the MDD (Table 4) and the BD (Table 5) group. Notably, the fetched clusters comprised different component-items from the original HAM-D scale across the BD and the MDD groups, as detailed in Tables 4 and 5, also reporting the proportion of resistant cases across different clusters, respectively.

Prediction of Treatment Resistance Based on Clinical Subtyping of Depression and Mixed Features Across Unipolar and Bipolar Clusters
Overall, the clinical subtypes of depression fetched by cluster analysis failed to allow a conclusive distinction between resistant vs. non-resistant cases (please refer to Tables 4 and 5 for details).

The presence of DSM-5-defined mixed features among MDD and BD cases was inversely related to the resistance outcome. In contrast, the presence of the “overlapping” symptoms of depression among MDD and BD—excluded by the DSM-5 specifiers of mixed depression—such as “distractibility,” “impulsivity,” “increased psychomotor activity,” and “hypersexuality,” predicted higher rates of treatment resistance, consistently in the MDD and the BD groups. Such “permissive” criteria for mixed depression, already outlined by the 1978 Research Diagnostic Criteria (44), consistently predicted treatment resistance both in the MDD and the BD groups even in the presence of different operational definitions and pharmacological courses differed between TRD and TRBD cases. Please refer to Table 6 for details. Finally, in the MDD group, the DSM-5 mixed features and the broadly defined mixed features were endorsed by 1.5% and 6.1% of cluster 1 patients, and 0.8% and 6.1% of cluster 2 patients, respectively. In the BD group, group the DSM-5 mixed features and the broadly defined mixed features were disclosed by 7.6% and 12.2% of cluster 1 patients, and 0.8% and 1.5% of cluster two patients, respectively.
TABLE 1 | Essential clinical and demographics across unipolar and bipolar cases.

|                           | MDD (n = 78) | BD (n = 53, of whom BD-I = 24; BD-II = 29) | t or χ² (df) | p    |
|---------------------------|-------------|-------------------------------------------|-------------|------|
| **Essential demographics**|             |                                           |             |      |
| Age, (mean ± sd)          | 49.41 ± 13.90 | 50.30 ± 12.14                           | .379 (129)  | .705 |
| Sex F/M, n (%)            | 49 (37.4%)/29 (22.1) | 35 (26.7%)/18 (13.7)                   | .142 (1)    | .706 |
| Ethnicity (Caucasian, other), n (%) | 78 (59.5) | 53 (40.5)                           | –           | –    |
| Primary school, n (%)     | 14 (10.7) | 11 (8.4)                           | 4.948 (3)   | .176 |
| Secondary school, n (%)   | 29 (22.1) | 13 (9.9)                           | –           | –    |
| College, university, or higher education, n (%) | 6 (4.6) | 10 (7.6)                           | –           | –    |
| Unmarried, n (%)          | 14 (10.7) | 15 (11.5)                           | 13.462 (2)  | .001 |
| Married/cohabiting, n (%) | 61 (46.6) | 27 (20.6)                           | –           | –    |
| Widower/divorced, n (%)   | 3 (2.3) | 11 (8.4)                           | –           | –    |
| **Essential lifetime comorbidities and clinical features** |            |                                           |             |      |
| Lifetime substance use disorder, n (%) | 4 (3.1) | 6 (4.6)                         | 1.716 (1)   | .190 |
| Lifetime panic disorder, n (%) | 28 (21.4) | 17 (13)                         | .204 (1)    | .651 |
| Lifetime generalized anxiety disorder, n (%) | 58 (44.3) | 33 (25.2)                        | 2.176 (1)   | .140 |
| Lifetime anorexia nervosa, n (%) | 15 (11.5) | 6 (4.6)                         | 1.467 (1)   | .226 |
| Lifetime bulimia nervosa, n (%) | 5 (3.8%) | 4 (3.1)                        | .064 (1)    | .801 |
| Lifetime binge eating disorder, n (%) | 8 (6.1%) | 10 (7.6)                        | 1.974 (1)   | .160 |
| Lifetime obsessive-compulsive disorder, n (%) | 13 (9.9%) | 9 (6.9)                         | .002 (1)    | .962 |
| Lifetime specific phobia, n (%) | 17 (13%) | 7 (5.3)                         | 1.555 (1)   | .212 |
| Lifetime impulse control disorder, n (%) | 5 (3.8%) | 20 (15.3)                        | 20.054 (1)  | <.001 |
| Borderline personality disorder DSM-5, n (%) | 3 (2.3) | 5 (3.8)                         | 1.718 (1)   | .190 |
| History of previous psychiatric hospitalization, n (%) | 25 (19.1) | 29 (22.1)                        | 6.691 (1)   | .01  |
| Lifetime suicide behavior, n (%) | 28 (21.4) | 23 (17.6)                        | .746 (1)    | .388 |
| Duration of untreated illness, in years, (mean ± sd) | 3.14 (3.77) | 2.81 (5.61)                    | 2.412 (129) | .81  |
| Duration of current MDE, in weeks, (mean ± sd) | 24.96 (40.34) | 40.13 (84.06)                  | 1.301 (114) | .196 |
| Age at onset of depression (self-report), in years, (mean ± sd) | 34.09 (14.32) | 32.85 (14.49)                 | –.483 (129) | .630 |
| **Essential specifics** |            |                                           |             |      |
| DSM-5 MDE with melancholic features, n (%) | 11 (8.4) | 4 (3.1)                         | 1.337 (1)   | .247 |
| DSM-5 MDE with mixed features, n (%) | 3 (2.3) | 7 (5.3)                         | 3.922 (1)   | .048 |
| DSM-5 MDE with anxious distress, n (%) | 33 (25.2) | 13 (9.9)                        | 4.378 (1)   | .036 |
| DSM-5 lifetime MDE with psychotic features, n (%) | 3 (2.3) | 9 (6.9)                         | 6.543 (1)   | .001 |
| DSM-5 MDE with atypical features, n (%) | 17 (13) | 11 (8.4)                        | .020 (1)    | .887 |
| DSM-5 MDE with catatonic features, n (%) | 0 | 0 | – | – |
| Rapid cycling, course of depression, n (%) | 1 (0.8) | 5 (3.8)                        | 4.798 (1)   | .028 |
| DSM-5 MDE with post-partum onset, n (%) | 13 (14) | 11 (8.4)                        | .331 (1)    | .565 |

