ORIGINAL ARTICLE

Distractibility, anxiety, irritability, and agitation symptoms are associated with the severity of depressive and manic symptoms in mixed depression

Diego Freitas **Tavares**,[1,2] iD Paulo **Suen**,[1] iD Doris Hupfeld **Moreno**,[2] iD Eduard **Vieta**,[3] iD
Ricardo Alberto **Moreno**,[2] iD André R. **Brunoni**[1,4] iD

[1]*Serviço Interdisciplinar de Neuromodulação, Departamento de Psiquiatria, Instituto de Psiquiatria, Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil.* [2]*Programa de Transtornos Afetivos, Departamento de Psiquiatria, Instituto de Psiquiatria, Faculdade de Medicina, USP, São Paulo, SP, Brazil.* [3]*Hospital Clínic, Instituto de Neurociencias, Universidad de Barcelona, L'Institut d'Investigacions Biomèdiques August Pi i Sunyer, Investigación Biomédica en Red en el Área de Salud Mental, Barcelona, Catalonia, Spain.* [4]*Laboratório de Neurociências, Departamento de Psiquiatria, Instituto de Psiquiatria, Faculdade de Medicina, USP, São Paulo, SP, Brazil.*

Objective: To explore whether there is an association between distractibility, anxiety, irritability, and agitation (DAIA) symptoms and the severity of depressive and manic symptoms.
Methods: Patients with unipolar and bipolar disorder (I and II) and mixed depression were evaluated. DAIA symptoms were assessed using previously described definitions.
Results: The full analysis set comprised 100 patients. The severity of depressive symptoms in mixed depression, assessed by Montgomery-Åsberg Depression Rating Scale (MADRS), was significantly associated with the presence of two or more DAIA symptoms in the bipolar sample, influenced mainly by anxiety. The severity of manic symptoms in mixed depression, assessed by Young Mania Rating Scale (YMRS), was significantly associated with the presence of two or more DAIA symptoms in the bipolar sample and three or four DAIA symptoms in the unipolar sample.
Conclusion: DAIA symptoms were associated with greater severity of manic symptoms in mixed depression. DAIA symptoms must be evaluated in all patients with mixed features and are associated with the severity of depressive and manic symptoms in mixed depression.
Clinical trial registration: ClinicalTrials.gov (NCT04123301).

Keywords: Mixed depression; mixed state; mixed affective state; bipolar disorder; major depressive disorder

Introduction

Bipolar disorder (BD) is a severe psychiatric disorder characterized by alternating periods of depressive and manic episodes. Patients with BD can also experience "mixed states," in which manic and depressive symptoms occur simultaneously in different combinations and intensities.[1] In the DSM-IV, the concept of "mixed states" comprised the simultaneous occurrence of full manic and full depressive episodes, which, in practice, corresponds to mixed mania, since manic symptoms take precedence over depressive ones. Such a presentation could only be possible in BD type I (BD I).[2]

Recently, the DSM-5 reconceptualized "mixed states," allowing their occurrence in any major episode (mania, hypomania, or depression) in BD I or type II (BD II), as well as in major depressive disorder (MDD).[3] Patients

with mixed depression have a worse clinical course, since they tend to experience more episodes and episodes of longer duration.[4] Moreover, mixed depression has been associated with greater depression severity,[5] rapid cycling,[6] higher comorbidities with anxiety,[7] impulsivity, and substance abuse,[8] worse sleep outcomes,[9] higher relapse rates,[10] refractoriness,[11] and higher suicide risk.[8,12] Previous studies have also found that patients with unipolar mixed depression were similar to patients with bipolar mixed depression regarding early onset, high recurrence, positive family history of BD, and refractoriness to treatment.[13]

Although the mixed specifier was an advancement over the DSM-IV, the exclusion of distractibility, anxiety, irritability and agitation (DAIA) symptoms from the DSM-5 "with mixed features" specifier has recently been challenged by new studies, which have shown that these

symptoms may not only be potentially useful for assessing mixed states, but may also be part of the pathophysiology of these mixed states.[5,7,14-17] For instance, anxiety within mixed states occurs in manic, hypomanic, and depressive episodes and correlates with depressive symptom severity in manic episodes and with manic symptom severity in depressive episodes.[17]

On the one hand, the exclusion of DAIA symptoms captures non-overlapping symptoms from opposite poles and overcomes early definitions in the DSM-IV without the risk of overdiagnosing mixed presentations.[18] On the other hand, although DAIA symptoms are nonspecific, their exclusion from DSM-5 mixed states criteria decreases sensitivity to their identification.[19]

Considering these issues, we explored whether there is an association between DAIA symptoms and the severity of depressive and manic symptoms. Our findings can contribute to a better understanding of the clinical relevance and role of DAIA symptoms in current conceptualizations of mixed states in mood disorders.

