

# The importance of identifying major depressive disorder with mixed symptoms in primary care

La importancia de identificar trastorno depresivo mayor con síntomas mixtos en el primer nivel de atención

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## Abstract

In daily medical practice, patients diagnosed with major depressive disorder frequently present with concomitant symptoms of activation, including agitation, insomnia, increased talkativeness, or irritability. These clinical presentations, commonly referred to as mixed symptoms, challenge traditional categorical models in which mania and depression are conceptualized as mutually exclusive states. This article reviews the historical evolution of the concept of mixed states, current diagnostic controversies, and available data on their clinical frequency, with particular attention to their relevance in family medicine. The importance of recognizing these presentations in order to prevent therapeutic errors, such as the use of antidepressant monotherapy, is examined, and practical tools for their clinical assessment are outlined. In addition, the potential consequences of underrecognition are discussed, including a more protracted course, increased suicide risk, and suboptimal treatment response. Finally, it is argued that the identification of mixed symptoms in primary care settings enhances diagnostic accuracy and supports more individualized, effective, and empathetic management of mood disorders.

## Resumen

En la consulta médica cotidiana es frecuente encontrar pacientes con diagnóstico de depresión mayor que también presentan síntomas de activación, como agitación, insomnio, verborrea o irritabilidad. Estos cuadros, conocidos como síntomas mixtos, desafían la visión clásica que separa manía y depresión como polos opuestos. Este artículo revisa el desarrollo histórico del concepto de estados mixtos, sus controversias diagnósticas actuales y su frecuencia clínica, con especial atención a su relevancia en la medicina familiar. Examina la importancia de reconocer estas presentaciones para prevenir errores terapéuticos, como el uso de antidepressivos en monoterapia, y ofrece herramientas prácticas para su evaluación. Además, analiza los riesgos asociados al subdiagnóstico, incluyendo una evolución más tórpida, mayor riesgo de suicidio y respuesta terapéutica inadecuada. Finalmente, plantea que la identificación de síntomas mixtos en el primer nivel de atención mejora la precisión diagnóstica y posibilita una atención más individualizada, empática y eficaz de los trastornos del estado de ánimo.

Key words: Mixed Symptoms, Mood Disorders, Major Depressive Disorder, Unipolar Depression, Bipolar Disorders. Palabras clave: Síntomas mixtos, Trastornos del ánimo, Trastorno depresivo mayor, Trastornos bipolares, Depresión Unipolar.

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## Introduction

In everyday primary care practice, it is common to encounter patients who present with depressive symptoms but have not yet been formally diagnosed. Major depressive disorder (MDD) has traditionally been defined by a set of characteristic symptoms, such as depressed mood, loss of interest or pleasure (anhedonia), psychomotor retardation, and persistent feelings of hopelessness<sup>1</sup>. However, a significant proportion of these patients also present manifestations that, far from fitting the classic model of depression, reflect symptoms of activation typical

of mania or hypomania, such as increased energy, verbosity, euphoria, or impulsivity<sup>2,3</sup>.

When these symptoms coexist within the same clinical episode, they are called mixed symptoms, and their presence challenges the traditional dichotomous view of depression and mania. In these cases, a patient may simultaneously experience deep sadness along with psychomotor agitation, difficulty falling asleep, or racing thoughts, elements that often lead to diagnostic confusion if not systematically evaluated<sup>4</sup>.



Early identification of these mixed states is crucial, as their omission can lead to misdiagnosis and, consequently, inappropriate therapeutic strategies. In particular, the use of antidepressants as monotherapy in patients with mixed symptoms may increase the risk of manic shift, clinical worsening, or suicidality<sup>5-7</sup>. Conversely, an accurate diagnosis allows for a more effective and safer approach, in line with the patient's clinical profile.

In this article, we will examine the historical evolution of the concept of mixed states, their absence and rediscovery in contemporary psychiatry, their prevalence and clinical implications, current diagnostic controversies, and practical recommendations for their recognition in primary care, with the aim of providing family physicians with a clear, dynamic, and rigorous perspective on why it is important to identify major depression with mixed symptoms in their patients.

### **Mixed states in mood disorders: a forgotten history that returns to the consultation**

In daily practice, it is not uncommon to encounter patients who do not fully meet the criteria in diagnostic manuals. People with deep sadness, but also with agitation, insomnia, racing thoughts, or irritability. Are we dealing with depression? An episode of mania? Or something else?

Since its inception, psychiatry has recognized these mixed forms, in which manic and depressive symptoms coexist. Even in ancient times, Aretaeus of Cappadocia suggested that mania and melancholia were two manifestations of the same disease<sup>8</sup>. This early insight anticipated what centuries later would be conceptualized as bipolar disorder.

