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"Evaluation and impact of subthreshold contrapolar symptoms during a Major Depressive Episode in unipolar and bipolar patients"

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LIST OF ABBREVIATIONS:

ACE = Activity, Cognition, Energy

AD = Antidepressant

ADS = with anxious distress specifier

BD = Bipolar disorder

BD-1 = Bipolar disorder type I

BPD = Borderline Personality Disorder

CANMAT = Canadian Network for Mood and Anxiety Treatments

DSM 5 = Diagnostic and Statistical Manual for Mental Disorders – fifth edition

DSM II = Diagnostic and Statistical Manual for Mental Disorders – second edition

DSM III = Diagnostic and Statistical Manual for Mental Disorders – third edition

DSM IV-TR = Diagnostic and Statistical Manual for Mental Disorders – fourth edition – text revised

DSM IV = Diagnostic and Statistical Manual for Mental Disorders – fourth edition

HCL -32 = Hypomania Check-List 32 items

ICD = International Statistical Classification of Diseases and Related Health Problems

ICNP = International College of Neuro-Psychopharmacology

ISBD= International Society for Bipolar Disorders

KMxD = Koukopoulos mixed depression

MAOI = Monoamine oxidase inhibitors

MDD = Major Depressive Disorders

MDE= Major Depressive Episode

ME = mixed episode

MFS = "With mixed features" specifier

MOODS-SR = Mood Spectrum-Self Report-Current

MS = mixed states

NCS - R= National Comorbidity Survey Replication study

RANZGP = Royal Australian and New Zealand College of Psychiatrists

RBDC-MXS = Research-based Diagnostic Criteria for depressive mixed states

SCI- MOODS = Structured Clinical Interview for Mood Spectrum

SGA = Second-generation antipsychotic

SSRI = Selective serotonin reuptake inhibitors

WFSBP = World Federation of Societies of biological psychiatry

Abstract

A considerable proportion of individuals suffering from a major depressive episode (MDE) experience co-occurring subthreshold hypomanic symptoms. Although these presentations - commonly referenced as "mixed depressive states"- have been described since the Classical Age, an operational definition of mixed depression was not included in the official psychiatric nomenclature until 2013 with the introduction of the "with mixed features" specifier (MFS) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The MFS – which may be applied to any mood episode (manic, hypomanic, or depressive episode) - denotes the co-occurrence of a threshold mood episode along with subthreshold symptoms of the opposite polarity, providing a less restrictive definition of mixed mood states, compared to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). However, several objections have been raised against the "DSM-5 defined mixed depression", whose diagnostic validity and accuracy are still debated with conflicting positions. The presence of mixed features during a depressive episode (either in MDD or in BD) has been associated with worse illness course, treatment resistance, and higher suicidal risks, although the generalizability of these outcomes is affected by the heterogeneity of operational definitions used for mixed depression. Thus - far from being a merely speculative issue - a reliable nosologic framework validly accounting for within-MDE subthreshold bipolarity has substantial concrete implications at several levels, from patient's management to international regulatory agency's choices.

The main object of this doctoral research was to investigate the presence and impact on illness-course of contrapolar symptomatology during an MDE in a multicenter sample of 300 patients with MDD or BD. In order to adopt a dimensional and spectrum-based approach, the current mood symptomatology was assessed by completing the last-month version of the Mood Spectrum-Self Report-Current (MOODS-SR) questionnaire.

The first study was aimed to evaluate the differences in mood spectrum between the two main diagnostic groups (MDD vs. BD). We found that (hypo)manic symptoms were endorsed by a large number of patients with BD, but also by a considerable number of patients with MDD. Significant differences between the two groups were restricted to "energy depressive" and "mood manic" MOODS domain scores.

In the second study, we disaggregated our sample into three transdiagnostic groups by using a clustering analysis approach based on MOOD-SR scores. Consistent with our hypothesis, we observed an overall disease-severity gradient, paralleling the increasing magnitude of contrapolar symptomatology across the clusters.

In the third study reported here, we compared the diagnostic constructs of DSM-5 defined mixed depression and Koukopoulos' mixed depression (KMxD) in terms of prevalence, associated clinical variables, and discriminative capacity for bipolar depression in patients with an ongoing MDE. We found that the two constructs exhibited an overlapping discriminative capacity for bipolar depression. However, the current diagnostic threshold of DSM-5 MFS did not prove to be adequately inclusive if compared to the greater diagnostic sensitivity of KMxD, which also yielded better association with clinical variables related to mixedness.
Overall, the results of these studies confirmed: the high prevalence and clinical relevance of subthreshold hypomania within an MDE regardless of the main diagnosis; the intrinsic inadequacy of the current DSM-5 MFS criteria in describing mixed depressive states; the need for a unitary, dimensional, more descriptive and dynamic approach to affective disorders.

Finally, the fourth paper reported in the present thesis is derived from a secondary research project consisting of a survey designed to investigate the attitudes of Italian psychiatrists towards the clinical entity of mixed depression in terms of diagnostic, therapeutic approaches, and psychopathological reference model. The results of the survey indicated: the relevance of mixed depressive presentations in the real-world clinical settings, a poor rating regarding the quality of training on the management of these forms during the residency, a broad disagreement with the DSM-5 operational definition of mixed depression, and a general alignment of prescribing practice for the treatment of mixed states with the recommendations provided by available guidelines.

Chapter 1

GENERAL INTRODUCTION

1.1 Subthreshold hypomania: an open issue

The co-occurrence of hypomanic symptoms during a depressive episode was already described in medical texts dating back to the Classical age[1]. However, this condition still poses several issues in terms of psychopathological and phenomenological characterization, diagnostic classification, assessment, and patient management.

Estimates of the prevalence of depressive episodes with concomitant subthreshold (hypo)manic symptoms have ranged widely (20 – 80%), depending on the criteria applied[2–5]. This heterogeneity underscores the absence of a univocal operational definition for mixed depressive states.

In the well-known 2009 Munich study[6], a ten-year perspective and longitudinal study including three follow-up phases, the prevalence of patients with current Major depressive disorder (MDD) presenting subthreshold hypomania (defined as the presence of elated\expansive mood with troublesome consequences or as the presence of ≥ 3 DSM-IV-TR hypomanic symptoms plus unusual irritability) on at least one evaluation visit was approximately 40%.

In a 2018 systematic review of studies reporting the frequency of contrapolar symptoms during an index mood episode, the mean prevalence of depressive episodes with mixed symptoms ranged from 35% to 23% in bipolar and unipolar depression, respectively[7]. Of note, this review selected only the studies which designated as “mixed depressive state” a Major Depressive Episode (MDE) with at least three concomitant contrapolar symptoms among those included in the diagnostic criteria for (hypo)manic episode according to the last four editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM).

Shifting to a lifetime perspective, the National Comorbidity Survey Replication (NCS-R) study, a nationally representative face-to-face household survey of the US population, found that almost 40% of respondents currently suffering from MDD reported a lifetime history of subthreshold hypomania according to the operational definition specifically adopted[8].

The significant proportion of patients with MDD who exhibit concomitant subthreshold hypomanic symptoms challenges the DSM categorical classification of mood disorders based on the unipolar-bipolar dichotomy whereby unipolar depression and bipolar disorder are conceived as distinct psychopathological processes. Conversely, these data would endorse a spectrum perspective in which all mood episodes lie along the same continuum where pure MDD and Bipolar disorder type I (BD-1) are placed at opposite poles, in line with the original unitary construct of "manic depressive insanity" developed by Emile Kraepelin, and subsequently reprised by Hagop Akiskal[9].

A more spectrum-oriented approach to affective disorders was formally adopted in the last edition of DSM[10] (DSM-5) by introducing the "with mixed features" specifier (MFS), which replaced the past "mixed episode" (ME) diagnostic category. Indeed, the addition of this specifier to MDD would represent a structural bridge between MDDs and BDs. For the first time in the American Psychiatry Association nosology, the possibility of mixed symptoms in MDD has been openly recognized, providing an operational definition of mixed depression. However, the validity of this new diagnostic entity is still being debated.

Far from being a mere heuristic issue, the availability of a valid nosologic framework, accounting for subthreshold hypomania in the context of an MDE, is fraught with implications at different levels, including diagnostic recognition, treatment strategy, and research direction.

1.2.1 Mixed depression: origin and development of the concept

Depressive mixed states (or mixed depression) may be described as a subtype of mixed states (MS) in which hypomanic symptoms are inserted in the context of a mood episode with prevalent depressive symptomatology.

Historically, MS refer to mood episodes characterized by the co-occurrence of symptoms of opposite polarity. Despite this simple definition, they still represent a 'nosologic dilemma' and a diagnostic and therapeutic challenge[11,12].

Although some earlier descriptions of clinical pictures characterized by the coexistence (or by the rapid alternation) of melancholic and manic symptoms already occur in the writings of Hippocrates (460-337 BC) and Aretaeus of Cappadocia (2nd century AD), and later also in the manuscripts of several authors (especially in the Medieval period and in the 1700s)[13,14], a first detailed psychopathological treatise of MS was provided by Johannes Christian August Heinroth (1773–1843), the first professor of psychiatry in Germany (Leipzig). In his *Lehrbuch der Stoerungen des Seelenlebens*[15] (Textbook of the disorders of the psychic life, 1818), Heinroth classified mental disorders into three large categories according to the changes in energy: "exaltation" (*hyperthymias*), "depression" (*asthenias*), and "mixture of exaltation and depression" (*hyper-asthenias*). The latter category of ''mixed states'' was divided into ''mixed mood disorders'' (*animi morbi complicati*), ''mixed mental disorders'' *(morbi mentis mixti*), and ''mixed volition disorders'' (*morbi voluntatis mixti*)[15]. It is mainly in the subcategories of "mixed mood disorders" and "mixed volition disorders" that we can find the description of clinical entities (*Melancholica furens, Melancholia mixta catholica, Athymia melancholico – maniaca*), encountering the contemporary notion of mixed affective states and schizoaffective disorders.

In his book *Pathology and Treatment of Mental Illnesses*[16], another eminent German psychiatrist, Wilhelm Griesinger (1817–1868), depicted states of mental alterations characterized by the coexistence of melancholic and manic elements,

distinguishable from rapid cycling forms and seasonal affective disorders. Such pathological conditions were named "*mid-forms*" and comprised "melancholia with destructive impulses" and "melancholia with long-lasting exaltations of volition." In addition, Griesinger described the potential onset of manic states progressing from melancholic ones, stating that "*during the development of melancholia into mania, a conglomerate of manic and depressive symptoms can be observed*".

A lesser-known contribution to the psychopathology of MS in the pre-Kraepelinian era is that of the French psychiatrist Louis-Victor Marce´ (1828-1865), student of Baillarger and Moreau de Tours. In his manual *Traite´ pratique des maladies mentales* (1862), he described a type of mood disorder defined by the alternation of recurrent melancholia and mania of limited intensity (resembling modern Bipolar Type II disorder) and clarified the concept of MS, referring to them as the result of combined depressive and excitatory symptoms, below the intensity of full-blown manic or depressive forms[17]. Furthermore, Marcè was the first author to report the occurrence of MS during the peripartum period[18].

Other authors have offered descriptions of clinical pictures resembling the current notion of MS, as summarized by Kahlbaum in his textbook, reporting the most prominent diagnostic classifications present in his time[19]. However, the first complete and detailed systematization of MS as psychopathological entities in the manic-depressive area is due to the work of Kraepelin and Weygandt.

1.2.2. The Kraepelinian classification of mixed states

Emil Kraepelin (1856–1926) and his fellow Wilhelm Weygandt (1870–1939) systematized MS. For the first time, Kraepelin used the term ''mixed states''(*Mischzustände*) or ''mixed forms'' (*Mischformen*) in the 5th edition of his textbook in 1896[20]. He developed and articulated this concept in subsequent editions[21,22] - also relying on the important contribution of his student William Weygandt[23] - until the final categorization reported in the 8th edition of his manual

(1913)[24]. Kraepelin conceived MS as the cornerstone of his unitary view of "manic-depressive insanity," referring to them a sort of "third polarity," nosographically independent from depression and mania, but placed along the same continuum[25]. Adopting a dimensional approach, based on a tripartite model of psychic life, Kraepelin identified six subtypes of MS, depending on the different potential combinations of fluctuations in the three domains of mood\emotion, thought, and psychomotricity. Thus, he distinguished: "*manic depression or anxiety*" (depressed mood, ideic acceleration, and hyperactivity), "*excited depression*" (depressed mood, inhibition of thought, and hyperactivity), "*unproductive mania*" (euphoria, inhibition of thought, and hyperactivity), *"manic stupor*" (euphoria, inhibition of thought, and apathy), "*depression with flight of ideas*" (depressed mood, flight of ideas, and apathy) and "*inhibited mania*" (euphoria, ideic acceleration, and apathy). Later, Kraepelin and Weygandt adopted a more elastic approach whereby the entity of MS could actually encompass all the infinite possible combinations of depressive and manic symptoms present in the same person, and not necessarily only those ascribable to the six types mentioned above. Furthermore, based on a longitudinal perspective, Kraepelin and Weygandt differentiated the transitional forms (arising during the transition from manic to depressive episodes) from the autonomous ones, which are characterized by the coexistence of contrapolar manifestations since the onset[26]. These forms would constitute the "real mixed states," representing the clinical phenotype of manic depressive insanity with the most unfavorable course and tendency to chronicization.

1.2.3 The decline and revival of mixed states

As early as the second decade of the twentieth century, a gradual and marked decline in interest in MS was observed. This was partly due to the strongly critical positions expressed by the exponents of the influential Heidelberg School. In particular, Karl Jaspers criticized the combinatorial model proposed by Kraepelin,

consisting in the decomposition of affective psychopathology in disorders of thought, mood, and volition/psychomotricity[27]. Kurt Schneider was even more severe, rejecting the admissibility of the concept of MS, which he considered as temporary transitional phases, without their own nosographic autonomy[28].

The lack of interest in MS was also related to the growing interest and resonance of the work of Karl Leonhard, who countered the unitary Kraepelinian model of "manic-depressive illness" by introducing a taxonomy of mood disorders based on the distinction between unipolar and bipolar affective disorders[29]. Consequently, in a systematization of affective disorders based on polarity rather than recurrence, non-transitional MS were downgraded to extremely uncommon, if not anecdotal, forms[30].

A significant exception to the general lack of interest in research on MS was a monograph by Stavros Mentzos, an exponent of the Hamburg School, published in 1967[31]. Mentzos proposed a new classification of MS based on the distinction between "stable mixed states" (*Mischzustände*) and "mixed pictures" (*Mischbild*). While the former are equivalent to the mixed forms described by Kraepelin and Weygandt since they are defined by the co-occurrence of manic and depressive symptoms in stable patterns of combination, the "*mixed pictures*" consist of rapid alterations (over a few hours or minutes) of contrapolar symptoms. The important innovation introduced by Mentzos was to theorize the mixed affective forms as the result of the dissociation of the two components of the so-called "drive-mood system," where "drive" refers to the underlying force behind psychic processes, while the mood is the affective-emotional tone that colors the psychic life. Therefore, if mania and depression derive from synchronous and concordant variations of the two components of the mood-drive system, MS derive from their stable dissociation. Otherwise, mixed pictures were conceived as the expression of desynchronization of the continuous cycling drive and mood, appearing as extremely chameleon-like and polymorphous forms[32]. The conceptualization of MS

proposed by Mentzos was partially incorporated in the "Vienna Criteria" for MS, published in 1983[33].

Similar to Mentzos, the authors of the Vienna School distinguished two types of MS, namely stable and unstable, proposing specific diagnostic criteria.

The Vienna School criteria for stable and unstable MS were based on a complex psychopathological model, known as *Janzarik's structural dynamic coherence* model[34]. The core element of this is the so-called "dynamics," conceived as a psychic driving force and inclusive of two components: a free and available component (the "dynamic usual level," representing the functional substrate of temperament) and a component linked to elements of the "structure," i.e., innate acquired behavioral schemas and representations. The "dynamics" may be subject to three types of stable derailments represented by mania, depression, and dysphoria. As clarified by Berner, stable MS include conditions originating from the mixture of at least two kinds of derailments. Thus, besides the classic frameworks characterized by the co-presence of mania and depression, it is possible to observe conditions such as "*angry mania*" (mixture of mania and dysphoria) and "*hostile depression*" (a mixture of depression and dysphoria). On the other hand, in the unstable MS, "the excessively rapid shifting from one of the three stable dynamic derailments to the other one" can be observed[35]. Since they are underpinned by a rather complex and sophisticated model, the Vienna criteria for MS had a limited diffusion in clinical practice, and their use was limited to research purposes. However, the Vienna school had the merit of stimulating renewed interest in MS that experienced a real revival since the mid-1980, as evidenced by the flourishing of abundant literature on this topic.

Hagop Akiskal in the United States and the Italian-Greek psychiatrist Athanasios Koukopoulos in Italy were among the authors who contributed most to the so-called revival of MS[14].

Akiskal developed a new theoretical framework of MS, fully integrated into the context of his construct of the bipolar spectrum[36,37]. According to Akiskal, MS are the result of the combination of an index affective episode with a dominant temperament of opposite polarity. Alternatively, a mixed state may arise when a depressive episode is inserted into a cyclothymic-type temperament. Therefore, it would be possible to distinguish three types of MS, depending on the different potential interactions between basic temperament and current mood episode[38–40] :

- Type B-I: depressive temperament + psychotic mania;
- Type B-II: cyclothymic temperament + major depression; and
- Type B-III: hyperthymic temperament + major depression.

Type B-I MS are characterized by florid psychotic symptoms such as auditory hallucinations, persecutory delusions, megalomaniac delusions, perplexity, confusion, and a mixture of signs and symptoms of the two opposite polarities. Clinically these may be indistinguishable from the acute phases of schizophrenic spectrum disorders, overlapping with the schizoaffective disorder.

Type B-II MS are generally non-psychotic and are described as the result of the irruption of a cyclothymic temperament into an episode of inhibited depression. Consequently, from a clinical-phenomenological point of view, they are characterized by depressed mood, hyperphagia, asthenia, easy fatigability intermixed with ideational acceleration, explosions of anger, hilarity, impulsivity, sexual disinhibition, and repeated suicide attempts.

Type B-III MS derive from the onset of an MDE in the context of a hyperthymic temperament and is characterized by incessant dysphoria together with irritability, impulsiveness, psychomotor agitation, panic and insomnia, suicidal obsessions and impulses, sexual hyperarousal, and genuine expressions of suffering. According to Akiskal, this type of MS is typical of hyperthymic patients who have suffered from multiple depressive episodes, repeatedly treated with antidepressants (ADs)[41].

On the other hand, Athanasios Koukopoulos, one of the strongest opposers of the dichotomous classification of mood disorders, focused on depressive MS, and in particular, on the clinical phenotype of "*agitated depression*". In 1992, Koukopoulos and colleagues of the Centro Lucio Bini in Rome published an article describing a depressive mixed syndrome characterized by the lack of psychomotor retardation (agitation), labile/irritable mood, and psychic agitation or inner tension[42]. Agitated depression contrasts in phenomenology with melancholia, defined by highly retarded psychomotor function and anhedonic depressive inhibition in the absence of any irritability or mood lability[43].

1.2.4 Mixed states and mixed depression in the current classification systems: from the revolution of DSM III to DSM-IV Mixed episode

The definition of MS in the various editions of the DSM has undergone several modifications, in step with changes in the systematization of mood disorders. In the first edition of the DSM (1952)[44], MS were confined to a peripheral nosologic position, as part of the diagnostic category "*manic depressive reaction, other*," together with the continuous circular forms. The DSM-II (1968)[45] introduced the diagnostic category of "*mixed manic-depressive illness*" and confirmed a marginal position by placing it among the "*Other major affective disorders*." Mixed manic-depressive illness was described as that condition in which "manic and depressive symptoms appear almost simultaneously," without, however, any specification on the number and type of symptoms required. In 1980, the DSM III[46] made substantial changes in the systematization of mood disorders: paradoxically, this consisted in replacing the unitary model of affective disorders, theorized by Emile Kraepelin, in the context instead of a general revolution in the classification of psychiatric disorders built on a neo-Kraepelinian approach[47,48].

According to the Kraepelinian unitary model, each pathological and recurrent mood episode with or without psychosis is an expression of the same disease – *the manic*

depressive illness - the psychopathological key feature of which is represented by the recurrence of episodes regardless of their polarity (depression vs. mania), as clearly stated by Kraepelin in this passage: *"The course of manic–depressive insanity is marked by a recurrence of attacks separated by lucid intervals.... It seldom happens that all are of the same type; at some time or other a depressive attack is sure to appear… several depressive attacks may recur before a manic attack appears; in other words, the occurrence of several attacks of one type to the exclusion of other types indicates that the greater number of attacks throughout life will be of the same character."*[49]

In DSM III, Kraepelin's broad concept of manic–depressive insanity (MDI) was separated into two distinct entities: bipolar disorder (BD) and major depressive disorder (MDD).

The diagnostic categories of MDE, manic episode, and hypomanic phase (hypomanic episode as a component of cyclothymic disorder) were also introduced. This radical nosographic innovation implied:

- the adoption of a diagnostic model of mood disorders based on the dichotomy of depression vs. mania (unipolar vs. bipolar) and therefore on the preeminence of polarity rather than recurrence of episodes was established, in line with Leonhard's view;

- the formalization of a binary model that differentiates unipolar depression from bipolar depression, conceiving them as two distinct psychopathological entities (although the criteria for unipolar MDE and bipolar MDE are exactly the same);

- the codification of MDD, as defined by the new diagnostic criteria, as a catch-all diagnostic entity, including extremely heterogeneous and diverse clinical forms[9].

DSM III introduced the diagnostic category of "*Bipolar disorder, mixed*," defined as "current (or most recent) episode involving the full symptomatic picture of both

manic and major depressive episodes, intermixed or rapidly alternating every few days." This definition was substantially retained in the DSM-III-R[50] published in 1987, except for the duration criterion of 2 weeks for depressive symptoms. In DSM-IV [51]and DSM- IV-TR[52], MS were incorporated into the diagnostic category of Mixed Episode (ME). This diagnosis required that the criteria be met for both manic and MDE each day for at least one week. Thus, in the last two DSM editions, ME designated a diagnosis of bipolar I disorder (BD-I), thus excluding a diagnosis of major depressive disorder (MDD) and the possibility that MS can coexist in the context of bipolar type II disorder.

The DSM-IV-TR operational definition of ME has proved to be extremely narrow as it targeted an almost unrealistic clinical condition, failing to discriminate the most prevalent presentations of MS, i.e., sub-threshold forms characterized by the occurrence of few symptoms of the opposite polarity during the same affective episode[53–55]. An equally rigid definition of MS is that proposed by the International Statistical Classification of Diseases and Related Health Problems – 10th edition (ICD-10), which requires that two sets of opposite symptoms occur for the greater part of the current episode of illness (for ≥2 weeks) and that there has been ≥1 past affective episode[56]. The main limitations of the ICD-10 criteria for the ME are essentially represented by the absence of the specification of the number of symptoms required and the temporal requirement of the duration of at least two weeks, considered excessive by many[57,58].

1.2.5 The DSM-5 -defined mixed depression

In 2013, the DSM-5 introduced the " '*with mixed features' specifier*" (MFS), to be applied when at least three symptoms of opposite polarity (among those listed) are present during a mood episode, and it may be referred to manic, hypomanic episodes and MDEs, both in bipolar disorder (BD) type I and II, and in Major Depressive Disorder (MDD). This substantive update was meant to overcome the

DSM-IV TR narrow diagnostic category of "Mixed Episode," providing clinicians with more sensitive criteria, able to address subsyndromal presentations of MS.

In order to qualify as having a manic or hypomanic episode with mixed features, the patient is required to have at least 3 of the following symptoms during the majority of the days of the current or most recent episode of mania/hypomania:

- Prominent dysphoria or depressed mood as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
- Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others).
- Psychomotor retardation nearly every day (observable by others, not merely subjective feelings of being slowed down).
- Fatigue or loss of energy.
- Feeling of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

On the other hand, to be diagnosed as suffering from an MDE with mixed features, the patient is required to have at least 3 of the manic or hypomanic symptoms during the majority of days of the current or most recent episode of depression:

- 1. Elevated, expansive mood.
- 2. Inflated self-esteem or grandiosity.

- 3. More talkative than usual or pressure to keep talking.
- 4. Flight of ideas or subjective experience that thoughts are racing.
- 5. Increase in energy or goal-directed activity (socially, at work or school, or sexually).
- 6. Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
- 7. Decreased need for sleep (feeling rested despite sleeping less than usual, to be contrasted with insomnia).

As expressly indicated by criterion C for the manic/hypomanic episode with mixed features, if a patient meets both the criteria for an MDE and a manic episode (a case that in the DSM-IV-TR designated a ME), the correct diagnosis is that of "mania with mixed features." Furthermore, the fulfillment of the MFS criteria in MDD is expressly indicated by the DSM-5 as a risk factor for the development of BD type I and II, warning clinicians about the need for a clinical evaluation over time, also in the perspective of a potential diagnostic transition.

The introduction of the DSM-5 MFS was interpreted as a theoretical structural bridge between MDD and BD, positing a more spectrum-oriented approach to mood disorders that – consistent with the Kraepelinian view – can be conceptualized along a spectrum ranging from pure unipolar depressive forms to

pure mania, passing through mixed presentations marked by varying degrees of contrapolarity[55,59,60].