Methods

We performed a secondary analysis of baseline data from a 6-week, randomized, double-blind, sham-controlled clinical trial (ClinicalTrials.gov identifier NCT04123301) of theta-burst stimulation in bipolar and unipolar patients in a major depressive episode with mixed features, the results of which have been reported elsewhere.[20]

Study design and patients

The primary study design has been described previously.[21] In brief, the study enrolled patients aged 18 to 65 years old who were diagnosed with BD I, BD II, or MDD and were in a major depressive episode with mixed features according to DSM-5 criteria that included DAIA symptoms. The standard DSM-5 major depressive episode with mixed features specifier was used to determine the presence of a major depressive episode with at least three manic symptoms, regardless of DAIA symptoms, considering that such symptoms are common to both (hypo)manic and depressive episodes.[3] We enrolled patients who were having a moderate or severe acute major depressive episode (i.e., Montgomery-Åsberg Depression Rating Scale [MADRS] score > 20 at baseline)[22] with mixed features (i.e., Young Mania Rating Scale [YMRS] score $\geqslant$ 1 on three or more items in the entire scale).[23,24]

The patients had to be using an appropriate first- or second-line pharmacological treatment for an acute MDD or BD depressive episode according to the Canadian Network for Mood and Anxiety Treatments guidelines.[25,26] Patients with the following characteristics were excluded: a primary diagnosis other than BD or MDD, psychotic depression, acute suicidal ideation, and suspected/confirmed pregnancy or breastfeeding. Personality, anxiety, and substance use disorders were allowed as comorbidities as long as the primary diagnosis was BD or MDD.

Assessments

Outcomes in the primary study were assessed using psychiatric rating scales, including the MADRS, YMRS, and Hamilton Anxiety Scale.[27] DAIA symptoms were assessed using the following definitions[17]: (i) Distractibility was defined as a score $\geqslant$ 2 on YMRS item 7 (distractible, loses goal of thought; changes topics frequently; racing thoughts); (ii) Anxiety was defined as a score $\geqslant$ 18 on the Hamilton Anxiety Scale; (iii) Irritability was defined as a score $\geqslant$ 4 on the YMRS item 5 (irritable at times during interview, recent episodes of anger or annoyance on ward); (iv) Agitation was defined as a score $\geqslant$ 3 on the YMRS item 2 (excessive energy, hyperactive at times, restless [can be calmed]).

Statistical analyses

Analyses were conducted using R version 4.1.1. Statistical significance was set as an alpha threshold < 0.05. The patients were grouped according to diagnosis, and the groups were compared using χ^2-tests.

To explore the relationship between the severity of depressive and manic symptoms and the presence of DAIA symptoms, we used general linear models with symptom scores measured by MADRS and YMRS as dependent variables. Independent variables included DAIA symptoms, depression type (BD I, BD II, or unipolar), and interaction between the number of DAIA symptoms and depression type, controlled by sex, age, and treatment type (first- or second-line treatment for the specific diagnosis).

Results

The sample was 50% MDD patients, 31% BD II patients, and 19% BD I patients. The patients were homogeneous at baseline in terms of demographic features, diagnosis, clinical course, scale scores, pharmacological treatment, and previous electroconvulsive treatment. The frequency of patients without DAIA symptoms at baseline did not vary across diagnoses (p = 0.247), nor did the frequency of each DAIA symptom at baseline: agitation (p = 0.655), irritability (p = 0.310), distractibility (p = 0.315), and anxiety (p = 0.125) (Table 1). Personality, anxiety, and substance use disorders were allowed as comorbidities and the overall prevalence of anxiety disorders, personality disorders, and substance use disorders was 61.1, 7.7, and 5.5%, respectively.

