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Mixed Depression: Clinical Features and Predictors of Its Onset Associated with Antidepressant Use

Gabriele Sani[a–c] Flavia Napoletano[a, d] Paul A. Vöhringer[d, f] Matthew Sullivan[d] Alessio Simonetti[a] Athanasios Koukopoulos[b] Emanuela Danese[a] Paolo Girardi[a] Nassir Ghaemi[d, e]

[a]NESMOS Department (Neuroscience, Mental Health, and Sensory Organs), Sapienza University, School of Medicine and Psychology, Sant'Andrea Hospital, [b]Centro Lucio Bini, and [c]IRCCS Santa Lucia Foundation, Department of Clinical and Behavioral Neurology, Neuropsychiatry Laboratory, Rome, Italy; [d]Mood Disorders Program, Department of Psychiatry, Tufts Medical Center, and [e]Tufts University School of Medicine, Boston, Mass., USA; [f]Hospital Clinico, Facultad de Medicina, Universidad Chile, Santiago, Chile

Key Words
Antidepressants · Bipolar disorder · Clinical predictors · Major depressive disorder · Mixed depression

Abstract
Background: Mixed depression (MxD) is narrowly defined in the DSM-IV and somewhat broader in the DSM-5, although both exclude psychomotor agitation as a diagnostic criterion. This article proposes a clinical description for defining MxD, which emphasizes psychomotor excitation. ***Methods:*** Two hundred and nineteen consecutive outpatients were diagnosed with an MxD episode using criteria proposed by Koukopoulos et al. [Acta Psychiatr Scand 2007;115(suppl 433):50–57]; we here report their clinical features and antidepressant-related effects. ***Results:*** The most frequent MxD symptoms were: psychic agitation or inner tension (97%), absence of retardation (82%), dramatic description of suffering or weeping spells (53%), talkativeness (49%), and racing or crowded thoughts (48%). MxD was associated with antidepressants in 50.7% of patients, with similar frequency for tricyclic antidepressants (45%) versus selective serotonin reuptake inhibitors (38.5%). Positive predictors of antidepressant-associated MxD were bipolar disorder type II diagnosis, higher index depression severity, and higher age at index episode. Antipsychotic or no treatment was protective against antidepressant-associated MxD. ***Conclusions:*** MxD, defined as depression with excitatory symptoms, can be clinically identified, is common, occurs in both unipolar depression and bipolar disorder, and is frequently associated with antidepressant use. If replicated, this view of MxD could be considered a valid alternative to the DSM-5 criteria for depression with mixed features.

Introduction

In the DSM system, psychomotor agitation is not diagnostically central for major depressive disorder (MDD). In DSM-IV [1], agitation was listed and weighted equally to psychomotor retardation within the fifth criterion for a major depressive episode: 'psychomotor

Athanasios Koukopoulos died before the submission of this article.

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Gabriele Sani, MD
NeESMOS Department (Neurosciences, Mental Health, and Sensory Organs)
School of Medicine and Psychology, Sapienza University, UOC Psychiatry
Sant'Andrea Hospital, Via di Grottarossa 1035–1039, IT–00189 Rome (Italy)
E-Mail gabriele.sani@uniroma1.it

Table 1. MxD without psychomotor agitation diagnostic criteria, proposed by Koukopoulos et al. [6]

Along with major depression, at least 3 of the following symptoms must be present:
1 Inner tension/agitation
2 Racing or crowded thoughts
3 Irritability or unprovoked feeling of rage
4 Absence of signs of retardation
5 Talkativeness
6 Dramatic description of suffering or frequent spells of weeping
7 Mood lability and marked emotional reactivity
8 Early insomnia

agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)'. This relegation of psychomotor agitation to just part of a subcriterion of major depression made it easy to diagnose the same condition, a major depressive episode, in someone who had severe agitation as well as in someone who had no agitation at all. DSM-5 [2] criteria for the mixed features specifier in MDD do not include psychomotor agitation, and irritability and mood lability [3–5].

