

The concept of mixed state in bipolar disorder: from Kraepelin to DSM-5

Il concetto di stato misto nel disturbo bipolare: da Kraepelin al DSM-5

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Summary

Objectives

Herein the authors review the most important studies on the conceptualization and diagnosis of bipolar mixed states.

Methods

A search in MEDLINE and PUBMED was performed using the following keywords: "bipolar disorder, mixed state/s, mixed episode/s, criteria, validation, mixed mania, dysphoric mania, mixed depression, agitated depression". Studies on mixed states were reviewed and selected emphasizing historical development, conceptualizations, proposed diagnostic criteria and their validation.

Results

The origin of the concept of affective mixed state can be identified in ancient times. However, the development and systematization of mixed states occurred with the work of Emil Kraepelin

and Wilhem Weygandt. After the Kraepelinian era, for several decades mixed states were largely neglected in both research and clinical practice. Even the restrictive criteria of DSM-IV-TR and ICD-10 do not fully account for the variable presentations of bipolar mixed states. Nevertheless, during the last 20 years, many studies have been published on this topic and several authors have proposed and validated less restrictive diagnostic criteria for mixed states.

Conclusions

There is general consensus among clinicians and researchers that DSM-IV-TR and ICD-10 criteria do not capture the complexity of bipolar mixed states. Nevertheless, the debate on the boundaries of mixed states remains open.

Keywords

Mixed State • Bipolar Disorder • Diagnosis • Mixed Mania • Mixed Depression

Introduction

In bipolar disorder, mixed states are essentially considered the co-presence of symptoms of opposite polarity. This apparently simple concept, however, in reality poses several problems in terms of psychopathology and diagnostic categorization, especially considering the high grades of polymorphism of clinical entities referred to as mixed states. Mixed states are therefore one of the most controversial areas of psychiatry to which a great deal of attention has been given. A renewed interest in mixed states, which historically has undergone periods of greater and lesser intensity, is motivated in large part by the inadequacy of current diagnostic definitions, and is concentrated on formulating alternative diagnostic models that more accurately reflect the clinical reality.

As for any other psychiatric diagnosis, correct identification of mixed states has important clinical relevance for both timely diagnosis and planning adequate treatment. In contrast, the inability to recognize this clinical entity

(still frequent in psychiatry) exposes the patient to significant risks, and especially for the possible worsening of symptoms due to iatrogenic damage as a consequence of inappropriate therapy. In the present review, the authors will focus on diagnosis of mixed states starting from the work of Emil Kraepelin, who first conceived this diagnostic entity in a structured manner. Following this, the diagnostic evolution of mixed states will be discussed beginning with the most widely used classification systems [Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR) ¹ and the International Classification of Diseases 10th Revision (ICD-10) ²] and problems encountered, before considering alternative diagnostic proposals and the new criteria in the DSM-5 and ICD-11.

"Pre-Kraepelinian" authors

Even if traces of what is considered to be a "mixed state" are present in antique medical textbooks (especially Are-

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taeus of Cappadocia) and in some treatises on psychopathology in the 1700s (Lorry, 1765)³, the first descriptions that are close to current terminologies and concepts are those dating to the nineteenth century. One of the first psychiatrists to explore mixed states in detail was Heinrich, and in his treatise entitled “Disturbances of Mental Life or Mental Disturbances”⁴ he used a German term translatable as “mix or mixture” to define difficult to define psychopathological conditions in which discordant elements coexisted. Another German psychiatrist, Griesinger, in his treatises^{5,6}, described states of mental alteration in which melancholic and maniac elements coexisted as well as forms that would be currently defined as rapidly cycling affective disorders. Griesinger defined such psychopathological conditions as “mid-forms”, such as “melancholia with destructive impulses” and “melancholia with long-lasting exaltations of volition”.

In addition to the above authors, several European psychiatrists before Kraepelin described symptoms that had characteristics similar to a mixed state, as summarized by Karl Kahlbaum⁷. These authors, however, did not provide a precise categorization of psychopathological conditions in the manic-depressive area, which first appeared with the work of Emil Kraepelin.