During the 19<sup>th</sup> century, French psychiatrists such as Jean-Pierre Falret and Jules Baillarger observed alternating depressive and manic episodes, laying the foundations for the concept of *folie circulaire* or circular madness<sup>8</sup>. These pioneering descriptions already hinted at the existence of transitional forms between affective poles. The great conceptual leap occurred towards the end of the 19<sup>th</sup> century, with Emil Kraepelin and his disciple Wilhelm Weygandt. The latter was the first to publish an exclusive monograph on these conditions<sup>9</sup>, whose impact was decisive in the sixth edition of Kraepelin's treatise that same year<sup>10,11</sup>. Kraepelin unified mania and melancholia into a single entity: manic-depressive psychosis, in which he recognized not only pure episodes, but also mixed forms<sup>10</sup>. In these conditions, symptoms of opposite polarity can coexist: for example, depressive mood with marked psychomotor agitation and racing thoughts. Both authors emphasized that these presentations were not exceptional, but rather frequent forms of the manic-depressive spectrum<sup>9,10</sup>.

Both Kraepelin and Weygandt agreed that there is no hierarchy among the three central dimensions of

mood disorder: affect, thought, and motor function. By combining these three domains, six basic clinical patterns are described which, together with the pure forms, make up the full spectrum of the disease. Among them, three presentations —agitated depression, unproductive mania, and manic stupor— were noted as particularly frequent and relevant<sup>12</sup>.

The conception of mixed states underwent a notable transformation in the mid-20<sup>th</sup> century. While the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-1) and DSM-2 offered a vague definition of these conditions as the coexistence of manic and depressive symptoms, it was DSM-3 that introduced a clear separation between bipolar disorders and unipolar disorders establishing specific criteria regarding duration and timing for each diagnosis<sup>13</sup>. This trend toward greater diagnostic rigidity was further developed in the DSM-4, which defined a mixed episode as the simultaneous and complete presence of all the criteria for a manic episode and a depressive episode for at least one week<sup>14</sup>. This strict definition marked a substantial departure from the classic formulations of mixed states and contradicted what is often observed in clinical practice: the coexistence of some symptoms of opposite polarity during the same episode, without reaching the full syndromic threshold. This evidence led to criticism of the DSM-4 model, pointing out that it did not adequately represent clinical reality or allow for the identification of a subset of patients who required more intensive care and differentiated therapy<sup>15</sup>.

Towards the end of the 20<sup>th</sup> century, psychiatrists such as Hagop Akiskal began to question this limited view and proposed broadening the bipolar spectrum to include atypical forms of depression with activation symptoms<sup>16</sup>. The change finally came with the DSM-5 in 2013, which introduced the specifier "with mixed features", applicable to major depressive, manic, or hypomanic episodes. This allowed for the recognition of depressive episodes with at least three symptoms of manic polarity (such as euphoria, verbosity, racing thoughts, or decreased need for sleep), without requiring a full manic syndrome<sup>1</sup>. At the same time, the International Classification of Diseases for Mortality and Morbidity Statistics, 11<sup>th</sup> revision (ICD-11) of 2019, does not include a formal category for depressive episodes with mixed features in patients without a bipolar diagnosis, creating a mismatch between the two systems. While the DSM-5 sets the stage for recognizing these conditions within major depressive disorder, the ICD-11 only includes the current mixed episode within bipolar disorder type I, also excluding it from bipolar disorder type II<sup>17</sup>.

However, this advance did not escape criticism. The DSM-5 excluded common manifestations such as agitation, irritability, and distractibility from its list of valid mixed symptoms, considering them to overlap with depression. This decision was highly

controversial, as these symptoms are precisely the most prevalent in actual clinical practice<sup>18</sup>.

Studies such as BRIDGE-II-MIX showed that up to one-third of patients with a major depressive episode have mixed features, although these often do not meet the DSM-5 criteria<sup>19</sup>. These patients tend to have an earlier onset, a greater number of episodes, poorer functioning, and a higher risk of suicide.

### **Current controversies surrounding definition and diagnosis**

#### **Insufficient definition in DSM-5**

Despite recent advances, the concept of mixed symptoms continues to be a subject of debate in contemporary psychiatry. One of the central controversies relates to its definition. Although the introduction of the specifier "with mixed features" in DSM-5 represented a significant advance, several experts have pointed out that the proposed criteria are still insufficient or clinically limited<sup>20</sup>.

#### **Koukopoulos's criticisms and the problem of underreporting**

Psychiatrist Athanasios Koukopoulos, a pioneer in the study of mixed depression, criticized the DSM-5 for excluding symptoms such as psychomotor agitation, irritability, and distractibility from its criteria, considering them to overlap with depression. However, according to this author, it is precisely these symptoms that are most common in mixed presentations, and their exclusion may lead to significant underreporting<sup>21</sup>. Thus, many patients with agitated depression may not meet the formal requirement of at least three manic symptoms, leaving them outside the diagnosis of mixed features despite presenting a clinically evident picture.