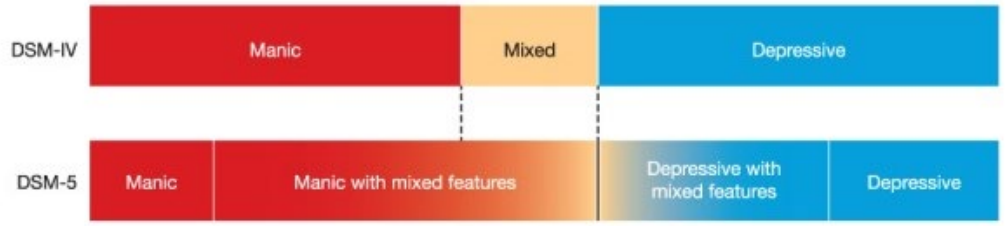

Figure 1. Classification of MS in DSM: moving from a categorical to a more dimensional approach. Adapted from Hu et al.[61]

However, the possibility of applying the DSM-5 MFS to a unipolar depressive episode appears to be inconsistent with the choice made by the DSM-5 task force to separate mood disorders into two distinct chapters (*Depressive disorders and Bipolar disorders*, previously included within the same chapter of "Mood disorders"), since a classification model based on the unipolar\bipolar dichotomy is reconfirmed. Logically, it would have been more consistent to restrict the use of this specifier only to bipolar MDEs.

Following its introduction, several researchers have discussed the diagnostic and clinical validity of the MFS, with the main focus being on the DSM-5 defined mixed depression.

In the 11th revision of the ICD[62], an ME is described as a mood episode characterized by "*either a mixture or very rapid alternation between prominent manic and depressive symptoms on most days during a period of at least one week*" and occurring only in the context of a BD-I. Thus, in contrast to DSM 5, the ICD-11 maintained a specific diagnostic category for ME, preferring it to a "specifier" for depressive and manic episodes. Some authors commented positevely on this choice by arguing that the shift from the diagnostic category of ME to the MFS

implies the rejection of MS as a distinct and separate entity, having its own clinical-phenomenological specificity[63]. Nonetheless, with regard to the definition of ME, the ICD 11 appears very similar to the DSM -5, and the essential feature is "the presence of several prominent manic and depressive symptoms consistent with those observed in manic episodes and depressive episodes, occurring simultaneously or alternating very rapidly ...". In pursuit of harmonization between the two classifications, ICD -11 simply adopted the DSM -5 definition based on the simultaneous presence of depressive and manic criteria (combinatorial approach) instead of trying to identify specific criteria for different subtypes of ME. As pointed out by Perugi, the solution makes ICD -11 redundant and unoriginal[64].

1.2.6 Alternative definitions and theoretical models for mixed depression

The lack of sensitivity of DSM-IV-TR-defined ME prompted several research groups to propose alternative diagnostic criteria for mixed depression. After the introduction of the MFS in DSM-5, some of these diagnostic constructs were revisited, and other new operational definitions were added in the wake of mounting criticism towards this specifier[65–67].

The Italian psychiatrist Franco Benazzi proposed a definition of mixed depression based on the presence of ≥3 DSM-IV TR hypomanic symptoms (excluding elevated mood and inflated self-esteem) or a Hypomania Interview Guide (HIG) score ≥3 in the context of an MDE with a duration of hypomanic symptoms of at least one week[68].

In the *Bipolar Disorders: Improving Diagnosis, Guidance, and Education (BRIDGE)-II-Mix-Study*[69], Perugi et al. presented an alternative set of criteria for mixed depression diagnosis, named *"Research-based Diagnostic Criteria for depressive mixed states"* (RBDC-MXS). RBDC-MXS are defined by the presence of an MDE plus 3 out of 14 hypomanic symptoms (irritable mood, emotional lability, distractibility, psychomotor agitation, impulsivity, verbal or physical

aggression, racing thoughts, talkativeness, hyperactivity, increased energy, risky behavior, grandiosity, euphoria, and hypersexuality).

As previously mentioned, Koukopoulos and fellows designated the term *"agitated depression*" to describe an MDE with psychomotor agitation identified by the presence of at least 2 of the following psychomotor symptoms, which should be present for several days: "pacing; handwringing; being unable to sit still; pulling or rubbing on hair, skin, clothing, or other objects; outbursts of complaining or shouting; and overtalkativeness"[70]. Subsequently, the same research group developed the diagnostic construct of mixed depression without psychomotor agitation, named *" Koukopoulos mixed depression"* (KMxD), requiring at least 3 of the following symptoms: "inner tension/agitation; racing or crowded thoughts; irritability or unprovoked feelings of rage; absence of signs of retardation, talkativeness, dramatic description of suffering or frequent spells of weeping; mood lability, and marked emotional reactivity, and early insomnia[71]. Based on these validated diagnostic criteria, Koukopoulos and collaborators developed a rating scale specifically designed for the assessment of the presence and severity of KMxD[72,73].

More recently, Malhi and colleagues offered a reconceptualization of MS based on the so-called *Activity Cognition Emotion* (ACE) model. The ACE model deconstructs any mood episodes into three main domains of symptoms (activity, cognition, and emotion), reprising the early Kraepelinian tripartite classification[74]. Accordingly, pure manic and depressive forms result from excitation or inhibition occurring simultaneously across all three domains; MS are instead described as the product of non-unison changes, reflecting a desynchronization of activity, cognition, and emotion.

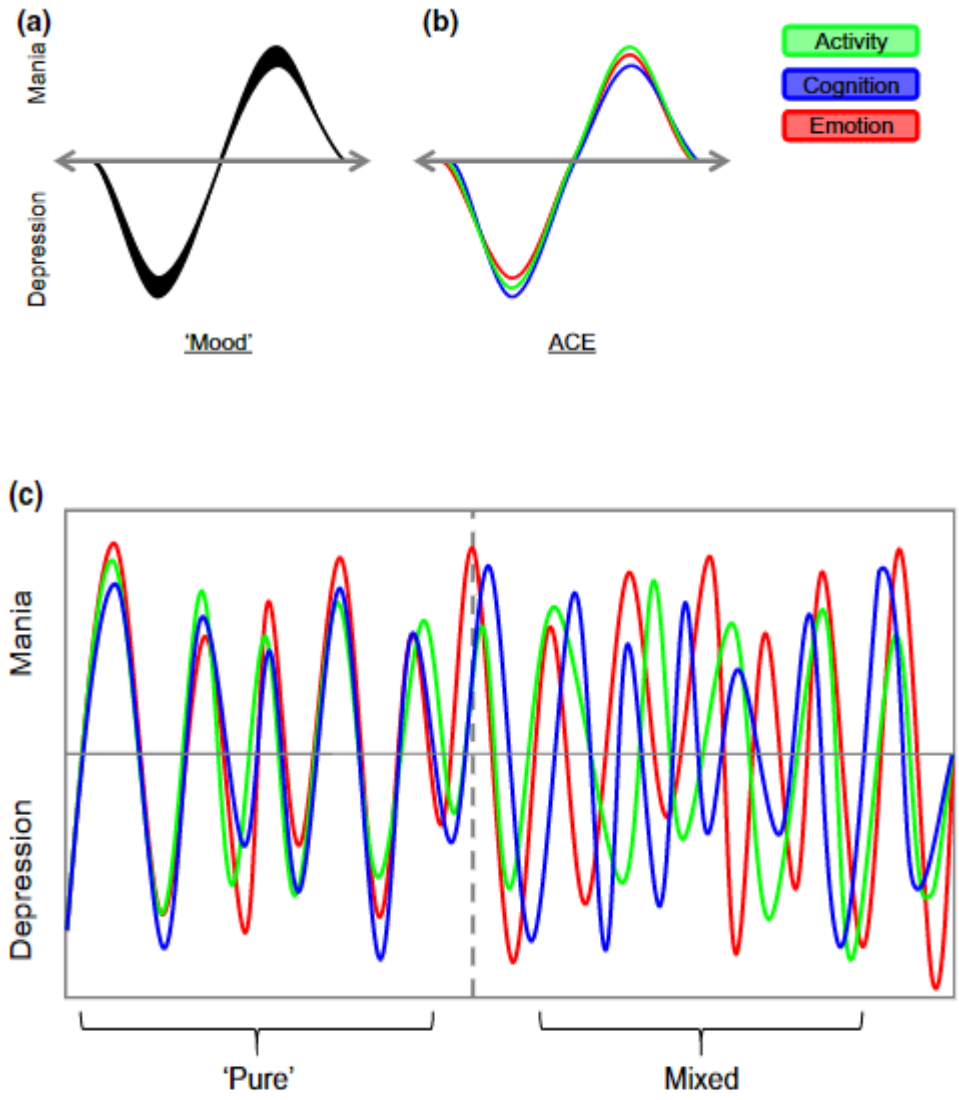

Figure 2: Conceptualization of MS: a) Current "unidimensional" classification of Mood disorders based on the primacy of polarity b) Destructuration of affective psychopathology according to the ACE model c) Mixed states as the result of asynchrony in the ACE domains. Adapted from Malhi et al.[59]

Thus, from the different combinations of symptoms afferent to each domain, it is possible to obtain eight different clinical profiles of mood episodes. Among them, only two are pure (pure mania and depression) since they are characterized by

synchronized and unidirectional changes in all domains, while the remaining six are mixed. While asserting that the ACE model more closely reflects the multidimensional complexity of MS in the clinical practice than the dichotomous, polythetic, polarity-driven approach[75], the same authors recognize that it is still an approximate representation of reality. Indeed, patients could experience opposite patterns of symptoms even within a single domain, and, in turn, an individual symptom may be ascribed to more than one component. Moreover, a myriad of clinical phenotypes may result from shifts in phase, changes in frequency, alterations in amplitude, and combinations of symptoms. Malhi and colleagues also proposed an etiological classification of MS according to which it is possible to distinguish: a) transitional MS in which the period of transition between manic and depressive episode necessarily involves a short time during which symptoms of opposite polarity are juxtaposed; b) treatment induced MS in which the uncoupling of the domains is due to the effect of antidepressants (which have a differential impact on single domains); b) cycling MS originating from ultra-rapid and ultradian cycling with mood swings occurring in days and hours whereby contrapolar symptoms may appear as concomitant, while instead they are not really comingled. Accordingly, cycling MS cannot be considered as 'true mixed states.'[76]

Actually, long before the ACE model was developed, the "Spectrum Project Collaborative Group" (SPCG) developed a psychometric tool aimed at a multidimensional assessment of mood psychopathology in order to provide clinicians with an instrument able to ensure a spectrum-based exploration of affective phenomenology, overcoming the classic unipolar/bipolar dichotomy. The Structured Clinical Interview for Mood Spectrum (SCI MOODS)[77], the "its self-report version" (MOODS-SR)[78], and the MOODS-SR last-month version consisted of 161 items coded as present or absent for one or more periods of at least 3-5 days through the patient's lifetime or over the month. These items are organized into four

domains: (1) The "Neurovegetative" domain, that assesses disturbances and rhythmic changes in feelings, eating attitudes, sexual activity, and sleep pattern, encompassing rhythmic variations in affective and sub-affective symptoms; (2) the "Energy" domain, that assesses changes in everyday activities; (3) the "Mood" domain, that explores the whole realm of depressive and (hypo)manic symptoms, and signs comprising sub-threshold manifestations of mood dysregulations; and (4) the "Cognitive domain", that assesses changes in the cognitive realm occurring together with mood dysregulations. With the sole exception of the "Neurovegetative domain," each MOODS-SR domain is divided into a depressive subcomponent and a manic subcomponent. The internal structure of MOODS-SR has been further divided into six depressive factors (depressive mood, psychomotor retardation, suicidality, drug illness-related depression, psychotic features, and neurovegetative symptoms) and five manic factors (psychomotor activation, mixed instability, spirituality/mysticism/psychoticism, mixed irritability and euphoria), identified by subsequent factorial analyses studies[79,80].

As far as we know, the SCI-MOODS and the derived versions are the only available psychometric tools that explore the "core" criterion diagnostic symptoms of mood disorders and their associated features, as well as the vast range of manifestations surrounding the typical features of manic and depressive episodes, in a unitary format.

1.2.7 Implications for diagnosis, patients' management, and research.

The importance of promptly recognizing the presence of mixed features during an MDE can be schematically referred to the following motivations:

- as expressly reported by the DSM-5 *("Mixed features associated with a major depressive episode have been found to be a significant risk factor for the development of bipolar I or bipolar II disorder. As a result, it is clinically useful to note the presence of this specifier for treatment planning and*

monitoring of response to treatment"), patients suffering from an MDE with mixed features require close monitoring and follow-up because the presence of subthreshold (hypo)manic symptoms suggests a possible underlying bipolar diathesis. Therefore, the presence of hypomanic symptoms - although it is not necessarily pathognomonic of bipolar disorder - should be assumed as a risk factor to be evaluated in association with other clinical features in accordance with the probabilistic approach proposed by Mitchell and Goodwin[81]. In a 2011 study that screened patients initially diagnosed with MDD for the presence of hypomanic symptoms, the total number of (hypo)manic symptoms that were detected at the baseline predicted the onset of hypomania or mania within the next five years, with each additional symptom conveying an increasing risk of 29%.[82] Accordingly, the presence of a standardized nosologic framework with adequate diagnostic sensitivity for mixed depressive episodes represents an important resource for clinicians in order to identify possible bipolar forms. This need appears to be very relevant if we consider that the DSM-5 has not provided different diagnostic criteria for unipolar and bipolar depressive episodes, although the dichotomous model of depression was reconfirmed. It should also be considered that an MDE is the most frequent first presentation of BD, especially in the under-25 age group, and 30%-50% of bipolar patients have been misdiagnosed as affected by MDD. This misdiagnosis contributes to an average interval of more than five years between the first manifestations of BD and the prescription of appropriate psychopharmacological therapy[83];

- regardless of the risk of a possible transition to a full-blown bipolar disorder, according to several studies, the presence of mixed features in the context of an MDE is associated with a more severe illness phenotype characterized by the following features: higher recurrence; poorer response, or switch to mania with antidepressants; high prevalence of psychiatric comorbidities

such as anxiety, substance use, and borderline personality disorder; increased risk of suicide; worse psychosocial functioning and quality of life[4,8,67,69,84–88];

- changes in the classification systems, including a new nosologic framework accounting for MDE with subthreshold polarity, has challenging implications for clinicians, researchers, and regulators who may refer to it as a basis for guiding their choices in the field of psychopharmacotherapy.

The pharmacological management of MS has always represented an insidious challenge for clinicians who must address the risk of mood-switching from the need to treat both manic and depressive symptoms[89]. Indeed, the use of AD medications to treat depressive symptoms can induce a switch to mania; conversely, a pharmacotherapy based on antipsychotics (especially in the case of strong Dopamine Type 2 receptor blockers) may increase the risk of switching to depression[90,91]. Another crucial issue related to the use of AD in the treatment of mixed depression is the risk of suicide. Several studies have shown an association between lifetime mixed episodes, higher rates of AD use, and increased risk of suicide behaviours[92–94]. Accordingly, the International Society for Bipolar Disorders (ISBD) task-force recommended that AD in BD patients should be prescribed only as an adjunct to mood-stabilizing medications[95]. However, the evidence supporting a detrimental or beneficial effect of ADs in the treatment of MDE with mixed features in MDD is still conflicting. Likewise, the question of whether the presence of mixed features confers greater treatment resistance remains open[55,94,96,97].

A further difficulty is that the available literature evidence is scant and weakened by serious methodological limitations which affect previous randomized clinical trials. Mostly, the evaluation of the response to medications of (hypo)manic patients with depressive symptoms is based on the post-hoc or pooled analysis of

randomized clinical studies originally meant to study treatment efficacy in manic episodes. On the other hand, given that the presence of contrapolar symptoms generally constitutes an exclusion criterion in randomized clinical trials conducted on subjects affected by MDEs, the evidence for mixed depression is even more lacking. Hence, historically, pharmacotherapy of MS has represented an unmet need in the international guidelines for the treatment of mood disorders[89,98].

To date, only three international guidelines specifically address the treatment of MS: *"Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) recommendations for the management of patients with bipolar disorder with mixed presentations"* (2021)[99]*, "The World Federation of Societies of biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder" (2019)*[100] and the *"Guidelines for the recognition and management of mixed depression"*[101] developed by Stahl and colleagues but focused exclusively on mixed depression. In addition to these, treatment recommendations for episodes with mixed features are available in the updated editions of some international guidelines for bipolar disorders: *Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology (2016)*[102]*; The International College of Neuro-Psychopharmacology (ICNP) treatment guidelines for Bipolar disorder in adults (2017)*[103]*; Royal Australian and New Zealand College of Psychiatrists (RANZGP) clinical practice guidelines for mood disorders (2021)*[104].

A recent systematic review and quality appraisal of the above-mentioned guidelines (updated March 2018) showed a significant degree of heterogeneity in the recommendations provided for the treatment of mixed depression and MS in general, especially in the indication of the compounds of choice.

This is to be ascribed mainly to a different approach in the study selection (even related to different diagnostic definitions and quality rating of available evidence).

Despite their heterogeneity, all guidelines agreed on avoiding the use of AD in mixed depression, in both BD and MDD, the use of AD or at least combining a Mood stabilizer or a Second Generation Antipsychotics (SGAs) with the ongoing AD treatment. Of note, only the Stahl Guidelines expressly include the use of AD in combination with mood stabilizers or second-generation antipsychotics among their Level 3 recommendations (Lithium or lamotrigine or valproate or atypical antipsychotic + bupropion; Lithium or lamotrigine or valproate or atypical antipsychotic + SSRI; Lithium or lamotrigine or valproate or atypical antipsychotic + MAOI).

SGAs are the psychotropic agents that have been generally considered as first-line or second-line choice in the treatment of acute depression with mixed features by most of the guidelines considered. Below is a summary of the recommendations from the different guidelines for the individual SGA compounds:

- Ziprasidone in monotherapy for acute depressive mixed episode was rated as a first-line treatment in the Stahl et al. guidelines and by the WFSBP in combination with treatment as usual but as a second-line treatment according to the CINP and as third-line treatment by the CANMAT- ISBD;
- Olanzapine was rated as a first-line treatment both in monotherapy (Stahl et al. guidelines) and in combination with MS (CINP, Stahl et al. guidelines) or AD (first-line with fluoxetine). Olanzapine monotherapy (WFSBP, CINP) or the combination olanzapine+ fluoxetine (CINP) was rated as a second-line treatment according to the WFSBP and the CINP guidelines, as an "alternative choice" by the RANZGP guidelines, and as a third-line treatment according to the CANMAT- ISBD guidelines;
- Lurasidone was rated as a first-line treatment in monotherapy or in combination by Stahl et al., as "choice agent" according to the RANZGP guidelines and as a second-line treatment in monotherapy according to the WFSBP. Interestingly, while the "*CANMAT/ ISBD 2018 guidelines for the*

management of patients with bipolar disorder"[105] considered Lurasidone in monotherapy or in combination with Lithium/Valproate as a first-line treatment, in the "*CANMAT/ISBD recommendations for the management of patients with bipolar disorder with mixed presentations*"[99] – released on October 2021 and based predominantly on studies of participants who met DSM-5 proxy criteria – Lurasidone was included along with Lithium, Risperidone and Paliperidone among the agents for which "further research is needed";

- Quetiapine (even in the extended-release formulation) was recommended as "choice agent" according to the RANZGP guidelines (in monotherapy or in combination with Lithium), as first-line treatment in monotherapy or in combination with mood stabilizers (Lithium or Valproate) according to the Stahl and colleagues' guidelines, as second-line treatment according to the CINP and as third-line treatment according to the CANMAT- ISBD guidelines;
- Asenapine, Ariprazole, and Cariprazine were considered as first-line treatment according to the Stahl and colleagues guidelines in monotherapy or in combination with antidepressants and as second-line treatment according to the CINP. The CANMAT- ISBD guidelines ranked Asenapine and Cariprazine as second-line treatments for depression with mixed features, while for Aripiprazole, evidence was considered insufficient.

Regarding the use of mood stabilizers in the treatment of mixed depression:

- Valproate and Lithium were proposed as possible first-line or second-line treatment for acute mixed depression in monotherapy or more often in combination with an SGA, by most of the available guidelines. However, it should be pointed out that the WFSB guidelines have concluded that there are no valid studies supporting the use of both these compounds in the

treatment of mixed depressive states, while the recent CANMAT-ISBD guidelines have concluded that there is insufficient evidence on the use of Lithium; instead they included Valproate among the second-line treatments. Conversely, Lithium and Valproate together with Olanzapine and Quetiapine are the most recommended compounds for the maintenance treatment of mixed depression;

- Carbamazepine in monotherapy was rated as a second-line treatment by the CINP, by the Stahl and colleagues' guidelines and by the WFSBP, and as third-line treatment by the CANMAT-ISBD guidelines;
- Lamotrigine, in monotherapy or in association with SGAs or Lithium or Valproate, was recommended as possible second-line treatment only by Stahl and colleagues' guidelines.

These recommendations should be accepted with caution in view of the limitations mentioned above. In particular, one of the main problems in recommending treatment for mixed depression is the lack of evidence for several compounds. Therefore, clinical well-designed, sufficiently powered double-blind placebo-controlled studies evaluating the efficacy and tolerability of psychopharmacological agents for treatment of MDE with mixed features are needed. However, a prerequisite, is the adoption of a valid and standardized diagnostic operational definition and related assessment approaches for mixed depression. At the same time, an adequate diagnostic framework for subthreshold bipolarity can help researchers to generate more homogeneous clinical samples of MDD patients for biomarkers and neuroimaging research[97].

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Chapter 2

OVERVIEW OF THE PhD RESEARCH PROJECT

2.1 Aims and objects of the studies

The all-embracing purpose of the present PhD project was to evaluate the presence, intensity, and impact on clinical phenotype and illness outcomes of (hypo)manic symptoms during an MDE in a sample of patients with a previously established diagnosis of either MDD or BD.

The following studies derive from this project:

I. *Mood spectrum symptoms during a major depressive episode: Differences between 145 patients with bipolar disorder and 155 patients with major depressive disorder. Arguments for a dimensional approach.*
Object of the study: To evaluate the differences in mood spectrum symptomatology between patients with BD and MDD during an MDE.
*(*Cuomo A, Aguglia A, Aguglia E, Bolognesi S, Goracci A, Maina G, Mineo L, Rucci P, Sillari S, Fagiolini A. Mood spectrum symptoms during a major depressive episode: Differences between 145 patients with bipolar disorder and 155 patients with major depressive disorder. Arguments for a dimensional approach. Bipolar Disord. 2020 Jun;22(4):385-391. doi: 10.1111/bdi.12855)

II. *Exploration of mood spectrum symptoms during a major depressive episode: the impact of contrapolarity: the impact of contrapolarity. Results from a transdiagnostic cluster analysis on an Italian sample of unipolar and bipolar patients*
Object of the study: a) to identify distinct clinical subgroups using a cross diagnostic cluster analysis, based on the exploration of mood symptoms, according to a spectrum approach within a cohort of patients admitted with current unipolar and bipolar depression; and b) to evaluate how cluster membership could be related to diagnostic categories and clinical and psychopathologic factors, hypothesizing that the degree of contrapolar symptomatology may be related to a more severe clinical phenotype of MDE.
(currently under review on "European Psychiatry)

III. *Which Mixed Depression model? A comparison between DSM-5 - defined mixed features and Koukopoulos' criteria*

Object of the study: To compare the diagnostic constructs of DSM-5 defined mixed depression and Koukopoulos' mixed depression in terms of prevalence, associated clinical variables and discriminative capacity for BD in patients with MDE.

(Mineo L, Rodolico A, Spedicato GA, Aguglia A, Bolognesi S, Concerto C, Cuomo A, Goracci A, Serafini G, Maina G, Fagiolini A, Amore M, Aguglia E. Which mixed depression model? A comparison between DSM-5-defined mixed features and Koukopoulos' criteria. Bipolar Disord. 2021 Nov 30. doi: 10.1111/bdi.13166)

As an additional research project, a survey was conducted to explore the attitudes of the Italian psychiatrists towards the clinical entity of mixed depression. This study survey has resulted in the 4th paper reported in the present thesis:

IV. *Mixed Depression: A Survey on Psychopathological, Diagnostic and Therapeutic Approaches Among a Sample of Italian Psychiatrists*

Object of the study: to investigate the attitudes of Italian psychiatrists towards the clinical entity of mixed depression in terms of diagnostic, therapeutic approaches and psychopathological reference model.

(Mineo, L., Rodolico, A., Concerto, C., Natale, A., Pennisi, M., Tusconi, M., ... & Aguglia, E. (2021). Mixed Depression: A Survey on Psychopathological, Diagnostic, and Therapeutic Approaches among a Sample of Italian Psychiatrists. *Clinical Practice and Epidemiology in Mental Health*, *17*(1).

DOI: 10.1111/bdi.12855

ORIGINAL ARTICLE

BIPOLAR DISORDERS WILEY

Mood spectrum symptoms during a major depressive episode: Differences between 145 patients with bipolar disorder and 155 patients with major depressive disorder. Arguments for a dimensional approach

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Abstract

Background: Several studies have challenged the traditional unipolar-bipolar dichotomy in favor of a more dimensional approach.

Objective: To evaluate the differences in mood spectrum between patients with bipolar disorder (BD) and major depressive disorder (MDD) during a major depressive episode (MDE).

Method: Study participants were 145 patients with BD and 155 patients with MDD recruited at three University Medical Centers in Italy. All study subjects met Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for MDE and completed the Mood Spectrum-Self-Report-Last Month questionnaire.

Results: Patients with BD endorsed more items in the mood manic/hypomanic and energy depressive subdomains of the MOODS-SR questionnaire. Significant differences were also found for specific depressive and manic items, which were more frequently endorsed by patients with BD. A large number of patients with BD, but also a considerable number of patients with MDD, endorsed manic items during a depressive episode.