Severity of depressive symptoms in mixed depression according to baseline DAIA symptoms

The severity of depressive symptoms in mixed depression (assessed by MADRS score) was not significantly associated with DAIA symptoms in the total sample (categorical analysis, groups of 36, 39, and 25 patients with BD I, BD II and MDD, respectively) (Figure 1A). The association between MADRS scores and the number of DAIA symptoms was statistically significant only in the bipolar

Table 1 Baseline clinical and demographic characteristics and frequency of DAIA symptoms

	Baseline (n=100)			p-value
Demographic characteristics				
Age, mean (SD)	39.4 (10.4)			0.196
Sex, female	64 (64.0)			0.768
Race, Caucasian	59 (59.0)			0.848
Marital status, married	69 (69.0)			0.727
Number of children, mean (SD)	0.6 (0.9)			0.529
Years of education, mean (SD)	14.8 (4.0)			0.231
Employment status, unemployed	51 (51.0)			0.898
Diagnosis and clinical course				
BD I	17 (17.0)			0.815
BD II	30 (30.0)			0.262
MDD	43 (43.0)			0.146
Recurrent depression	78 (78.0)			0.127
Melancholic depression	86 (86.0)			0.120
Atypical depression	3 (3.0)			0.245
Previous psychotic depression	9 (9.0)			1.000
Previous hospitalization due to depression	19 (19.0)			0.108
Baseline scales scores, mean (SD)				
MADRS	34.9 (6.0)			0.491
YMRS	9.9 (3.1)			0.561
CGI-S	4.5 (0.7)			0.939
GAF	34.4 (10.1)			0.840
HAM-A	21.2 (7.2)			0.449
WHOQOL-Bref	66.8 (12.0)			0.430
BIS	68.3 (9.4)			0.955
Pharmacological treatment				
BD I				
First line treatment[†]	14 (14.0)			0.984
Second line treatment[‡]	4 (4.0)			0.620
BD II				
First line treatment[§]	1 (1.0)			0.467
Second line treatment[‖]	28 (28.0)			0.104
MDD				
First line treatment[¶]	43 (43.0)			0.146
Second line treatment[††]	4 (4.0)			0.044
Previous neuromodulation treatment				
Electroconvulsive therapy	6 (6.0)			0.681

DAIA symptoms	MDD	BD II	BD I	
None	3 (6.9)	5 (16.7)	1 (5.8)	0.247
Agitation	15 (34.8)	7 (23.3)	4 (23.5)	0.655
Irritability	4 (9.3)	6 (20.0)	3 (17.6)	0.310
Distractibility	40 (93.0)	21 (70.0)	16 (94.1)	0.315
Anxiety	36 (83.7)	16 (53.3)	14 (82.3)	0.125

Data presented as n (%), unless otherwise specified.
p-values represent the significance of chi-square or Fisher exact tests for categorical and t tests for continuous variables.
BD = bipolar disorder; BIS = Barratt Impulsivity Scale; CGI-S = Clinical Global Impression – Severity of Illness; DAIA = distractibility, anxiety, irritability, and agitation; GAF = Global Assessment of Functioning; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; WHOQOL-Bref = World Health Organization Quality of Life Instrument-Abbreviated version; YMRS = Young Mania Rating Scale.
[†] Lithium OR quetiapine OR lamotrigine OR lurasidone OR lithium/divalproex + lamotrigine OR lithium/divalproex + lurasidone.
[‡] Olanzapine + fluoxetine OR divalproex OR lithium/divalproex + selective serotonin reuptake inhibitor (SSRI) OR lithium/divalproex + bupropion.
[§] Quetiapine.
[‖] Lithium OR lamotrigine OR bupropion OR sertraline OR venlafaxine.
[¶] Agomelatine OR bupropion OR citalopram OR desvenlafaxine OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR mirtazapine OR paroxetine OR sertraline OR venlafaxine OR vortioxetine.
[††] Tricyclic antidepressant OR trazodone OR quetiapine.