#### **Alternative diagnostic proposal: agitated depression**

Koukopoulos had already proposed in the 1990s that agitated depression should be considered a clinical entity distinct from traditional melancholic depression, and he outlined specific diagnostic criteria for its identification<sup>4,22</sup>. Among the characteristic symptoms he mentioned were racing thoughts, verbosity, marked irritability, affective lability, insomnia, impulsivity, and flight of ideas. Unlike typically manic symptoms, these are not usually accompanied by euphoria or grandiosity, but rather correspond to a profile of dysphoric activation, with a high degree of subjective suffering. Therefore, they tend to go unnoticed if the clinician only looks for classic signs of expansive or euphoric mania.

#### **Risk of misdiagnosis due to clinical overlap**

Another area of debate concerns the clinical overlap between mixed states and other psychiatric disorders. Given that mixed symptoms can include irritability, impulsivity, emotional lability, and psychomotor agitation, there is a risk that these conditions may be confused with personality

disorders —particularly, borderline personality disorder— anxiety disorders, attention deficit hyperactivity disorder in adults, or even manifestations resulting from substance use<sup>23</sup>. In these cases, the distinction may not be obvious. The high psychiatric comorbidity in patients with mixed symptoms further complicates the picture, making diagnostic delimitation difficult. That is why it is important to conduct a longitudinal assessment and determine the context in which the symptoms appear: if they emerge exclusively during well-defined affective episodes, it is more likely to be a mixed state; if, on the other hand, they are persistent personality traits or respond to external stressors, it may be another underlying disorder.

#### **Debate on its nosological classification**

Finally, the debate continues on the nosological classification of depression with mixed symptoms. Is it a subtype of unipolar major depressive disorder, or does it actually indicate an incipient form of bipolar disorder? The DSM-5 allows the specifier "with mixed features" to be applied to patients with no history of mania or hypomania, recognizing the possibility of an intermediate spectrum. However, other specialists, such as Koukopoulos himself, argue that any depressive episode with mixed symptoms is essentially an expression of the bipolar spectrum, even if it has not yet manifested itself in the form of full-blown mania<sup>20</sup>.

This discussion is not merely theoretical. It has concrete clinical implications, as it directly influences the treatment strategy, the type of drugs to be used, and the psychoeducation offered to the patient. In short, although there is growing consensus regarding the existence and relevance of mixed states, the criteria for accurately capturing them are still being refined, without incurring diagnostic errors or overlapping with other clinical conditions. **Table 1** presents a detailed comparison of the criteria used by the DSM-5, Koukopoulos' proposal, and the ICD-11.

#### **Prevalence and clinical relevance of mixed symptoms**

One of the fundamental reasons for identifying mixed symptoms in mood disorders is their high frequency and significant clinical relevance. Recent studies have shown that these presentations, far from being exceptional, are common in both major depression and bipolar disorder. Estimates of the prevalence of mood states with mixed polarity traits have varied widely (between 20% and 80%) among patients with depression, depending on the criteria applied<sup>2</sup>.

A systematic review and meta-analysis that included 17 studies reported that between 24% and 35% of unipolar and bipolar major depressive episodes, respectively, present at least three symptoms of opposite polarity, thus meeting the criteria for mixed features proposed by the DSM-5.

These data suggest that about one-third of patients diagnosed with depression —whether bipolar or unipolar— may exhibit concurrent manic symptoms, reinforcing the importance of actively exploring these signs even in non-specialized clinical settings<sup>2,19</sup>.

From a clinical point of view, patients with mixed symptoms tend to be more complex cases and at greater risk than those with pure depression. Several studies have associated these conditions with a more sluggish course, a greater number of episodes throughout life, an earlier onset of the disorder, higher rates of comorbidity (such as anxiety or substance abuse), and a notable increase in the risk of suicide<sup>23</sup>. The coexistence of activation symptoms, such as difficulty falling asleep, psychomotor agitation, and impulsivity, against a background of depression can generate a state of intense dysphoric agitation, which is particularly dangerous from the point of view of suicidal impulsivity<sup>2</sup>. In particular, symptoms such as marked irritability and psychomotor agitation have been identified as clinical predictors of suicide attempts in

patients with depression, highlighting the urgency of recognizing these signs in the initial assessment.

In addition, mixed presentations tend to respond less favorably to antidepressants in monotherapy and more often require combination treatments with mood stabilizers or antipsychotics, making them a therapeutic challenge at both the primary and specialized levels<sup>24</sup>.

On the other hand, early recognition of mixed symptoms also has prognostic implications. A considerable number of patients who currently present a depressive episode with mixed symptoms, particularly those with activation features, could evolve into a clearly defined bipolar disorder over time<sup>20</sup>. For this reason, many experts consider that these presentations belong more to the bipolar spectrum than to truly unipolar forms of depression. In short, identifying mixed symptoms not only improves the current clinical understanding of the patient, but also allows us to anticipate their evolution, optimize the therapeutic strategy, and adjust their follow-up throughout treatment.