Although studies indicate that the incidence of mixed depression (MxD) among mood disorders is high [6–9], data regarding age at onset [9–14], gender [9, 15], role of temperament [16–21], and family history of bipolar disorder (BD) [14, 21–23] are unclear or contrasting.

The role of antidepressants in the treatment and pathogenesis of MxD is controversial. While most studies agree that MxD has worse outcomes than non-MxD and is less responsive to, or even worsened by, common antidepressant treatments [24–31], one recent large study found that the likelihood of remission was greater in depressive patients with DSM-5 mixed features treated with antidepressants [32]. However, data on this topic are limited [7, 33–36]. Furthermore, few studies have focused on characteristics that make patients more susceptible to antidepressant-associated MxD (AD-MxD) [37–42]; finally, no study heretofore has investigated the antidepressant-associated transition from depression to MxD.

Koukopoulos et al. [6] have proposed that mixed depressive syndromes with psychomotor agitation be given the traditional name of 'agitated depression' according to the original Research Diagnostic Criteria [43]. However, psychomotor agitation is present in many cases, but not in all. In cases *without* psychomotor agitation, specific diagnostic criteria have been proposed, which are currently under validation (table 1).

This is the first study to assess the impact of antidepressants on broadly defined MxD, and provides clinical data regarding the frequency of diagnostic symptoms of MxD.

Methods

In a prospective cohort study design, among 1,257 consecutive patients with any DSM-IV-TR mood disorder diagnosis (Bipolar Disorder, type I, n = 480; Bipolar Disorder, type II, n = 332; Major Depressive Disorder, n = 355; First Depressive Episode, n = 90) seen at the Centro Lucio Bini in Rome from 1990 to 1999, 647 (51.4%) had a 'simple' (i.e., nonmixed) major depressive episode; among these patients, 219 (33.8% of the depressive episodes and 17.4% of the total sample) were diagnosed with MxD according to criteria proposed by Koukopoulos et al. [6]. No patients diagnosed with 'simple' depression had any symptoms of psychomotor agitation. No patients diagnosed with MxD met criteria for mania according to the DSM-IV-TR; thus they were not diagnosable with a DSM-IV mixed episode. DSM-IV criteria, as well as the above criteria, were applied to all patients by treating clinicians (G.S., P.G., A.K.). A semistructured diagnostic interview, used at Centro Lucio Bini since 1980 to assess patients with mood disorders, was used. Briefly, the semistructured interview, carried out by a senior psychiatrist, is based on DSM criteria and on clinical evaluation (not on simple yes/no answers to structured questions). The wording of the questions can be changed to improve/check understanding, and the final evaluation was based also on information from family members/close friends (always present during at least one visit) and from any medical documentation. All data collected about past, social and family history, past psychiatric history and current psychiatric history were entered in preprinted medical records.

Exclusion criteria were diagnosis of mental retardation or documented IQ <70, presence of an unstable general medical condition and presence of clinically significant prestudy physical examination, electrocardiogram, laboratory or urinalysis abnormalities indicating serious medical disease, that could impair evaluation. All patients gave free, informed consent.

Using both patient and family interviews, and all other reliable sources (i.e. social workers, physicians, other relevant informants), demographic and clinical data were obtained at baseline, at the end of the index episode and, at least, once during the follow-up period. The affective temperament of patients was assessed using the method described by Akiskal and Mallya [33]. Information regarding psychic and/or chemical and/or physiological factors present or associated with the index episode were recorded. Baseline and end-of-index-episode mood symptom severity was assessed through the 21-item Hamilton Rating Scale for Depression (HDRS-21), Young Mania Rating Scale (YMRS), and Clinical Global Impression (CGI). The occurrence of three or more proposed mixed symptoms, during a major depressive episode that was continuously treated with antidepressants, indicated an antidepressant-associated transition from depression to MxD. Patients treated with antidepressants, who had discontinued them from 6 to 3 months before the onset of MxD, were included in the nonantidepressant-associated MxD group.