MDD, major depressive disorder; BD, bipolar disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MDE, major depressive episode.

Note: Statistically significant difference in bold or p ≤ .05.

**DISCUSSION**

Consistent with our hypothesis, the propensity toward TRD may vary across different clinical subtypes of depression. Cluster 1 membership among MDD cases, including the core depressive symptoms, psychomotor retardation, suicidal behavior (ideation or attempt), and somatic-anxiety (namely, gastrointestinal, indigestion, cardiovascular, palpitations, headaches, respiratory, and genitourinary symptoms), predicted TRD in half of such cases (14.1% of 28.2% of cluster 1 MDD patients). This is in line with previous evidence which, even those of mild to moderate intensity (27)—anxiety (25), and severity of the current MDE in the prediction of the treatment outcome (26, 28), as well as the impact of psychotic features of depression in the prediction of subsequent TRD (45). This is also in line with previous evidence involving patients diagnosed using the codes provided by the Fourth Edition of the Manual (DSM-IV) (46), yet failing to adopt a data-generated clustering of psychopathology (47). However, it must be noticed that the clustering had a poor predictive value overall in the MDD group and no significant predictive value for TRBD cases. Similarly, the affective temperaments measured by means of the TEMPS had no discriminative value for treatment resistance, neither in the MDD, neither in the BD subgroups, in line with previous reports comparing unipolar and bipolar cases (48).

On the other side, the present study highlights the impact of mixed features of depression, broadly defined to encompass also the not overlapping symptoms otherwise excluded by the DSM-5. Mixed features of depression were somewhat similar in terms of frequency among different data-generated subtypes of depression, in the MDD and the BD groups. Overall, mixed features consistently predicted treatment resistance among BD and MDD cases across different clinical subtypes of depression, especially when these latter included “excitement” symptoms among MDD patients. Indeed, mixed features of depression have been suggested to represent hallmarks of bipolarity among DSM-
TABLE 2 | Essential pharmacological treatment history across the included cases.

|                        | BD (any), n = 53 | MDD, n = 78 |
|------------------------|-----------------|-------------|
| Current MDE           |                 |             |
| TRBD or not            |                 |             |
| Not resistant = 38     |                 | 37 (83.79)  |
| TR(B)De = 15           |                 | 18 (90)     |
| TRD or not             |                 |             |
| Not resistant = 58     |                 |             |
| TRD = 20               |                 |             |