**Table 1:** Comparison of different diagnostic criteria for depressive episodes with mixed symptoms.

Criterion / Feature	DSM-5	Koukopoulos criteria	CIE-11
Applicability	MDD, type I BD, type II BD	Mainly MDD (unipolar o bipolar)	Only within tipo I BD
Terminology	Specifier "with mixed features"	"Agitated depression" or "mixed depression"	"Current mixed episode"
Number of manic symptoms required	≥3 manic/hypomanic symptoms during a depressive episode	≥3 core symptoms of psychomotor agitation	Simultaneous presence of complete criteria for major depression and mania
Accepted manic symptoms	Elevated/expansive mood Grandiosity Verbal fluency Flight of ideas Increased energy Risky behaviors Decreased need for sleep	Psychomotor agitation Racing thoughts Verbosity Internal tension Irritability Impulsivity Insomnia	Must meet all criteria for both manic and depressive episodes simultaneously
Excluded symptoms (DSM-5)	Irritability, distractibility, and agitation (considered to overlap with depression)	Actively included	N/A (full syndrome required; does not include symptom specifiers)
Does it require grandiosity/euphoria?	Not required	Not usually present	Yes, as part of the complete criteria for mania
Required duration	Not specified beyond the duration of the depressive episode	Not fixed; symptoms must coexist within the same depressive episode	At least two weeks of depressive symptoms plus one week of manic symptoms
Clinical utility in unipolar MDD	Allows the specifier to be applied in unipolar depression	Considers that many unipolar cases with mixed symptoms are actually forms of the bipolar spectrum	Does not recognize mixed symptoms in patients without a bipolar diagnosis
Main criticisms	Very restrictive; excludes frequent mixed presentations	Broadens the clinical spectrum and recognizes high-risk conditions even if they do not meet DSM criteria	Very limited; does not include patients with clinically relevant mixed symptoms
Aligned instruments	SCID-5 (Structured Clinical Interview for DSM Disorders), CUDOS-M (Clinically Useful Depression Outcome Scale - Mixed Features)	KMDRS (Koukopoulos Mixed Depression Rating Scale)	Not specified

Abbreviations MDD: Major Depressive Disorder; BD: Bipolar Disorder; N/A: Not applicable

## **Tools and methods of assessment in clinical practice**

### **Active search for mixed symptoms during the consultation**

For the family physician and primary care clinician, what do all these advances imply? Fundamentally, the need for a more comprehensive and proactive assessment of mood. Identifying a major depressive disorder with mixed symptoms requires actively looking for signs of opposite polarity during the consultation for depression. It is not enough to diagnose depression based on typical symptoms; it is also necessary to inquire whether the patient, even while depressed, has experienced elements such as episodes of unusual energy, decreased need for sleep, verbosity or rapid speech, unusually rapid or multiple thoughts at the same time, increased activity or motor restlessness, unusual irritability, or periods of strangely euphoric or irritable mood. These targeted questions can reveal a mixed picture that would otherwise be masked behind the primary depressive complaint.

### **Structured instruments available**

There are structured tools that can be very useful to support this clinical assessment. For example, standardized diagnostic interviews such as the SCID-5 (Structured Clinical Interview for DSM-5 Disorders) now include explicit assessment of the mixed specifier, allowing the presence of these symptoms to be documented. However, it does not take into account those considered overlapping, such as irritability, distraction, insomnia, and psychomotor agitation, which remain clinically relevant<sup>20,25</sup>. On the other hand, the CUDOS-M (Clinically Useful Depression Outcome Scale–Mixed) is an adaptation of a brief self-administered depression scale (CUDOS) to which items were added to detect mixed features according to the DSM-5. Its main limitation is that, like the SCID-5, it is based on DSM-5 criteria, and does not consider irritability or agitation as indicators; therefore, it could overlook many non-classical mixed cases. In essence, it will mainly detect depression with features of euphoria/hyperactivity, but not necessarily common agitated depression. Even so, it is useful for patients to report symptoms that the clinician might not ask about directly. In turn, the KMDRS (Koukopoulos Mixed Depression Rating Scale), developed by Koukopoulos' group and internationally validated in 2018, is a hetero-applied scale (administered by the clinician) specifically designed to quantify mixed depression according to Koukopoulos' vision. As a limitation, being relatively new, the KMDRS is not yet widely used or validated in all languages, and its application requires training of the evaluator to objectively rate sometimes subjective symptoms (e.g., how intense the internal tension is). Finally, the SMDS (Shahin Mixed Depression Scale) is one of the most recent and

innovative tools, as its objective is to capture both the mixed symptoms included in the DSM-5 and those considered to be overlapping. Being a self-administered tool, it has the practical advantage of saving the clinician time and could be used as a screening instrument<sup>26-28</sup>.