Conclusions: There are differences between BD and MDD in terms of the number and type of mood spectrum items that are endorsed during a MDE, which may help to identify patients with BD when a retrospective assessment of a history of mania or hypomania is not possible or not reliable. A high number of patients with BD and a considerable number of patients with MDD endorsed several items in the manic section of the mood, energy, and cognition domains, this confirming the centrality of mixed features in patients with mood disorders and the need for a unitary, dimensional, descriptive and dynamic approach to MDD and BD, such as the recently proposed ACE (Activity, Cognition, Energy) model.

KEYWORDS
bipolar, depression, difference, differential, episode, major depressive, mixed, mood, unipolar

1 | INTRODUCTION

The differential diagnosis of bipolar disorder (BD) and major depressive disorder (MDD) is predominantly based upon the presence or absence of the history of manic or hypomanic episodes. However, several authors have suggested that the difference between BD and MDD is not limited to the presence or absence of a history of manic episodes.[1] For instance, Forty and colleagues[2] compared clinical course variables and depressive symptom profiles in individuals with MDD (n = 593) and bipolar disorder type I (BD1) (n = 443) and observed that the clinical characteristics associated with a bipolar course included the presence of psychosis, diurnal mood variation and hypersomnia during depressive episodes. Mitchell and colleagues[3] evaluated 39 patients with BD1 matched with 39 patients with MDD and observed that BD1 patients were more likely to demonstrate psychomotor-retarded melancholic and atypical depressive features and to have had previous episodes of psychotic depression. Mc Intyre and colleagues[4] noted that BD may be both overdiagnosed (false positives) and underdiagnosed (false negatives), primarily due to the retrospective assessment of the history of manic or hypomanic episodes, in patients who are more likely to recognize and remember depressive episodes than hypomanic or even manic episodes. Also, patients are usually more likely to seek treatment while experiencing symptoms of depression and anxiety than while they are experiencing symptoms of mania or hypomania.[5] Moreover, there may be patients who are close to meeting the criteria for BD at the time of assessment but have not yet crossed the threshold for this diagnosis. When a BD diagnosis is missed, under-prescribing of mood-stabilizing medications, overprescribing of antidepressants, and increased risk of rapid cycling may occur.[5] Vice versa, overdiagnosis may lead to treatment with unneeded medications and with an increased risk of side effects and physical risks.[6] Also, once a diagnosis is made, it becomes difficult to establish longitudinally, if the absence of further manic episodes is due to the preventative action of mood stabilizers or to a mistaken BD diagnosis.[4]

Indeed, the distinction between bipolar and unipolar disorder has been challenged in light of studies[6-8] pointing to the limitations of the categorical diagnoses of unipolar and bipolar disorders, along with genetic studies[9,10] indicating that the familial aggregation of bipolar disorder and severe depression is at least partly related to genetic factors. Also, mixed mood states are widely present in clinical practice and mixed features may be related to a higher likelihood of endorsing, or being at the risk to develop, BD. However, Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 allows a diagnosis of "mixed features" in both bipolar and MDD,[11] this making yet another argument for a unitary and more dimensional view of mood disorders, where mixed features in MDD may signal a higher risk to develop a BD.[11] Indeed, several studies have highlighted that mixed features are very frequently present in both MDD and BD, which somewhat challenges the classic MDD-BD dichotomy, and highlights the need to bridge the gap between these two disorders.[12]

Approximately, 30%-70% of patients have mixed episodes,[13,14] and this percentage would very likely go higher if patients with just one or two symptoms of opposite polarity, or if key symptoms such as psychomotor activation, distractibility or irritability, counted towards the attribution of a mixed features specifier.[15] Also, a relatively high number of individuals initially diagnosed with MDD will later be diagnosed with BD, owing to the development of a manic or hypomanic episode. For instance, Musliner and Østergaard conducted a cohort study on 91 587 individuals diagnosed with MDD and reported an overall cumulative incidence of conversion from MDD to BD of 8.7% in females and 7.7% in males.[16] Interestingly, diagnostic conversion from MDD to BD was correlated to the presence of severe depression requiring in-patient treatment, psychotic symptoms, and parental history of BD. In a systematic review and meta-analysis, Ratheesh and colleagues[17] identified the rates and characteristics that were predictive of transition from MDD to BD and reported that nearly a quarter of patients with MDD followed over a period of 12-18 years developed BD. Family history of BD, earlier age of onset of depression and the presence of psychotic symptoms were significant predictors of a transition from MDD to BD.

One of the main problems of current nosography for mood disorders is the primary importance that is given to polarity, which is fundamentally incompatible with mixed states, and the failure to dynamically describe an illness that tends to change over time.[18] Hence, it may be useful to deconstruct the rigid manic or depressive dichotomy and regroup the constituent features into domains, for instance, according to the activity, cognition, and energy (ACE) model suggested by Malhi and colleagues.[18] To this end, we decided to evaluate if there were differences between patients with BD and MDD for the number and type of current depressive and hypomanic/manic spectrum items that were endorsed during a major depressive episode (MDE). Our goal was to identify the differences that may help the clinician to distinguish between the two disorders, even when the presence or absence of a history of manic/hypomanic episodes cannot be clearly established. Clearly, when a diagnosis of MDD or BD is uncertain, a longitudinal evaluation is paramount to confirm a provisional diagnosis of MDD or BD. However, we thought that the identification of specific symptoms that are more frequent in BD may help to better orientate the clinicians toward a diagnosis of BD or MDD in those cases when the diagnosis is unclear. Based on the results of previous research,[1-22] we postulated that subjects with BD would endorse more manic/hypomanic symptoms, despite the fact that no patient endorsed a DSM-IV diagnosis of mixed episode. Also, we evaluated if there were differences between BD and MDD for the percentage of patients who endorsed each specific mood spectrum—depressive or manic/hypomanic—item.

2 | METHODS

The Institutional Review Board at the University of Siena, Turin and Catania reviewed and approved all study procedures and all subjects gave written informed consent prior to participating in the study. All study subjects participated in a research diagnostic interview using

the Mini-International Neuropsychiatric Interview for DSM-IV[23] and completed the last month version of the Mood Spectrum-Self Report-Current (MOODS-SR) questionnaire.

The MOODS-SR is a psychometrically sound[24,25] questionnaire that has been used in several other studies and that evaluates the presence/absence of a wide range of features of mood psychopathology. These features include the DSM core symptoms of depression and mania, subthreshold manifestations, mood-related personality traits, prodromal and residual symptoms, and behaviors associated with—or arisen as a means of coping with—mood disorders. The questionnaire comprises 161 items coded as present or absent for a period of at least 3-5 days over the past 1 month (MOODS-SR). Items are organized into three manic-hypomanic and three depressive domains each exploring mood, energy, and cognition, plus a domain that explores disturbances in rhythmicity (ie, changes in mood, energy, and physical well-being according to the weather, the season, and the phase of menstrual cycle, etc) and in vegetative functions, including sleep, appetite, and sexual function. The seven domain scores are obtained as a count of the items endorsed. Seven items explore functional impairment and are not included in the count. The scoring procedures are described in detail in www.spectrum-project.org. Participants were also assessed using the Young Mania Rating Scale (YMRS) [26] and with the Hamilton Depression Rating (HRSD) scale.[27]

2.1 | Statistical analysis

Comparisons between patients with BD and MDD were performed using Chi-square test for categorical variables (gender and mood spectrum items), *t* test for continuous variables with a normal distribution, and Mann-Whitney test for continuous variables with a non-normal distribution. Shapiro-Wilk's statistics was used to test the normality of the distribution. Multivariate analysis of variance was used to compare the seven mood spectrum domain scores between patients with BD and MDD after adjusting for age, gender, and the HRSD score. The significance level was set at $P < .05$. To control for type-I error related to multiple testing of mood spectrum domains and items, Bonferroni-Holm correction was applied to the significance level. The study complete database is available at the University of Siena, Department of Molecular Medicine, Division of Psychiatry.

2.2 | Sample

Study participants included 145 patients with BD and 155 patients with MDD. All study subjects met DSM criteria for a MDE at study entry. The characteristics of the sample are provided in Table 1. Patients with MDD were significantly older, more likely to be female as compared with those with BD, and had significantly higher scores on YMRS.

3 | RESULTS

3.1 | Mood spectrum domains during a major depressive episode

During a *Major Depressive Episode*, patients with BD had significantly higher scores on the mood manic, energy manic, cognitive manic, and cognition depressive subdomains of the MOODS-SR (Table 2). Comparisons between groups were conducted using Mann-Whitney test to take into account the skewed distribution of some domains and the presence of outliers (Figure 1).

After adjusting for age, gender, and HRSD score in multivariate ANOVA, only the energy depressive and mood manic subdomain score resulted significantly higher in patients with BD, compared with patients with MDD (Table 3). Of note, the difference in the energy depressive subdomain score, which is not significant after applying Bonferroni-Holm correction to the probability level (Table 2), achieved statistical significance after adjusting for the three covariates because the severity of depression, measured by the HRSD score, partly accounts for the variability of the energy depressive score, thereby reducing its standard error.

When we compared the frequency of endorsement of individual mood spectrum items, to identify differences in symptom profiles between patients with MDD and those with BD, we found nine mood spectrum items that were endorsed by a significantly larger percentage of patients with BD, after applying Bonferroni-Holm correction to the probability level (Table 4).

TABLE 1 Demographic and clinical characteristics of patients broken down by diagnosis

	MDD	Bipolar	Test	Sig.	
Age (mean ± SD)	53.0 ± 15.3	47.0 ± 13.3	3.608[a]	<0.001	MDD > BIP
Years of education (mean ± SD)	11.2 ± 4.7	12.2 ± 4.0	−1.892[a]	0.059	
% female	67.1	53.8	5.557[b]	0.018	MDD > BIP
HRSD (mean ± SD)	21.5 ± 6.5	22.9 ± 6.1	−1.924[a]	0.055	
YMRS (median and range)	3.4 ± 3.6	6.2 ± 4.1	−6.231[c]	<0.001	BIP > MDD

[a]*t* test.
[b]Chi-square test.
[c]Mann-Whitney test.

TABLE 2 Mood spectrum domain scores in patients with BD and MDD

Domain	MDD	BD	Mann-Whitney test	*P*	
Mood depressive (mean ± SD)	15.5 ± 5.2	16.9 ± 5.4	12 791.5	0.029	
Mood manic (mean ± SD)	4.7 ± 4.7	7.3 ± 5.8	13 990.5	<0.001*	BIP > MDD
Energy Depressive (mean ± SD)	5.7 ± 2.8	6.6 ± 2.4	12 910.5	0.018	BIP > MDD
Energy Manic (mean ± SD)	2.1 ± 2.3	3.0 ± 2.3	13 357.0	0.003*	BIP > MDD
Cognition depressive (mean ± SD)	12.4 ± 6.6	15.0 ± 6.6	13 251.5	0.005*	BIP > MDD
Cognition manic (mean ± SD)	1.7 ± 2.6	2.6 ± 3.5	13 165.5	0.005*	BIP > MDD
Rhythmicity (mean ± SD)	14.8 ± 6.5	16.0 ± 5.7	12 044.5	0.236	

*significant after applying Bonferroni-Holm correction to the probability level.

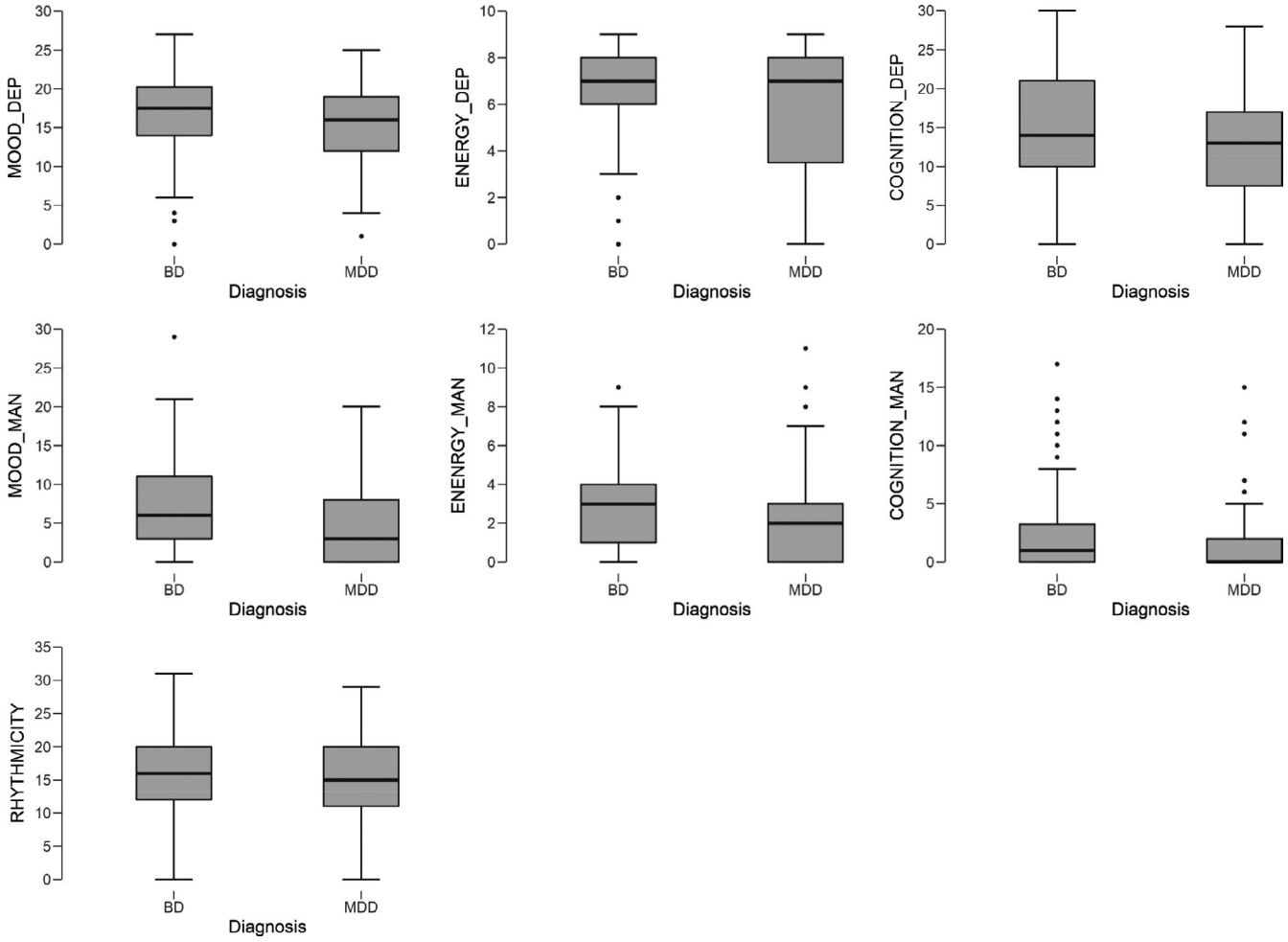

FIGURE 1 Box-plots of the mood spectrum domain scores. The line in the middle of the box is the median, the margins of the box are the 25th and 75th percentiles. The dots outside the whiskers are outliers

4 | DISCUSSION

The criteria for MDE provided by DSM for patients with BD and MDD are identical. However, differences between BD and MDD patients have been described by a number of authors[1-22] and are very frequently observed in clinical practice. In this study, we found significant differences between patients with BD and patients with MDD for several mood spectrum features. Specifically, patients with BD endorsed more manic spectrum items in the mood, energy, and cognitive domains and more depressive spectrum items in the energy and cognition domains. After adjusting for age, gender, and HRSD score in multivariate ANOVA, the energy depressive and mood manic score remained significantly higher in patients with BD, compared with patients with MDD. Our study confirmed that, during a MDE, patients with BD are more likely than patients with MDD to endorse "atypical" depressive features, which are

TABLE 3 Results of MANOVA comparing mood spectrum domains between patients with BD and MDD. Estimates of domain scores are adjusted for age, gender, and HRSD scores

Dependent variable	Mean	Std. error	95% Confidence interval	
			Lower bound	Upper bound
Mood depressive				
BD	16 661[a]	0.411	15.852	17.470
MDD	15 620[a]	0.409	14.815	16.425
Mood manic*				
BD	6908[a]	0.430	6.063	7.754
MDD	5104[a]	0.427	4.263	5.946
Energy depressive**				
BD	6626[a]	0.210	6.212	7.039
MDD	5713[a]	0.209	5.301	6.124
Energy manic				
BD	2852[a]	0.193	2.472	3.231
MDD	2316[a]	0.192	1.939	2.694
Cognition depressive				
BD	14 509[a]	0.515	13.495	15.523
MDD	12 672[a]	0.513	11.663	13.681
Cognition manic				
BD	2532[a]	0.260	2.019	3.044
MDD	1847[a]	0.259	1.338	2.357
Rhythmicity				
BD	15 752[a]	0.473	14.821	16.682
MDD	14 569[a]	0.471	13.643	15.495

[a]Covariates appearing in the model are evaluated at the following values: age = 50,07, HRSD score = 22,17.
*P = .003.
**P = .002.

well represented in the reduced energy depressive subdomain of MOODS-SR questionnaire.[3,20,21]

When we looked at differences in the endorsement of specific items, we found that patients with BD were more likely to endorse the items related to mood changes (both toward depression and toward mania) related to the abuse of drugs or alcohol. Not surprisingly, but still noteworthy, patients with BD were also more likely than patients with MDD to feeling passive and sluggish, having difficulty taking care of themselves, showing rapid shift of interests, being excessively preoccupied with money even in absence of any real financial problems, or rapidly making very important decisions. Interestingly, the differences were not exclusively limited to manic spectrum features.

Hence, the differences between BD and MDD are not simply limited to the presence or absence of a history of manic or hypomanic episodes, nor are they only related to the presence of comorbid symptoms of mania or hypomania during a MDE.

Of interest, a high percentage of patients with BD and a considerable percentage of patients with MDD endorsed manic/hypomanic items during a depressive episode. These findings confirm: (i) the high prevalence of mixed features in mood disorders[11,13,15]; (ii) the need for a unitary, dimensional, more descriptive and dynamic approach to MDD and BD[6,8,18] such as the ACE model proposed by Malhi and colleagues[18]; and (iii) the key role of mixed features in BD and, to a certain extent, in MDD as well.[11,12,14,18]

Several limitations of our study should be acknowledged. First, the self-report for the spectrum of mood disorders does not provide information on how the endorsed symptoms cluster. In other words, we were not able to establish if patients experienced isolated or clustered symptoms during the 1-month period that preceded and included the day of assessment. Also, the self-report does not explore the duration of occurrence of each item, since it only inquires whether the item occurred for a period of at least 3-5 days in the past month. Therefore, some items may have been endorsed for a longer period than others or, for patients whose episode started less than a month before the assessment, in periods when the individual was not fully depressed yet. Third, we cannot exclude a recall bias, given that the MOODS-SR instrument evaluates the current and past symptoms, which have occurred anytime during the previous month.

Clearly, larger, prospective studies are needed to better explore our preliminary findings. It is our hope that our study stimulates more research on the spectrum of mood symptoms that are

TABLE 4 Mood spectrum items endorsed with a significantly higher frequency in patients with BD compared with patients with MDD (Bonferroni-Holm correction)

Item		BD	MDD
Mood depressive			
20	Your mood became depressed as a result of using alcohol, sleeping pills, anti-anxiety drugs, nicotine, caffeine, stimulants, or similar substances even though you took them in order to feel better	24.8%	9.1%
Mood Manic			
49	Your mood changed rapidly from happy to sad and back again	37.9%	20.1%
55	Your mood became irritable or elevated when you were abusing and clearly in relation to alcohol, sedatives, hypnotics, anxiolytics, other substances, or within a month of withdrawal	21.4%	8.4%
56	Your mood became even more irritable or elevated when you increased your use of alcohol, sedatives, nicotine, caffeine, stimulants, and similar substances and you were already irritable or high	21.4%	7.8%
Energy depressive			
62	You felt passive, sluggish, and failed to take care of your usual commitments and responsibilities	84.8%	68.2%
64	You had difficulty taking care of yourself, for example, you showered less, wore the same clothes, did not put on make-up or shave).	74.5%	52.6%
Energy manic			
74	You found your interest shifting frequently from one thing to another and were easily distracted so that, for example, it was hard to finish a newspaper or magazine article or to watch a television program from beginning to end	56.6%	38.3%
Cognition depressive			
86	You were very preoccupied with money even though you did not have any real financial problems	41.4%	24%
Cognition manic			
126	You made very important decisions—such as selling or buying a house or car, or changing jobs—extremely rapidly	22.1%	8.4%

experienced by patients with BD and MDD and on the correlations between different symptom "phenotypes" and disease course and response to specific treatments.

CONFLICT OF INTEREST

Dr Cuomo is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Lundbeck, Otsuka. Dr Fagiolini is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Apsen, Boehringer Ingelheim, Doc Generici, FB-Health, Janssen, Lundbeck, Mylan, Otsuka, Polifarma, Recordati, Sanofi Aventis, Sunovion, Vifor. Dr Aguglia E is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Doc Generici, FB-Health, Janssen, Lundbeck, Otsuka, Fidia, Recordati. Dr Maina is/has been a consultant and/or a speaker and/or has received research grants from Janssen, Otsuka, Lundbeck, Angelini, Sanofi, Boehringer, Fb-health, Recordati. Dr Aguglia A, Bolognesi, Goracci, Mineo, Rucci, and Sillari have no conflict of interest.

DATA AVAILABILITY STATEMENT

The study complete database is available at the University of Siena, Department of Molecular Medicine, Division of Psychiatry.

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Exploration of mood spectrum symptoms during a major depressive episode: the impact of contrapolarity

Results from a transdiagnostic cluster analysis on an Italian sample of unipolar and bipolar patients

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ABSTRACT

BACKGROUND: The frequent occurrence of subthreshold hypomania during a major depressive episode challenges the dichotomic classification of mood disorders. In our study we employed a cross-diagnostic cluster analysis—based on a spectrum exploration of mood symptomatology—to identify distinct subgroups within a cohort of depressed patients.

METHODS: A k-means cluster analysis—built on the domain scores of the Mood Spectrum Self-Report (MOODS-SR) questionnaire—was performed on a data set of 300 adults with either bipolar or unipolar depression. After identifying the groups, between-clusters comparisons were conducted on MOODS-SR domains and factors and on a set of sociodemographic, clinical and psychometric variables.

RESULTS: Three clusters were identified: one with intermediate depressive and poor manic symptomatology (Mild), one with severe depressive and poor manic symptomatology (Moderate) and a third one with severe depressive and intermediate manic symptomatology (Mixed). Across the clusters, bipolar patients were significantly less represented in the Mild one, while the DSM-5 "Mixed features" specifier did not differentiate the groups. When compared to the other patients, those in the Mixed cluster were characterized by the following: younger current age and earlier age of disease onset; higher symptom severity, impulsivity and seasonality pattern scores; worse self-reported health and higher disability scores; and higher occurrence of: comorbid cluster B personality disorder, current psychotic ideation, suicidal ideation, lifetime suicide attempts and hospitalizations. After performing pairwise comparisons significant differences between Mixed and Moderate clusters were restricted to: current and disease-onset age, psychotic ideation, suicidal attempts, hospitalization numbers, impulsivity levels and comorbidity for Cluster B personality disorder.

CONCLUSIONS: In the present study a clustering approach based on a spectrum assessment of mood symptomatology led to the identification of three transdiagnostic groups of patients.

Consistent with our hypothesis, the magnitude of subthreshold (hypo)manic symptoms was related to a greater clinical severity, regardless of the main categorial diagnosis.

INTRODUCTION

Strong evidence supports the high frequency of contrapolar symptoms in patients suffering from a Major Depressive Episode (MDE)[1-3]. In a recent systematic review, the presence of three or more (hypo)manic symptoms in unipolar and bipolar depression is reported to range from 23% to 35%, respectively[4]. These percentages are significantly increased when a lower number of symptoms is considered[5-7]. Yet, despite its clinical relevance, subthreshold hypomania in patients with an ongoing MDE poses several issues in terms of psychopathological characterization, classification, diagnosis, and treatment[8, 9]. In 2013, the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5)[10] introduced the "with mixed features specifier" (MFS), applicable to manic, hypomanic and MDEs, both in bipolar disorder (BD) types I and II and in Major Depressive Disorder (MDD). This substantive update was meant to replace the DSM, Fourth Edition, Text Revision (DSM-IV TR)[11] narrow diagnostic category of "Mixed Episode", providing clinicians with more sensitive criteria, able to address the highly prevalent subsyndromal presentations of mixed states[12, 13]. Furthermore, the fulfillment of the MFS criteria in MDD was expressly indicated by the DSM-5 as a risk factor for the development of BD type I and II, warning clinicians about the need for a clinical evaluation over time, also in the perspective of a potential diagnostic transition. Consequently, the addition of the MFS to MDD was interpreted as a theoretical structural bridge between MDD and BD, positing a more spectrum-oriented approach to mood disorders[14, 15], coherent with the DSM-5 overarching principle of closer integration between the categorical and dimensional model[16].

Nevertheless, this nosologic change was judged to be controversial by several authors and much of the criticism focused on the diagnostic subtype of the MDE "with mixed features". Indeed, the threshold number of symptoms was deemed arbitrary, as was the choice to retain as mixed features only those manifestations belonging to the manic polarity, and excluding the so-called "overlapping

symptoms" such as irritability, psychomotor agitation and distractibility[17-19][17–19]. As remarked by several psychopathologists, the DSM neo-Leonhardian taxonomy of mood disorders, based on polarity (depression and mania as extreme poles of a bipolar dichotomy) rather than on the course and recurrence of the episode, constitutes a theoretical model, per se, unsuitable to offer a diagnostic prototype that would properly target the complexity of mixedness in the real-world clinical setting[20-22].