Data expressed as “n (%)

| Pharmacological Treatment | BD-53 | MDD-78 |
|---------------------------|-------|--------|
| Antidepressant(s)         | 31 (81.59) | 13 (86.67) |
| SGA(s)                    | 21 (55.26)  | 6 (40) |
| Lithium                   | 13 (34.21)  | 11 (73.33) |
| FGA(s)                    | 6 (15.79)   | 4 (26.67) |
| Mood Stabilizer(s)        | 22 (57.89)  | 8 (53.33) |
| Aripiprazole              | 3 (7.89)    | 4 (26.67) |
| Asenapine                 | 4 (10.53)   | 0 |
| Brexpiprazole             | 0           | 0 |
| Cariprazine               | 0           | 0 |
| Clozapine                 | 13 (34.21)  | 11 (73.33) |
| MoA(s)                    | 22 (57.89)  | 8 (53.33) |
| MAOI(s)                   | 0           | 0 |
| Carbamazepine             | 9 (23.68)   | 2 (13.33) |
| SGA                       | 26 (68.42)  | 12 (80) |
| TCA                       | 17 (44.74)  | 8 (53.33) |
| Valproate                 | 25 (65.79)  | 10 (66.67) |
| Mood Stabilizer(s)        | 11 (28.95)  | 9 (60) |
| Polypolypharmacy(>4 drugs)| 23 (60.53)  | 7 (46.67) |

MDE, major depressive episode; MDD, major depressive disorder; BD, bipolar disorder; SGA, second-generation antipsychotic; FGA, first-generation antipsychotic; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor; TRD, treatment-resistant depression; TRBD, treatment-resistant bipolar depression.

TRD = treatment resistant depression was defined as failure to respond to at least two adequate trials with antidepressant drugs. TRBD = treatment resistant bipolar depression was defined as lack of response to treatment to at least two previous established treatments for bipolar depression (e.g. olanzapine/fluoxetine combination, brexpiprazole, cariprazine, quetiapine, aripiprazole). Most of the bipolar depressed patients were currently in receipt of at least one mood stabilizer drug plus an antidepressant due to the high frequency of comorbid conditions, though the antidepressant would not represent the established treatment for bipolar depression.

TABLE 3 | Rating and temperamental profile of MDD and BD patients.

| Study subjects (n = 131) | MDD (n = 78) | BD (n = 53, of whom BD-I = 24; BD-II = 29) | t or χ² (df) | p |
|--------------------------|-------------|---------------------------------------------|--------------|---|
| Essential ratings        |             |                                             |              |   |
| HAM-D-17 total score     | 19.63 ± 6.19 | 19.55 ± 5.33                               | −0.078 (129) | .334 |
| YMRS item 2, "increased psychomotor activity" | 3 (3.96) | 42 (79.25) | 10.935(3) | .012 |
| YMRS item 3, "hypersexuality" | 1 (1.28) | 7 (13.21) | 7.827 (1) | .005 |
| YMRS item 4, "irritable mood" | 29 (31.18) | 30 (66.66) | 8.082 (3) | .044 |
| YMRS item 7, "distractibility" | 10 (12.82) | 14 (26.42) | 11.020 (2) | .004 |
| TEMPS-A-110 domains for affective temperaments |             |                                             |              |   |
| Depressive temperament domain score, range 1–21 (mean ± sd) | 10.14 ± 4.04 | 10.58 ± 3.78 | .568 (102) | .571 |
| Cyclothymic temperament score, range 1–21 (mean ± sd) | 6.64 ± 4.41 | 8.91 ± 4.44 | 2.590 (102) | .111 |
| Hyperthymic temperament, score 1–21 (mean ± sd) | 3.69 ± 3.21 | 5 ± 4.83 | 1.653 (102) | .101 |
| Irritable temperament score, range 1–21 (mean ± sd) | 4.08 ± 3.29 | 6.47 ± 4.37 | 3.170 (102) | .002 |
| Anxious temperament score, range 1–21 (mean ± sd) | 12.22 ± 6.2 | 12.22 ± 5.16 | .002 (102) | .999 |

Statistically significant difference in bold or p < .05.

MDD, major depressive disorder; BD, bipolar disorder; HAM-D, Hamilton Depression Scale; YMRS, Young Mania Rating Scale; TEMPS, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-auto-questionnaire 110-item version.

Selected items of the YMRS emphasized herein as they represent the “overlapping” mixed features not accounted by the DSM-5 for the diagnosis of the “with mixed features” specifier of MDE.
TABLE 4 | Clusters and their characterization generated by two-step cluster analysis based on the three components obtained upon principal component analysis (PCA) on MDD patients.

| Components generated by the PCA | Loading HAM-D-17 Items | Interpretation of clusters | Patients, n (%) |
|---------------------------------|------------------------|---------------------------|-----------------|
| Cluster 1                       | 1, 2, 3, 4, 5, 6, 7, 8, 10, 15 | 22 (28.2) of whom 11 | 22 (28.2) of whom 11 |
| Cluster 2                       | 12, 14, 16, 17 | 14.1% TRD | 14.1% TRD |
| Cluster 3                       | 9, 11, 13 | Somatic anxiety and agitation | 56 (71.8) of whom 9 |