### **Importance of longitudinal observation**

Beyond specific instruments, sustained clinical observation remains the primary diagnostic tool. As noted by Weygandt more than a century ago, time is crucial in identifying mixed states: over several weeks, fluctuations and interactions of symptoms may emerge that could be overlooked at a single point in time<sup>9</sup>. It is advisable to closely monitor patients with depression who show any warning signs (e.g., family history of bipolar disorder, previous episodes of overactivation, paradoxical response to antidepressants, etc.). Even a mood diary kept by the patient themselves can help detect brief periods of elation interspersed with depression.

### **Clinical examination guided by psychopathological spheres**

When interviewing, it is advisable to prioritize the examination questions by grouping them into the three key spheres classically described by Weygandt<sup>9</sup>: affective, psychomotor, and cognitive. In the affective sphere, in addition to the usual sadness, ask about irritability or brief periods of strangely elevated or inappropriately cheerful mood. In the psychomotor sphere, observe whether the patient is restless, constantly moving their hands or feet, or whether they report difficulty relaxing (agitation). In the cognitive sphere, ask whether they sometimes feel their thoughts are racing or whether they have too many thoughts at once, despite being depressed.

There is no laboratory test or single marker to detect mixed symptoms; their identification depends on clinical expertise and maintaining a high index of suspicion. Many patients do not voluntarily offer this information because they assume it is part of their personality or attribute it to their anxiety. Therefore, the physician should probe further with specific questions and clear examples (e.g., do you feel so agitated or nervous these days that you have trouble sitting still?), also correlating the information with what family members report, if possible.

### **Formal criteria and clinical monitoring**

As for formal criteria, although it is not necessary to memorize all the DSM-5 lists, it is useful to remember the essential points: for example, at least three manic symptoms to qualify a depressive episode as mixed<sup>1</sup>. In practice, this means that a single symptom (e.g., irritability alone) would not be sufficient, but a combination of several (e.g., little need for sleep, verbosity, and intermittent euphoria) should clearly suggest a mixed state. Finally, it should be noted that assessment tools are not only useful for diagnosis: they also serve to monitor

response to treatment. If we decide to treat a patient with depression with mixed symptoms and start a mood stabilizer, for example, we can track the evolution of these specific mixed symptoms at each visit to see if they decrease with the intervention.

### Applicability of scales in primary care

Although many of the available tools were developed in psychiatric settings, some can also be used in primary care for screening or initial diagnostic support.

- **Self-administered scales (CUDOS-M and SMDS):** most suitable for primary care. They do not require specialized training and can be administered in a few minutes. The SMDS, in particular, allows for the detection of both mixed symptoms defined by the DSM-5 and overlapping symptoms (irritability, agitation, internal tension), offering a broader view of mixed depression. In this context, they can serve as screening or alert tools that guide the clinician toward suspecting a mixed state and eventual referral to a psychiatrist.
- **Hetero-applied scales (KMDRS) and structured interviews (SCID-5):** require specific training and more time to be administered, so their use is mainly reserved for the psychiatric field or clinical research.

In summary, in primary care, it is recommended to use brief, self-administered tools —such as the SMDS or CUDOS-M— combined with a guided clinical interview and longitudinal follow-up.

### Additional diagnostic options for detecting mixed symptoms

In contexts where specific instruments for mixed symptoms are not available, a possible alternative is to use the Young Mania Rating Scale (YMRS)<sup>29</sup> as a complement to depression inventories. Its application allows for the quantification of elements of psychomotor agitation, irritability, racing thoughts, and other subtle indicators of hypomania that may go unnoticed in a brief clinical evaluation.

Likewise, the development of a brief checklist for primary care could be useful for the rapid detection of symptoms of dysphoric activation within major depression—e.g., initial insomnia, motor restlessness, accelerated thinking, atypical irritability, and rapid emotional fluctuation. In this regard, the SMDS represents a concrete example of this type of tool, as it integrates both the items covered by the DSM-5 and those considered overlapping, allowing for screening that is more faithful to the actual clinical presentation. Its routine implementation in PHC would promote earlier, safer, and more operationalizable detection, facilitating appropriate therapeutic decisions and eventual timely referral to a specialist.

### Therapeutic implications and risks of misdiagnosis

Identifying the presence of mixed symptoms in a major depressive episode is a theoretical exercise with clinical implications, as it has direct consequences on therapeutic decisions, patient safety, and the prognosis of the disorder.

The main risk of not recognizing mixed symptoms in major depression is the use of antidepressants as monotherapy as a first-line strategy. This practice, widely accepted in unipolar depressive disorders, can be harmful in patients with mixed activation. Numerous studies have shown that antidepressants—especially tricyclics and duals—can induce manic shifts, increase emotional lability, or intensify psychomotor agitation when administered without mood stabilizers in people with bipolar vulnerability or mixed symptoms<sup>5,30</sup>. In practice, this translates into patients reporting feeling more anxious, agitated, or insomniac after starting treatment, which can be misinterpreted as comorbid anxiety and lead to an increase in dosage, perpetuating an iatrogenic cycle. Therefore, early recognition of a mixed state allows potentially harmful interventions to be avoided and treatment to be directed toward safer and more effective strategies.