sample (two symptoms: β = 3.26, 95%CI 0.24-6.29, p = 0.04; three or four symptoms: β = 4.85, 95%CI 1.46-8.24, p = 0.007) (Figure 1B). In the bipolar sample, anxiety (β = 5.28, 95%CI 2.72-7.86, p < 0.001) was associated with greater severity of depressive symptoms in mixed depression according to MADRS score and was adjusted according to age, sex, diagnosis, and treatment, whereas irritability, distractibility, and agitation were not (Figure 2).
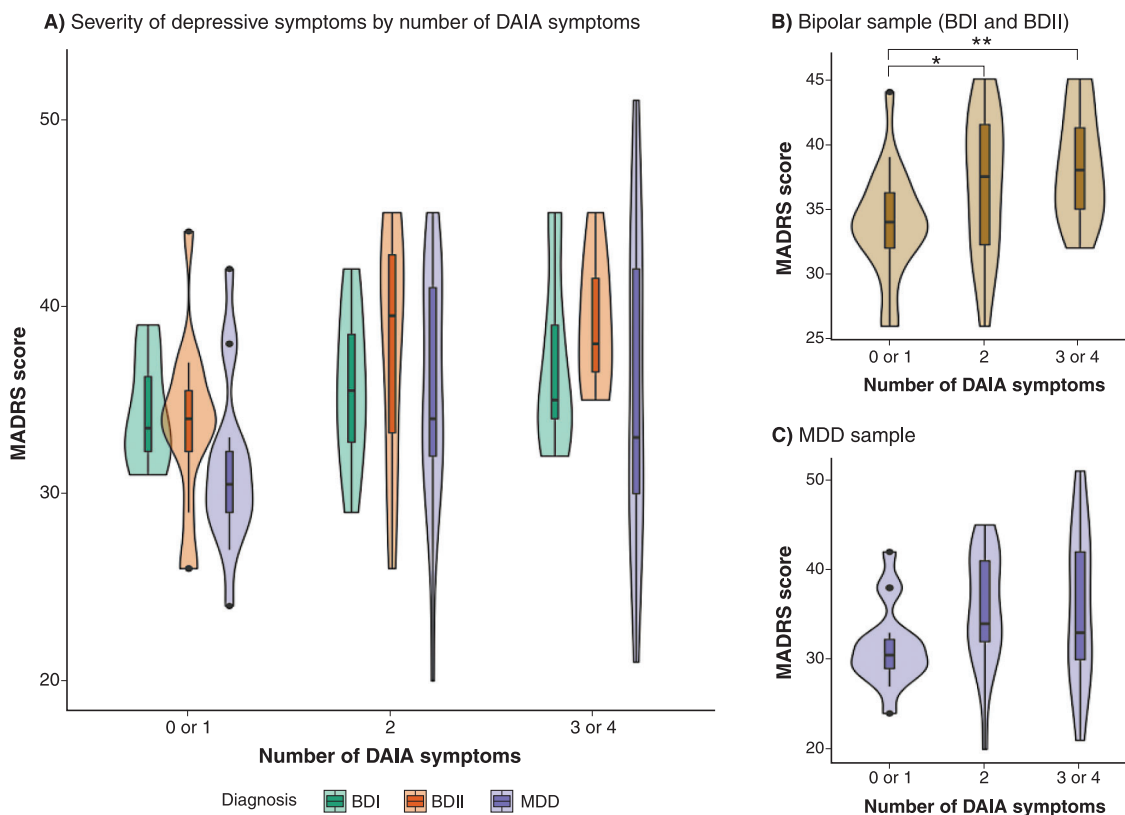
Figure 1 The severity of depressive symptoms in mixed depression according to number of distractibility, anxiety, irritability and agitation (DAIA) symptoms (categorical analysis). Severity of depressive symptoms in mixed depression (Montgomery-Åsberg Depression Rating Scale [MADRS] scores), y axis. Number of DAIA symptoms, x axis. A) Entire sample: bipolar disorder (BD) I, BD II, and major depressive disorder (MDD). B) Bipolar sample: BD I + BD II. C) MDD sample: MDD. * p < 0.05, ** p < 0.01.

Severity of manic symptoms in mixed depression according to baseline DAIA symptoms