TABLE 5 | Clusters and their characterization generated by two-step cluster analysis based on the three components obtained upon Principal Component Analysis (PCA) on BD patient.

| Components generated by the PCA | Loading HAM-D-17 Items | Interpretation of clusters | Patients, n (%) |
|---------------------------------|------------------------|---------------------------|-----------------|
| Cluster 1                       | 1, 2, 3, 4, 5, 6, 7, 8, 10, 14 | 16 (30.2), of whom 5 | 16 (30.2), of whom 5 |
| Cluster 2                       | 11, 13, 15 | Hypochondria, somatic anxiety and fatigue, headache | 37 (69.8), of whom 10 |
| Cluster 3                       | 9, 12, 16, 17 | Agitation, gastro-intestinal, weight loss, insight | 37 (69.8), of whom 10 |

defined cases of BD, which may, on turn, be prone to treatment failure with standard MDD medications (49). In particular, MDD patients may require strategies other than the two “adequate” trials with antidepressants before receiving a diagnosis of treatment resistance in the presence of mixed features, especially when these latter encompass the “excitement” overlapping symptoms. In the MDD group, patients without broadly-defined mixed features, or DSM-5 defined mixed features of depression neither, may be more likely to respond to standard antidepressant care, thus endorsing lower rates of TRD. Stating the categorical nature of the operational definitions adopted by the present study for TRD or TRBD, it cannot be excluded, however, that the propensity for treatment resistance may span across a linear gradient ranging from almost neutral risk (OR = .916; C.I. = .148–5.658 in BD patients with narrowly-defined mixed features of depression) toward a 7-fold increased odd (OR = 7.130; C.I. = 1.485–34.247) in the BD group endorsing broadly-defined mixed features. Moreover, since the DSM-5-defined mixed features had negligible predictive value for treatment resistance, the use of the sole boundary-defined mixed features proposed by the DSM-5 itself may lead to improper pharmacological management of depression (50).

The categories proposed the DSM consist of “ideal types,” abstractions from reality, which we can use to assess empirical observations but which are not themselves, empirical facts. This latter concept, which is central to Jaspers’ thinking in his textbook “General Psychopathology” (51), was derived from the work of Max Weber (52). While the ideal types may aid in discriminating depression from, say mania, the most common clinical presentations are an admixture of both conditions (53). From this perspective, we remark the relevance of the present study, although its preliminary nature solicits for additional research on the matter. However, more sensible operational definitions for TRD, especially in BD, are warranted (Fornaro M. et al., submitted for publication).

There several limitations of the present study, which was conducted in a tertiary care outpatient setting that needs to be accounted for in the interpretation of the results. The sample size is a relatively small one, with no longitudinal follow-up or systematic stratification of pharmacological history across different classes of antidepressants, titration modality. No stratification according to the predominant mood polarity or polarity index of BD was reported. Recall bias may have hampered the validity of some diagnoses, including general medical comorbidities (which may have nonetheless affected the propensity of treatment response). Specifically, those BD patients who were also in receipt of antidepressant(s) drugs beyond the mood stabilizer(s) need to be further stratified by

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upcoming studies in order to better account for several comorbidities (e.g., obsessive–compulsive disorder) that may have led to pseudo-resistance in some cases. However, per study-protocol, even those BD patients who were currently in receipt of antidepressant(s) at the time of the assessment had already failed at least two adequate courses with established treatments for acute bipolar depression (e.g., the atypical antipsychotic quetiapine, or the olanzapine/fluoxetine combination). Besides, there was no virtually no record of the psychosocial or neuro-modulatory interventions, any correlation measures with neither neuroimaging, molecular nor genetic marker. Yet, neuro-modulatory interventions such as electroconvulsive therapy represent consolidated treatment avenues for TRD (54). Besides, the psychopathological clustering of depression based entirely on the sole HAM-D, which may not be sufficient to catch the complexity of depression exhaustively.

However, stating the data-generating hypothesis of the present preliminary report, we further reinforce the need for upcoming studies to replicate the present results across different clinical subtypes of depression and a large number of putative biological and neuropsychological measures.

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DATA AVAILABILITY STATEMENT
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT
The studies involving human participants were reviewed and approved by Federico II University of Naples. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS
MF and AF conceived the study and extensively edited the main-text and its attachments together with SN, ABl, AA, PM, FI, and ABA. Finally, all the co-authors contributed substantially to the present piece of work.
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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