The third Argentine consensus on the management of bipolar disorder (2023)<sup>3</sup> is the most recent and up-to-date guide on the pharmacological treatment of mood disorders, and its authors agree that the scientific evidence available for the management of episodes with mixed features is still limited. To date, only a few drugs have demonstrated relative efficacy in this clinical subgroup, including lurasidone, quetiapine, and the combination of olanzapine and fluoxetine<sup>3</sup>. In cases in which the use of antidepressants is essential, it is advisable to administer them in combination with a stabilizer, avoiding agents with high activating potential, such as venlafaxine or tricyclic antidepressants<sup>30</sup>.

Clinical follow-up and psychoeducation are fundamental in the therapeutic process for the choice of pharmacological strategy to be effective. Informing the patient about the nature of their condition—even in the absence of a formal diagnosis—allows for the construction of a more solid therapeutic alliance and prevents risky behaviors, such as abrupt discontinuation of medication. Involving the family in monitoring symptoms and early detection of hypomanic or incipient manic signs can be decisive in preventing relapses or major complications. Conversely, ignoring the mixed dimension of a depressive condition can lead to misguided psychotherapeutic interventions (such as attributing irritability exclusively to stress) or to failure to implement adequate containment measures regarding suicide risk<sup>5</sup>.

From a public health perspective, low reporting of mixed symptoms means that many patients with non-classical depression remain misdiagnosed, resulting in prolonged and ineffective treatments, increased disease burden, higher consultation rates, and avoidable indirect costs. In contrast, timely detection in primary care allows to implement preventive strategies, reducing the frequency of relapses and the long-term risk of suicide. It also reduces unnecessary polypharmacy: many patients with mixed depression are treated with combinations of anxiolytics, hypnotics, and antidepressants without satisfactory results.

## Conclusions

Identifying major depressive disorder with mixed symptoms in primary care plays a critical role in guiding clinical and therapeutic decisions. This is not a diagnostic fad, but rather the recognition of a common clinical reality that had been underestimated.

For family physicians, becoming familiar with this concept means having an additional lens through which to evaluate patients with depression, resulting in more accurate diagnoses and treatments that are better tailored to real needs. In a depressed patient who is also restless, irritable, and has racing thoughts, simply labeling the condition as depression is insufficient; recognizing the mixed symptoms, on the other hand, allows the physician to take proactive measures: monitoring for the possible onset of mania, avoiding certain medications, involving specialists when appropriate, and providing the patient with a more complete explanation of what is happening to them.

From classical Greece to Kraepelin, and from oblivion in the early DSMs to a renaissance in DSM-5, the pendulum of psychiatry has swung back and forth on mixed states. Today we know that ignoring them is closing our eyes to an important piece of the puzzle, one that can make a difference in a patient's progress. The first level of care, where the vast majority of depression cases are treated, is the first opportunity to pick up on these mixed signs. Doing so improves treatment safety, avoiding unwanted changes, and helps patients feel understood in their experience, as many report feeling depressed and agitated at the same time, experiencing relief in knowing that this has a name and a medical explanation.

Recognizing mixed symptoms in the context of major depression not only allows for the optimization of the therapeutic approach and the prevention of diagnostic errors, but also constitutes an expression of clinical sensitivity and commitment to the complexity of psychological suffering. For the primary care physician, it represents an opportunity to intervene with greater precision, anticipate more complex evolutionary trajectories, and provide truly personalized care. Listening beyond sadness or lack of energy, identifying what is most complex, and providing truly personalized care. Listening beyond sadness or lack of energy, identifying what does not quite fit, is also a way of practicing more attentive, more humane, and more effective medicine.

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## Declaration on the use of artificial intelligence

In preparing this manuscript, the ChatGPT tool (model GPT-5.2, OpenAI, December 2025) was used as a support tool for linguistic editing tasks, including improving the clarity of the text and standardizing the format of bibliographic references.

