

AI AND ALTERNATIVE SYMPTOMS IN THE DIAGNOSIS OF MDD: The role of forgiveness, hopelessness, mixity and diminished drive

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SUMMARY

The explosion of the use of artificial intelligence (AI) in medical practice has shaken the foundations of clinical assessment and management. In our study, we conducted structured interviews with 43 patients (23 female, 15 male) affected by MDD (DSM-5-TR criteria). We sent the recorded and transcribed semi-structured interviews to the analysis of appropriately trained AI programs. We evaluated the predictive weight of symptoms described by patients beyond those present among the DSM-5-TR diagnostic criteria. We also analyzed the relationship with forgiveness, hopelessness, and diminished drive. The results revealed a positive predictive factor in patients with higher levels of somatization and physical oppression, ambivalent and blocked anhedonia, distress and agitated restlessness, mixed states, and subthreshold symptomatic oscillations.

Key words: MDD – AI - depressive symptoms - DSM-5-TR – forgiveness - mixity

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INTRODUCTION

The symptomatic heterogeneity determined by the main operational criteria for mood disorders and, particularly, for major depressive disorder is considered fundamental in the diagnostic and therapeutic approach of this disorder. However, the difficulty of framing and inserting some symptoms among the diagnostic criteria, indicated by the main international classification systems (DSM and ICD), often, emerges from clinical interviews in professional practice in the "real world". Although patients report a large constellation of symptoms, often, the clinician risks not being able to identify symptoms that meet these diagnostic criteria (Michellini et al. 2021; Kotov et al. 2017). A new pragmatic perspective of psychopathology was proposed by McNally and co-authors (2015) according to the concept that «symptoms are not outcome factors of an underlying disease; the symptoms and their associations are the disease itself». To overcome these difficulties, the use of new IT tools, as well as artificial intelligence, can open up new scenarios to help clinicians formulate diagnoses more closely aligned with real patient experiences.

LOOKING FOR MOOD DISORDERS IN THE REAL WORLD

In daily clinical practice, frequently, we witness the identification and collection of symptoms described by patients that are not recognizable in the symptoms described in traditional diagnostic categories (Maj et al. 2020). Even though the patient, for example, clearly shows intense personal anxiety an irritability, or complains of heart problems, or clearly describes an impair-

ment of his social functioning, there is a risk of not being able to identify symptoms that satisfy the diagnostic criteria of the main diagnostic manuals for psychiatric disorders. Based on these premises, scientific research has begun to utilize network analysis, which has played a fundamental role in addressing symptomatic and, therefore, psychopathological heterogeneity through bottom-up processes (from patient to clinician) (Fusar-Poli et al. 2023). Network analysis attributes psychiatric data (e.g., the symptoms) to a network structure. In this way, correlated symptoms within the same network, as in the case of depressive symptoms, can be explained using a network analysis approach (Contreras et al. 2019; Kim et al. 2024). Using network analyses, these studies found a lack of specificity with definite differences between the centrality of symptoms included in the DSM diagnostic criteria for major depressive disorder (e.g., depressed mood) and depressive symptoms not included in the DSM diagnostic criteria (Fried et al. 2016). Among the depressive symptoms that have a discreet (and predictable) centrality in the diagnosis of major depressive disorder, lack of energy, absence of interest, sense of uselessness and symptoms associated with the anxious sphere (weakness, dizziness, feeling of suffocation, feeling of fear, fear that something bad will happen, nervousness, inability to relax and feeling of trembling) have been identified (Kim & Park 2020). These symptoms have been defined as the central node/core of depressive and anxious symptoms. Furthermore, the interconnection between irritability and nervousness can represent a strong diagnostic advantage as well as an undisputed transdiagnostic usefulness between anxious and depressive symptoms. The symptomatology dimension, along a descriptive spectrum,

poses the problem of integrating temperament and state condition through positioning within it (Tavormina & Franza 2022, Tavormina 2021). Since the first developments of the Hippocratic concepts, temperament has represented the central point in the discussion of psychopathological phenomena in psychiatry. However, the presence of elusive psychopathological boundaries is indisputable. Although the modern concept of affective temperament has been operationalized primarily in a clinical descriptive framework (Akiskal 1996), important theoretical and empirical convergences with phenomenology suggest that the Typus Melancholicus infrastructure is a potentially relevant modulator of the intramodality and long-term trajectories of mood disorders, thus constituting a vulnerability factor (Raballo & Pelizza 2019).