Treating clinicians (G.S., P.G., A.K.) have worked together in the same outpatient setting for more than 15 years, reaching a high level of agreement.

Statistics

Statistical analysis is mainly descriptive, consistent with the recommendations of the International Committee of Medical Journal Editors (www.icmje.org); t tests were applied for continuous variables and the χ^2 and Fisher's exact tests for binary variables, along with 95% confidence intervals.

Clinical and demographic variables were analyzed for MxD associated with antidepressants [AD-MxD (+)] as the primary outcome and reported in a stratified descriptive analysis. All the variables from univariate analysis with p values 0.05 or less were included in logistic regression modeling using a backward selection procedure (with AIC criterion) to obtain the best-fitting model and to correct for possible clinical and demographic confounders. Robustness of our final antidepressant-association predictor model and logistic model assumptions were tested, as well as collinearity, interactions, discriminative capacity (auROC) and calibration (Hosmer-Lemeshow test). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated. All statistical analyses were performed using STATA 11 (Stata Corp., College Station, Tex., USA) and R statistical package (R Project for Statistical Computing, http://www.r-project.org/).

Results

Clinical Features of the MxD Sample

Among 219 patients with MxD, 56 met DSM-IV criteria for BD type I (BDI; 11.7% of the total BDI sample), 68 for BD type II (BDII; 20.5% of the total BDII sample), 72 for MDD (20.3% of the total MDD sample), and 23 for a first depressive episode (25.6% of the total first depressive episode sample).

Female gender, BDII diagnosis, and high frequency (63%) of hyperthymic temperament were the main characteristics of the patients with MxD. Most of them (84%) had one or more close relatives suffering from a mood disorder; first-degree relatives were more likely to have unipolar (i.e., MDD), rather than bipolar disorder. Finally, 11% of the sample had a rapid cycling course.

In the entire sample, the most frequent mixed depressive symptoms during index episodes were psychic agitation or inner tension (97%), absence of retardation (82%), dramatic description of suffering or weeping spells (53%), talkativeness (49%), and racing or crowded thoughts (48%). Onset of the index episode was typically during the mid-forties on the average, lasting about 7 months, and with an interepisode time (i.e. time from the end of the index episode and the beginning of the next one) of at least 2 months. About one third of index episodes were psychotic, and about one half were associated with antidepressants. Patients were followed up for a mean period of 15.4 ± 8.9 months. After the recovery from the index episode, during the follow-up period, 99 patients (45.2%) had no new episodes, 42 (19.2%) had a minor depressive episode, 37 (16.9%) a nonmixed major depressive episode, 18 (8.2%) a hypomanic episode, 16 (7.3%) an MxD, and 2 (1%) an attempted suicide. Mean duration of the new episode was about 7 months. Concerning treatment after MxD diagnosis, there was a frequent use of mood stabilizers (31.5%), antipsychotics (30.1%), and electroconvulsive therapy (24.7%); few patients (2.7%) were treated with antidepressants.

All patients responded well to treatments (HDRS-21, baseline, 27.9 ± 6.5, endpoint, 8.0 ± 6.8; YMRS, baseline, 16.0 ± 5.2, endpoint, 5.6 ± 5.2; CGIs, baseline 5.0 ± 1.0, endpoint, 1.6 ± 1.2). However, although the final CGI score improved in all patients, there was a trend towards lack of improvement in those patients treated with antidepressants (mean final CGI, 1.5 ± 1.1 for electroconvulsive therapy, 1.5 ± 1.0 for antipsychotics, 1.6 ± 1.1 for antiepileptics, 1.5 ± 1.0 for lithium, and 4.0 ± 2.9 for antidepressants; p = 0.06).