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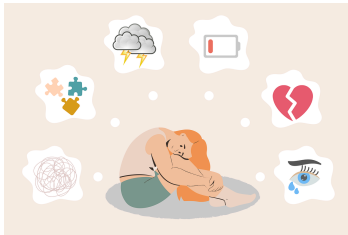
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## References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington (DC): American Psychiatric Association; 2013. DOI: <https://doi.org/10.1176/appi.books.9780890425596>
2. Vázquez GH, Lolich M, Cabrera C, et al. Mixed symptoms in major depressive and bipolar disorders: a systematic review. *J Affect Disord* [Internet]. 2018 [citado 2025 dic 22];225:756-760. DOI: <https://doi.org/10.1016/j.jad.2017.09.006> PMID: [28922738](https://pubmed.ncbi.nlm.nih.gov/28922738/)
3. Cetkovich-Bakmas M, Abadi A, Camino S, et al. Tercer Consenso Argentino sobre el manejo de los Trastornos Bipolares. Segunda Parte B. *Vertex* [Internet]. 2023 [citado 2025 dec 22];34(160):25-53. DOI: <https://doi.org/10.53680/vertex.v34i160.459> PMID: [37562388](https://pubmed.ncbi.nlm.nih.gov/37562388/)
4. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. *Psychiatr Clin North Am* [Internet]. 1999 [citado 2025 dec 22];22(3):547-564. DOI: [https://doi.org/10.1016/s0193-953x\(05\)70095-2](https://doi.org/10.1016/s0193-953x(05)70095-2) PMID: [23561484](https://pubmed.ncbi.nlm.nih.gov/23561484/)
5. Stahl SM, Morrissette DA, Faedda G, et al. Guidelines for the recognition and management of mixed depression. *CNS Spectr* [Internet]. 2017 [citado 2025 dec 22];22(2):203-219. DOI: <https://doi.org/10.1017/s1092852917000165> PMID: [28421980](https://pubmed.ncbi.nlm.nih.gov/28421980/)
6. Benazzi F, Akiskal HS. Psychometric delineation of the most discriminant symptoms of depressive mixed states. *Psychiatry Res* [Internet]. 2006 [citado 2025 dec 22];141(1):81-88. DOI: <https://doi.org/10.1016/j.psychres.2005.07.024> PMID: [16313969](https://pubmed.ncbi.nlm.nih.gov/16313969/)
7. Tondo L, Vazquez GH, Baldessarini RJ. Suicidal behavior associated with mixed features in major mood disorders. *Psychiatr Clin North Am* [Internet]. 2020 [citado 2025 dec 22];43(1):83-93. DOI: <https://doi.org/10.1016/j.psc.2019.10.008> PMID: [32008690](https://pubmed.ncbi.nlm.nih.gov/32008690/)
8. Angst J, Marneros A. Bipolarity from ancient to modern times: conception, birth and rebirth. *J Affect Disord* [Internet]. 2001 [citado 2025 dec 22];67(1-3):3-19. DOI: [https://doi.org/10.1016/s0165-0327\(01\)00429-3](https://doi.org/10.1016/s0165-0327(01)00429-3) PMID: [11869749](https://pubmed.ncbi.nlm.nih.gov/11869749/)
9. Weygandt W. Über die Mischzustände des manisch-depressiven Irreseins. Munich: J.F. Lehmann; 1899.
10. Trede K, Salvatore P, Baethge C, et al. Manic-depressive illness: evolution in Kraepelin's textbook, 1883-1926. *Harv Rev Psychiatry* [Internet]. 2005 [citado 2025 dec 22];13(3):155-178. DOI: <https://doi.org/10.1080/10673220500174833> PMID: [16020028](https://pubmed.ncbi.nlm.nih.gov/16020028/)
11. Salvatore P, Baldessarini RJ, Centorrino F, et al. Weygandt's On the Mixed States of Manic-Depressive Insanity: a translation and commentary on its significance in the evolution of the concept of bipolar disorder. *Harv Rev Psychiatry* [Internet]. 2002 [citado 2025 dec 22];10(5):255-275. DOI: <https://doi.org/10.1080/10673220216283> PMID: [12202452](https://pubmed.ncbi.nlm.nih.gov/12202452/)
12. Sotelo D, Grasso V, Dines M, et al. Controversias acerca de los estados mixtos en el trastorno bipolar. *Vertex* [Internet]. 2025 [citado 2025 dec 22];36(167):56-66. DOI: <https://doi.org/10.53680/vertex.v36i167.801> PMID: [40238699](https://pubmed.ncbi.nlm.nih.gov/40238699/)
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-III. 3rd ed. Washington (DC): American Psychiatric Association; 1980.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. Washington (DC): American Psychiatric Association; 1994.
15. Chakrabarty T, Keramatian K, Yatham LN. Treatment of mixed features in bipolar disorder: an updated view. *Curr Psychiatry Rep* [Internet]. 2020 [citado 2025 dic 22];22(3):15. DOI: <https://doi.org/10.1007/s11920-020-1137-6> PMID: [32025903](https://pubmed.ncbi.nlm.nih.gov/32025903/)
16. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. *J Clin Psychopharmacol*. 1996 [citado 2025 dec 22];16(2 Suppl 1):4S-14S. DOI: <https://doi.org/10.1097/00004714-199604001-00002> PMID: [8707999](https://pubmed.ncbi.nlm.nih.gov/8707999/)
17. World Health Organization. ICD-11: International Classification of Diseases [Internet]. Ginebra: WHO; 2022 Ene 1. [citado 2025 dic 26]. Available from: <https://icd.who.int/en/>
18. Suppes T, Eberhard J, Lemming O, et al. Anxiety, irritability, and agitation as indicators of bipolar mania with depressive symptoms: a post hoc analysis of two clinical trials. *Int J Bipolar Disord* [Internet]. 2017 [citado 2025 dic 22];5(1):36. DOI: <https://doi.org/10.1186/s40345-017-0103-7> PMID: [29105003](https://pubmed.ncbi.nlm.nih.gov/29105003/)
19. Perugi G, Angst J, Azorin JM, et al. Mixed features in patients with a major depressive episode: BRIDGE-II-MIX study. *J Clin Psychiatry* [Internet]. 2015 [citado 2025 dic 22];76(3):e351-e358. DOI: <https://doi.org/10.4088/jcp.14m09092> PMID: [25830457](https://pubmed.ncbi.nlm.nih.gov/25830457/)
20. Koukopoulos A, Sani G, Ghaemi SN. Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV) *Br J Psychiatry* [Internet]. 2013 [citado 2025 dic 22];203(1):3-5. DOI: <https://doi.org/10.1192/bjp.bp.112.124404> PMID: [23818531](https://pubmed.ncbi.nlm.nih.gov/23818531/)
21. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr Scand* [Internet]. 2014 [citado 2025 dec 22];129(1):4-16. DOI: <https://doi.org/10.1111/acps.12140> PMID: [23600771](https://pubmed.ncbi.nlm.nih.gov/23600771/)
22. Koukopoulos A, Sani G, Koukopoulos AE, et al. Melancholia agitata and mixed depression. *Acta Psychiatr Scand Suppl* [Internet]. 2007 [citado 2025 dic 22];(433):50-57. DOI: <https://doi.org/10.1111/j.1600-0447.2007.00963.x> PMID: [17280571](https://pubmed.ncbi.nlm.nih.gov/17280571/)