The results of research carried out with factor analysis on the predictive value of depressive disorders have highlighted a quantitative difference between the different symptoms. Depressive symptoms have been identified with a higher predictive value than the symptoms described in the DSM, and, particularly, a high predictive relevance of the "diminished drive" symptom (a reduced volitional drive) has been found (McGlinchey et al. 2006).

The absence of reactive mood, psychic anxiety, somatic anxiety, and expressed anger is another frequent symptom in depressed patients. Diminished drive is thus among the strongest symptom predictors to differentiate MDD from non-MDD. Other symptoms that should be explored as internal symptoms in the diagnosis of depression are forgiveness and hope, or their absence, which could be associated with a greater vulnerability to develop this disorder (Franza et al. 2022).

To address these difficulties, studies utilizing artificial intelligence in the medical and psychiatric fields are beginning to emerge (Bzdok & Meyer-Lindenberg 2018; Guntuku et al. 2017). Our study aimed to use, through a Transformer architecture NLP (Natural Language Processing) module, designed for the semantic and contextual processing of semi-structured clinical interviews (Topaz et al. 2021), the presence of symptoms indicative and predictive of a major depressive disorder but not present among the diagnostic criteria of the DSM-5-TR. Furthermore, based on the results obtained, we examined the levels of forgiveness, the hopelessness, and the presence of subthreshold mixed states. Our study is a preliminary investigation, and its complete results will be developed and published subsequently.

METHODS

In our study, we recruited 43 patients (23 female, 15 male) affected by MDD or related affective disorders (DSM-5-TR criteria), through semi-structured clinical interviews conducted in an outpatient setting (and in

psychiatric rehabilitation center inpatients). All interviews were recorded and transcribed in textual form and sent to the analysis of appropriately trained AI programs. The interviews were collected in textual form, anonymized and archived in accordance with the European Data Protection Regulation (GDPR 2016/679). The study was conducted in accordance with relevant ethical guidelines and regulations. For the study conducted, the patients provided informed consent in accordance with the healthcare guidelines of the center. The participants were recruited from both a residential setting (SIR "Villa dei Pini", Avellino, Italy) and an outpatient setting. The study adhered to the provisions of Law No. 219/2017, which governs informed consent and advance healthcare directives in Italy (18G00006) (Table 1).

The semi-structured interview was based on the questions of the PHQ-9 and integrated with open questions and other questions from the GT. Mixed States Rating Scales, HFS and BEES. All patients the following psychopathological assessment scales were administered:

- Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham 1962): for psychopathological assessment.
- Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al. 2001): for the assessment of depression and basis for the semi-structured interview in our study.
- Heartland Forgiveness Scale (HFS) (Thompson et al. 2005): HFS consists of three six-item subscales (Forgiveness of Self, Forgiveness of Others, and Forgiveness of Situations).
- G.T. Mixed States Rating Scales" (G.T. MSRS) (Tavormina 2014): for the assessment of mixed states.
- Beck Hopelessness Scale (BHS) (Beck 1988): for hopelessness assessment [in 22/43 patients].

Computational linguistic analysis

The transcriptions of the patient interviews were processed using a transformer architecture NLP (Natural Language Processing) module, designed for the semantic and contextual processing of unstructured clinical documents.

Technical description

The system used is based on a Large Language Model (LLM) model, trained on general and medical textual datasets, and optimized for:

- syntactic-semantic interpretation of natural language,
- abstraction of latent clinical entities (e.g. emotional experiences, bodily metaphors),
- comparison between textual contents and nosographic systems (DSM-5, ICD-11),
- structured production of tables, symptom clusters and screening forms.