Kraepelin and the later periods

Considering the origin of the concept of mixed states, a prominent place belongs to the German psychiatrist Emil Kraepelin who, starting from the 5th edition of his Textbook of Psychiatry⁸, first used the term “mixed states” (*Mischzustände*). In successive editions^{9,10}, together with the significant contribution of his apprentice Wilhelm Weygandt, author of a pioneering monograph on the subject¹¹, Kraepelin categorized and conferred nosographic autonomy to mixed states in the context of manic-depressive disorder. Kraepelin viewed mixed states as a ‘third polarity’ of manic-depressive disorder, and used this idea to consolidate his unified vision of this disorder. The possible co-presence of symptoms in the manic

and depressive phases, seemingly antithetical, in his view confirmed the common association of two polarities of the same underlying disease, supporting a hypothesis that had been around since ancient times.

Kraepelin identified a total of six different basic types of mixed states, depending on the combination of alterations in the three different psychic domains that, in his opinion, were involved in manic-depressive illness. The three domains consisted of mood, course of thought and psychomotor changes. Thus, there were the emerging concepts (Table I) of “manic depression or anxiety” (depressed mood, flight of ideas and hyperactivity), “excited depression” (depressed mood, inhibition of thought and hyperactivity), “unproductive mania” (euphoria, inhibition of thought and hyperactivity), “manic stupor” (euphoria, inhibition of thought and apathy), “depression with flight of ideas” (depressed mood, flight of ideas and apathy) and “inhibited mania” (euphoria, flight of ideas and apathy).

Later, Kraepelin and Weygandt partially overcame this tripartite model of the psyche, and favoured a dimensional approach, which involved a broadening of the concept of mixed states to the infinite possibilities that a mixture of manic and depressive elements could manifest in the same patient. In their opinion, apart from multiform phenomenal appearances, the essential point for diagnosis of a mixed state was the co-presence of manic and depressive elements in a patient with clinical features that reflected manic-depressive disorder, and in particular a previous history of manic and depressive episodes. A second concept in Kraepelin’s theory was the distinction between two basic types of mixed states: “transitional” forms, i.e. clinical pictures that frequently arise in the transition from mania to depression and vice versa, and “autonomous” forms, i.e. those that appear and manifest as such. According to Kraepelin, the latter form constituted that of a mixed state, and was characterized by the most unfavourable form of manic-depressive disorder, presenting with a lengthy course and the tendency to become chronic. The concept of mixed Kraepelin states

TABLE I.

Kraepelin criteria for mixed states. *Schema riassuntivo degli stati misti descritti da Kraepelin.*

	Mood	Motor activity	Ideation
1. Depressive mania	-	+	+
2. Excited depression	-	+	-
3. Unproductive mania	+	+	-
4. Manic stupor	+	-	-
5. Depression with flight of ideas	-	-	+
6. Inhibited mania	+	-	+

was the object of harsh criticism by other prominent figures in European psychiatry. Among these critics are Karl Jaspers¹², who refused the concept of a mixed state from a methodological standpoint, and Kurt Schneider¹³, who negated the existence of this diagnostic category, viewing it as a simple transitional phase (from mania to depression and vice versa) in manic-depressive disorder. Other authors, such as Eugen Bleuler, provided their own description of mixed states and did not pursue their research in this area in any detail.

Starting from the 1920s there was a relative lack of interest in mixed states, defined by Marneros¹⁴ as a “period of ignorance”, during which the number of publications on the subject was drastically reduced. One of the few exceptions was a monograph by the German psychiatrist Mentzos¹⁵, who utilized some concepts from Weygandt and proposed a new classification of mixed states. Building upon the static conception and clinical descriptions of Kraepelin and Weygandt, Mentzos added a dynamic view. In fact, the classification of Mentzos referred to a psychopathological model that he developed which was not based on the description of a clinical picture as a group of different symptoms; indeed, the mixed state was interpreted using the so-called ‘mood boost’ system. According to this point of view, mood alterations in bipolar disorder could be seen as pathological variations of the ‘boost’, or as the underlying force behind psychic processes, and ‘mood’ as the prevalent affective tone that affects thoughts of consciousness. In this light, mania and

depression were seen as concordant alterations of boost and mood (increased energy and euphoric mood vs. decreased energy and deflected mood), while mixed states were viewed as discordant alterations (e.g. increased energy and deflected mood). Moreover, Mentzos used a bipartition between ‘mixed states’ where the deviations in boost and mood were discordant but stable, and “mixed pictures”, where they were discordant and, importantly, variable over time. Unfortunately, due to the complexity of this psychopathologic model, clear criteria for the identification of mixed states were not proposed, and the terminology adopted was difficult to translate with the nomenclature used on an international level¹⁴.