Antidepressant- versus Nonantidepressant-Associated MxD Groups

A stratified analysis was performed comparing the AD-MxD (+) group and the group with nonantidepressant-associated MxD [AD-MxD (–)], with at least 10% quantitative differences seen as potentially meaningful (based on current epidemiological standards) [44]. Compared to AD-MxD (–), AD-MxD (+) patients were more likely to be BDII, to have MDD family history, rapid cycling course, more hospitalizations and more past suicide attempts. No differences were found in age at first AD treatment and in time of illness spent on AD treatments (table 2).

Table 3 provides stratified characteristics of the index episode. AD-MxD (+) had a higher age of onset and a lower probability that the index episode was the first episode; moreover, they were more likely to have psychotic symptoms and less likely to be treated with antipsychotics during the MxD episode. No differences were found in type of antidepressants between the groups and within the AD-MxD (+) group, comparing the two most commonly used agents, tricyclic antidepressants and selective serotonin reuptake inhibitors. Specifically, AD-MxD (+) episodes were about similarly common in those treated with tricyclic antidepressants (45%, OR = 2.5, 95% CI 2.0, 3.1) as with selective serotonin reuptake inhibitors (38.5%, OR = 2.3, 95% CI 1.9, 2.8).

Table 2. Clinical and demographic characteristics of the sample (n = 219)

Variable	Total sample (n = 219)	AD-MxD (–) (n = 108)	AD-MxD (+) (n = 111)	Mean difference or RR (95% CI)
Age (mean ± SD), years	63.1±14.9	60.2±15.5	65.8±13.9	–5.63 (–9.56, –1.70)
Gender, %				
Women	72.6	72	73	1.01 (0.75, 1.36)
Men	27.4	27	27	0.98 (0.73, 1.31)
Marital status, %				
Married	63.9	57	71	**1.39 (1.02, 1.88)**
Single	26.0	32	20	0.70 (0.49, 1.00)
Divorced	6.0	8	4	0.59 (0.25, 1.35)
Widow	4.1	3	5	1.33 (0.82, 2.15)
Occupation, %				
Employed	42.0	40	44	1.09 (0.83, 1.41)
Unemployed	27.4	26	29	1.07 (0.80, 1.42)
Student or homemaker	20.5	27	14	**0.65 (0.42, 0.98)**
Retired	10.1	7	13	1.29 (0.91, 1.82)
Diagnosis[1]				
BDI	25.6	28	23	0.89 (0.64, 1.22)
BDII	31.0	18	43	**1.69 (1.32, 2.15)**
MDD	32.9	38	28	0.79 (0.58, 1.07)
First MxD[2]	10.5	16	6	**0.48 (0.24, 0.98)**
Family history of mental illness			13	
None	16.4	20	14	0.73 (0.47, 1.12)
BDI	14.2	14	5	1.01 (0.70, 1.46)
BDII	6.0	7	32	0.90 (0.49, 1.65)
MDD	26.0	20	36	**1.30 (1.00, 1.70)**
Other psychiatric conditions[3]	37.4	39		0.94 (0.71, 1.23)
Temperament, %				
Normal	10.0	12	8	0.79 (0.46, 1.32)
Hyperthymic	63.0	59	67	1.17 (0.88, 1.55)
Cyclothymic	13.2	15	12	0.86 (0.56, 1.33)
Dysthymic	6.9	8	6	0.91 (0.52, 1.59)
Anxious	4.6	5	4	1.07 (0.61, 1.87)
Irritable	2.3	1	3	1.18 (0.57, 2.46)
Polarity pattern[4]				
Regular bipolar	59.8	57	63	1.14 (0.87, 1.50)
Regular unipolar	30.6	35	26	**0.72 (0.52, 0.98)**
Irregular	9.6	8	11	1.06 (0.71, 1.57)
Course				
Rapid cycling, %	11.0	5	17	**1.67 (1.30, 2.16)**
Seasonal	4.1	3	5	1.33 (0.82, 2.15)
Nonspecific[5]	84.9	92	78	**0.61 (0.47, 0.78)**
Age at first episode (mean ± SD)	33.5±14.8	32.1±15.2	34.9±14.3	–2.75 (–6.67, 1.17)
Age at first treatment with AD (mean ± SD)	36.1±11.7	35.1±12.5	37.1±12.9	–1.97 (–5.1, 1.14)
Illness under antidepressants (mean ± SD), %	18.74±14.1	19.41±13.7	18.0±14.5	1.32 (–2.44, 5.04)
Number past hospitalizations (mean ± SD)	1.4±2.4	0.9±1.6	1.8±2.9	**–0.79 (–1.43, –0.15)**
Number past suicide attempts (mean ± SD)	0.3±0.9	0.2±0.5	0.5±1.3	**–0.33 (–0.59, –0.06)**