23. Mackinnon DF, Pies R. Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. *Bipolar Disord* [Internet]. 2006 [citado 2025 dic 22];8(1):1-14. DOI: <https://doi.org/10.1111/j.1399-5618.2006.00283.x> PMID: [16411976](https://pubmed.ncbi.nlm.nih.gov/16411976/)
24. Yatham LN, Chakrabarty T, Bond DJ, et al. 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. *Bipolar Disord* [Internet]. 2021 [citado 2025 dic 22];23(8):767-788. DOI: <https://doi.org/10.1111/bdi.13135> PMID: [34599629](https://pubmed.ncbi.nlm.nih.gov/34599629/)
25. First MB, Williams JBW, Karg RS, et al. Structured Clinical Interview for DSM-5 Disorders: Clinical Trials Version (SCID-5-CT). Arlington (VA): American Psychiatric Association; 2015.
26. Zimmerman M, Chelminski I, Young D, et al. A clinically useful self-report measure of DSM-5 mixed features. *J Affect Disord* [Internet]. 2014 [citado 2025 dec 22];168:357-362. DOI: <https://doi.org/10.1016/j.jad.2014.07.021> PMID: [25103631](https://pubmed.ncbi.nlm.nih.gov/25103631/)
27. Sani G, Vöhringer PA, Barroilhet SA, et al. The Koukopoulos Mixed Depression Rating Scale (KMDRS): An International Mood Network (IMN) validation study of a new mixed mood rating scale. *J Affect Disord* [Internet]. 2018 [citado 2025 dic 22];232:9-16. DOI: <https://doi.org/10.1016/j.jad.2018.01.025> PMID: [29459190](https://pubmed.ncbi.nlm.nih.gov/29459190/)
28. Shahin I, Bonnin CDM, Saleh E, et al. Validity of the Shahin Mixed Depression Scale: A Self-Rated Instrument Designed to Measure the Non-DSM Mixed Features in Depression. *Neuropsychiatr Dis Treat* [Internet]. 2020 [citado 2025 dic 22];16:2209-2219. DOI: <https://doi.org/10.2147/ndt.s259996> PMID: [33061391](https://pubmed.ncbi.nlm.nih.gov/33061391/)
29. Colom F, Vieta E, Martínez-Arán A, et al. Versión española de una escala de evaluación de la manía: validez y fiabilidad de la Escala de Young. *Med Clin (Barc)* [Internet]. 2002 [citado 2025 dic 22];119(10):366-371. DOI: [https://doi.org/10.1016/s0025-7753\(02\)73419-2](https://doi.org/10.1016/s0025-7753(02)73419-2) PMID: [12372167](https://pubmed.ncbi.nlm.nih.gov/12372167/)
30. Vieta E, Valentí M. Mixed states in DSM-5: implications for clinical care, education, and research. *J Affect Disord* [Internet]. 2013 [citado 2025 dic 22];148(1):28-36. DOI: <https://doi.org/10.1016/j.jad.2013.03.007> PMID: [23561484](https://pubmed.ncbi.nlm.nih.gov/23561484/)



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