The studies of Mentzos were also worthwhile, starting from the beginning of the 1980s, in promoting a renewed interest in research on diagnosis of mixed states, the initial stages of which can be seen in the “Vienna Criteria”¹⁶, named after the city from which the authors originated. The Vienna School, in the wake of Mentzos, divided mixed states into two subtypes, stable and instable, and proposed precise diagnostic criteria for the identification of both (Table II). These criteria were based on a well-defined psychopathological model known as Janzarik’s concept of structural-dynamic coherence¹⁷. According to this model, similar to the idea of Mentzos, mixed states were perceived as the product of instable alteration of the ‘dynamic’. The term dynamic referred to the mixture of two components that normally form the individual’s personality: one that forms the functional substrate of the

TABLE II.

Vienna School criteria for stable and unstable mixed states (from Berner et al. 1983, mod.)¹⁶. *Criteria della Scuola di Vienna per gli stati misti instabili e stabili (da Berner et al., 1983, mod.)*¹⁶.

Unstable mixed states

A.	Appearance of at least one of the following rapidly cycling changes following a period of normal functioning: 1. Mood changes rapidly cycling between depression and/or anxiety, euphoric/expansive hostile mood 2. Rapid cycling and exaggerated emotional resonance in various affective states (depressive, anxiety, manic and hostile) 3. Rapid cycling between inhibition, agitation, increase in drive and occasional aggressiveness
B.	Biorhythmic disturbances* 1. Diurnal variations of affectivity, emotional resonance, or drive 2. Sleep disturbances (interrupted, prolonged, or shortened sleep or early awakening)

Stable mixed states

A.	Appearance of persistent variations in affectivity, emotional resonance or drive after a period of normal functioning Requires symptoms 1 and/or 2 and 3: 1. Depressed, anxious, euphoric/expansive or hostile mood 2. Lack of emotional resonance or limited to depressive, manic, hostile or anxious response 3. Persistent presence of drive in contrast with the affective status and/or emotional resonance
B.	Appearance of biorhythmic disturbances* 1. Daily changes in affectivity, emotional resonance or drive 2. Sleep disturbance (interrupted, prolonged, or shortened sleep or early awakening)

* Symptoms 1 and 2 are required.

temperament and a “structural” form that encodes both innate and acquired behavioural patterns. Strict adherence to this model, even if highly thought-provoking, limited the use of the Vienna Criteria to research purposes on an international level. Nonetheless, the Vienna Criteria represented a turning point that influenced and stimulated research in the forthcoming years, giving rise to a large number of publications especially by authors from the US.

Current classification systems

The most widely-used classification systems for psychiatric pathologies in clinical practice and research are the DSM-IV-TR¹ and ICD-10², and both provide a definition of the mixed state. The vision of plurality of mixed states is not used in either system, and depending on the combination of manic and depressive symptoms, a mixed episode is seen with a unitary vision. Thus, the presence of third polarity in bipolar mood disorders is anticipated. According to DSM-IV-TR criteria, it is possible to diagnose a mixed episode in the co-presence of criteria to diagnose either a manic or major depressive episode (except for the time criterion) for at least one week. In the ICD-10, however, the term “mixed episode” indicates the co-presence or rapid cycling of prominent depressive and manic or hypomanic symptoms for at least 2 weeks. If on one hand these classification systems simplify the concept of “mixed states” and groups them in a single diagnostic category, on the other they bring about a series of problems, especially in terms of sensitivity in revealing psychopathologic symptoms that the majority of clinicians would judge as belonging to that category, but which do not reach sufficient threshold criteria to make a diagnosis.

Considering the DSM-IV-TR, the possibility that mixed states can coexist in the context of type II bipolar disorder is excluded, except when commonly encountered in clinical practice^{18,19}. Moreover, this means that the presence of symptoms with opposite polarity in the context of a manic or depressive episode is not considered, unless the diagnostic threshold for a mixed episode is reached. Lastly, diagnosis of a mixed episode correlated with the use of mood-altering substances, pharmacological therapies or general medical conditions is not allowed, which are all rather common²⁰. The major limitations in ICD-10 criteria concern the low precision and reliability of the diagnostic definition itself, since the number of symptoms needed for diagnosis is not specified. Moreover, the poor sensitivity relative to temporal criteria requires a duration of two weeks, which many consider to be excessive^{20,21}. Due to the above-mentioned limitations, at present, the majority of experts consider both DSM-IV-TR and ICD-10 criteria for ‘mixed episodes’ to be inadequate^{14,19-23}.