Starting from a lifetime spectrum approach to mood disorders as opposed to the rigid dichotomic DSM classification category, researchers of the Spectrum Project Collaborative Group developed a self-report tool (Mood Spectrum Self-Report [MOODS-SR]) that is functional for a dimensional model-based evaluation of mood episodes. This tool factorizes affective symptomatology into distinct domains (mood, energy, cognition and rhythmicity), considering subthreshold-level manifestations of unipolar and bipolar mood psychopathology[23, 24]. Similarly, Malhi and colleagues proposed the so-called Activity Cognition Emotion (ACE) model, which deconstructs any mood episodes into three main components, describing mixed states as the product of non-simultaneous changes in these domains[25], reprising the early Kraepelinian classification[26, 27]. Far from being a mere speculative issue, the availability of a valid nosologic framework, accounting for subthreshold hypomania, is fraught with several implications at different levels, including diagnostic recognition, treatment strategy and research direction[28-30]. Indeed, the unavailability of shared operational criteria has also been a limitation for studies aimed at exploring the neurobiological underpinnings of mixed depression. The vast majority of findings on altered monoaminergic function, hypothalamic–pituitary–adrenal (HPA) axis dysfunction, hyperinflammation, and circadian dysregulation in mixed states are derived from research focused on mixed mania[31]. Therefore, the applicability of the aforementioned pathophysiological mechanisms to mixed depression is purely conjectural.

The present study aimed to identify distinct subgroups using a cross diagnostic cluster analysis, based on the exploration of mood symptoms, according to a spectrum approach within a cohort of patients admitted with current unipolar and bipolar depression. Cluster analysis is a statistical technique that identifies subgroups as defined by selected features and whose application to heterogeneous and multidimensional disorders, such as MDD, may help to deconstruct disease complexity, contribute to the development and validation of diagnostic criteria, and support tailored treatment plans[32].

After identifying different clusters, we evaluated how cluster membership could be related to diagnostic categories and clinical and psychopathologic factors, hypothesizing that the degree of contrapolar symptomatology may be related to a more severe clinical phenotype of MDE.

METHODS

Sample

A post-hoc cluster analysis was performed on a data set derived from a multicenter cross-sectional study conducted in three Italian University Hospitals (Siena, Catania and Turin). The sample consisted of 300 adult individuals with a previously established DSM-5 diagnosis of either MDD or BD. The patients were recruited during their hospital stay, after being informed about the study focus and its voluntary nature. Clear assurance of confidentiality, anonymity, and absence of clinical management implications was also provided. Inclusion criteria were: 1) age > 18 years at entry of the study, 2) current diagnosis of an MDE confirmed by the Mini International Neuropsychiatric Interview (MINI) for DSM IV-TR[11], and 3) ability and willingness to sign a written informed consent. The exclusion criteria comprised a current or past diagnosis of any schizophrenia spectrum disorder, organic psychiatric disorder, major neurocognitive disorder, intellectual disability, or any other neurological condition that may have interfered with a the comprehensive evaluation of the patient. It was also required that patients had not received any

major pharmacotherapy changes in the last three weeks. Each center enrolled one hundred patients. The Institutional Review Boards at the Universities of Siena, Catania and Turin reviewed and approved all the study procedures. The data were collected in compliance with the current version of the Helsinki Declaration and were obtained after written informed consent was received. The complete data set is available from the authors upon request.

Assessment

A comprehensive psychiatric diagnostic assessment was conducted using the MINI, while sociodemographic and additional clinical characteristics were collected utilizing a semi-structured interview, used in two previously published studies[33, 34]. Patients were also assessed using the Barratt Impulsiveness Scale (BIS-11)[35, 36], the Short Form 12-Item Health Survey (SF-12)[37], the Sheehan Disability scale (SDS)[38], the Clinical Global Impression-Severity scale (CGI-S)[39] and the Seasonal Pattern Questionnaire Assessment (SPAQ)[40].

A dimensional evaluation of the current MDE was carried out by completing the last-month version of the MOODS-Self Report (MOODS-SR), developed from the Structured Clinical Interview for Mood Spectrum (SCI-MOODS)[25]. It is a psychometrically robust questionnaire, specifically structured for a dimensional assessment of mood episode phenomenology. It consists of 161 items, coded as present or absent, for a span of at least 3-5 days over the past month and organized into three depressive and three (hypo)manic domains. MOODS-SR items are targeted at examining energy levels, cognitive features, and affective symptoms, including signs and subthreshold manifestations of mood dysregulation. An adjunctive domain assesses disturbances and rhythmic changes in neurovegetative functions. The MOODS-SR was shown to be reliable with a substantial agreement between the self-report and the interview formats, as expressed by intraclass correlation coefficients (ICC) ranging from 0.88 to 0.97[24].

The internal structure of MOODS-SR was further divided into six depressive factors (depressive mood, psychomotor retardation, suicidality, drug illness-related depression, psychotic features, and neurovegetative symptoms) and five manic factors (psychomotor activation, mixed instability, spirituality/mysticism/psychoticism, mixed irritability and euphoria), identified by subsequent factorial analyses studies[41, 42]. The domain and factor scores were obtained as a count of the specific MOODS-SR items endorsed. The scoring procedures are described in detail at www.spectrum-project.org and in the cited papers[41, 42].

Statistical analyses

Descriptive statistics were reported as frequencies and percentages for categorical variables and as a mean and standard deviation for continuous variables with a normal distribution; non-normal variables were reported as mean, median and interquartile range [IQR]. For each variable, the normality of the distribution was tested using a Shapiro-Wilk test. A Spearman's correlation test was used to determine the correlation between the number of depressive and the number of (hypo)manic items in the total sample and the two main diagnostic groups.

In this study, we carried out a k-means cluster analysis based on the scores of the six MOODS-SR depressive and (hypo)manic domains.

The optimal number of clusters was determined using the NbClust package[43] implemented in the R software. The NbClust package allows for the comparison of 30 distinct clustering validity indices and recommends the best solution according to a majority rule, i.e., the optimal number of clusters is the one supported by the relative majority of the cluster validity indices. The search for the optimal number of clusters was a-priori set between one and five, with three being selected as the optimal number of clusters. After the clusters were formed, an initial set of one-way analyses was performed to verify whether the distribution of a group of sociodemographic and clinical variables differed among the clusters. The variables that were tested included: gender, age, age at

disorder onset, primary diagnosis (BD *vs.* MDD), DSM-5- MFS diagnosis, Koukopoulos Mixed Depression (KMxD) diagnosis[44], current psychotic ideation, current suicidal ideation, lifetime hospitalizations, lifetime suicide attempts, comorbidity of any anxiety disorders, substance use disorders, cluster A, cluster B and cluster C personality disorders, family history of mood disorders, CGI-S score, BIS-11 total score, SDS total score, SPAQ total score, SF-12 Physical Component Summary (SF-12-PCS) score, and SF-12 Mental Component Summary (SF-12-MCS) score. The assessment of DSM-5-MFS and KMxD criteria was carried out through the analysis of clinical records and by using proxy criteria derived from H.D.R.S., Y.M.R.S. and M.I.N.I. items. This reviewing procedure was independently conducted by three trained adult psychiatrists with a substantial experience in the field of mood disorders. The overall mean percentage agreement was 88.50 % (range, 82 -100%) We also assessed if there were significant inter-cluster differences in the scores of the internal depressive and (hypo)manic MOODS-SR factors.

The differences between the clusters were verified with suitable one-way analyses (ANOVA, Kruskall Wallis and chi-square tests), depending on the normal/non-normal distribution of the variables. If significant intergroup differences were detected, we performed appropriate pairwise post-hoc comparisons, adjusted for multiple comparisons (post-hoc analysis with Tukey's adjustment). Finally, a subset of variables (i.e., the ones proven to significantly differ between the Mixed and the Moderate clusters, and also "suicidal ideation") were modeled as outcomes of generalized linear models (GLMs) (logistic, Poisson or normal, depending on the distribution of the outcome), while the MOODS-SR factors represented the assumed predictors.

The coefficients of the GLM were estimated using elastic-net penalty regularization. The H2O R package[45] was used to fit the logistic regression with the elastic-net penalty. The elastic-net technique optimally combines two penalties on the coefficients being estimated, the Least Absolute Shrinkage and Selection Operator (LASSO) (L1) and the Ridge (L2). Both penalties mitigate the impact of non relevant or collinear predictors, by shrinking their coefficients toward zero in the

estimation process. This provides a more robust and direct identification of relevant variables, compared to the iterated stepwise approach based on classical regression inference. Thus, under the elastic net method, relevant predictors are indicated by an absolute coefficient greater than 0, instead of by a *p*-value under the significance threshold used in the classical inferential approach. Finally, the GLM performance measures, i.e., Area Under the Roc Curve (AUC), R squared (R^2) and Akaike's information criterion (AIC) were estimated using 10-fold cross-validation to avoid overfitting, considering the relatively limited sample size.

All statistical analyses were performed using the R Statistical software[46] and associated specific R packages like Emmeans[47] and DescTools[48]. The H2O R package[45] was used to fit the logistic regression with the Elastic net penalty. Statistical significance was assessed by using a 5% threshold except for the Elastic net regression analysis.

RESULTS

Characteristics of the total sample

The sample consisted of 300 patients of which one 155 (51.7%) had a primary diagnosis of MDD while 145 (48.3%) were affected by BD. Females represented 60.7% of the sample while the mean age was 50.1 (14.7). DSM-5 threshold criteria for MFS were met only by forty-four subjects (14.7%), while 165 qualified for the KMxD diagnosis. The mean (median) number and [IQR] of the depressive MOOD-SR items endorsed by the patients with MDD and by the patients with BD were 33.65 (36) [18] and 38.28 (40) [17] respectively, whereas, the mean (median) number and [IQR] of the manic MOOD-SR items experienced by unipolar and bipolar patients were 8.61 (6) [12] and 12.76 (11) [12] respectively.

The Spearman's rank correlation test showed a weak positive correlation between total depressive and total manic MOODS-SR component scores within the total sample ($p = 0.292$; $p < 0.001$) and also within both main diagnostic groups (MDD: $p = 0.299$; $p < 0.001$; BD: 0.224; $p < 0.05$). The characteristics of the total sample are reported in Table 1.

Table 1: Sociodemographic characteristics of the sample

Gender (female), N (%)	182 (60.7)
Current age, mean ± SD - (median) [IQR]	50.1 ± 14.7 - (50) [21]
Years of education, mean ± SD - (median) [IQR]	11.5 ± 4.50 - (13) [5.0]
Marital status, N (%)	
Single	109 (36.3)
Married	130 (43.4)
Other	61 (20.3)
Occupation, N (%)	
Unemployed	118 (39.3)
Student	18 (6.0)
Employed	111 (37.0)
Retired	53 (17.7)
Living status, N (%)	
Alone	95 (31.7)
With Relatives	205 (68.3)
Primary diagnosis, N (%)	
Major Depressive Disorder	155 (51.7)
Bipolar Disorder	145 (48.3)
Mixed Depression diagnosis, N (%)	
DSM-5 Mixed Features Specifier	44 (14.7)
Koukopoulos Mixed Depression	165 (55,0)
Lifestyle habits	
Smoker, N (%)	127 (42.3)
Daily number of cigarettes, mean ± SD	16.6 ± 9.4
Alcohol consumption, N (%)	67 (22.3)
Daily alcohol units, mean±SD	3.0 ± 2.8
Physically inactive, N (%)	189 (63.0)
Young Mania Rating Scale, mean ± SD - (median) [IQR]	4.8 ± 4.1- (4.0) [6.0]
Hamilton Depression Rating Scale, mean ± SD	24.3 ± 4.3
Clinical Global Impression, mean ± SD- (median) [IQR]	4.8 ± 0.8 - (4.0) [1.0]
Shehaan Disability Scale, mean ± SD - (median) [IQR]	20.96 ± 6.90 - (22) [11]
Short Form 12 Item Health Survey	
Physical component summary, mean ± SD - (median) [IQR]	42.93±10.70 - (40.5) [14.5]
Mental component summary, mean ± SD - (median) [IQR]	25.31±10.15 – (23.9) [12.9]

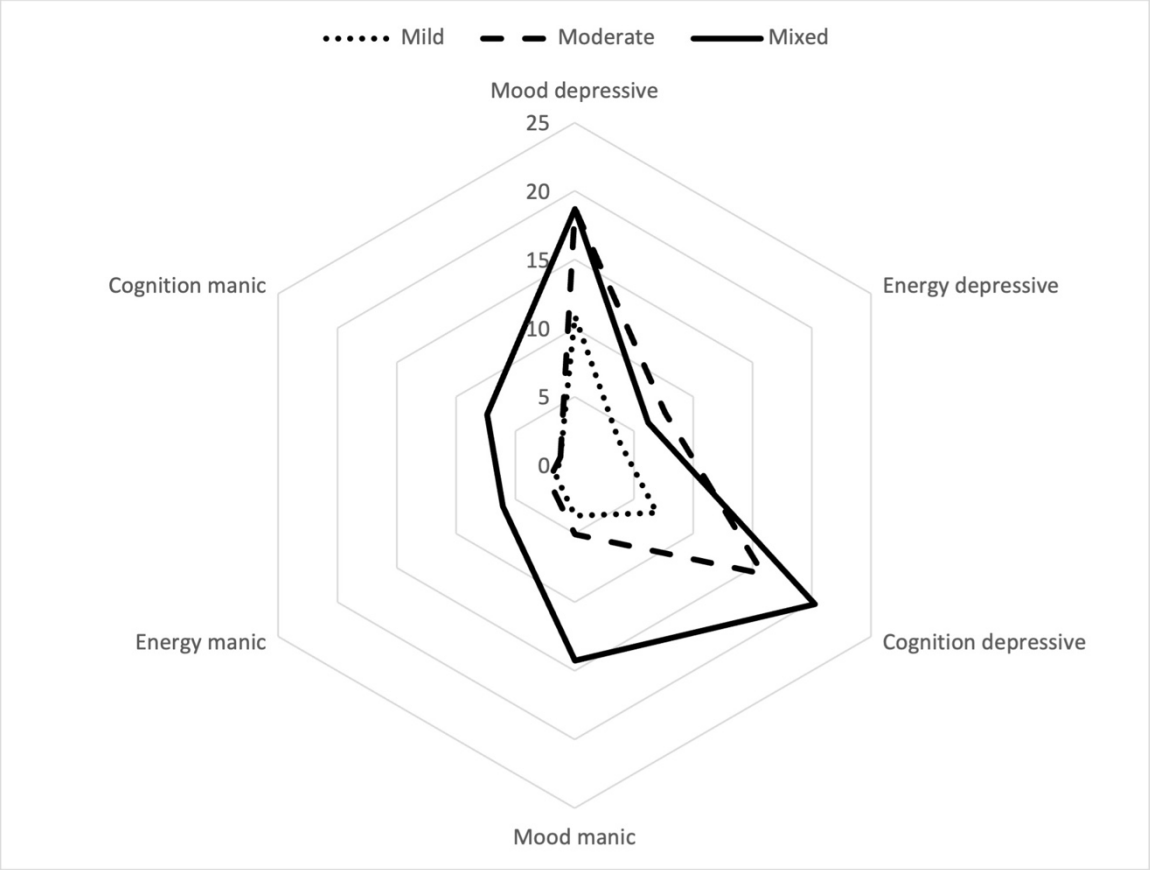
DSM-5= Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; IQR= interquartile range; MFS= Mixed features specifier; N= number of subjects; SD= standard deviation

Cluster analysis

13 out of the 30 validity indices implemented in the NbClust package selected a three-cluster solution, which was therefore adopted as the optimal clustering fit. The number of patients in

cluster one (n=98), two (n=158) and three (n=44) accounted for 32.7%, 52.7% and 14.6% of the total sample, respectively. After comparing the cumulative scores of the depressive and (hypo)manic MOODS-SR domains for each of the three clusters and the trend of the severity-illness related measures across them, they were labeled as Mild (cluster 1), Moderate (cluster 2) and Mixed (cluster 3) (see figure 1). Indeed, we were able to detect a group characterized by intermediate levels of depressive symptoms and low levels of (hypo)manic symptoms (Mild cluster), a group with high levels of depressive symptoms and intermediate levels of (hypo)manic symptoms (Mixed cluster) and a large group (Moderate cluster) with depressive and manic symptomatology levels overlapping with those recorded for the Mixed and Mild cluster, respectively.

Figure 1: Radar chart representing the distribution of the MOODS-SR domains across the three clusters.



A significant main group effect was observed on all scores of the MOODS-SR domains and post-hoc tests were run to determine the pairwise differences (see table 2 for numerical results and figure 1 and 2 for graphical representations). The Mild cluster was significantly lower than Mixed on all domains and was also significantly lower than Moderate on all domains, except for "cognition manic". The Mixed cluster was significantly higher than Moderate on all domains, except "mood depressive", "energy depressive" and "rhythmicity". The Mixed and Moderate clusters had similar total average scores in depressive domains, being both significantly higher than Mild. On the other hand, the total average scores of the Mild and Moderate clusters on (hypo)manic domains did not differ significantly but both were significantly lower than Mixed.

A significant main group effect was also observed in all scores of the MOODS-SR factors. With regard to (hypo)manic symptomatology, the Mixed cluster reported significantly higher scores in all (hypo)manic factors than both the Moderate and the Mild clusters, while these differed significantly from each other only in "mixed irritability" (Moderate > Mild) and in "euphoria" (Mild > Moderate). Regarding the depressive factors, the Mild cluster showed significantly lower scores for each factor compared to the Mixed and the Moderate clusters, which instead only differed significantly from each other in "psychomotor retardation" (Moderate > Mixed), "suicidality factor" (Mixed > Moderate), "depressive psychotic" features (Mixed>Moderate) and "drugs illness-related depression" (Mixed > Moderate).

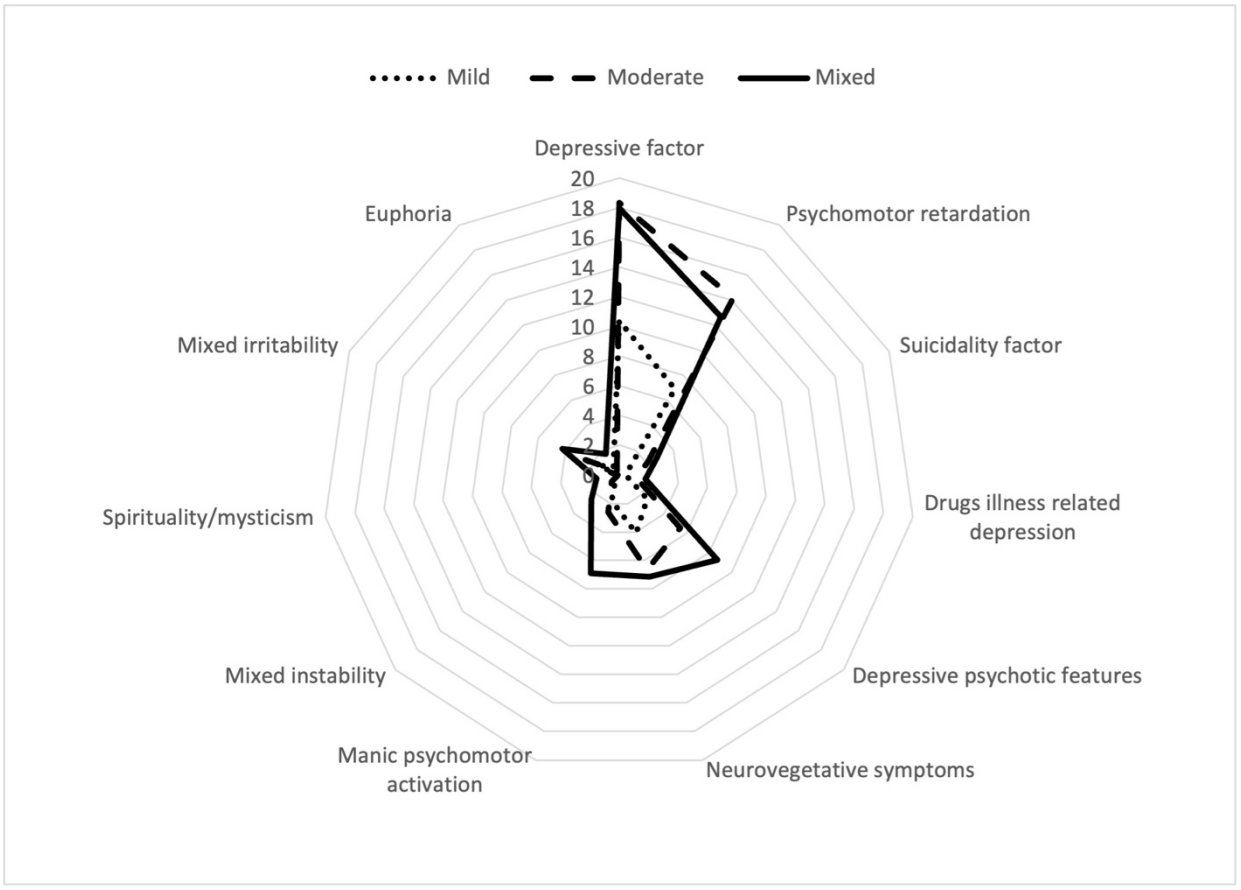
Table 2: Comparison between the clusters in MOODS-SR domains and factors

MOOD-SR DOMAINS	Clusters			Inter-cluster differences	
	Mild (N=98)	*Moderate.* (N=158)	*Mixed* (N=44)	Overall Kruskal-Wallis p-value	Post-hoc cluster comparisons
	Mean *(Median)* [IQR]	Mean *(Median)* [IQR]	Mean *(Median)* [IQR]		
Mood depressive	10.87 (11.50) [5.75]	18.72 (19.00) [5.00]	18.70 (19.00) [5.00]	<0.001	Mod.≃Mixed>Mild
Energy depressive	3.69 (4.00) [5.00]	7.61 (8.00) [2.00]	6.20 (6.50) [2.25]	<0.001	Mod.>Mixed>Mild

Cognition depressive	6.93 (7.00) [4.00]	15.89 (15.00) [6.00]	20.25 (21.50) [8.25]	<0.001	Mixed>Mod.>Mild
Depressive symptoms total score	21.51 (22.00) [9.03]	42.23 (42.00) [18.75]	45.16 (46.50) [12.25]	<0.001	Mod.≃Mixed>Mild
Mood manic	3.69 (2.00) [6.75]	5.04 (4.50) [6.00]	14.27 (14.00) [7.25]	<0.001	Mixed>Mod.>Mild
Energy manic	1.57 (1.00) [3.00]	2.18 (2.00) [2.00]	6.04 (6.00) [2.00]	<0.001	Mixed>Mod.>Mild
Cognition manic	1.20 (0.00) [2.00]	1.20 (1.00) [2.00]	7.40 (7.00) 7.00	<0.001	Mixed>Mod.≃Mild
(Hypo)manic symptoms total score	6.47 (5.00) [10.00]	8.43 (8.00) [9.00]	27.72 (26.00) [10.25]	<0.001	Mixed>Mod.≃Mild
Rhytmicity	12.68 (12.50) [7.0]	16.26 (16.00) [8.75]	18.38 (19.00) [7.25]	<0.001	Mod.≃Mixed>Mild
DEPRESSIVE MOODS-SR FACTORS					
Depressive factor	10.37 (11.00) [5.00]	18.35 (18.00) [5.00]	17.97 (19.00) [5.00]	<0.001	Mod.≃Mixed>Mild
Psychomotor retardation	6.91 (7.00) [6.00]	14.15 (15.00) [3.00]	12.65 (13.50) [4.00]	<0.001	Mod.>Mixed >Mild
Suicidality factor	0.58 (0.00) [0.00]	2.12 (2.00) [4.00]	2.79 (2.00) [4.00]	<0.001	Mixed≃Mod.>Mild
Drugs illness related depression	0.49 (0.00) [1.00]	1.16 (1.00) [2.00]	1.79 (2.00) [2.00]	<0.001	Mixed >Mod. Mild
Depressive psychotic features	2.46 (2.0) [2.0]	5.45 (5.0) [3.0]	8.73(9.5) [4.25]	<0.001	Mixed> Mod.>Mild
Neurovegetative symptoms	4.07 (4.00) [4.00]	6.63 (7.00) [2.19]	7.15 (8.00) [3.00]	<0.001	Mod.≃Mixed>Mild
MANIC MOODS-SR FACTORS					
Manic psychomotor activation	1.78 (1.00) [3.00]	2.62 (2.00) [3.00]	6.90 (7.00) [2.25]	<0.001	Mixed>Mod.≃Mild
Mixed instability	0.31 (0.00) [0.00]	0.66 (0.00) [1.00]	2.50 (2.00) [3.00]	<0.001	Mixed>Mod.≃Mild
Spirituality/mysticism psychoticism	0.08 (0.00) [0.00]	0.13 (0.00) [0.00]	1.55 (1.00) [2.00]	<0.001	Mixed>Mod.≃Mild
Mixed irritability	1.48 (1.00) [2.00]	2.50 (2.00) [1.00]	4.25 (4.00) [1.25]	<0.001	Mixed> Mod.>Mild
Euphoria	0.72 (0.00) [1.00]	0.32 (0.00) [0.00]	1.68 (1.50) [2.00]	<0.001	Mixed>Mild>Mod.