Table 1. Epidemiological and psychopathological data

	Age		BPRS - Descriptive Statistics	
	years		T1	T0
Total	43	Valid	43	43
	43.23	Mean	47.256	50.442
	12.32	Std. Dev	12.767	11.675
Females	26	Valid	<i>Test of Normality (Shapiro-Wilk)</i>	
	42.88	Mean	T0 (baseline vs T1 (after 6 months))	
	11.49	Std. Dev	W	p
Males	17	Valid	0.842	<0.001
	43.76	Mean		
	11.54	Std. Dev		

The interface was used in interactive mode, on a private cloud platform, without connection to external databases. The model's responses were validated and supervised by clinical specialists and psychopathologists.

All inferences produced by the NLP model have been discussed and validated in a clinical setting. The results were compared with the professional experience of the team and led to the formulation of descriptive and operational hypotheses, useful for the revision of the traditional depressive model.

Being a preliminary study, the description of the method and complete results will be presented in subsequent works.

Statistical analysis

The statistical data were analyzed using JASP (an open-source project supported by the University of Amsterdam) and Validity and Reliability Analysis with Factor Analysis (e.g. exploratory or confirmatory factor analysis) [Cronbach's Alpha (Coefficient α)/McDonald's Omega (Coefficient ω)] to evaluate the internal reliability of the scales and the sub-groups of items.

RESULTS

The results obtained in our study highlighted differences in the analysed sample which will be described below in subgroups of symptoms.

Body weight, somatization and sense of physical "oppression"

69.77% of patients (30/43 pts) described a central physical symptom, often more disturbing than humoral symptoms. The most frequent statements in this subgroup of symptoms were: "heaviness in the chest", "muscle tension", "unexplained body tiredness", "daily stomach-ache", "stuck breathing". The DSM-5-TR does not evaluate somatization as a key symptom, while in our sample, it is highlighted that depression has a primary bodily expression, particularly at the thoracic and gastric level.

Ambivalent and "stuck" anhedonia

Patients are not simply "disinterested" or report a lack of pleasure in doing things. There are frequent statements that highlight a "diminished drive": "I would like but I cannot"; "I lack drive"; "I know what I should do but I am stuck." The DSM-5-TR considers anhedonia as a distinct absence of pleasure. However, in our sample, a type of "dynamic anhedonia" is highlighted, characterized by a conflict between desire and paralysis, which corresponds to the motivational-blocked subtype.

Anguish and agitated restlessness as dominant symptoms

More than 25 patients describe their symptoms with statements such as: "I feel like I am moving inside", or "I cannot sit still", or "Anxiety consumes me". The DSM-5-TR includes only observable psychomotor agitation, while in our sample, it is found that subjective internal agitation is central. It sometimes precedes or accompanies depression.

Passive suicidal ideation (vague but recurrent)

In our group, there is a widespread form of passive ideation that is considered clinically relevant even without suicidal planning. Recurring expressions such as: "I wish I did not wake up," are highlighted; "Maybe it would be better not to be there anymore,"; "I would not do any harm, but I do not care if I live." The DSM-5-TR considers suicidal thinking as criterion 9, but does not distinguish between active/passive/or ambivalent.

Externalized anger and frustration

In our sample, some patients exhibit anger towards their family, the world, or doctors, especially in younger patients and in resistant cases (VS, DGS, FZ, RR). It often coexists with sadness and anxiety. The DSM-5-TR does not include anger as an expression of depression. As we will see later, the coexistence with other

symptoms should orient the clinician towards other diagnostic hypotheses (for example, "mixity"). Our sample suggests a possible agitated-irritable phenotype, potentially associated with mixed forms of the disorder.