The severity of manic symptoms in mixed depression, assessed by YMRS scores, was significantly associated with the presence of three or four DAIA symptoms (categorical analysis, groups with 36, 39, and 25 subjects each), stratified by diagnosis and adjusted according to age, sex, and treatment (presenting three or four DAIA symptoms: β = 3.57, 95%CI 0.45-6.70, p = 0.027) (Figure 3A). In additional analyses of the bipolar sample (type I or II), two or more DAIA symptoms were associated with more severe manic scores in mixed depression as assessed by the YMRS (two symptoms: β = 3.75, 95%CI 1.87-5.63, p < 0.001; three or four symptoms: β = 4.07, 95%CI 1.97-6.18, p < 0.001), whereas in the unipolar sample three or more DAIA symptoms were associated with more severe manic scores in mixed depression (three or four symptoms: β = 3.96, 95%CI 2.12-5.80, p < 0.001) (Figure 3B and C). In addition, the presence of anxiety (β = 3.12, 95%CI 1.95-4.29, p < 0.001), distractibility (β = 1.45, 95%CI 0.02-2.88, p = 0.049), agitation (β = 1.79, 95%CI 0.44-3.13, p = 0.01), or irritability (β = 2.41, 95%CI 0.65-4.16, p < 0.01) was associated with greater severity of manic symptoms in mixed depression as assessed by YMRS

scores and adjusted according to age, sex, diagnosis, and treatment (Figure 4).

Discussion

In this post-hoc analysis of baseline data from a randomized clinical trial, we observed that the severity of depressive symptoms in mixed depression was significantly associated with the presence of two or more DAIA symptoms in the BD sample, but not in the MDD sample. In the bipolar sample, anxiety symptoms were associated with greater severity of depressive symptoms in mixed depression. The severity of manic symptoms in mixed depression in the total sample was not significantly associated with the presence of two symptoms, but was significantly associated with three or four DAIA symptoms. In the bipolar sample, two or more DAIA symptoms were associated with more severe manic scores in mixed depression, whereas in the unipolar sample three or more DAIA symptoms were associated with more severe manic scores in mixed depression. The presence of all four DAIA symptoms was associated with greater severity of manic symptoms in mixed depression.

Our findings indicate that the presence of two or more DAIA symptoms are related to the severity of depressive
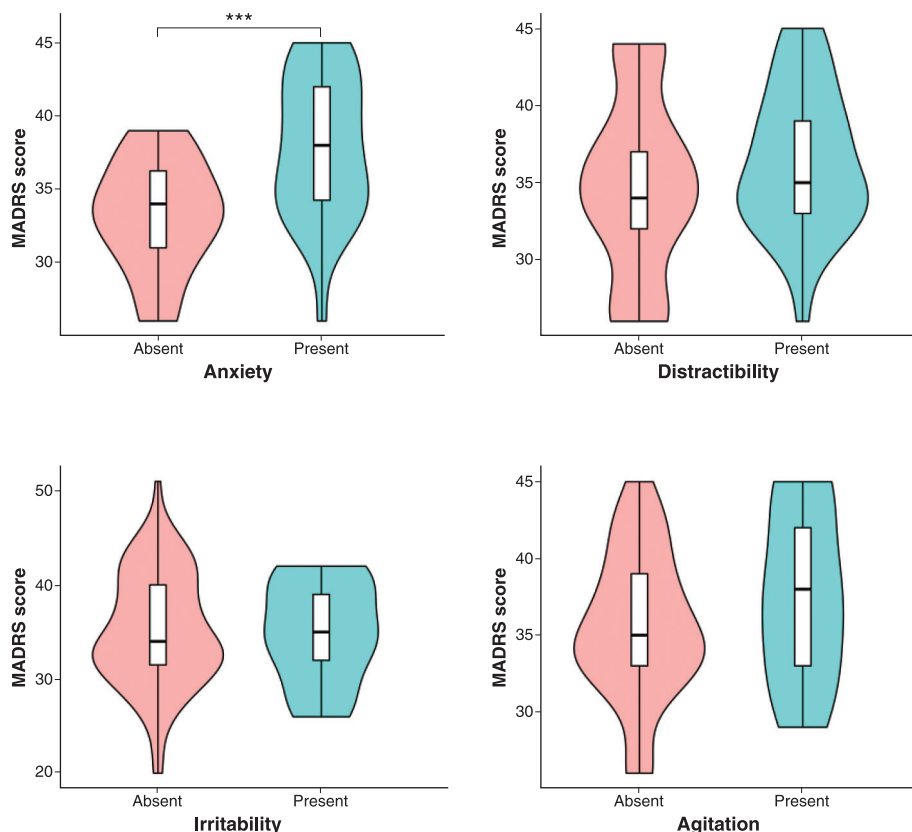
Figure 2 Severity of depressive symptoms in mixed depression according to specific distractibility, anxiety, irritability and agitation symptoms (for bipolar sample). Severity of depressive symptoms in mixed depression (Montgomery-Åsberg Depression Rating Scale [MADRS] scores), y axis. Specific distractibility, anxiety, irritability and agitation symptoms (absent or present), x axis. ***p < 0.001.

symptoms as assessed by the MADRS in mixed bipolar depression, but not in mixed unipolar depression. In other words, patients with mixed bipolar depression and two or more DAIA symptoms experience more intense depression than those with zero or one symptom. Analysis of each specific DAIA symptom showed that our findings were influenced by anxiety, rather than distractibility, agitation, or irritability.