The ">" symbol means that the median/mean value of the cluster on the left side of the symbol is statistically different and higher than the cluster on the right side of the symbol, the "≃" symbol means that the median/mean value of the cluster on the left and right sides of the symbol are not statistically different. IQR= interquartile range.

Figure 2: Radar chart representing the distribution of the MOODS-SR factors (according to factor analysis by Cassano) across the three clusters.



Comparisons among clusters

Clinical, diagnostic and severity variables

There were no gender differences among the three clusters. Significant inter-cluster differences were found for current age and age at onset of disorder, with post-hoc analysis indicating that patients belonging to the Mixed group were significantly younger and had an earlier onset of disease compared to the other two clusters (Mild and Moderate).

Patients with BD were significantly less likely to be present in the Mild cluster than in the Moderate and Mixed clusters. The DSM-5 MFS did not differentiate the three subgroups, unlike the diagnosis of KMxD, which was significantly more prevalent in the Mixed cluster.

Regarding the psychiatric comorbidities, we did not find any significant difference in the prevalence of anxiety disorders across the three groups. Conversely, a significantly higher rate of a comorbid cluster B personality disorder, as well as a significantly lower rate of a comorbid cluster C personality disorder among patients belonging to the Mixed cluster, was observed.

When a subset of disease-severity and psychometric variables was considered, significant between-group differences were found for CGI-S, BIS-11, SPAQ, SDS, SF-12 Physical Component Summary (PCS) and SF-12 Mental Component Summary (MCS) scores, current psychotic and suicidal ideation, lifetime suicide attempts and the number of hospitalizations, with Mixed cluster patients reporting higher or worse values on each of these measures (except for the SF-12 MCS). Subsequent post-hoc pairwise comparisons showed that the Mixed and Mild clusters significantly differed on each of these outcomes. On the other hand, significant differences between the Mixed and Moderate clusters were restricted to BIS-11 total score, current psychotic ideation, lifetime hospitalizations, suicide attempts. Significant differences between the Mild and Moderate clusters were instead limited to CGI-S scores and current suicidal ideation (see table 3).

Table 3: Comparison between the clusters on clinical characteristics, diagnostic features and psychometric measures

	Clusters			Inter-cluster differences	
	Mild (N=98)	*Moderate* (N=158)	*Mixed* (N=44)	Overall	Post-hoc cluster comparisons
	N (%) *(Median)* [IQR]	N (%) *(Median)* [IQR]	N (%) *(Median)* [IQR]	p	
Female	60 (61.2%)	97 (61.4%)	25 (56.8%)	0.94	-
Age	49.72 *(49.5)* [14.0]	52.78 *(54.0)* [18.0]	41.02 *(41.0)* [13.75]	**<0.01**	**Mild≃Mod.>Mixed**
Age at disorder onset	35.50 (25.75)	28.50 (23.75)	22.00 (13.25)	**<0.01**	**Mild≃Mod.>Mixed**
Bipolar diagnosis	35 (35.7%)	85 (53.8%)	25 (56.8%)	**<0.01**	**Mixed≃Mod.> Mild**
MFS	15 (15.3%)	18 (11.4%)	11 (25.0%)	0.08	NC
KMxD	42 (46.9%)	85 (53.8%)	34 (77.3%)	**<0.01**	**Mixed>Mod. ≃Mild**
Cluster A pers. dis.	2 (2,0%)	2 (1,3%)	1 (2,3%)	0.8	-
Cluster B pers. dis.	13 (13,3%)	28(17.7 %)	24 (54.5%)	**<0.01**	**Mixed>Mod.≃Mild**
Cluster C pers. dis.	16 (16.3%)	21 (13.3%)	0 (0.0%)	**0.02**	**Mild.≃Mod.>Mixed**
Anxiety disorder	28 (28.6%)	37 (23.4%)	10 (22.7%)	0.6	-
Substance use disorder	5 (5.1%)	13 (8.2%)	8 (18.2%)	**0.04**	**Mixed>Mild**
Mood disorders familiarity	45 (45.9%)	87 (55.1%)	25 (56.8%)	*0.3*	-
CGI-S	4.00 (1.00)	4.00 (1.00)	5.00 (1.00)	**<0.01**	**Mixed≃Mod>Mild**
Current suicidal ideation	31 (31.6%)	94 (59.5%)	33 (75.0%)	**<0.01**	**Mixed≃Mod>Mild**

Current psychotic ideation	12 (12.2%)	39 (24.7%)	20 (45.5%)	**<0.01**	**Mixed>Mod.≃Mild**
Hospitalizations	0.75 *(0.00)* [1.00]	1.77 *(1.00)* [1.00]	2.47 *(2.00)* [2.25]	**<0.01**	**Mixed>Mod.>Mild**
Suicidal attempts	0.13 *(0.0)* [0.0]	0.42 *(0.0)* [1.0]	0.77 *(0.0)* [1.25]	**<0.01**	**Mixed>Mod.>Mild**
BIS-11	60.19 *(61.00)* [13.00]	64.01 *(63.00)* [12.00]	69.34 *(70.00)* [11.00]	**<0.01**	**Mixed>Mod.>Mild**
SPAQ	9.77 *(11.00)* [8.00]	12.46 *(13.00)* [6.75]	12.79 *(13.00)* [4.00]	**<0.01**	**Mixed≃Mod.>Mild**
SDS	16.96 *(15.00)* [11.75]	22.79 *(24.00)* [6.00]	23.27 *(25.00)* [7.00]	**<0.01**	**Mixed≃Mod.>Mild**
SF-12 PCS	45.01 *(47.4)* [17.2]	41.42 *(40.1)* [14.5]	37.99 *(36.3)* [12.9]	**<0.01**	**Mild>Mod.≃Mixed**
SF-12 MCS	31.59 *(30.6)* [12.5]	22.23 *(21.1)* [9.4]	22.43 *(19.9)* [8.9]	**<0.01**	**Mild>Mod.≃Mixed**

The ">" symbol means that the median/mean value of the cluster on the left side of the symbol is statistically different and higher than the cluster on the right side of the symbol, the "≃" symbol means that the median/mean value of the cluster on the left and right sides of the symbol are not statistically different. BIS-11= Barratt Impulsiveness Scale score; KMxD= Koukopoulos Mixed Depression; MFS= Mixed features specifier; SDS = Sheehan Disability scale; SF-12 MCS = Short Form 12 Item Health Survey Mental component summary; SF-12 PCS = Short Form 12 Item Health Survey Physical component summary; SPAQ = Seasonal Pattern Questionnaire Assessment.

Regression analyses

The results of the GLMs are detailed in table 4. The MOODS-SR factors, identified as positive or negative predictors for the outcomes considered, are indicated by non-zero values for standardized coefficients, with higher values expressing a greater magnitude of influence on the respective outcomes.

Table 4: Regression of MOODS-SR Factors with the selected variables.

	Current psychotic ideation	Current suicidal ideation	Lifetime suicide attempts	Lifetime hospitalizations	BIS-11	Cluster B-pers. dis.
MOODS-SR Factors	St.coeff.	St.coeff	St.coeff	St.coeff	St.coeff	St.coeff
Depressive factor	**0.19**	**0.05**	0.00	**0.12**	**0.82**	**0.35**
Psychomotor retardation	**0.10**	0.00	0.00	**0.13**	**0.02**	**-0.21**
Suicidality factor	**0.12**	**1.15**	**0.54**	**0.03**	0.00	**0.51**
Drugs illness related depression	0.00	**0.17**	0.00	**0.02**	0.00	**-0.05**
Depressive psychotic features	**0.01**	0.00	0.00	**0.04**	0.00	**-0.34**
Neurovegetative symptoms	**0.01**	0.00	0.00	**0.08**	0.00	**-0.02**
Manic psychomotor activation	**0.32**	**0.18**	**0.22**	**0.06**	**0.63**	**0.25**
Mixed instability	0.00	0.00	**0.12**	**0.07**	**0.61**	**0.29**
Spirituality/Mysticism psychoticism	**0.12**	0.00	**-0.12**	**0.03**	**0.34**	**0.02**
Mixed irritability	**0.14**	**0.06**	0.00	**0.04**	**2.16**	**0.32**
Euphoria	**0.15**	0.00	0.00	**-0.03**	0.00	**0.34**
Intercepts	**-1.29**	**0.24**	**-1.21**	**0.36**	**63.55**	**-1.53**
GLM type	logistic	logistic	poisson	poisson	gaussian	logistic
AUC	0.71	0.81				0.78
R2					28%	
AIC			1139.00	458.00		

Significant variables in bold. AIC: Akaike's information criterion; AUC: Area Under the Roc Curve; BIS-11= Barratt Impulsiveness Scale score; GLM: General Linear Model; R^2: R squared; Stand. coeff.: standardized coefficients;

DISCUSSION

In the present study, we aimed at clustering a sample of inpatients admitted for a MDE in the context of either MDD or BD, based on a spectrum evaluation of mood symptomatology to ascertain whether subthreshold contrapolar symptoms may act as discriminant and moderating severity factors of a current MDE. Before performing the cluster analysis, we checked the relationship between the depressive and (hypo)manic components, finding a similar positive correlation between the number of depressive and manic/hypomanic items, experienced by patients with BD or MDD. This linear relationship had already been found in a previous study by Cassano et al. in a sample that included patients with remitted recurrent unipolar depression and patients with current bipolar depression[49].

Actually, the relationship between depressive and manic symptoms has been investigated by several cross-sectional and longitudinal studies, none of which foundsupport for the core assumption of a robust negative correlation between contrapolar symptoms, posited by the unidimensional model of

bipolar disorder, as no fixed relation pattern was identified[50-52]. Thus, depressive and (hypo)manic symptoms might be conceived as two separate dimensions, independently fluctuating even in their subdomains and this conceptualization would imply an orthogonal, rather than a linear approach to nosology, better encompassing the highly heterogeneous realm of mixed forms[20, 53].

The K-mean clustering analysis identified three numerically inhomogeneous transdiagnostic clusters, showing distinct profiles of MOODS-SR domains scores. As expected, BD patients were proportionally more represented in the Mixed cluster compared with the other two, but the post-hoc analysis revealed a statistically significant difference in BD diagnosis distribution only between the Mixed and Mild clusters. Considering only the Moderate and Mixed clusters, as they share similar levels of depressive symptomatology and BD prevalence rates, the analysis of the between-groups differences on MOODS-SR factors suggests the presence, in our sample, of two phenotypes of bipolar depression distinguished by different combined degrees of inhibition and hyperactivation. Our findings can be added to those of previous studies, to show evidence for heterogeneity in bipolar depression with the identification of subtypes, based on clinical and psychopathological dimensions rather than nosologic categorization (i.e., BD type I and II)[54-56].

In the present study, we also investigated the pattern of distribution across the clusters of two alternative diagnostic constructs for “Mixed depression”. The prevalence of DSM-5 MFS was higher among the Mixed cluster patients with a percentage of 25%, but no significant mean effect of group was found. This finding may appear in contrast to the results of a recent study involving unipolar and bipolar patients suffering from MDE[57], which identified the clinical presentation with DSM-5 MFS criteria as the second strongest association with the cluster burdened by greater illness severity. Some methodological differences can partially account for this contrast in findings (i.e. different mood symptomatology assessment tools, disparities in sample size, recruitment procedures, inter-rater reliability levels, care settings, and the heterogeneity of the study population). Consequently, we may surmise that the DSM-5 MFS plays the role of a highly specific

marker of mixedness, identifying more dramatic mixed presentations while leaving a large portion of mixed episodes underdiagnosed[5, 57].

Interestingly, the alternative diagnostic construct of mixed depression, proposed by Koukopoulos (KMxD)[44], presented higher prevalence rates than DSM-5 MFS in each of the three clusters and it was found to discriminate the Mixed group from the Mild and Moderate ones after a post-hoc analysis. Taken together, these findings appear to be consistent with the arguments questioning the diagnostic validity of the DSM-5-MFS, deemed to be poorly sensitive, and phenomenologically focused on pure manic manifestations but unable to capture the critical excitatory and dysphoric components of mixed depression[58, 59]. These components have instead been incorporated into the KMxD criteria and, accordingly, the scores of the "mixed instability" and "mixed irritability" MOODS-SR subdomains were significantly higher in the Mixed cluster compared to the Mild and Moderate ones.

The study of the distribution across the clusters of the select sociodemographic, psychometric, and clinical variables revealed an overall disease-severity gradient from the Mild to the Mixed cluster. The Mixed cluster exhibited a strong association with most of the illness-severity, quality of life, and outcomes measures considered, qualifying as a more severe clinical phenotype, consistent with well-established mixed presentations described in the literature[2, 60, 61]. Compared to the patients in Mild and Moderate clusters, those belonging to the Mixed one were characterized by younger age and an earlier onset of disease, a higher number of hospitalizations and previous suicide attempts, the more likely presence of psychotic and suicidal ideation, greater levels of impulsivity, worse self-reported health and higher disability scores. Furthermore, within the Mixed cluster, we recorded higher comorbidity rates of any Cluster B personality disorders or any substance use disorder. However, after post-hoc pairwise comparisons between the Moderate and Mixed clusters, both characterized by similar MOODS-SR depressive total scores, statistically significant differences

were limited to the number of hospitalizations and suicide attempts, psychotic ideation, comorbidity of Cluster B personality disorders, and higher impulsiveness levels.

Finally, the potential correlations between the previously mentioned discriminant variables and the MOODS-SR depressive and hypomanic factors were explored. The regression model for the variable “suicide attempts” revealed that - excluding the intuitive correlation with the “suicidality factor”- the main predictors were represented by two (hypo)manic factors, namely “manic psychomotor activation” and “mixed instability”, consistent with the available evidence on the impact of these domains on the psychopathogenic pathway to suicidal behaviors in mood disorders[62-65]. In particular, as suggested by a comparative assessment of the two separate regression models for suicidal ideation and lifetime suicidal attempts, marked emotional lability and dysphoria may be supposed to exert a critical role in governing the transition from suicidal thought to suicidal acts.

Interestingly, the only negative predictor of lifetime suicide attempts was represented by “spirituality-mysticism-psychoticism”, confirming the religious-spiritual dimension as a protective factor against suicidal attempts[66, 67]. Regarding the predictors for the outcome “lifetime hospitalizations”, contrary to the expectation of overlap with the predictors for suicidal attempts, we observed a slightly greater relevance of MOODS-SR factors belonging to the depressive pole. Specifically, psychomotor retardation may be seen as a symptomatic marker of remarkable importance in guiding clinicians whether to opt for patient' hospitalizations[68-70]. On the other hand, the level of impulsivity exhibited by our patients was associated with a greater number of positive predictors among the MOODS-SR hypomanic factors. Specifically, the mixed irritability factor presented the highest coefficient, followed by the depressive factor. The presence of subthreshold hypomanic symptoms during an MDE could, therefore, exert a multiplying effect on the proportion of impulsiveness already intrinsic to the depressive episode in both bipolar and unipolar patients[71-73]. Finally, the regression analysis carried out for the variable “comorbid

cluster B personality disorder" (represented mainly by a borderline personality disorder - BDP) showed a pattern of positive and negative predictors that appears consistent with the phenomenological characterization of BPD. The significant comorbidity of BPD observed among Mixed cluster patients is not surprising but widely reported in the literature[74-76]. Indeed, the phenomenological and clinical similarities between some mixed episodes and BDP represent critical arguments in the psychopathological debate about the possible inclusion of this personality disorder within the bipolar spectrum[77-79].

This study is subject to several limitations that should be considered when interpreting the results. Firstly, the sample size was not large enough to allow for additional homogeneous subgroups (and therefore to estimate alternative optimal clustering solutions) since sufficient power would have been lost if further trait differences between smaller cluster groups were defined.

Secondly, the MOODS-SR questionnaire inquires only whether the item occurred for at least 3-5 days in the past month, without providing any additional information on the entire duration of occurrence and the intensity of each item. Also, given that the instrument assesses the current and lifetime symptoms, that occurred any time in the last month, there might be a recall bias.

Thirdly, since complete pharmacotherapy data are missing, our findings cannot be adjusted for them. Finally, the multicenter nature of the study may have resulted in differences in the policies adopted for patient' hospitalizations and the definition-criteria of suicide attempts.

CONCLUSION

Using a cluster analysis based on a mood spectrum evaluation, this study identified three transdiagnostic clusters in a sample of acutely depressed patients. In support of our hypothesis, the magnitude of subthreshold (hypo)manic symptoms was related to greater clinical severity, regardless of the main categorical diagnosis. The transdiagnostic composition of each cluster and the orthogonal relationship observed in each group between depressive and manic symptoms, would

seem to challenge the unipolar-bipolar dichotomy, supporting the existence of a continuum between the two opposite poles and the consequential need for a dimensional probabilistic approach to mood disorder diagnosis. Furthermore, in line with other studies, our results portray the attempt made by the DSM-5 to provide a reliable nosological framework for intra-MDE hypomania through the introduction of the DSM 5-MFS as unsuccessful, because of the intrinsic limits of that diagnostic category in targeting the whole realm of mixed states. On the other hand, this study represents an attempt at subtyping MDEs based on an in-depth exploration of mood spectrum phenomenology, and challenging the limitations of current categorical systems and polythetic diagnostic criteria. The identification of validated subtypes may aid in improving the classification performance and in guiding therapeutic choices (e.g., the use of antidepressants and the selection of a specific class), allowing a reasonable risk stratification regardless of the diagnostic categorical label. Furthermore, patients clustering based on the deconstruction of affective psychopathology may be functional for research into distinct underlying biological processes and for the subsequent development of personalized treatments[80].

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ORIGINAL ARTICLE

BIPOLAR DISORDERS WILEY

Which mixed depression model? A comparison between DSM-5-defined mixed features and Koukopoulos' criteria

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Abstract

Background: The criteria of the *Diagnostic and Statistical Manual of Mental Disorders* 5th edition "with mixed features specifier" (DSM-5 MFS) are considered controversial since they include only typical manic symptoms. By contrast, Koukopoulos developed an alternative model of mixed depression (MxD) focusing primarily on the excitatory component.

Objective: To compare DSM-5 MFS and Koukopoulos' MxD (KMxD) in terms of prevalence, associated clinical variables, and discriminative capacity for bipolar depression in patients with major depressive episode (MDE).

Methods: A total of 300 patients with MDE—155 with major depressive disorder and 145 with bipolar disorder (BD)—were recruited. The discriminative capacity of DSM-5 MFS and KMxD criteria for BD was estimated using the area under the curves of receiver operating characteristic (ROC_AUC). The clinical variables associated with these two diagnostic constructs were assessed by performing a logistic regression.

Results: A total of 44 and 165 patients met the DSM-5 MFS and KMxD criteria, respectively. The ROC_AUCs and their confidence intervals for BD according to DSM-5 MFS and KMxD were 77.0% (72.0%-82.1%) and 71.9% (66.2%-77.7%), respectively. The optimal thresholds (combining sensitivity and specificity measures) for BD diagnosis were ≥1 (77%/68%) for DSM-5 MFS and ≥3 symptoms (78%/66%) for KMxD. However, considering the DSM-5 MFS cut-off (≥3 symptoms), the specificity (97%) increased at the expense of sensitivity (26%).

Conclusions: KMxD and DSM-5-MFS showed an overlapping discriminative capacity for bipolar depression. The current diagnostic threshold of DSM-5 MFS did not prove to be very inclusive, if compared with the greater diagnostic sensitivity of KMxD, which also yielded better association with clinical variables related to mixedness.

KEYWORDS
bipolar, depression, Elastic Net, generalized linear model, mixed features, mood disorders, receiver operating characteristic curve, sensitivity, specificity, unipolar

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1 | INTRODUCTION

Mixed states (MS) refer to mood episodes characterized by the co-occurrence of symptoms of opposite polarity. Despite this simple definition, their conceptualization and subsequent nosographic categorization still represent one of the most controversial issues in psychiatry with significant implications for daily clinical practice in terms of recognition, diagnostic assessment, illness course, prognosis, and therapeutic strategies.[1]

In the two previous versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), MS appeared as a marginal entity coherently with the rejection of the Kraepelinian unitarian concept of manic-depressive illness in favor of the unipolar–bipolar dichotomy.[2] Indeed, in DSM IV[3] and DSM IV-TR[4] MS were incorporated into the diagnostic category of Mixed Episode (ME). This diagnosis required the co-presence for at least 1 week of symptoms that fulfilled the criteria for either a major depressive episode (MDE) or a manic episode. Thus, in the past DSM classification, ME designated a diagnosis of bipolar I disorder (BD-I), excluding a diagnosis of bipolar II disorder (BD-II) or major depressive disorder (MDD). The DSM-IV-TR ME criteria proved to be of little clinical utility as they were extremely narrow and targeted an almost unrealistic clinical condition. This diagnostic category appeared particularly inadequate in discriminating those mood episodes with a prevalent depressive polarity plus concurrent (hypo)manic symptoms but nosologically included in the catch-all entity of MDE.[5] Hence, a growing number of psychiatrists have challenged the official classification of ME, offering alternative, less narrow definitions of mixed depressive states. For instance, Benazzi proposed as diagnostic criteria for "mixed depression" the presence of ≥3 DSM-IV-TR within hypomanic symptoms (adding irritable mood but excluding elevated mood and inflated self-esteem).[6] Akiskal, on the other hand, conceptualized MS as the combination of an episode of affective alteration with a dominant temperament of different polarity. In line with this view, it is possible to classify two different mixed depressive states resulting from the overlap of major depression with either a cyclothymic or a hyperthymic temperament.[7]

In 2013, DSM-5 replaced the narrow diagnostic category of ME by introducing the "mixed features specifier" (DSM-5 MFS) to be applied to either (hypo)-manic episodes or MDE in the presence of at least three contrapolar symptoms (see Table 1).[8] This substantial change was intended to provide clinicians with more sensitive criteria better accounting for the heterogeneity of MS and the highly prevalent subthreshold presentations. Furthermore, the addition of the MFS to MDD was interpreted as a theoretical structural bridge between MDD and BD, positing a more spectrum-oriented approach to mood disorders[9] in accordance with the DSM-5 guiding principle of a closer integration between categorical and dimensional models.

However, this revision was judged to be controversial and still carrying the limitations of categorical and polythetic diagnostic classification. Because it is based on dichotomizing mood disorders along a single domain with depression and mania at the opposite pole, the DSM-5 taxonomy would not be able to address the complexity of mixedness.[2,10] As indicated by the recent activity–cognition–energy model, which deconstructs each mood episode in three key dimensions, the phenomenology of MS might be better conceptualized according to independent fluctuations in the domains of activity, cognition, and emotion.[11]

Several objections have been raised against the new diagnostic subtype of the MDE "with mixed features". Despite its broader definition compared with the definition of ME in the DSM IV-TR,[12,13] DSM-5 MFS criteria have been criticized as inadequate and still restrictive. Indeed, the DSM-5 task force opted to consider as mixed features only those symptoms belonging to the manic polarity, excluding other relevant manifestations such as irritability, psychomotor agitation, and distractibility only because they are already covered by the MDE criteria.[14,15]

This position has been strongly contested by A. Koukopoulos, a Greek-Italian psychiatrist, who criticized the DSM-5 MFS construct for not capturing the excitatory component of mixedness expressed by key symptoms such as psychic agitation, marked irritability and mood lability.[16] This resulted in a diagnostic category that was judged to be scientifically weak and without adequate sensitivity in identifying "not pure" unipolar forms. Therefore, DSM-5 MFS applied to an MDE would not represent a reliable marker of a potential underlying bipolarity, despite the clear indication stated in the footnote to its criteria: "Mixed features associated with a major depressive episode have been found to be a significant risk factor

TABLE 1 DSM-5 "with mixed features" specifier criteria and Koukopoulos' diagnostic criteria for mixed depression.

DSM-5 "with mixed features" specifier criteria Major depressive episode + at least three of seven items	Koukopoulos' diagnostic criteria for mixed depression Major depressive episode + at least three of seven items
• Elevated, expansive mood	• Psychic agitation or inner tension
• Inflated self-esteem or grandiosity	• Racing or crowded thoughts
• More talkative than usual or pressure to keep talking	• Irritability or unprovoked rage
• Flight of ideas or subjective experience that thoughts are racing	• Absence of retardation
• Increase in energy or goal-directed activity	• Talkativeness
• Increased or excessive involvement in activities that have a high potential for painful consequences	• Dramatic description of suffering or frequent spells of weeping
• Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia)	• Mood lability or marked reactivity • Early insomnia

for the development of bipolar I or bipolar II disorder. As a result, it is clinically useful to note the presence of this specifier for treatment planning and monitoring of response to treatment".[8]

Based on his previous research on MS,[17] Koukopoulos and colleagues proposed an alternative clinical definition of mixed depression, called Koukopoulos Mixed Depression (henceforth KMxD), validating specific operational criteria[18] (see Table 1). The phenomenological key feature of this depressive syndrome has been identified to be inner psychic tension (without motor agitation) along with other excitatory symptoms.

The aim of this study was to evaluate the frequency of mixed depression in a sample of subjects affected by MDE according to the different clinical definitions of DSM-5 MFS and KMxD. Secondly, we also compared the discriminative capacity of both diagnostic constructs for bipolar depression and the clinical variables mostly associated with mixed features.

2 | METHODS

We reviewed the data on a sample of adult patients recruited at three Italian Psychiatry Inpatient Units (University of Catania, Siena and Turin) for a multisite naturalistic cross-sectional study. The sample consists of 300 patients with a previously established diagnosis of either MDD or BD. According to the inclusion criteria, all patients had to present a MDE with age > 18 years old at the time of study entry, confirmed by the Mini International Neuropsychiatric Interview (MINI) for DSM IV.[19]

The exclusion criteria were as follows: (1) current or past diagnosis of any schizophrenia spectrum disorder, (2) major neurocognitive disorder, intellectual disability, or any other severe neurological condition that might interfere with the assessment procedure, and (3) lack of written informed consent.