CI = Confidence interval; RR = relative risk; SD = standard deviation.

[1] The diagnosis was assessed according to DSM-IV criteria except for depressive mixed diagnosis that grouped patients with a regular series of mixed depressive episodes diagnosed according to criteria proposed by Koukopoulos et al. [6].

[2] We grouped patients that had their first depression at the index episode meeting the criteria of Koukopoulos et al. [6] for MxD.

[3] In this group we included anxiety disorders, personality disorders, psychotic disorders and eating disorders according to medical records and/or other important sources.

[4] Regular bipolar cycle pattern = patients have had regular series of alternate manic and depressive episodes until the index episode; regular unipolar cycle pattern = patients have had regular series of episodes of the same polarity until the index episode; irregular cycle pattern = patients have had irregular series of episodes of both the polarities until the index episode.

[5] Nonspecific means neither rapid cycling nor seasonal.

Table 3. Characteristics of the index episode of the sample (n = 219)

Variable	Total sample (n = 219)	AD-MxD (–) (n = 108)	AD-MxD (+) (n = 111)	Mean difference or RR (95% CI)
Age (mean ± SD), years	45.7±14.9	42.7±15.4	48.8±13.7	**–6.10 (–9.98, –2.21)**
Duration (mean ± SD), months	6.3±3.5	6.5±8.1	7.2±8.3	–0.65 (–2.83, 1.52)
Index episode is first episode, %				
Yes	12.3	19	6	**0.47 (0.24, 0.91)**
No	87.7	81	94	**2.08 (1.08, 4.00)**
Psychotic symptoms, %				
Yes	31.1	24	38	**1.35 (1.04, 1.74)**
No	68.9	76	62	**0.75 (0.57, 0.95)**
Treatment before diagnosis of MxD, %				
None	28.8	50	8	**0.21 (0.11, 0.40)**
Antidepressants	56.6	8	100	**12 (6.42, 22.43)**
Tricyclic antidepressants	25	3.5	45	2.5 (2.0, 3.1)
Selective serotonin reuptake inhibitors	21	3.5	38.5	2.3 (1.9, 2.8)
Serotonin-norepinephrine reuptake inhibitors	8	1	14.5	2.0 (1.7, 2.4)
Monoamine oxidase inhibitors	1	0	2	
Antipsychotics	5.5	9	2	**0.56 (0.42, 0.75)**
Mood stabilizers	9.1	19	0	
Treatment after diagnosis of MxD, %				
Electroconvulsive therapy	24.7	20	29	1.23 (0.93, 1.61)
Antipsychotics	30.1	37	23	**0.70 (0.50, 0.98)**
Mood stabilizers	31.5	29	34	1.13 (0.86, 1.48)
Antidepressants	2.7	3	3	0.84 (0.35, 1.99)
Benzodiazepines	11	11	11	0.97 (0.64, 1.49)
Interepisode time after index episode (mean ± SD), months	2.4±5.1	1.6±4.5	3.1±5.6	**–1.53 (–2.89, –0.17)**
Type of next episode after index episode				
None	45.2	52	39	0.76 (0.58, 1.00)
Similar to index episode	7.3	6	8	1.25 (0.83, 1.88)
Subsyndromal depressive episode	19.2	14	24	1.28 (0.97, 1.70)
Hypomania	8.2	8	8	0.98 (0.60, 1.59)
Depression	16.9	17	17	1.01 (0.71, 1.43)
Suicide attempt	1	3	4	1.13 (0.58, 2.18)
Next episode duration (mean ± SD), months	6.8±8.2	6.5±8.1	7.2±8.3	–0.65 (–2.83, 1.52)