This secondary analysis also demonstrated that DAIA symptoms are related to the severity of manic symptoms as assessed by the YMRS in mixed bipolar depression (two or more DAIA symptoms) and in mixed unipolar depression (three or more DAIA symptoms). These findings suggest that while fewer DAIA symptoms contribute to greater agitation in mixed bipolar depression, more DAIA symptoms are required for more intense manic symptoms (i.e., greater agitation) in mixed unipolar depression. In analysis of each specific DAIA symptom, distractibility, agitation, irritability, and anxiety were all associated with more severe manic symptoms in mixed depression, i.e., they correlate with "agitation" in mixed depression.

These results are in line with other findings that DAIA symptoms are associated with greater severity in patients with depression with mixed features than in those without mixed features. This is also the first study to have

analyzed the impact of DAIA symptoms on the depressive and manic symptomatology of mixed depression separately.[28-30] Furthermore, our findings suggest that despite their high rate among mixed samples, DAIA symptoms seem to be more closely related to severity than to mixed state diagnosis itself, since they occur in both mixed depression and mixed (hypo)mania. Although studies have defined the presence of DAIA symptoms using distinct criteria, there is broad agreement in the literature that they are common among patients with mixed depression and that they should be considered when diagnosing mixed depression, both because they are among the cardinal symptoms of mixed depression and because they are related to symptom severity, a finding that our study reinforced.[5,6,31]

Concurrent manic symptoms during depression ranged from 4-60% in BD and from 0-34% in MDD, depending on the criteria used by each study and the low sensitivity of the "with mixed features" specifier used in the DSM-5.[6,31-33] The appearance of manic symptoms during depressive episodes intensifies depressive symptoms and worsens clinical and treatment outcomes.[7] A recent network analysis of an observational study showed that agitation and irritability are core symptoms of mixed states.[33] In our study, we classified the intensity of mixed depression according to the severity of depressive and
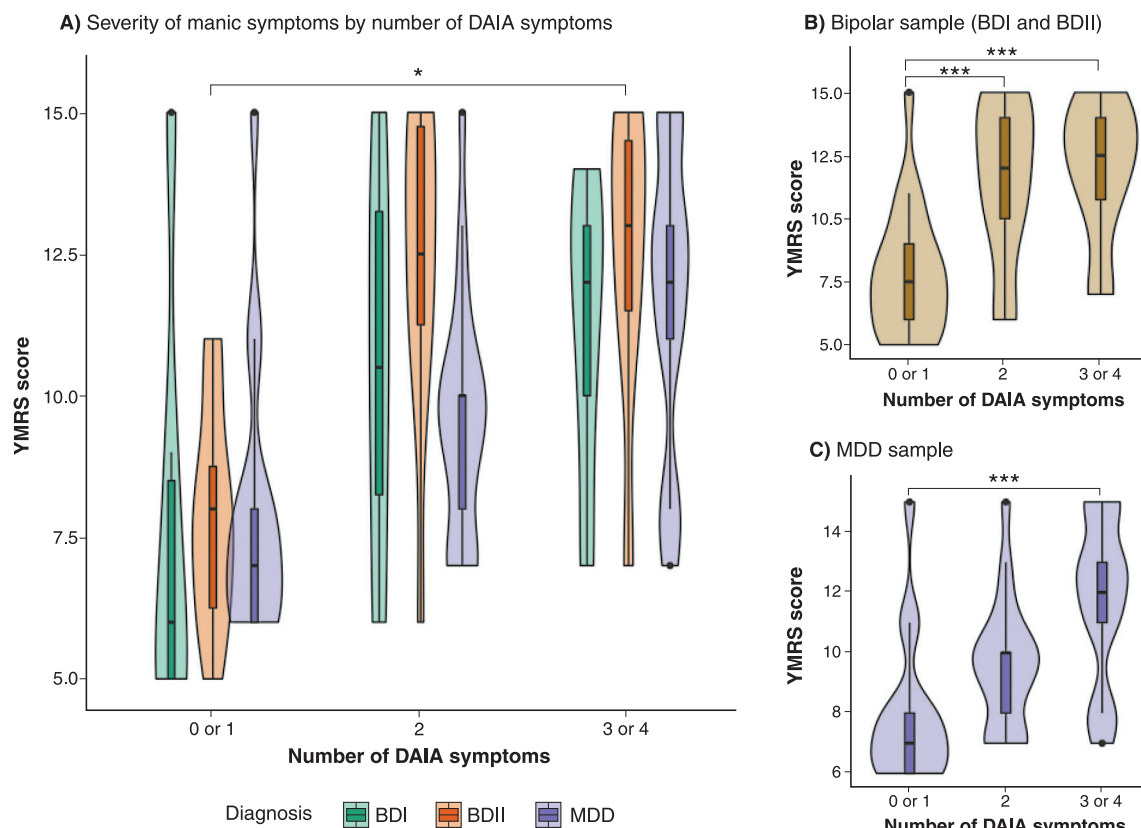
Figure 3 Severity of manic symptoms in mixed depression according to distractibility, anxiety, irritability, and agitation (DAIA) symptoms (categorical analysis), stratified by diagnosis. Severity of manic symptoms in mixed depression (Young Mania Rating Scale [YMRS] scores), y axis. Number of DAIA symptoms, x axis. A) Entire sample: bipolar disorder (BD) I, BD II, and major depressive disorder (MDD). B) Bipolar sample: BD I + BD II. C) MDD sample: MDD. * p < 0.05, *** p < 0.001.