Each patient had undergone an extensive evaluation procedure including mental state examination and collection of data referring to sociodemographic and clinical characteristics by means of semi-structured interviews, used in previous published papers.[20,21] Mood symptomatology and episode severity were investigated by using the Young Mania Rating Scale (YMRS),[22] the Hamilton Depression Rating Scale (HDRS),[23] and the Clinical Global Impression-Severity (CGI-S).[24] Furthermore, functioning, impulsivity and seasonality pattern were also assessed by the administration of the Sheehan Disability Scale (SDS),[25] Barratt Impulsiveness Scale (BIS)[26,27] and Seasonal Pattern Questionnaire Assessment (SPAQ),[28] respectively. The Institutional Review Board at the University of Catania, Siena and Turin reviewed and approved all study procedures, and all patients gave their written informed consent prior to participating in the study.

2.1 | Reviewing procedure

For the application of the DSM-5 MFS, our reviewing procedure was partially inspired by that adopted by McIntyre et al. in a similar study in which the authors inferred the DSM-5 MFS criteria referring to selected items from the YMRS.[12] However, unlike the previously mentioned authors, we opted to exclude the seventh (language-thought disorder), eighth (content), ninth (disruptive-aggressive behavior), and tenth (appearance) YMRS items from our diagnostic retrospective reviewing procedure because they are not univocally coincident with DSM-5 mixed features. The fulfillment of those DSM-5 MFS criteria without a clearly corresponding item from YMRS was assessed by referring to the matching (hypo)manic symptoms investigated by the MINI and to the mental examinations reported in the available clinical records. Furthermore, for each of the DSM 5-MFS criteria we conducted a cross-check between YMRS items, MINI items, and data from clinical records.

Three trained adult psychiatrists with a solid experience in the field of mood disorders (A.A., L.M., A.R.) independently ascertained whether any patient met the KMxD criteria by revising the results from the assessment tools (YMRS, HDRS, MINI) used for the characterization of the ongoing MDE and the available clinical records. In the few cases of disagreement, the authors reached a consensus by a discussion of related clinical and psychometric data. During this process, the authors remained blind to patient characteristics and primary diagnosis (MDD vs. BD).

2.2 | Statistics

Sociodemographic and clinical characteristics were expressed as mean and standard deviation for continuous variables, and frequency and percentage for categorical ones. Classical inferential tests like Pearson's chi-squared test and Fisher exact test were used to compare the prevalence of DSM-5 MFS and KMxD, and the distribution of mixed features between the two main diagnostic groups (MDD vs. BD). The Bonferroni correction for multiple comparisons was applied. The Area Under the Receiver Operating Characteristic (ROC_AUC) was used to assess the discriminative capacity of DSM-5 MFS and KMxD criteria for BD. The ROC-AUC is a widely used measure of predictive performance when modeling binary outcome; each of its point represents one of the possible sensitivity-specificity pairs. Its natural ranges are 0.5 (meaning no discriminative power) to 1.0 (meaning perfect discriminative power). The ROC-AUC curve was used to determine the optimal cutoffs (and corresponding sensitivity-specificity values) according to the Youden index.[29]

We performed a logistic generalized linear model with Elastic Net penalty to explore the association between an assigned operational definition of mixed depression (DSM-5 MFS vs. KMxD) and patients' characteristics.

The patients' characteristics included in the regression model were selected a priori among the available variables describing the clinical course of the illness or recognized as related to bipolarity.[1,30–33] These variables were: gender, age, age at disorder onset, family history for mood disorder, current suicidal risk (dichotomizing the related Mini international Neuropsychiatric Interview[19]),

lifetime suicide attempts, previous hospitalizations, severity of the illness (splitting the Clinical Global Impression severity CGI-S score), co-occurrent Cluster B Personality Disorder or Substance Use Disorder or Anxiety Disorder, impulsivity levels,[27] and seasonality pattern.[28]

Elastic Net regularization is a machine learning technique based on the combination of the Least Absolute Shrinkage and Selection Operator (LASSO) penalty (L1) and the Ridge penalty (L2) that provides a numerical approach strongly mitigating the impact of nonrelevant or collinear predicting variables, maintaining the same interpretation of coefficients commonly used in any regression framework. In particular, non-relevant predictors coefficients are shrunk towards a numerically zero value,[34] instead of using the p-value threshold commonly applied in the traditional probabilistic framework of the standard logistical regression. This approach is considered more appropriate when the number of predictors is large compared with the sample size because traditional variable selection methodologies may perform poorly because of overfitting data. Furthermore, another advantage of this technique is faster and more robust identification of relevant predicting variables compared with the iterated stepwise approach. Eventually, the models' ROC-AUCs (estimated using a 10-fold cross-validation to enhance generalization and overcome overfitting) were calculated as a measure of their predictive performance.

The R Statistical software[35] and associated R packages like pROC[34] and DescTools[36] were used to perform statistical analysis. The h2o R package was used to fit the logistic regression with the Elastic Net penalty. Statistical significance was assessed by using a 5% threshold except for the Elastic Net regression analysis where *p*-values are not available.

3 | RESULTS

3.1 | Prevalence of mixed depression definitions and frequency of contrapolar symptoms

The sociodemographic and clinical characteristics of the total cohort ($N = 300$) and of DSM 5-MFS and KMxD subgroups are summarized in Table 2. A total of 155 patients (51.7%) had a primary diagnosis of MDD, whereas 145 (48.3%) patients had a bipolar diagnosis. Only 44 subjects (14.7%) fulfilled the DSM-5 criteria for MFS, whereas 165 (55%) met the KMxD criteria.

The three most frequently recorded symptoms were “irritability,” “dramatic expressions of suffering,” “mood lability,” all belonging to the KMxD set of criteria. Conversely, “elevated mood” was the least reported symptom, followed by “racing thoughts” and then by “inflated self-esteem or grandiosity.”

After comparing the frequency of the different contrapolar symptoms between BD and MDD subgroups, a statistically significant difference was found for “increased energy or goal-directed activity,” “involvement in risky activity,” “mood lability,” “talkativeness,” “elevated mood,” “psychic agitation or inner tension,” and “irritability” (see Table 3).

3.2 | ROC curves

The AUCs of ROC curves for BD according to DSM-5 MFS and KMxD were 77.0% (CI: 77.6%–82.1%) and 71.9% (CI: 66.2%–77.7%), respectively. The optimal symptom thresholds (and corresponding sensitivity and specificity values) for the primary diagnosis of BD were ≥1 (77%/68%) and ≥3 (78%/66%), respectively. At the cutoff point corresponding to the DSM-5 MFS diagnostic threshold (≥3 criteria), sensitivity/specificity values were 26%/97%. (see Figure 1).

3.3 | Regression

In our multivariate binary logistic regression analysis, the clinical variables, which were identified as positive or negative predictors for either DSM-5 MFS or KMxD diagnosis are indicated by nonzero values for both standardized and nonstandardized coefficients (see Table 4).

A comorbid Cluster B personality disorder, disease severity (CGI-S score higher or equal to 4), medium-high suicidal risk, impulsivity (BIS total score), and seasonality pattern (SPAQ total score) were found to be positive predictors of both diagnostic constructs, but each of these variables showed a more pronounced correlation with KMxD. The number of lifetime suicidal attempts, the number of psychiatric hospitalizations, the presence of comorbidity with anxiety disorders and a family history of mood disorders had instead a statistically significant exclusive association with KMxD.

On the other hand, patient functioning (SDS score) and older age at onset were revealed to be significant negative predictors of both diagnoses. In particular, a later onset of disease exhibited a stronger negative association with DSM-5 MFS compared with KMxD.

The predictive performance, estimated by 10-fold cross-validated ROC-AUC, was 0.79 for Koukopoulos regression and 0.71 for DSM-5 MFS.

4 | DISCUSSION

To our knowledge, this is the first study conducted by an independent research group aimed to compare DSM-5 MFS and KMxD diagnoses in terms of prevalence, associated clinical variables, and discriminative capacity for a primary diagnosis of BD.

The prevalence of DSM-5 MFS observed in our research falls within quite a wide range of variability, as reported in other studies investigating the prevalence and illness characteristics of DSM-5 defined mixed depression.[37,38] These heterogeneous results are probably linked to different clinical settings, recruitment procedure, and methodological approaches adopted for the retrospective diagnostic evaluation.

In our study, the KMxD criteria identified more than three times as many patients recognized as having mixed depression by applying the DSM-5 MFS definition. Regardless of the diagnostic model considered, the percentage of patients qualifying for a diagnosis of mixed depression was found to be significantly higher among

TABLE 2 Characteristics of the total sample and of the patients meeting DSM-5 and Koukopoulos's mixed depression criteria

	Total	DSM-5 MFS (*N* = 44)	KMxD (*N* = 165)
Sociodemographic			
Gender (females), *N* (%)	182 (60.7%)	28 (63.6%)	102 (61.8%)
Current age, mean ± SD	50.1 ± 14.7	45.7 ± 14.5	47.18 ± 14.7
Years of education, mean ± SD	11.5 ± 4.5	11.49 ± 4	11.6 ± 4.5
Marital status, *N* (%)			
Single	109 (36.3%)	21 (47.7%)	73 (44.2%)
Married	130 (43.4%)	14 (31.8%)	58 (35.2%)
Other	61 (20.3%)	9 (20.5%)	34 (20.6%)
Employed, *N* (%)	111 (37.0%)	18 (40.9%)	63 (38.2%)
Living status, *N* (%)			
Alone	95 (31.7%)	19 (43.2%)	55 (33.3%)
With parents	205 (68.3%)	25 (56.8%)	110 (66.7%)
Unhealthy lifestyle			
Smoking status, *N* (%)	127 (42.3%)	24 (54.6%)	92 (55.8%)
Daily number of cigarettes, mean ± SD	16.6 ± 9.4	9.4 ± 10.6	9.8 ± 11.6
Alcohol intake, *N* (%)	67 (22.3%)	13 (29.6%)	44 (26.7%)
Daily alcohol units, mean ± SD	0.8 ± 1.9	1 ± 1.9	0.9 ± 2
Physical inactivity, *N* (%)	189 (63.0%)	29 (65.9%)	113 (68.5%)
Clinical			
Age at onset (disorder)	32.2 ± 14.7	25.3 ± 9.1	28.1 ± 12.3
Family history for mood disorders	157 (54.3%)	26 (59.1%)	97 (58.8%)
Substance use disorder	26 (8.7%)	5 (11.4%)	19 (11.5%)
Cluster B personality disorder	65 (21.7%)	17 (38.8%)	55 (33.3%)
Anxiety disorders	75 (25%)	11 (25%)	35 (21.2%)
CGI-S score ≥4	240 (80%)	40 (90.9%)	150 (90.9%)
Medium-high suicidal risk	94 (31.3%)	19 (43.2%)	68 (41.2%)
Lifetime suicide attempts	0.4 ± 0.8	0.5 ± 0.9	0.5 ± 1
Previous hospitalizations	1.5 ± 2.1	1.5 ± 1.9	1.9 ± 2.3
BIS total score	63.6 ± 9.3	66.5 ± 9.4	65.8 ± 9.3
SPAQ total score	11.6 ± 5.3	13.1 ± 4.1	12.7 ± 4.5
SDS score	21 ± 6.9	21.8 ± 6.2	21.9 ± 6.6
Primary diagnosis, *N* (%)			
Major depressive disorder	155 (51.7%)	6 (13.6%)	52 (31.5%)
Bipolar disorder	145 (48.3%)	38 (86.4%)	113 (68.5%)
Young Mania Rating Scale, mean ± SD	4.8 ± 4.1	9.9 ± 3.9	7.1 ± 3.7
Hamilton Depression Rating Scale, mean ± SD	24.3 ± 4.3	24 ± 6.5	23.5 ± 6.3
Clinical Global Impression, mean ± SD	4.8 ± 0.8	4.4 ± 0.7	4.4 ± 0.7

patients with bipolar depression. Of note, among patients with unipolar depression, the prevalence of DSM-5 MFS was approximately nine times lower than that of KMxD.

Similar findings were found in the BRIDGE II study in which the proportion of patients with MDE who met the DSM-5 MFS criteria was four times lower than that of the patients who met the alternative research-based diagnostic criteria (RBDC-MXS) defined by the presence of an MDE plus 3 out of 14 hypomanic symptoms (irritable mood, emotional lability, distractibility, psychomotor agitation, impulsivity, verbal or physical aggression, racing thoughts, talkativeness, hyperactivity, increased energy, risky behavior, grandiosity, euphoria, and hypersexuality).[39] Correspondingly, Takeshima et al. found a higher percentage of MDE patients who qualified for Benazzi's mixed depression in both unipolar and bipolar subgroups compared with DSM-5 MFS criteria, to an extent comparable with our results.[40]

We found that mood lability, irritability, dramatic expression of suffering, and talkativeness were the most common contrapolar

TABLE 3 Prevalence of contrapolar symptoms, DSM-5's mixed features, and Koukopoulos' mixed depression during major depressive episodes

Mixed depression models	Total (n = 300) n (%)	MDD (n = 155) n (%)	BD (n = 145) n (%)	p-value MDD vs. BD
DSM-5 MFS	44 (14.7)	6 (3.9)	38 (26.2)	**<0.001**
KMxD	165 (55.0)	52 (33.5)	113 (77.9)	**<0.001**
DSM-5 MFS symptoms				
Elevated, expansive mood	8 (2.7)	0 (0.0)	8 (5.5)	**0.045**
Inflated self-esteem or grandiosity	29 (9.7)	11 (7.1)	18 (12.4)	NS
Increased energy or goal-directed activity	33 (11.0)	4 (2.6)	29 (20.0)	**<0.001**
Excessive involvement in risky activity	72 (24.0)	4 (2.6)	68 (46.9)	**<0.001**
Decreased need for sleep	37 (12.3)	14 (9.0)	23 (15.9)	NS
KMxD symptoms				
Psychic agitation or inner tension	68 (22.7)	24 (15.5)	44 (30.3)	**0.03**
Irritability or unprovoked rage	184 (61.3)	82 (52.9)	102 (70.3)	**0.03**
Absence of retardation	88 (29.3)	34 (21.9)	54 (37.2)	**NS**
Dramatic expression of suffering	176 (58.7)	81 (52.3)	95 (65.5)	NS
Mood lability or marked reactivity	166 (55.3)	61 (39.4)	105 (72.4)	**<0.001**
Early insomnia	79 (26.3)	39 (25.2)	40 (27.6)	NS
Shared symptoms				
Talkativeness	110 (36.7)	33 (21.3)	77 (53.1)	**<0.001**
Racing thoughts	17 (5.7)	5 (3.2)	12 (8.3)	NS

Abbreviations: BD, bipolar disorder; DSM-5 MFS, mixed depressive episode—with depressive features; KMxD, Koukopoulos' mixed depression; MDD, major depressive disorder; NS, not significant.

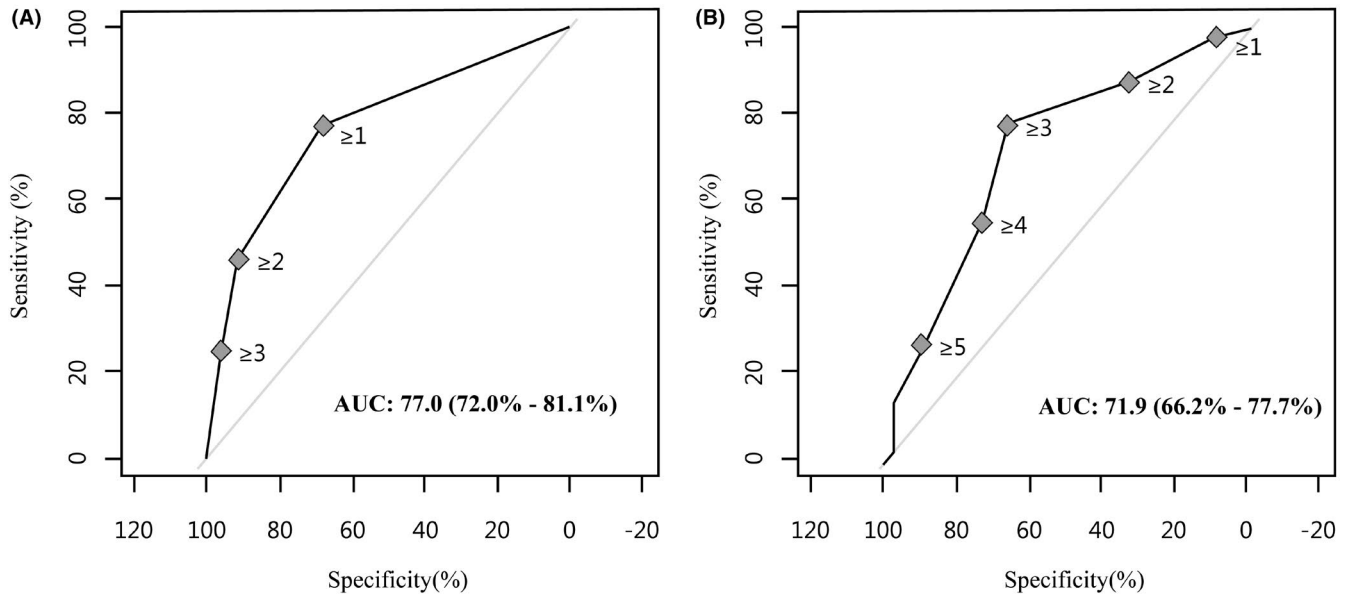

FIGURE 1 Receiver–operator curves of bipolar disorder diagnosis according to *Diagnostic and Statistical Manual of Mental Disorders fifth edition* mixed features specifier (A) and Koukopoulos' mixed depression (B) criteria

symptoms, occurring in more than a third of the patients. With the sole exception of talkativeness (shared by both diagnostic constructs), all these mixed features are included in KMxD but not in DSM-5 MFS criteria. Elevated mood, inflated self-esteem and racing thoughts were instead the less frequent (hypo)manic symptoms, observed in less than 10% of the sample. Aside from talkativeness, "engagement in risky activity" was the only DSM-5 MFS symptom with a prevalence rate greater than 20%. Consistent with the available literature,[33,41] the cumulative occurrence rate of the so-called "overlapping symptoms" included in KMxD criteria (namely irritability and psychic tension, together with other excitatory features shared with mania and atypical features such as

TABLE 4 Multivariate logistic regressions of variables associated with mixed depressive episode—with depressive features (DSM-5 MFS) and Koukopoulos' mixed depression (KMxD)

	DSM-5 MFS		KMxD	
Variables	**Unst. coeff**	**Stand. coeff**	**Unst. coeff**	**Stand. coeff**
Gender (female)	0.00	0.00	0.00	0.00
Current age	0.00	0.03	0.00	−0.05
Age at onset (disorder)	**−0.02**	**−0.25**	**−0.02**	**−0.05**
Family history for mood disorders	0.00	0.00	**0.24**	**0.24**
Substance use disorder	0.00	0.00	0.00	0.00
Cluster B personality disorder	**0.36**	**0.36**	**0.88**	**0.88**
Anxiety disorders	0.0	0.00	**0.12**	**0.13**
CGI-S score ≥4	**0.22**	**0.22**	**0.96**	**0.96**
Medium-high suicidal risk	**0.06**	**0.06**	**0.23**	**0.23**
Lifetime suicide attempts	0.00	0.00	**0.08**	**0.07**
Previous hospitalizations	0.00	0.00	**0.02**	**0.04**
BIS total score	**0.01**	**0.13**	**0.03**	**0.30**
SPAQ total score	**0.01**	**0.06**	**0.02**	**0.12**
SDS score	**−0.01**	**−0.07**	**−0.02**	**−0.11**
Intercepts	−2.07	−1.71	−1.04	0.17
ROC-AUC	0.71		0.79	

Note: Significant variables in bold.

Abbreviations: BIS, Barratt Impulsiveness Scale; CGI-S, Clinical Global Impression—Severity Scale; DSM-5 MFS, mixed depressive episode—with depressive features; KMxD, Koukopoulos' mixed depression; ROC-AUC, Receiver Operating Characteristic—Area Under the Curve; SDS, Sheehan Disability Scale; SPAQ, Seasonal Pattern Assessment Questionnaire; Stand. coeff., standardized coefficients; Unst. coeff., unstandardized coefficients.

marked emotional reactivity and absence of motor retardation) was far higher than that of "non-overlapping symptoms". Overall, our findings confirm the relevance of psychic excitement and unproductive behavioral activation in characterizing the mixed depression profile. On the one hand, we may, therefore, affirm that the choice to discard overlapping (hypo)manic symptoms from DSM-5 MFS, because of their supposed low specificity, entails the failure to recognize the excitatory and the dysphoric component—mainly represented by irritability and marked mood reactivity—as the key phenomenological dimensions of mixed depression.[42–44] On the other hand, the low frequencies of proper manic symptoms recorded in our sample, that is, elevated mood and grandiosity, in our sample was not surprising: the impact of expansiveness component in the real world of depressed patients with mixed features appear marginal as is consistently noted in previous studies.[41,45]

Furthermore, the aforementioned motivation behind the DSM-5 task force resolution appears contradictory to the inclusion of inner tension and restlessness among the criteria of the DSM-5 specifier "with anxious distress" (ADS), increasing the risk of misdiagnosis.[46] Indeed, as shown in a recent network analysis on a sample of patients with MDE, the anxiety symptoms listed in ADS tended to cluster together with KMxD criteria, suggesting a partial overlap between these two depressive subtypes.[47]

The confidence intervals of the area under both ROC curves—the one built using KMxD criteria and the other using the DSM-5 MFS criteria to identify bipolar patients—overlap. This suggests a comparable diagnostic capacity of both constructs. However, the interesting point that emerged from this procedure was the concordance of the KMxD optimal threshold we found to identify patients with bipolar depression, and the KMxD diagnostic cutoff (≥3 symptoms in both cases); on the other hand, the DSM-5 cut-off for BD diagnosis resulting from our analysis was lower than the one currently used to diagnose DSM-5 MFS (≥1 vs. ≥3 symptoms). This discrepancy accounts for the lack of sensitivity of DSM-5 MFS criteria for bipolar disorder, although the DSM-5 clearly suggests that the fulfillment of MFS is a risk factor for bipolar depression.

This finding is in line with a previous study showing that the use of a lower DSM-5 MFS cutoff enables the identification of more bipolar depressed patients than when the established DSM-5 threshold is considered. In particular, in that study, the participants detected by the lower threshold presented important clinical aspects commonly present in mixed depression (e.g., more lifetime anxiety disorder comorbidity and more current irritability).[45] In the present study, we also performed a multivariate logistic regression aimed at comparing the two different definitions of mixed depression in terms of association with a set of clinical variables recognized as related to MS. Both diagnostic constructs shared a positive correlation with younger age at onset, current higher severity of illness, a medium-high suicide risk, comorbid cluster B personality disorder, higher impulsivity levels, and the presence of a seasonality pattern. However, the magnitude of the association with each variable was remarkably stronger for KMxD diagnosis, except for the age of disease onset. Unexpectedly, a high SDS score was a negative predictor of both mixed depression diagnoses. As potential explanation of this finding, we hypothesized that the presence of a behavioral activation in these subgroups of patients may mitigate the self-perception of illness-due to the interference with work/school, social life/leisure activities, and family life/home responsibilities.

The multivariate logistic regression revealed the exclusive association of KMxD with family history of mood disorders, anxiety disorders, previous hospitalizations, and lifetime suicide attempts. Taken together, all these outcomes suggest that Koukopoulos' model of mixed depression identifies a prototype of depressed patient as follows: probably not an isolated case in family; a younger age at illness onset and presenting a more severe course; influenced by seasonality; and burdened by anxiety disorders comorbidity. The most challenging trait featuring this cluster of patients, however, is not only represented by the high probability of suicidal behavior, as expressed by the stronger correlation of KMxD diagnosis with the variables "current higher suicidal risk" and "lifetime suicide attempts" but also potentially amplified by the interplay between cluster B personality traits and greater levels of impulsivity.

The findings of our analysis should be seen in light of several limitations. Firstly, the diagnosis of DSM-5 MFS and KMxD were

assigned post hoc based on a retrospective evaluation of the available clinical and psychometric data. Although the reviewing procedure was conducted by trained psychiatrists, the availability and use of the specific tools developed for the assessment of both constructs would have maximized the reliability of our findings.

Secondly, data were collected with a cross-sectional design, precluding any prospective evaluation of patients, with the consequent impossibility of verifying the stability of the main diagnosis and the predictive capacity of both diagnostic models of mixed depression for mood switches.

Thirdly, the pharmacological treatment data were partially missing, so we could not speculate on potential drugs interference on clinical presentations.

Another limitation of the study may be represented by the heterogeneity of the sample composition with regard to sociodemographic, clinical characteristics, and pharmacotherapeutic approach, even more so considering the multicenter nature of the primary study. Lastly, since all patients were recruited after their admission to inpatients units, our results may be affected by a severity illness bias.

In conclusion, KMxD was found to be a more inclusive operational definition than DSM-5 MFS, detecting a wider proportion of patients missed by DSM-5-MFS criteria and exhibiting a more robust association with clinical correlates of mixedness. By contrast, the diagnostic construct of DSM-5-MFS—due to a controversial epistemological orientation in the development of its criteria—appears not capable of discriminating a considerable number of "mixed depressed patients" from "pure unipolar patients," thus failing in the assigned role of bipolar diathesis marker with potentially serious treatment implications.

Therefore, we strongly believe that a deeper diagnostic reconsideration of mixed features in depression should be warranted by the new official nosologic classification systems.