Mixed states and subthreshold oscillations

In many patients in the analysed sample, an alternation and confluence of apparently opposite symptoms are observed, such as tiredness and hyperactivity, apathy and restlessness, and inhibition and accelerated thoughts. The DSM-5-TR requires ≥ 3 manic symptoms to diagnose a "depressive episode with mixed features". Instead, our sample documents subclinical (or undiagnosed) mixed states or unstable fluctuations, not codifiable according to current criteria. These conclusions agree with the results obtained with the G.T. MSRS (34.3% of "mixity").

Sense of moral and relational guilt

The LLM model analysis detected and focused on strong expressions expressed by the patients of the analysed sample, such as: "I ruined my family", "They will never forgive me", and "It is my fault if they are sick too". The DSM-5-TR talks about "excessive or inappropriate guilt," but does not distinguish the type. Our study, however, suggests that relational guilt is a core trait, often more painful than feelings of personal failure.

Table 2 shows the summary comparison with the DSM-5-TR and analysed sample.

Data on HFS, PHQ-9, and BHS scales

From the data analysis we investigated the presence of depressive symptoms, forgiveness, hopelessness and Mixed States in the same group of patients. The data obtained with the HFS, BHS, and G.T.-MSRS scales showed

Table 2. Summary comparison with the DSM-5-TR and analysed sample

Aspect	DSM-5-TR	Our sample
Somatization	✗ (not central)	✓ (very frequent)
Classical anhedonia	✓	⚡ (blocked/ambivalent)
Inner agitation	✗	✓ (very common)
Nuanced passive ideation	✗	✓ (very common)
Anger/Irritable depression	✗	✓ (in specific clusters)
Subclinical mixed states	✗	✓ (widespread but not diagnosable)
Relational guilt	✓ (generically)	⚡ (specific and moral)

Table 3. Frequentist Scale Reliability Statistics (HFS, PHQ-9, GT-MSRS, BHS scales)

Coefficient	Estimate	Std. Error	95% CI	
			Lower	Upper
<i>HFS</i>				
Coefficient ω	0.468	0.103	0.265	0.670
Coefficient α	0.595	0.123	0.355	0.836
Mean	70.419	1.781	66.927	73.910
SD	11.681	1.706	9.631	14.846
<i>Note:</i> The following items correlated negatively with the scale: Q3, Q5, Q7, Q9, Q16, Q18.				
<i>PHQ-9</i>				
Coefficient ω	0.817	0.041	0.736	0.897
Coefficient α	0.891	0.088	0.618	0.963
Mean	12.818	1.024	10.812	14.824
SD	6.790	1.752	5.610	8.603
<i>GT-MSRS</i>				
Coefficient ω	0.941	0.013	0.915	0.967
Coefficient α	0.911	0.037	0.839	0.983
Mean	10.455	1.421	7.669	13.241
SD	9.429	3.745	7.790	11.947
<i>Note:</i> Of the observations, 43 complete cases were used.				
<i>BHS</i>				
Coefficient ω	0.647	0.076	0.497	0.797
Coefficient α	0.676	0.069	0.541	0.810
Mean	8.326	0.553	7.243	9.409
SD	3.623	0.325	2.988	4.605

Note: The following items correlated negatively with the scale: Q4, Q6, Q20.

Table 4. HFS Scale - frequency of forgiveness subgroups

	A	B	C
Forgiveness of Self	41.86%	51.26%	6.98%
Forgiveness of Others	9.26%	79.07%	11.63%
Forgiveness of Situations	6.98%	74.42%	18.6%
<i>Total HFS</i>	<i>6.98%</i>	<i>86.05%</i>	<i>6.98%</i>

A: one is usually unforgiving of oneself, other people, or uncontrollable situations, respectively;

B: one is about as likely to forgive as to not forgive oneself, other people, or uncontrollable situations, respectively;

