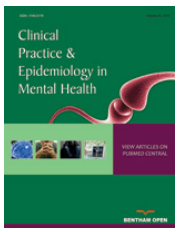

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RESEARCH ARTICLE

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.....

-	**Did the participant take into account DSM-5 MxD criteria in her/his clinical practice?**		
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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CONFLICT OF INTEREST

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Eugenio Aguglia, Ludovico Mineo, Alessandro Rodolico planned the study. Andrea Aguglia, Carmen Concerto, Ludovico Mineo, Manuela Pennisi, and Alessandro Rodolico designed the questionnaire. Alessandro Rodolico, Gianluca Serafini, and Massimo Tusconi implemented the online version of the survey and carried out the statistical analysis. All authors recruited the survey's participants. Andrea Aguglia, Andrea Amerio, Carmen Concerto, Ludovico Mineo, Manuela Pennisi wrote the paper. Eugenio Aguglia and Mario Amore supervised the study. All the authors revised and approved the final version of the paper.

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