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CONFLICT OF INTEREST

Dr Aguglia E is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Doc Generici, FB-Health, Janssen, Lundbeck, Otsuka, Fidia, and Recordati. Dr Amore is /has been a consultant and/or a speaker and/or has received research grants from Angelini, FB-Health, Janssen, Lundbeck, Otsuka, Pfizer, Recordati, and Glaxo. Dr Cuomo is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Lundbeck, and Otsuka. Dr Fagiolini is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Apsen, Boehringer Ingelheim, Doc Generici, FB-Health, Janssen, Lundbeck, Mylan, Otsuka, Polifarma, Recordati, Sanofi Aventis, Sunovion, and Vifor. Dr Maina is/has been a consultant and/or a speaker and/or has received research grants from Janssen, Otsuka, Lundbeck, Angelini, Sanofi, Boehringer, Fb-health, and Recordati. Dr Aguglia A, Bolognesi, Concerto, Goracci, Mineo, Rodolico, Serafini, and Spedicato have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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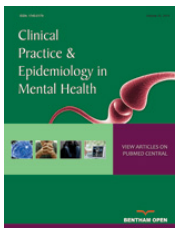

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RESEARCH ARTICLE

Mixed Depression: A Survey on Psychopathological, Diagnostic, and Therapeutic Approaches among a Sample of Italian Psychiatrists

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Abstract:

Background:

The Diagnostic and Statistical Manual for Mental Disorders (5th edition) introduced the specifier "with Mixed Features" to the diagnosis of Major Depressive Episode to designate the presence of (hypo) manic symptoms as part of the clinical presentation. This change has led to renewed attention on the operational definition, diagnosis, and treatment of Mixed Depression.

Objective:

To investigate the diagnostic and therapeutic approaches towards Mixed Depression among a representative sample of Italian psychiatrists.

Methods:

Between March and April 2021, 342 psychiatrists working in Italian adult mental health services were invited to participate in an anonymous online survey comprising 32 questions designed to investigate clinical and psychopathological approaches regarding the management of mixed depression in daily psychiatric practice.

Results:

83.74% of participants reported having performed a diagnosis of mixed depression in the last five years, with the majority of respondents affirming that they had not used any diagnostic tool. Only 7,5% of the surveyed psychiatrists considered the DSM-5 criteria to be fully adequate in the description of this clinical entity. The most used pharmacological approach was combined therapy, in particular antipsychotics plus mood stabilizers. For monotherapy, the preferred drugs were Valproate and Quetiapine. Regarding the conceptualization of mood disorders, 199 of the participants chose the Kraepelinian unitary spectrum view; meanwhile, 101 expressed their preference for the binary model.

Conclusion:

Our results suggest a prominent position of mixed depression in the context of mood disorders. Univocal operational criteria and additional research on pharmacological treatment are also needed to ensure the correct recognition and management of mixed depression.

Keywords: Mixed depression, Online survey, Prescription attitudes, Psychiatrists, Hypomania, Antidepressants.

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1. INTRODUCTION

The question of Mixed States (MS) has been much debated over the centuries, from Hippocrates and Aristotle till the present days; the construct has been revised in the Diagnostic and Statistical Manual for Mental Disorders (fifth edition) (DSM-5) [1]. In the first decades of the XX century, Kraepelin described six different types of MS based on the combination of non-unison stable variations in the three domains of mood, thought, and psychomotricity [2 - 4]. These types included depressive or anxious mania, excited depression, mania with thought poverty, mania with stupor, depression with flight of ideas, and

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inhibited mania. The operational definition of "mixedness" in the DSM classification underwent a substantial change, moving MS from a core episode to a clinical specifier for both depressive and bipolar disorders (from DSM-III [5] to DSM-5). The DSM-5 definition of mixed depression (MxD) consists in the addition of the "with mixed features" specifier (DSM-5 MFS) to a diagnosis of a major depressive episode (MDE) in either unipolar or bipolar patients with at least three of the following (hypo)manic symptoms: elevated or expansive mood; inflated self-esteem or grandiosity; being more talkative than usual or feeling pressure to keep talking; flight of ideas or racing thoughts; distractibility; increase in energy or goal-directed activity; increased or excessive involvement in activities that have a high potential for painful consequences, and decreased need for sleep. The new DSM-5 classification mirrors the conceptualization of mood disorders along a spectrum ranging from pure unipolar depression to pure mania, through different presentation patterns of depressive and manic symptoms [6 - 8].

However, various issues should be mentioned. For instance, the relevance of this nosographic entity is underestimated and several clinical manifestations of patients with mood disorders might not be recognized, leading to an under-diagnosis of mixed episodes and their phenomenological presentations [9 - 11]. Considering the lower response to standardized treatments of these forms compared to pure presentations of depressive syndromes [7, 12 - 14], the correct diagnosis and treatment of these patients is central to psychiatric care.

Therefore, potential alternatives to DSM criteria for MxD have been proposed in the literature with a significant contribution by some Italian authors. For example, Benazzi considered a minimum of three numbers of hypomanic symptoms (without specifying which ones) that are present within the depressive state and with a score on the Hypomania Interview Guide > 7 [15 - 17]. Koukopoulos' construct of MxD focuses on the dysphoric and excitative components, and its diagnosis requires the presence of at least three of the following symptoms during an MDE: psychic agitation or inner tension; racing or crowded thoughts; irritability or unprovoked feelings of rage; absence of retardation; talkativeness; dramatic description of suffering or frequent spells of weeping; mood lability and marked emotional reactivity and early insomnia [18 - 20].

More recently, the Activity, Cognition, and Emotion (ACE) model has become a valid proposed approach that considers mood disorders as a combination of symptoms across these three domains, varying over time [21, 22]. Each symptom may be defined in terms of severity dimension. For depression, activity symptoms include loss of energy, alteration of sleep and appetite, reduced engagement in normal activities, and psychomotor agitation or retardation; cognitive symptoms include diminished concentration and indecisiveness, while emotional symptoms are sadness, hopelessness, worthlessness, and guilt. For mania, activity symptoms include a decreased need for sleep, an increase in goal-directed activity, psychomotor agitation, and heightened talkativeness; cognitive symptoms include racing thoughts and distractibility, while emotion symptoms are represented by euphoria and inflated self-esteem. Therefore, clinicians could conceptualize various nuanced aspects of clinical presentations that may give us novel insights, facilitating research and enhancing the recognition and understanding of mood disorders [23 - 27].

Current pharmacological guidelines, largely based on evidence derived from clinical trials on bipolar patients who met the DSM–IV definition of either manic or depressive episodes [28], provide insufficient decision support to clinicians for adequate treatment in patients affected by MDE with mixed features [12, 29 - 32]. Given the epidemiological and psychopathological relevance of this topic in the field of mood disorders, the evident gap related to DSM-5 criteria, and the recent literature updates in the treatment of mood disorders, we conducted a survey on the attitudes of Italian psychiatrists towards the clinical entity of MxD. Specifically, this study aimed to investigate the relevance of this framework in daily clinical practice, focusing on the diagnostic and therapeutic approaches adopted as well as on the psychopathological role model of a clinical entity still being debated.

2. MATERIALS AND METHODS

2.1. Study Design

Between March and April 2021, an anonymous online survey was conducted to explore Italian psychiatrists' approach to MxD in terms of diagnosis, treatment, and psychopathological reference framework. The participants received an email in which they were informed of the purpose of the study and were invited to take part in the survey *via* a linked Airtable form. The survey was designed to be completed in less than 5 minutes, and the snowball technique was implemented for recruitment [33]. Eligible individuals included psychiatrists working in an Italian adult in-/outpatients mental health service. Psychiatry residents with at least two years of training in mood disorders management were also considered qualified to take part in the survey. All the participants provided their informed consent to take part in the study anonymously. On account of the study design, the topic, and the population investigated, institutional review board approval was considered unnecessary. The decision to conduct this survey in the online mode instead of the traditional version of the paper survey was firstly determined by the suspension (due to the restrictions for the COVID-19 pandemic) of professional meetings such as congresses, conferences, or seminars during which the questionnaires would normally be distributed and collected. In any case, the use of online surveys has increased in recent years. Internet based surveys have several advantages: firstly, they enable researchers to establish contact with a large number of people—who would otherwise be difficult to reach—in a short time and bypassing geographical distances; secondly, online surveys are money-saving and eco-friendly, as the costs associated with printing and large-scale distribution of paper surveys can be enormous; and finally, since online responses are automatically documented, the time and costs associated with transcription are eliminated. However, internet-based surveys also have some disadvantages over the traditional version. When conducting online surveys, investigators are still confronted with a number of problems,

mainly concerning the quality of the sampling. One major issue is the risk of receiving multiple responses from the same participant sent from different accounts, if the survey is conducted anonymously. A solution for investigators could be to require participants to contact them prior to completing a survey to obtain a unique code number which they would be asked to insert on the online questionnaire; alternatively, they could be asked to use web-survey platforms offering a response tracking service. Another major limitation of online surveys is a self-selection bias since, in any given community, it is possible to find individuals who are less inclined to complete an online survey for several reasons. This sampling issue may potentially jeopardize researchers' ability to make generalizations about study findings but could be countered by ensuring that a predetermined proportion of the participants receive and complete the paper version of the survey [29].

2.2. Questionnaire

The survey was comprised of 32 questions to probe the participants' standpoint on MxD in adults. Sociodemographic variables were collected along with relevant data regarding professional training and practice. We investigated the participants' training and knowledge regarding the clinical entity of MxD, the diagnostic approach commonly used, the assessment tools eventually adopted to corroborate the diagnosis, and the symptoms most frequently observed and considered as distinctive of MxD. The participants could choose from the following assessment tools: Affective Self Rating Scale [30], Bech-Rafaelsen Mania Scale [31], Clinician-Administered Rating Scale for Mania [32], Hypomania Check-list (HCL32) [33], Hypomania Interview Guide [34], Internal State Scale [35], Koukopoulos Mixed Depression Rating Scale (KMxD-RS) [36, 37], Mood Disorder Questionnaire [38], Multiple Visual Analogue Scales for Bipolarity [39], Schedule for Affective disorder and Schizophrenia [40], Structured Clinical Interview for DSM-5 (SCID-5-CV) [41], Young Mania Rating Scale (YMRS) [42], other not listed scales. Among these instruments, the KMxD-RS is the only one targeted at assessing the diagnosis of a specific model of MxD and not for the assessment of hypomanic symptoms alone (*i.e.*, whereas the other scales merely test for hypomanic symptoms, this scale is intended to ascertain the diagnosis of a specific construct of mixed depression).

The percentage rate of patients diagnosed with MxD among those suffering from an MDE in the daily clinical practice was also evaluated.

Furthermore, the most common pharmacological approach used for the treatment of MDE with mixed features in patients receiving the diagnosis for the first time was explored. We asked participants to indicate their preferred pharmacological treatment between monotherapy (antipsychotics or antidepressants or mood stabilizers) and combined treatment (antipsychotics + mood stabilizers or antidepressants + mood stabilizers or antidepressants + antipsychotics). The choice of monotherapy allowed participants to select up to two drugs for each class among a list of medications commonly used in the treatment of MxD. In this case, respondents could express a preference for more than one class of drugs as long as they were considered to be equally appropriate as therapeutic option: for the combined treatment, we allowed participants to indicate up to two drugs for each class.

Additionally, the participants were asked whether they agreed with the "unitary view of depression" that conceptualizes all depressive disorders as belonging to a unique mood spectrum or with the "binary model" that considers unipolar and bipolar depression as two separate psychopathological entities. The questionnaire is available upon request to the corresponding author.

2.3. Statistical Analysis

Regarding sociodemographic data, counts and percentages were used for categorical variables. In contrast, almost all continuous variables were given the median and interquartile ranges (IQR) because those were non-normally distributed, as assessed with the Kolmogorov-Smirnov test. The Wilcoxon Mann–Whitney test was used to compare not normally distributed continuous variables. Chi-square and Fisher's exact tests were used to analyze differences in categorical variables. An alpha level of .05 was used for all statistical tests. Given the exploratory nature of the inferential analyses, we did not apply any correction for multiple comparisons. Statistical analyses were performed with Wizard Statistics for Mac version 2.0.4 [43].

3. RESULTS

The survey was completed by 395 psychiatrists. We excluded residents attending the first and second years of specialization. This reduced the number of available questionnaires to 369. Twenty-seven questionnaires were excluded because they had not been filled in properly. The sociodemographic characteristics of the participants are reported in Table **1**. Among the 342 responders, 57.31% were females, and the median age was 38 (IQR: 34-50). Most of the participants had completed their training (89.47%). The median number of working years for all the participants was 6 (IQR: 2-19). Almost half of the responders had attended and completed a psychotherapy school (42.11%), 44 had obtained a Ph.D. degree, and 78 had a master's degree. Two hundred and fifty-six participants worked in services afferent to a public Department of Mental Health (193 in Adult Mental Health Centres, 63 in Psychiatric Diagnosis and Treatment Hospital Units), 65 were employed at University Hospitals, and 21 in other settings. Responders from northeast Italy were 64, 83 from the northwest, 59 from the center, 59 from the south of Italy, and the remaining 77 from the Islands.

A detailed description of the answers to the questionnaire items is reported in Table **2**, in which only the participants that answered "Yes" to the question "Do you know what MxD is?" are included (N=320). More than half of the responders (56.25%) reported having performed a clinical diagnosis of MxD without using any psychometric scales or questionnaires. Conversely, the most commonly used assessment tools were the YMRS (N = 69) and the HCL-32 (N = 41). The KMxD-RS was used by only 21.43% (30 participants over 140) of those reporting the use of diagnostic tools.

Table 1. Sociodemographic characteristics of the survey participants.

Demographics	Results
Number of females	196 (7.31%)
Age (median)	38 (IQR: 34-50)
Education	-
Specialist	306 (89.47%)
In training (last two years)	36 (10.53%)
Length of service (median)	6 (IQR: 2-19)
Specialization	-
Psychiatry	337 (98.54%)
Other	5 (1.46%)
Psychotherapy school diploma	144 (2.11%)
PhD	44 (12.84%)
Second level Italian master's degree	78 (22.81%)
Work setting	-
Department of Mental Health Territorial Services	193
Psychiatric Diagnosis and Treatment Hospital Units	63
University Hospital (hospitalists)	29
University Hospital (residents in training)	36
Other	21
Italian region where the participants work	-
North East (Emilia-Romagna, Friuli-Venezia Giulia, Trentino-South Tyrol, Veneto)	64 (18.71%)
North West (Aosta Valley, Liguria, Lombardy, Piedmont)	83 (24.27%)
Center (Marche, Lazio, Tuscany, Umbria)	59 (17.25%)
South (Abruzzo, Apulia, Basilicata, Calabria, Campania)	59 (17.25%)
Islands (Sardinia, Sicily)	77 (22.51%)

Table 2. Questionnaire on mixed depression.

Item	Questions	Results
01.	Do you know what "Mixed Depression" is?	320 (93.57%)
02.	Have you diagnosed "Mixed Depression" in the past 5 years? †	268 (83.74%)
03.	What is the percentage of patients suffering from Major Depressive Episode that you have diagnosed as affected by "Mixed Depression"? †	20% (IQR 10%-30%)
04.	Do you refer to DSM-5 "mixed features specifier" criteria for the clinical recognition of "Mixed Depression"? †	227 (70.94%)
05.	How would you rate the DSM-5 based definition of depressive mixed states compared to DSM-IV-TR? †	-
	▪ Fully adequate and better than DSM-IV-TR	24 (7.5%)
	▪ Sufficiently adequate and better than DSM-IV-TR	107 (33.44%)
	▪ Inadequate but better than DSM-IV-TR	128 (40%)
	▪ Less adequate than DSM-IV-TR	16 (5%)
	▪ I do not know	45 (14.06%)
06.	How would you rate the training on the diagnosis and treatment of "Mixed Depression" during your residency program? †	-
	▪ Adequate	75 (23.43%)
	▪ Less adequate compared to the training on the management of other mood episodes	104 (32.5%)
	▪ Barely enough	71 (22.19%)
	▪ Inadequate	54 (16.88%)
	▪ Severely Inadequate	16 (5%)

(Table 2) contd.....

Item	Questions	Results
07.	How would you rate the attention given to "Mixed Depression" in post-residency training formative events (seminars, conferences, master classes?) †	-
	▪ Adequate	16 (5%)
	▪ Less adequate compared to that given to other mood episodes	101 (31.56%)
	▪ Barely enough	113 (35.31%)
	▪ Inadequate	86 (26.88%)
	▪ Severely Inadequate	4 (1.25%)
08.	Do you routinely use any assessment tool in the evaluation of contrapolar symptoms for the diagnosis of "Mixed Depression"? †	-
	▪ Only clinical diagnosis (no interview or scale)	180 (56.25%)
	▪ Scale	140 (43.75%)
	1. Young Mania Rating Scale	69
	2. Hypomania Check-list Scale	41
	3. The Structured Clinical Interview for DSM-5	38
	4. Koukopoulos' Mixed depression Rating Scale	30
	5. Mood disorder questionnaire	27
	6. Other	21
	7. Affective Self Rating Scale	11
	8. Bach-Rafaelsen Mania Scale	5
	9. Internal State Scale	4
	10. Hypomania Interview Guide	3
	11. Clinician-Administered Rating Scale for Mania	2
	12. Multiple Visual Analogue Scales for Bipolarity	1
	13. Schedule for Affective disorder and Schizophrenia	0
09.	What is the most common triad of symptoms you have found in patients affected by "Mixed depression"? †	-
	▪ Irritability, emotional liability, psychomotor agitation	49
	▪ Irritability, emotional liability, racing thoughts	27
	▪ Irritability, psychomotor agitation, racing thoughts	16
	▪ Irritability, emotional liability, absence of psychomotor retardation	12
	▪ Irritability, emotional liability, decreased need for sleep	12
	▪ Emotional liability, psychomotor agitation, racing thoughts	12
10.	What is the most distinctive symptom of "Mixed depression" based on your clinical practice? †	-
	▪ Irritability	106 (33.12%)
	▪ Emotional liability	73 (22.81%)
	▪ Psychomotor agitation	55 (17.19%)
	▪ Racing thoughts	34 (10.62%)
	▪ Increased energy or goal-directed activity	18 (5.62%)
	▪ Pressured talk	12 (3.75%)
	▪ Others	22 (6.75)
11.	What is the least distinctive symptom of "Mixed depression"? †	-
	▪ Inflated self-esteem	88 (27.5%)
	▪ Increased sexual activity	72 (22.5%)
	▪ Elevated mood	40 (12.5%)
	▪ Involvement in risky activities	37 (11.56%)
	▪ Increased appetite	30 (9.38%)
	▪ Increased energy or goal-directed activity	16 (5%)
	▪ Other	37 (11.56%)
12.	As regards the psychopathological framework of depressive syndromes, which model you mostly support? †	-
-	▪ Unitary model	199 (62.19%)
-	▪ Binary model	101 (31.56%)
-	▪ Do not know	20 (6.25%)

† Only participants that answered "Yes" to Question 1 were considered.

The most common prescription strategies are reported in Table **3**. Regarding polytherapy, the most commonly prescribed antipsychotics were, in descending order, olanzapine, quetiapine, aripiprazole, risperidone, and

lurasidone, irrespective of the polypharmacy prescription approach. The most used mood stabilizers, in descending order, were valproate, lithium, lamotrigine, (ox)carbazepine, pregabalin/gabapentin, and topiramate, regardless of the polypharmacy prescription pattern. Finally, psychiatrists who opted for prescribing antidepressants by choosing a polypharmacy strategy preferred selective serotonin reuptake inhibitors (SSRI) over serotonin-norepinephrine reuptake inhibitors (SNRI); vortioxetine, trazodone, and bupropion.

We asked the participants if they took into account DSM-5 MxD criteria in the diagnostic approach and 227 (70.94%) answered in affirmative. The estimated frequency of MxD diagnosis among depressed patients was significantly lower for psychiatrists who answered that they referred to DSM-5 (17.50% *vs*. 30.00%, $p < 0.001$).

We also inquired about the standpoint regarding the conceptualization of depressive disorders: 199 of the participants answered that they supported the "unitary model", 101 the "binary model" and 20 did not know. We excluded the latter and compared the other variables among the remaining 300 subjects. The respondents who agreed with the "unitary model" were younger than the others (37 vs 42 years old, $p = 0.039$). Among the respondents who opted for the "binary model", we found a higher percentage of participants who affirmed that they considered DSM-5 criteria for the recognition of MxD compared to those who opted for the "unitary model" (81.19% *vs*. 64.82%, $p = 0.003$). Conversely, those who chose the "unitary model" used the Koukopoulos criteria for the diagnosis more frequently than the other group (13.07% *vs*. 3.95%, $p = 0.013$). The rate of respondents who indicated that they do not prescribe antidepressants for treating MxD was greater in the "unitary model subgroup" than in the "binary model" subgroup (35.68% vs 20.79%, $p = 0.008$). (Table **4**).

4. DISCUSSION

This is the first study to explore the knowledge and prescriptive attitudes towards MxD of psychiatrists working in different clinical settings across Italy. We aimed to investigate psychiatrists' awareness of the concept of MxD, also examining the assessment of first-time diagnosed patients and the prescription patterns adopted.

Almost all the participants (93.6%) answered that they were acquainted with the clinical entity of MxD. Only 23.43% of the respondents considered the level of training provided on this topic to be adequate, whereas twice that percentage (46.07%) rated it to be from "barely enough" to "seriously inadequate". Similarly, only 5% of the sample ranked the attention and time dedicated to MxD in post-residency scientific meetings as "fully adequate"

The reported prevalence of MxD diagnosis varies from 0% to 95% of total MDEs with a median value of 20% (IQR: 10-30%). This wide range of variability is not surprising since it is in line with the existing literature [7, 18, 44, 45] and might be mostly due to the absence of criteria univocally defining MxD [46 - 49].

Table 3. Drug prescription attitudes for "Mixed Depression".

Type	Treatments	Results
Polypharmacy	Antipsychotic + Mood Stabilizer	123 (38.44%)
Polypharmacy	Antidepressant + Mood Stabilizer	89 (27.81%)
Monotherapy	-	88 (27.5%)
-	Preferred drugs[†]:	-
-	o Valproate	58 (65.91%)
-	o Quetiapine	58 (65.91%)
-	o Lithium	48 (54.55%)
-	o Olanzapine	46 (52.27%)
-	o SSRI	32 (36.36%)
-	o Aripiprazole	26 (29.55%)
-	o Lamotrigine	23 (26.14%)
-	o Trazodone	15 (17.05%)
Polypharmacy	Antidepressant + Antipsychotic	20 (6.25%)

[†] Truncated, considers only drugs with more than 10 selections.

Table 4. Inferential statistics on diagnostic definition of mixed depression and psychopathological reference model for depressive disorders.

-	**Did the participant take into account DSM-5 MxD criteria in her/his clinical practice?**		
-	Yes (N = 227)	No (N = 93)	p-value
Estimated frequency of MxD diagnosis among depressed patients	17.5%	30%	<0.001
-	**Psychopathological reference model for depressive disorders**		
-	Unitary model (N = 199)	Binary model (N = 101)	p-value

(Table 4) contd.....

-			
Median age	37	42	0.039
Use of DSM-5 MxD criteria	64.82%	81.19%	0.003
Use of KMxD criteria	13.07%	3.95%	0.013
Aptitude to not prescribe antidepressants	35.68%	20.79%	0.008

Overall, the nosologic reorganization of MS implemented by DSM-5 reaches only a partial consensus among the participants in our survey. Only 7,5% of the surveyed psychiatrists considered the DSM-5 criteria for MxD to be fully adequate in the description of this clinical entity. On the other hand, a large majority of them evaluated the new systematization to be better than that of DSM-IV-Text Revision. We could hypothesize that one of the main reasons supporting only the partial agreement with DSM- 5 MFS criteria was the validity of the selected mixed symptoms. In fact, participants identified irritability, emotional liability, and psychomotor agitation/psychic tension as the symptoms "suggestive" of the diagnosis of MxD and more frequently recorded, based on their own clinical experience. None of these symptoms are included among the DSM-5 criteria for MxD because of the choice made by the DSM-5 - task force to exclude overlapping manifestations between episodes of opposite polarity.

Nevertheless, those symptoms indicated by participants to be rarely found during MDE with mixed features, namely "inflated self-esteem", "hypersexuality", "elevated mood" and "involvement in risky or dangerous activities", belong to the category of non-overlapping (hypo)manic symptoms. Consistent with previous studies, our survey highlights the criticisms toward the DSM-5 construct of MxD. Indeed, as argued by other authors, the decision to discard the "overlapping symptoms" and include pure manic manifestations, such as "elevated mood" or "inflated self-esteem", led to the development of an operational model of MxD that is not consistent with the phenomenological reality, disregarding the dysphoric and excitatory components in these patients [8, 50 - 54].

Regarding the assessment of contrapolar symptoms, the use of specific scales or questionnaires was practiced only by around 45% of participants. This may be related to the scarce attitude of the psychiatrists to the use of psychometric instruments in routine clinical practice, likely due to lack of time and adequate training [42, 55, 56]. Among the assessment tools listed, the YMRS was the one most used, followed by the HCL-32 and the SCID-5- CV). Few participants chose the KMxD-RS, a questionnaire specifically developed for assessing the diagnostic criteria of this alternative construct of MxD. The KMxD-RS appears to be less known, with increased use among participants working in Central Italy, probably due to the influence of the work of Athanasios Koukopoulos' Roman group in the training of psychiatrists working in that area.