manic symptoms, finding that the presence and number of DAIA symptoms increase the severity of both depressive and manic symptoms, worsening mixed depression. The presence of DAIA symptoms increased mixed depression severity by increasing depressive symptoms and manic symptoms, but in different ways according to the specific diagnosis (unipolar or bipolar). These findings reinforce the idea that unipolar and bipolar mixed states are distinct and that DAIA symptoms work as severity indexes, with potential therapeutic implications.[34]

In our analyses, anxiety was associated with greater severity of depressive symptoms in mixed bipolar depression, and all DAIA symptoms (anxiety, distractibility, irritability and agitation) were associated with greater severity of manic symptoms in mixed unipolar and bipolar depression. To our knowledge, no study has yet examined the impact of all DAIA symptoms on the severity of depressive and manic symptoms in mixed depression; most have focused only on the frequency and impact of DAIA symptoms in mixed depression outcomes. In factor analysis studies,[35,36] anxiety has been significantly correlated with mania scores in depressed individuals, i.e., the greater the manic symptomatology, the greater the anxiety, but they did not examine how anxiety, as a mixed feature, was correlated with greater manic severity. Few studies have directly analyzed anxiety as an integral

symptom of mixed states, although anxiety often appears indirectly as a comorbidity common to these clinical conditions.[7,37] Irritability, also called dysphoria in some studies, is consistently found in both unipolar and bipolar mixed depression (40 to 73% prevalence, respectively, vs. 15-17.5% in pure depression).[6] In the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-Mix study, the most frequent manic symptom in mixed depression was irritable mood (32.6%).[7] In a BRIDGE-II-Mix study cluster analysis,[33] although non-overlapping DSM-5 mixed symptoms were more consistent among depressive patients with mixed features, the symptoms that best predicted the mixed cluster were irritable mood, mood lability, psychomotor agitation, and distractibility, none of which correspond to DSM-5 mixed features criteria.