CI = Confidence interval; RR = relative risk; SD= standard deviation.

In the AD-MxD (+) group, mean duration of antidepressant treatments before the onset of MxD was 3.1 months (SD 5.6).

As shown in table 4, although the AD-MxD (+) group had initially more severe illness compared to the AD-MxD (–) group, no significant differences were found according to the HDRS-21, YMRS and CGI scores at the end of the episode.

Predictors of MxD Associated with the Use of Antidepressants

The most important positive predictors for AD-MxD (+) were a BDII diagnosis (OR = 2.33, 95% CI 1.09, 4.97), higher HDRS-21 score at the beginning of the index episode (OR = 1.07, 95% CI 1.01, 1.13), and older age at the index episode (OR = 1.02, 95% CI 1.00, 1.05). The most important negative predictors were treatment with antipsychotics (OR = 0.06, 95% CI 0.01, 0.35) or absence of treatment before MxD diagnosis at the index episode (OR = 0.08, 95% CI 0.03, 0.19), and nonspecific course of illness (OR = 0.34, 95% CI 0.11, 0.98) (table 5).

The receiver operating characteristic (ROC) curve for the model for antidepressant association predictors is shown (fig. 1). The model had good discriminative capacity (auROC = 0.83), sensitivity (84.7%), specificity

Table 4. Baseline and endpoint scores at psychometric and functional scales

	Baseline				Endpoint			
	total sample (n = 219)	AD-MxD (–) (n = 108)	AD-MxD (+) (n = 111)	mean difference (95% CI)	total sample (n = 219)	AD-MxD (–) (n = 108)	AD-MxD (+) (n = 111)	mean difference (95% CI)
HDRS-21	27.9±6.5	26.6±6.9	29.2±5.8	–2.56 (–4.26, –0.85)	8.0±6.8	7.3±6.1	8.7±7.3	–1.42 (–3.20, 0.39)
YMRS	16.0±5.2	15.6±4.9	16.4±5.5	–0.76 (–2.15, 0.63)	5.6±5.2	5.3±5.0	5.9±5.4	–0.64 (–2.05, 0.77)
CGI	5.0±1.0	4.9±1.1	5.2±1.0	–0.30 (–0.57, –0.02)	1.6±1.2	1.6±1.1	1.7±1.3	–0.13 (–0.45, 0.19)

Values represent means ± SD.

Table 5. Final predictor model for AD-MxD

Predictor	Coefficient (β)	OR	SE	p value	95% CI
Antipsychotics treatment before diagnosis of MxD	–2.72	0.06	0.05	0.002	0.01, 0.35
Absence of treatment before diagnosis of MxD	–2.51	0.08	0.03	0.000	0.03, 0.19
Nonspecific course of illness[1]	–1.07	0.34	0.18	0.047	0.11, 0.98
BDII diagnosis	0.84	2.33	0.90	0.029	1.09, 4.97
HDRS-21 total at index episode baseline	0.07	1.07	0.03	0.013	1.01, 1.13
Age at index episode	0.02	1.02	0.01	0.028	1.00, 1.05

CI = Confidence interval; OR = odds ratio; SE = standard error.
[1] Nonspecific course of illness = patients who have neither a rapid cycling nor a seasonal course of illness.