In this survey, we also investigated the prescriptive attitudes adopted for the treatment of depressive episodes with mixed features. Firstly, we asked which approach was most frequently used between mono- and polytherapy, obtaining heterogeneous responses. The pharmacological management of MS is an insidious challenge for psychiatrists. Historically, pharmacotherapy of MS has represented an unmet need in the international guidelines for the treatment of mood disorders, and currently, no drugs have been approved for the treatment of MxD, although pharmacological recommendations are available [57 - 61].

Almost one-third of respondents selected antidepressants in combination with mood stabilizers or antipsychotics. SSRIs represented the antidepressant class most widely prescribed. Among the mood stabilizers, valproate and lithium were the first choices in association with antidepressants, whereas olanzapine and quetiapine were the preferred choice of antipsychotics. Antidepressant monotherapy was selected by around 10% of the psychiatrists. Overall, the prescriptive attitude towards antidepressants in MxD appears to be in line with the guidelines and pharmacological recommendations. Indeed, antidepressant monotherapy is discouraged, and reservations are expressed about their prescription in the maintenance treatment, if associated with mood stabilizers or antipsychotics [12, 62 - 64].

We also found that the use of antidepressants was less reported by those participants who preferred the unitary model. This might be attributed to the opposition to the use of antidepressants expressed by previous authors who support a spectrum approach to mood disorders [65 - 71].

The association of mood stabilizers with second-generation antipsychotics (SGAs) was found to be the prevailing prescriptive pattern. Valproate and lithium among mood stabilizers, and quetiapine and olanzapine among antipsychotics, were indicated as the drugs most used in such a combination. Similarly, valproate, quetiapine, lithium, and olanzapine resulted in the most used drugs also in monotherapy. These findings suggest an alignment of prescribing practice with the available literature evidence. Indeed, most of the aforementioned recommendations for the treatment of MxD indicate olanzapine and quetiapine as first-line or second-line options, either in monotherapy or in association with a mood stabilizer. On the other hand, lurasidone and asenapine were chosen by few participants, although they are included among the most widely recommended antipsychotics along with olanzapine and quetiapine. This data fits into a less prescriptive attitude towards these SGAs by Italian psychiatrists, as documented by the Italian Medicines Agency (AIFA) report on drug' consumption. Regarding lurasidone, this trend might be explained by the fact that it was just recently introduced to the Italian market [72], while the progressive decreasing prescription of asenapine might be due to a profile of particularly unpleasant side effects [73, 74].

As regards the mood stabilizers, valproate and lithium were the most considered drugs, irrespective of the chosen therapeutic regimen. Both these drugs are mentioned among

potential first-line or second-line options either in monotherapy or in association with an SGA (olanzapine, quetiapine, or lurasidone). However, mood stabilizers monotherapy is mostly recommended for maintenance treatment since the available evidence on their efficacy in the acute treatment is weak, especially compared to SGAs [63]. The percentage of our respondents reporting the use of lithium is quite remarkable. This result is almost coinciding with the rate of participants who answered that they considered lithium for the treatment of depressive episodes with mixed features in a recent survey involving young Italian psychiatrists [75]. Therefore, our results confirm an incremental trend in lithium's prescription after decades of relative marginalization of this pharmacological agent in psychiatric practice [76, 77].

Finally, we asked participants to indicate which theoretical model they found the most reliable for the classification of depression. We suggested two possible models: the Kraepelinian unitary spectrum view of mood disorders and Leonhard's binary model, which considers bipolar and unipolar depression as two separate psychopathological entities [78, 79]. Over 60% of our sample expressed their preference for the spectrum view, while 30% supported the Leonhardian dichotomic model, and around 6% did not express any preference. The respondents in favor of the unitary model were significantly younger than those who opted for the binary model. It can be hypothesized that younger psychiatrists rely on a dimensional and spectrum approach to the diagnosis of affective and psychiatric disorders in general. On the other hand, those who preferred the dual view might be still anchored on the categorical approach introduced by DSM III, which divided for the first time, Kraepelin's broad concept of manic-depressive insanity (MDI) into the two distinct diagnoses of bipolar disorder and major depressive disorder, therefore introducing a distinction between unipolar and bipolar depression [80].

This study has several strengths and limitations. As previously underlined, this is the first survey aimed at exploring the psychopathological, diagnostic, and therapeutic approaches toward the clinical entity of MxD among a large sample of Italian psychiatrists, with a quite homogeneous geographical representation, working in different clinical settings. One of the limitations is that we collected few responses from academic psychiatrists who may offer a perspective that is more aligned with the latest literature evidence on psychopathology and treatment strategies of MS. Moreover, the choice to rely on an online survey could have implied a sort of recruiting bias with the self-selection of a younger and more technologically inclined sample. Finally, although the survey was conducted anonymously, we cannot exclude that several answers, especially those concerning the pharmacological approach, could be affected by a potential desirability bias rather than reflect the real attitudes in the daily clinical practice.

CONCLUSION

The explorative nature of this survey highlights the clinical relevance of mixed depression within the field of affective disorders. The resulting heterogeneity of diagnostic and therapeutic approaches of MxD reflects the need for further studies on this topic. They would be aimed at clarifying the psychopathological structure of MxD in order to develop future univocal diagnostic criteria for the correct identification of patients and for conducting specifically targeted clinical trials. Another aspect arising from this study is the lack of attention given to MxD and MS during residency training and postgraduate training events. Therefore, there appears to be an urgent need for more specific activities and training programs to fill this gap.

LIST OF ABBREVIATIONS

MS	=	Mixed States
DSM III	=	Diagnostic and Statistical Manual for Mental Disorders – third edition
DSM IV	=	Diagnostic and Statistical Manual for Mental Disorders – fourth edition
DSM 5	=	Diagnostic and Statistical Manual for Mental Disorders – fifth edition
MxD	=	Mixed Depression
MDE	=	Major Depressive Episode
MFS	=	"With Mixed Deatures" Specifier
ACE	=	Activity, Cognition, Energy
HCL -32	=	Hypomania Check-List 32 items
KMxD-RS	=	Koukopoulos' Mixed Depression Rating Scale
SCID-5-CV	=	Structured Clinical Interview for DSM-5 – Clinical Version
YMRS	=	Young Mania Rating Scale
IQR	=	Interquartile Ranges
SSRI	=	Selective Serotonin Reuptake Inhibitors
SNRI	=	Serotonin-Norepinephrine Reuptake Inhibitors
SGA	=	Second-Generation Antipsychotic
MDI	=	Manic Depressive insanity

ETHICAL STATEMENT

The University of Catania's ethical review committee approval is not needed for surveys conducted anonymously on a non-clinical population.

CONSENT FOR PUBLICATION

All participants provided their informed consent and were informed of the study's purpose.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study are available within the article.

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Chapter 3

DISCUSSION AND CLOSING REMARKS

The main aim of this Ph.D. research project consisted in investigating subthreshold hypomanic symptomatology in terms of prevalence, phenomenological features, and clinical impact during an MDE in a sample of patients with a previously established diagnosis of either MDD or BD, recruited at three University Medical Centers in Italy.

One of the strengths of this research can be seen in the use of the MOODS-SR questionnaire, which provides clinicians and researchers with the possibility of exploring affective psychopathology according to a spectrum and multidimensional approach. The internal organization of MOODS-SR allows for an assessment of affective psychopathology based on the analysis of 4 domains (energy, mood, cognitive, and neurovegetative), and therefore it qualifies as a potential psychometric tool that is adaptable to the ACE model. The latter is designed to deconstruct the rigid manic or depressive dichotomy, regrouping the constituent features into the domains of Activity, Energy, and Cognition[1].

A first relevant finding of the research derived from the analysis of MOODS-SR scores that revealed a positive linear correlation between depressive and manic symptomatology, both within the total sample and within the two main diagnostic groups (MDD vs. BD). This evidence is in accordance with previous studies that examined the relationship between depressive and manic symptoms in cross-sectional or longitudinal design, and failed to support the core assumption of the one-dimensional model of bipolar disorder, i.e., that depressive and manic symptoms would be robustly and negatively correlated[2–5]. In this regard, it is worth noting that—unlike past simplified neurobiological theories—psychodynamic and

psychoanalytic conceptualizations of mood disorders have not considered the possible coexistence of depression and mania to be a contradiction[6].
More realistically, depression and mania might be conceived as two separate symptom dimensions, fluctuating independently even in their subdomains. In line with this conceptualization, an orthogonal rather than a linear approach to nosology would be more adequate and would better encompass the highly heterogeneous realm of mixed forms. However, this view was not incorporated into DSM-5, which opted for a pragmatic and linear approach whereby mania and depression are at opposite poles of the spectrum[7,8].

In the study *Mood spectrum symptoms during a major depressive episode: Differences between 145 patients with bipolar disorder and 155 patients with major depressive disorder. Arguments for a dimensional approach*, we aimed at evaluating differences in MOODS-SR domain scores between the two main diagnostic groups (MDD vs. BD). Secondly, we wanted to verify whether specific symptoms were more frequent in one or the other diagnostic group. Our guiding assumption that patients with BD would endorse more manic\hypomanic symptoms compared to patients with MDD was confirmed, but to a lesser extent than expected. Indeed, although the BD group reported higher scores in all MOODS-SR domains, after statistical corrections, significant differences were observed only for "energy depressive" and "mood manic" domains. Additionally—after comparing the frequency of endorsement of individual mood spectrum items between the two main diagnostic groups—the following nine mood spectrum items were found to be endorsed by a significantly larger percentage of patients with BD: mood deflection after use of psychotropic agents, rapid mood swings, expansive or dysphoric mood after abuse or increased use of psychotropic agents, passivity, severe difficulty in taking care of oneself, distractibility, unrealistic financial worries, and impulsive decision making. Therefore, these specific manifestations should be given more

attention in the differential diagnostic process when the presence or absence of a history of manic/hypomanic episodes cannot be clearly established.
Two main conclusions were drawn from this study: the presence of a considerable amount of contrapolar symptomatology, ascertained by means of a spectrum approach, in both diagnostic groups (although higher among bipolar patients); and the greater likelihood of BD patients to exhibit atypical depressive features along with reduced energy levels, as demonstrated by a significantly higher score in the "depressive energy" domain.

In the study *Mood spectrum symptoms exploration during a major depressive episode: the impact of contrapolarity. Results from a transdiagnostic cluster analysis on a sample of unipolar and bipolar patients,* we used K-means clustering analysis to disaggregate our sample into distinct groups based on the domain scores of the MOODS-SR questionnaire. By means of this statistical technique, we identified three transdiagnostic clusters characterized by distinct profiles of MOODS-SR domain scores: a group characterized by intermediate levels of depressive symptoms and low levels of (hypo)manic symptoms (Mild cluster); a group with high levels of depressive symptoms and intermediate levels of (hypo)manic symptoms (Mixed cluster); and a large group (Moderate cluster) with depressive and manic symptomatology levels overlapping with those recorded for the "Mixed" and "Mild" clusters respectively. A more in-depth dimensional analysis of the psychopathological profile of the three different clusters was performed by assessing inter-cluster differences in the scores of the six depressive and manic MOODS-SR domains. In summary, the "Mixed" cluster reported significantly higher scores than the "Mild" in each of the six domains considered; on the other hand, compared to the "Moderate" cluster, the "Mixed" cluster scores were found to be significantly higher in all three hypomanic domains and in the

"cognitive depressive domain," similar in the "mood depressive domain," but significantly lower in the "energetic depressive" domain.

Since the "Moderate" and "Mixed" clusters share similar levels of depressive symptomatology and BD prevalence rates, the analysis of the between-group differences on MOODS-SR domains and factors in our sample suggested the presence of two phenotypes of bipolar depression distinguished by different combined degrees of inhibition and hyperactivation. Our findings reflect those of previous studies that provide support for heterogeneity in bipolar depression with the identification of subtypes based on clinical and psychopathological dimensions rather than nosologic categorization[9–11].

Of note, while the primary affective diagnosis exerted a main effect on the group with BD prevalence that was significantly less represented in the "Mild" cluster than in the "Moderate" and "Mixed" clusters, the DSM-5 MFS did not differentiate among the three groups. Conversely, the alternative diagnostic construct of KMxD presented higher prevalence rates than DSM-5 MFS in each of the three clusters, and it was found to discriminate the "Mixed" group from the "Mild" and "Moderate" ones after performing a pairwise comparison. We surmised that this superior discriminative ability is probably related to the inclusion among the KMxD criteria of symptoms that express the dysphoric, excitatory, and irritability components present in mixed depressive states[12]. In support of this assumption, patients belonging to the "Mixed cluster" reported significantly higher scores in "mixed instability" and "mixed irritability" MOODS-SR factors compared to those belonging to the "Mild" and "Moderate" ones.

Studying the distribution across the clusters of a set of selected sociodemographic, psychometric, and clinical variables, we observed an overall disease-severity gradient from the "Mild" to the "Mixed" cluster. In line with well-established presentations of mixed states reported in the literature[13–17], the "Mixed" cluster patients presented younger age and an earlier onset of disease, a higher number of

hospitalizations and previous suicide attempts, the more likely presence of psychotic and suicidal ideation, greater levels of impulsivity, worse self-reported health, higher disability scores, and higher comorbidity rates of any Cluster B personality disorders or any Substance use disorder. Based on the evidence of a strong association between "Mixed" cluster membership and most of the illness-severity, quality of life, and outcome measures considered, we assumed that the magnitude of subthreshold contrapolar symptomatology might act as a key moderating factor of MDE clinical phenotype regardless of the main affective diagnosis. Nevertheless, after performing post-hoc pairwise comparisons, statistically significant differences between the "Moderate" and the "Mixed" cluster (characterized by similar MOOD-SR depressive scores but unequal MOOD-SR manic scores) were restricted to the following variables: impulsivity levels, presence of psychotic ideation, comorbid Cluster B personality disorder, number of lifetime hospitalizations, and suicide attempts.

With regard to the latter outcome, the subsequent regression analysis—conducted in order to ascertain potential correlations between the discriminative variables listed above versus the depressive and manic factors of the MOODS-SR—identified the "suicidality factor" as its main positive predictor followed by the "manic psychomotor activation factor" and the "mixed instability factor." Not surprisingly, the "spiritualism/mysticism/psychoticism" factor was instead found to be the only negative predictor. On the other hand, as well as recognizing the "depressive factor" as a positive predictor, the outcome "suicidal ideation" presented a more robust correlation with the "suicidality" factor, a weaker correlation with the "manic psychomotor activation," and no correlation with the "mixed instability" factor.

These findings offer interesting insights into the impact of specific psychopathological subdimensions on the pathway from suicidal ideation to suicidal acts, corroborating the findings of earlier studies[18–21]. The comparative

assessment of the two separate regression models for suicidal ideation and lifetime suicidal attempts suggests that marked emotional lability, rapid mood shifts, and dysphoria may exert a critical role in governing the transition to suicidal behaviors. However, the interplay between manic and depressive symptoms in moderating suicidal risk during a major depressive episode appears extremely complex and is yet to be fully elucidated. In particular, the question of whether the presence of subthreshold manic symptoms confers a greater risk for suicide outcome beyond that attributed to the depressive component is still being debated with conflicting data. For instance, in a 2021 study, after examining the data of 6,105 patients (998 affected by BD and 5,117 with MDD) from the National Network of Depression Centers Mood Outcomes Program, Fiedorowicz et al. reported that manic symptoms during an MDE conveyed no excess risk of suicidal ideation or behavior beyond the risk conveyed by the depressive symptoms alone[22]. The same authors suggested that previous established associations[23–27] between mixed depressive states and prior suicide attempts may be put into question by a more persistent course of depressive symptoms since MS are characterized by more frequent or longer duration of mood episodes. One major limitation of this cited study was the use of a scale for manic symptomatology (Altman Self-Rating Mania scale) designed to capture only symptoms related to selected facets, such as elevated mood and increased energy and therefore, it was unable to assess other more typically mixed dimensions such as irritability and dysphoria which are instead targeted by the MOODS-SR.

Another factor that explains the significantly higher rate of suicide recorded in the "Mixed" cluster may be the greater levels of impulsivity exhibited by patients belonging to this group. Impulsivity is a complex construct whose phenomenological characterization has revealed the predominance of different components in bipolar disorder (motor impulsivity) and MDD (non-planning impulsivity)[28–30]. Therefore, the co-presence of hypomanic symptoms during MDE

could imply a multiplying effect because of the synergic interaction between the distinct impulsivity components.

With regard to the significantly higher comorbidity of a Cluster B Personality Disorder (in most cases with a Borderline Personality Disorder) found in patients of the "Mixed" group, this finding must be accepted with caution, although it is widely reported in the literature[15,31–33]. These high rates of comorbidity, together with the not insignificant heterogeneity of the data obtained from prevalence studies available to date, can be partly ascribed to errors in the clinical assessment of both conditions and consequent misdiagnosis.

In fact, the differentiation of BD spectrum disorders from Borderline Personality Disorder (BPD) represents a diagnostic challenge in view of the overlap of phenomenological and clinical features such as emotional dysregulation, mood instability, aggressiveness, impulsivity, unstable interpersonal relationships, repeated self-harm, and suicide attempts[34]. The relationship between these nosological entities is still a matter of academic debate, with some authors questioning the true nosographic independence of BPD and, consequently, the possibility of real comorbidity, considering it as a "nosographic artifact" and placing the borderline syndrome along the bipolar spectrum[35–37].

In the paper *Which mixed depression model? A comparison between DSM-5-defined mixed features and Koukopoulos' criteria*, we addressed the issue of the diagnostic sensitivity and clinical validity of the DSM-5 defined "mixed depression" construct.

The introduction of the DSM-5 MFS was originally meant to provide clinicians with more sensitive criteria to better account for the heterogeneity of MS and the highly prevalent subthreshold presentations compared to the strict definition of ME in DSM-IV-TR[38,39].

A recent meta-analysis and systematic review investigated the prevalence of DSM-5 defined mixed features in MDE and manic-hypomanic episodes to verify the effective improvement in diagnostic coverage of mixed depressive episodes[40]. After selecting a total of 17 studies with 20 samples, the pooled prevalence of MFS in MDE was 11.6% (95% CI = 7.9%-16.7%). Two samples in East Asian countries (Republic of Korea and Japan) had the lowest prevalence, which were 2.2% (12 out of 552)[41] and 0% (0 out of 125)[42] respectively. However, the authors of the review suggested caution on the interpretation of these findings since the heterogeneity issues were not solved by subgroup analysis (suggesting that there were influential factors for the prevalence of mixed features that were not included in the meta-analysis) and most of the studies demonstrated moderate to high risk of bias. It should be noted that in most of the studies examined, the assessment of the MFS criteria was conducted through a retrospective evaluation of samples of patients recruited prior to the publication of the DSM-5 (by means of retrospective chart review or using proxies by means of psychometric tools). In all cases, with the exception of one study, the prevalence of MDEs with DSM-5 MFS was higher than that of ME according to the DSM-IV-TR criteria.

Although these data confirm that this diagnostic change would effectively achieve the original goal of overcoming the extremely narrow definition of ME in DSM IV-TR by offering a broader definition of depressive mixed states, several criticisms and objections have been raised against the DSM-5-defined mixed depression construct, judged by some authors to be scientifically weak and without adequate diagnostic sensitivity[43–46].

In our study, we found that the KMxD criteria identified more than three times as many patients with mixed depression by applying the DSM-5 MFS. Both diagnostic constructs were proven to exhibit an overlapping discriminative capacity for bipolar depression; nevertheless, the optimal DSM-5 cut-off for BD diagnosis resulting from our analysis was lower than the one currently used to diagnose DSM-5 MFS

(≥1 *vs.* ≥3 symptoms). Conversely, the KMxD optimal threshold we found to identify patients with bipolar depression in our sample and the KMxD diagnostic cut-off were concordant (≥3 symptoms in both cases). Furthermore, after performing a multivariate binary logistic regression, KMxD yielded a stronger association than DSM-5 MFS with a set of variables related to bipolarity. Of note, the number of lifetime suicidal attempts, the number of psychiatric hospitalizations, the presence of comorbidity with anxiety disorders, and a family historyof mood disorders were found to exhibit a statistically significant association with KMxD but not with DSM-5 MFS. In our study, the KMxD proved to be a more inclusive diagnostic construct than the DSM-5 MFS as it was able to intercept a large portion of "mixed depressed patients" missed by the DSM-5 criteria.

The low sensitivity of DSM-5 MFS has been related to the fixed diagnostic threshold and especially to the symptoms included in the criteria[47,48]. Indeed, the DSM-5 task force opted to consider as mixed features only those symptoms belonging exclusively to the manic polarity, excluding other relevant manifestations such as irritability, psychomotor agitation, and distractibility only because they overlap with the criteria for MDE and thus are considered as non-specific. However, it is precisely this set of symptoms, along with other excitatory features (overlapping with the criteria for "atypical features," such as mood reactivity, absence of psychomotor retardation, and emotional liability) that would best characterize the phenomenological and clinical profile of mixed depressive states[12,49]. On the other hand, to qualify as "mixed features," those manifestations that are expressions of the more properly expansive component of manic symptomatology, i.e., elevated/expansive mood or grandiosity, lead to symptom combinations that are rather illogical or paradoxical (such as euphoria with melancholia)[45,50,51]. The frequency of these manifestations recorded in our sample of patients was consistently marginal, in line with data from other previous similar studies[15,52,53].

The distance of the DSM-5-defined mixed depression from the "real-world" phenotype of mixed depressive states has also emerged from the results of our survey-study *Mixed Depression: A Survey on Psychopathological, Diagnostic and Therapeutic Approaches Among a Sample of Italian Psychiatrists.* Indeed, only 7.5% of the surveyed psychiatrists considered the DSM-5 criteria to be clearly better in describing this clinical entity compared to the DSM-IV TR. In addition, the symptoms indicated by most of the respondents as distinctive features of mixed depression were "irritability, emotional liability, and psychomotor agitation," whereas inflated self-esteem, increased sexuality, and elevated mood were deemed to be the least observed mixed features.

As already reported, the inability of DSM-5 MFS to adequately address subthreshold bipolarity in patients suffering from MDE was also highlighted in our cluster analysis, where DSM-5 MFS did not exert any main effect of group, as no differences were indicated between the three clusters characterized by different gradients of contrapolarity.

The DSM-5, like the DSM-IV, proposed a conceptualization of mixed depression as a simple addition of depressive and manic symptoms without taking into account the real phenomenology of mixedness and, in particular, the key dysphoric and excitatory components[54]. Therefore, with the aim of avoiding overdiagnosis, the DSM-5 MFS has excluded the overlapping manic symptoms that actually represent the core features of mixed depression, favoring specificity at the expense of sensitivity. In this way, however, it could end up failing to detect a wider fraction of patients, with huge clinical and therapeutic implications.

Furthermore, the aforementioned motivation behind the DSM-5 task force resolution appears contradictory to the inclusion of inner tension and restlessness (conceptually linked to psychomotor agitation) among the criteria of the DSM-5 specifier "with anxious distress" (ADS) increasing the risk of misdiagnosis[55,56].

Although the addition of the MFS to MDD was interpreted as a theoretical structural bridge between MDD and BD—positing a more spectrum-oriented approach to mood disorders in accordance with the DSM-5 guiding principle of closer integration between categorical and dimensional models—the new systematization of mixed states paradoxically further emphasizes the limitations of the DSM approach to the psychopathology of affective disorders. Indeed, the shift from ME to mixed features has been argued to radicalize the dichotomization of mood disorders along a single domain in which depressive and manic episodes are at the opposite ends of the mood spectrum and, therefore, mutually exclusive[7].

Beyond the specific limitations discussed in the individual papers (first and foremost the relatively small sample size), the present doctoral research was affected by two major limitations that should be acknowledged.

Firstly, although it was required that patients should not receive any major changes in pharmacotherapy in the three weeks prior to the clinical examination, we could not speculate on the effects of any possible drugs on clinical presentations since pharmacological treatment data were not available.

Secondly, because of Covid-19 pandemic-related restrictions, follow-up assessments of patients according to specific time intervals were precluded. Consequently, we could not perform a longitudinal evaluation aimed at verifying the stability of the main diagnosis and at identifying specific symptom clusters of factors presumably predictive of manic switch or progression from MDD to BD.

These two limitations appear to be closely related in recalling two main issues that are still controversial related to depressive episodes with subthreshold hypomania.

A first issue is whether MDD with mixed features should be considered as an intermediate presentation that is inevitably on the path to evolving into bipolar disorder, or as a relatively stable nosographic entity.

A second one concerns the preclusion or not of the use of ADs in monotherapy in patients with MDD with mixed features.

The answer to these questions may be provided by prospective studies of patients with well-defined MDD with mixed features based on renewed diagnostic criteria that account for those mixedness components currently ignored by the DSM-5.

However, this revisitation cannot be separated from a real implementation of a dimensional approach that considers the different domains of affective psychopathology and their intersections. The definition of mood disorders drawn by current classification systems still remains a primary option in describing these conditions for both clinical and research purposes, since the practical strengths of these taxonomies—such as their international diffusion, reliability, familiarity, and widespread uptake—outweigh their drawbacks, and make their replacement by alternative systems very unlikely[57].

As recently outlined by Mario Maj: "we still need current diagnostic categories, which can certainly be much improved, but without which we would either be lost in a *mare magnum* of variables, or presented with synthetic formulations which are less efficient, in addition to being potentially controversial and not rooted in clinical tradition."[58] At the same time, it seems that there is an urgent need for the development of tools which—by also incorporating elements from the models that are currently presented as "alternative" to the ICD and DSM—may guide clinicians and researchers in a more refined clinical and psychopathological characterization of individual cases in order to offer targeted treatment plans and allow for better risk stratification and the formation of more homogeneous clinical trial samples.

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