The results of these analyses are limited by the modest sample size, but the patients were systematically characterized with standardized rating scales and diagnostic instruments, which were applied by psychiatrists specialized in mood disorders. The definition of DAIA symptoms is not well established and we do not know if using the distractibility, anxiety, irritability and agitation items of YMRS and Hamilton Anxiety Scale is a sufficient measure of actual DAIA symptoms. Since distractibility, irritability, and agitation were based on YMRS items, they were also
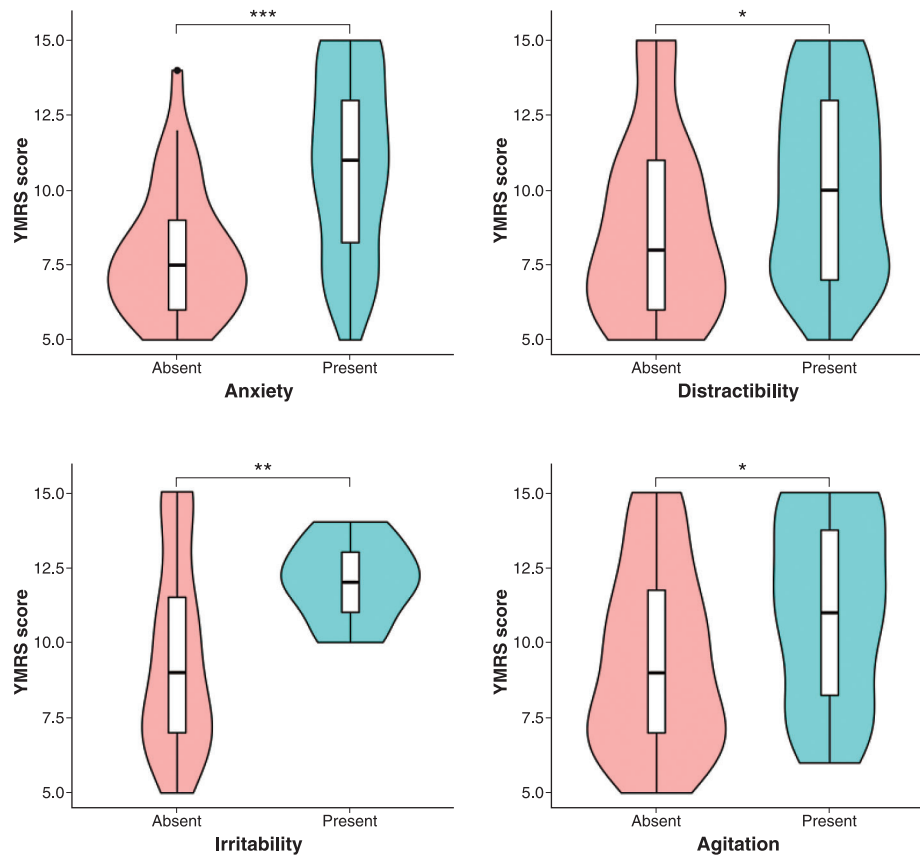
Figure 4 Severity of manic symptoms in mixed depression according to specific distractibility, anxiety, irritability and agitation (DAIA) symptoms (entire sample). Severity of manic symptoms in mixed depression (Young Mania Rating Scale [YMRS] scores), y axis. Specific DAIA symptoms (absent or present), x axis. * p < 0.05 (distractibility and agitation), ** p < 0.01 (irritability), *** p < 0.001 (anxiety).

not independent regarding manic symptom severity as assessed by the YMRS. It is important to bear in mind that the strategy of assessing depression symptoms with MADRS and mixed symptoms with YMRS does not itself assess the DSM-5 mixed specifier criteria and must be viewed as a limitation of the study design. For safety reasons, patients with current psychotic depression and acute suicide ideation were excluded from the study, which is an additional limitation, since psychotic symptoms and suicidality are closely related to mixed depression.[12] Finally, the analysis does not rule out the possibility of pseudospecificity, i.e., that DAIA and depressive/manic symptoms are discrete, overlapping phenomena.

In sum, these data provide relevant criticism of the DSM-5 "with mixed features" specifier, since this definition excludes DAIA symptoms, which are common symptoms of mixed depression. Our findings corroborate that DAIA symptoms should be considered important identifiers of mixed depression because, although nonspecific, they contribute to the severity of these conditions.

Disclosure

DFT has worked as speaker and a scientist in the last 2 years for Cristália, Aché, Torrent, Abbott, and Lundbeck. DHM has worked as speaker and a scientist in the last 2 years for Aché, Torrent, Abbott, and Lundbeck. EV has received grants and served as consultant, advisor, or continuing medical education speaker for the following entities (unrelated to the present work): AB-Biotics, Abbvie, Aimentia, Angelini, Biogen, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo Smith-Kline, Janssen, Lundbeck, Organon, Otsuka, Sage, Sanofi-Aventis, Sunovion, and Takeda. ARB is chief medical advisor of Flow™ and has a small equity in the company. The other authors report no conflicts of interest.

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