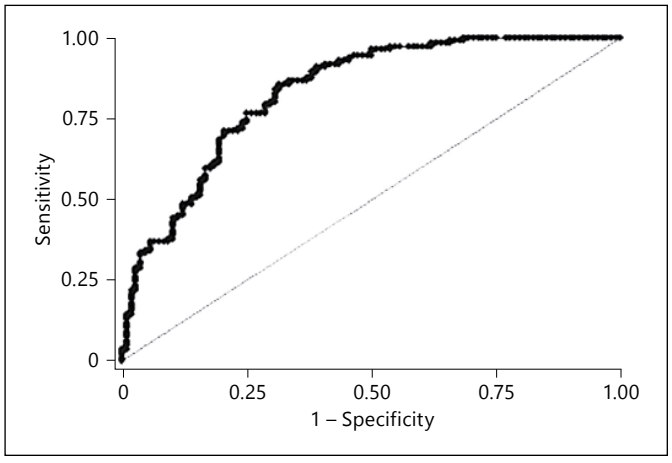

Fig. 1. ROC analysis of predictive model of AD-MxD (sensitivity = 84.7%; specificity = 69.2%; AUC = 0.832).

(69.2%), positive predictive value (74.02) and negative predictive value (81.32). Patients were correctly classified in 77% of cases. Goodness-of-fit analysis indicated that the model is well calibrated (Hosmer-Lemeshow test = 4.69; numbers of group = 10; p value = 0.79).

Discussion

MxD was indentifiable in about one third of patients who met DSM-IV criteria for bipolar depression or MDD, similarly in both the AD-MxD (+) and AD-MxD (–) groups. Antidepressant-associated mixed states were also common, occurring in about one half of MxD episodes. In contrast to the mixed episode specifier of the DSM-5 [2], the sample showed psychomotor agitation, absence of retardation, dramatic description of suffering or weeping spells, and racing or crowded thoughts. These findings support the need for future dimensional investigations of MxD [31].

MxD patients, although defined as not meeting DSM-IV criteria for mania, had high baseline YMRS scores (16.0), similar to those found in many manic episodes. This observation suggests that broadly defined MxD, even excluding DSM-like manic symptoms, identifies many patients with severe excitatory symptoms. This is consistent with the view expressed by Koukopoulos and Ghaemi [45], i.e., that the very presence of psychomotor excitation, not DSM-defined mania per se, is clinically important in the differential diagnosis of mood disorders

(i.e., pure depression/melancholia vs. MxD vs. mania, bipolar depression vs. unipolar depression) [46]. These data support the view that broadly defined excitement should be considered as crucial in both clinical and research settings to better understand the pathophysiology of mood disorders and to establish more effective treatments. A recent review reported a high rate of excessive arousal response, other than mania or hypomania, in patients with juvenile depressive or anxiety disorders treated with antidepressants [47]. Interestingly, the risk was as high among patients with anxiety as with depression. These findings support the possibility that anxiety may be the expression of an underlying excitatory process [45], hence being susceptible to antidepressant treatment-related overactivation. If this is correct, anxiety conditions might be more safely and effectively treated with antianxiety (namely antiexcitatory) than with antidepressant agents [48]. The issue of anxiety in MxD is central. Although it seems apparently identical to the anxiety present in nonmixed depressive episodes (i.e., the emotional reaction to painful experience of depression itself), anxiety in MxD may be of a different kind, inherent to the psychic agitation itself [34]. This type of anxiety could better respond to antiexcitatory treatments (such as anxiolytics, antipsychotics or antiepileptic agents), whereas it may possibly worsen whit antidepressants [34].

Besides manic-like excitation, another prominent clinical feature in this sample was psychosis, which was present in about one third of the sample; interestingly, Kraepelin [10] described the mixed state as a 'morbid state… in which ideas of sin and persecutions are usually present'. This may suggest that MxD can be more severe than pure mood states. We also found a large proportion of women and a relatively later onset age, in agreement with Kraepelin [10]. In the literature, it is unclear whether mixed depressive patients have earlier [11, 12, 14], similar [9, 13] or later [10] onset of illness, compared to other mood disorder patients. Family history of mood disorder was very common, though rapid cycling was less common than in DSM-defined bipolar disorder (11% vs. a typical rate of about 25%) [49]. These results agree with many [13, 15, 21, 50, 51], but not all [9, 11–14, 22, 23] previous reports on broadly defined mixed depressive states.