C: one is usually forgiving of oneself, other people, or uncontrollable situations, respectively

the presence of a high frequency of these aspects. The data obtained with the FHS are shown in tables 3 and 4. The results obtained highlight a low reliability of the total score for the Total HFS scale [mean total score: 73.721±1.901, coeff ±: 0.576]. The other HFS subscales (Forgiveness of Self, Forgiveness of Others and Forgiveness of Situations) also have a low internal consistency. However, the percentages of the score on the Forgiveness of Situations subscale are interesting. 41.86% of the patients interviewed presented an usually unforgiving of oneself vs 51.26% as likely to forgive as to not forgive oneself. The data obtained with the GT- MSRS showed excellent internal consistency (Cronbach Alpha: 0.911). It should be noted that 34.34% of patients presented scores indicating the presence of a mixed state. The PHQ-9 data also showed good internal consistency (Cronbach Alpha: 0.891). While the data obtained with the BHS indicate a questionable internal consistency. From the data analysis we investigated the presence of Depressive symptoms, Forgiveness, Hopelessness and Mixed States in the same group of patients. The data obtained with the HFS, BHS, and G.T. scales MSRS showed the presence of a high frequency of these aspects. The data obtained with the FHS are shown in tables 3 and 4.

DISCUSSION AND CONCLUSIONS

Our study is a preliminary evaluation of data requiring a larger analytical sample. However, it is a down-up study that shows how patients who meet the DSM-5-TR diagnostic criteria for MDD may present a symptomatologic pattern that may fall outside of classical diagnostic criteria. Patients may bring to the clinical listener other symptoms which may present, for example, bodily, relational, mixed, anxious, or disorganized characteristics. Patients report several experiences that cannot be attributed to the symptoms outlined in the DSM diagnostic criteria. Descriptions such as the subjective experience of irritability, of an enormous burden to carry, of feeling "drained of energy", of a complete "absence of vital energy" are frequent. However, other experiences, also identified in our study, concern the heart ("heavy heart", "heart pain", chest tightness,

tiredness or excessive tension, palpitations) are not reported in manuals describing depression but are experienced very frequently by depressed individuals (Maj 2023). The depressed person feels painfully imprisoned in his own body and may manifest somatic symptoms as well as the feeling of suffocation, tiredness, and oppression. Often, people suffering from depression have described their body as heavy, oppressive, like "a cage of suffering" from which they cannot escape. As indicated by our study, these symptoms are very frequent and may represent subtypes of MDD. However, intercepting these symptoms is not always easy. New AI tools (such as computational linguistic analysis) can help the clinician identify them. The results of our preliminary study confirm this hypothesis. Furthermore, the results of our study highlighted the importance of considering other non-DSM-5-TR symptoms in the diagnosis of MDD. Our study confirms, in fact, previous studies by our group in which the need to deepen the diagnosis is underlined (Franza et al. 2024; 2021). Furthermore, our data shows that mixed states are more frequent than analysed. As previously reported, this raises new questions and diagnostic concerns. The psychopathological symptom dimensions require careful evaluation to avoid the risk of falling into diagnostic excessive simplifications. Mixed states and bipolar disorders appear to represent the "real world" of mood disorders more effectively. Other interesting data emerged from our preliminary study, which utilized computational linguistic analysis. Although the results were obtained from a small sample, the data analysed would give rise to the possibility of identifying new diagnostic subtypes for depression with our method used. Symptomatic dimensions such as disgraced drive, forgiveness, anguish, sensations of localized physical discomfort could be indicated as predictive factors of diagnosis. Ultimately, AI tools can help clinicians formulate diagnoses in a more detailed manner, beyond the DSM-5-TR approach, and, finally, improve therapeutic approaches.

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Contribution of individual authors:

Francesco Franza: design of study, literature research, interpretation of data, manuscript writing.

Andreana Franza: manuscript writing, translation.

Luigi Calabrese: clinical interview, data collection.

Antonio Nicola Iannaccone: literature searches, statistical analyses, AI analysis.

Antonio Ricca: interpretation and data collection.

Barbara Solomita: clinical interview, data collection, interpretation of data.

Giuseppe Tavormina: supervision and final reading.

All authors approved the final manuscript.

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