Alternative diagnostic proposals

To compensate for the shortcomings of current classification systems, there are several recent publications in which the authors propose alternative models for the identification of mixed states. Generally, in these reports, the rigid categorical approach of the DSM-IV-TR is not used, but rather a categorical-dimensional mixed system is adopted that is closer to that the original system proposed by Kraepelin. Thus, the concept of mixed state as a rigid diagnostic entity is replaced by a more variable condition in which, in the context of an affective episode, symptoms of opposite polarity are present, often to a lesser extent but which are not negligible for diagnostic purposes. In this way, the concepts of mixed manic state or mixed manic and mixed depressive state or mixed depression are outlined. From a more practical aspect, mixed manic and depressive states are described separately in the following paragraphs. A model centred around the role of affective temperament as a causal factor for mixed states, in part theorized by Kraepelin and further developed by Hagop Akiskal and other authors, will also be considered.

Mixed manic states

Over the last 20 years, the low sensitivity of DSM-IV-TR criteria in the identification of the possible relevance of the presence of depressive symptoms in the context of a manic or hypomanic episode prompted many authors to propose more adequate diagnostic criteria. At present, in the absence of widely-accepted opinion, the literature is filled with a variety of terms that are often interchangeable and used inappropriately to indicate similar concepts: these include *mixed state*, *mixed mania*, *dysphoric mania* and *mania with depressive symptoms*.

For greater clarity, herein the term mixed mania will be used, although this was not always the term used in the original publication. McElroy et al.²⁴ were among the first authors to propose a differentiation between ‘pure’ and ‘mixed’ mania (defined in that study as *dysphoric mania*), which greatly influenced later clinical studies. These authors carried out a revision of previous studies and concluded that mixed mania was a clinical entity which is separate from pure mania, and with distinguishing features that include different clinical characteristics such as prevalence and poorer prognosis. Considering this, they proposed working criteria for the identification of mixed mania, which were also valid for hypomania, known as the Cincinnati criteria, that required the simultaneous presence of rapid cycling (within several minutes) of a variable number of depressive symptoms in the context of a (hypo)manic episode diagnosed according to DSM-III-R criteria²⁵. The presence of symptoms for at least 24 hours is also required to diagnose mixed mania,

and the criteria also dictate, depending on the number of depressive symptoms present, different diagnostic thresholds: certain diagnosis of *dysphoric mania* or *hypomania* (presence of 3 or more depressive symptoms), probable diagnosis (presence of two symptoms) and possible diagnosis (one symptom present). The list of possible depressive symptoms includes those for diagnosis of a major depressive episode according to the DSM-III-R except for psychomotor agitation, insomnia and loss of appetite/weight loss. In a later revision of mixed mania, McElroy et al.²⁶ stabilized that the diagnostic threshold consists in the presence of at least any three depressive symptoms, or only two symptoms comprising at least one of the following: depression, anhedonia, guilt, loss of hope or recurring ideation of death or suicide.

Another classification system proposed, which in many aspects is similar to that of McElroy et al., is that of Cassidy et al.²⁷ which distinguishes mixed mania from pure mania according to the presence of at least two of six depressive symptoms (depressed mood, anhedonia, anxiety, guilt, suicidal ideation and asthenia). This classification is obtained using data from a study on 247 patients with a diagnosis of mania according to DSM-III-R criteria. The optimal cut-off of at least two symptoms was obtained by statistical analysis using a ROC (receiving operating characteristic) curve, and was validated with criteria for a mixed episode according to DSM-III-R criteria.

An analogous definition was used in the epidemiological multicentre investigation published by Akiskal et al.²⁸ known as EPIMAN. This study compared the prevalence of mixed states in patients recruited according to DSM-IV-TR criteria for mixed episodes to that observed using less restrictive criteria (manic episode + at least two depressive symptoms). The authors noted a substantial difference between the two definitions, in that the prevalence was 6.7% in the former and 37.5% in the latter. The study also reported a higher prevalence of depressive temperamental forms in patients with a mixed state compared to those with pure mania. It was concluded that the mixed state can be defined using three different approaches: from a categorical point of view through identification of at least two depressive symptoms, from a psychometric standpoint with a score >10 on the Hamilton Depression Rating Scale and from a dimensional viewpoint through identification of a dominant depressive temperament.