Abnormal mood temperaments were also quite common, as in other reports [17, 52]. In our sample hyperthymia predominated, while others reported more cyclothymic [52, 53] or dysthymic [21] temperaments in MxD. Since hyperthymic temperament is more common in BD than MDD [54, 55], this finding suggests that MxD may share much clinical and biological background with bipolar disorder.

In general, differences between clinical associations in this study and prior research may be due to how mixed states are broadly defined. The MxD definition given here was not used in most previous studies, although it may have been approximated by some of them.

Regarding antidepressant treatment and overall outcomes, AD-MxD (+) was associated with more severe index episodes and a more severe course of illness (more past hospitalizations and more past suicide attempts). These results are consistent with a potential harmful impact of antidepressant treatment on depression in general [56, 57], and in MxD in particular [7, 35, 36], although, given the observational nature of these analyses, direction of causality cannot be inferred. A possibility is that more severely ill patients were systematically given antidepressants, but this is less likely due to the prospective treatment outcome data in this sample, showing observable improvement in the overall sample despite the use of antidepressants in a minority of patients, and a similar outcome in the group that received antidepressants. These data contrast with those of an analysis of a subgroup of patients in the STAR*D database (n = 449) showing a greater rather than a lesser likelihood of remission in MDD patients with DSM-5 mixed features treated with antidepressants [32]. The mixed features in that analysis most associated with benefit were 'expansive mood' and 'cheerfulness', which, in the context of major depression, suggested a diagnosis of 'mixed hypomania', rather than MxD, as in our sample. Since there was no nontreatment control group in the STAR*D study, apparent improvement with antidepressants in the 'mixed hypomania' subgroup cannot be causally attributed to antidepressants; as opposed, the brief duration of 'mixed hypomania' compared to nonmixed major depression is a well-known natural history fact.

A recently published consensus statement of the International Society of Bipolar Disorders on antidepressant use in bipolar disorders, which did not issue any recommendation regarding antidepressant use in mixed bipolar depression [58], based mainly on the absence of much evidence. These data would provide new evidence that the consensus statement indicates as being much needed.

The most important predictors concerning AD-MxD (+) in multivariate analysis were BDII diagnosis, higher baseline index depression severity, and greater index age. The most important negative predictors were nonspecific course of illness, treatment with antipsychotics, and absence of treatment before the diagnosis

of MxD at index episode. Sensitivity and specificity of our model for antidepressant-association predictors were high. Some studies indicated that a BDI diagnosis [37–39], a positive history of suicide attempts possibly related to patient impulsiveness [37], higher YMRS scores on the disruptive behavior item [37], and excitatory symptoms (motor activation, pressured speech, and racing thoughts) [40] increase antidepressant-associated switch-risk. There is contrasting evidence about the role of age [37, 38, 41].

To our knowledge, this study is the first to address mixed depressive episodes within a prospective cohort design by describing differential clinical features among patients that experienced MxD while using antidepressants. Given its observational design, our data could have been influenced by confounding factors that can impact diagnosis and outcome, some of which were corrected in regression modeling of antidepressant-association outcomes.

In conclusion, MxD, as defined by Koukopoulos et al. [6], may be a valid and distinct syndrome in the longitudinal pattern of manic-depressive illness based on classical nosological validators. AD-MxD appears to be common. Our preliminary data provide a clinical context for further validation studies. If valid, the MxD construct would be quite different from the DSM-5 mixed features specifier, which explicitly excludes psychomotor agitation, and would be a valid alternative to it.

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