Another important study led to the definition of the "Pisa-San Diego criteria"²⁹, which differ from the previous ones by proposing a more dimensional approach. In this diagnostic algorithm, mixed states are defined as the simultaneous presence of manic and depressive symptoms, for at least 2 weeks, in at least two psychic areas comprising mood, train of thought, content of thought, misperceptions and psychomotor behaviour. In addition, the presence of two additional symptoms among the fol-

lowing is required: emotional lability, lowered threshold for anger/hostility, abrupt changes in the libidinal drive, marked disturbances of the sleep-wake cycle and circadian fluctuations of symptoms referable to the above-mentioned areas. Lastly, as exclusion criteria, adequate interpersonal and affective responses adequate during symptom-free periods are needed. Such criteria allow for diagnosis of a broad spectrum of mixed states, including manic and depressive, which is more in line with the concepts of Kraepelin (e.g. unproductive mania, inhibited mania, etc.). Thus, these diagnostic criteria for mixed mania are less restrictive than those in the DSM-IV-TR, and allow a greater degree of differentiation with greater sensitivity of pure states and mixed states.

Mixed depressive states

Over the last 20 years there has been a renewed interest in mixed depression due to the important diagnostic and therapeutic implications. Several authors with long-standing experience in bipolar disorders concur that mixed depression should be differentiated from 'pure' depression²⁹⁻³⁴. In 2005, Koukopoulos et al.³⁴ published an in-depth revision that highlighted the inadequacy of diagnostic criteria for identification of mixed depression (defined as *agitated depression*), and reiterated the urgency of defining new, broadly-accepted criteria. Several years earlier, the same author³³ had proposed diagnostic criteria for identification of mixed depression, which required the presence of a major depressive episode (according to DSM-III-R criteria) with agitation and at least three of the following symptoms: racing thoughts, irritability or sentiments of unmotivated anger, absence of signs of slowing down, talkativeness, dramatized description of suffering and frequent crying spells, emotional lability and marked emotional reactivity, and initial insomnia. According to the author, the presence of these symptoms indicates an excitatory disequilibrium in mood, non-depressive, which in the context of a major depressive episode would manifest as a mixed state.

The nosographic autonomy of mixed depression is also supported by several lines of evidence, as highlighted in a recent review³². From the available information, mixed depression (defined as the co-presence of at least 2-3 manic or hypomanic symptoms) is differentiated from pure depression on the basis of its particular characteristics, which in some ways are very similar to bipolar disorder. Firstly, mixed depression appears more frequently in bipolar disorder than in major depression. In particular, mixed depression is a condition that is especially frequent in type II bipolar disorder, and as reported in large cohorts of patients, almost one-half (48.7%) of patients with episodes of major depression also have at least three hypomanic symptoms³⁵. Secondly, mixed depression generally pre-

sents at an earlier age than pure depression, and is more frequent in individuals who present with a family history for mood disturbances and in those who present with non-mixed depression (see above). This latter aspect, at present, is the strongest evidence to sustain that mixed depression is an independent nosographic entity.

A later study¹⁹, carried out on 320 patients with bipolar II disorder and an on-going episode of major depression, confirmed the high prevalence of mixed depression in the disorder. In fact, the results showed that 62.5% patients presented with mixed depression or with a major depressive episode with the co-presence of at least three hypomanic symptoms for at least two days. Compared to patients with non-mixed episodes, patients presented with a significantly lower age of onset of the disorder, and there was a higher proportion of women, more frequent episodes with atypical symptoms and a higher rate of positive family history for bipolar disorder. Through multivariate logistic regression analysis of hypomanic, intra-episode signs and symptoms, there was evidence that the two subtypes of mixed depression can be differentiated, which is in agreement with the concepts outlined by Kraepelin over a century ago. The first subtype is defined as 'excited depression' (the core symptomatology of which is psychomotor agitation, whose accessory symptoms are logorrhoea, irritability and easy distractibility), while the second type is referred to as 'depression with flight of ideas' (with a core symptomatology consisting in flight of ideas, associated with lack of impulse control, including sexual control due to increased libido).

Another difference that seems to distinguish mixed depression from pure depression is the poorer response to antidepressant pharmacotherapy, which may even contribute to worsening of symptoms in some cases with a mixed state (see above). Koukopoulos et al.³⁶, in a cohort of 212 patients who presented with agitated depression, in accordance with the above-mentioned criteria proposed by the same authors, reported that in over one-half (53%) of cases the episode did not manifest as such, but rather developed from pure depression. Among these, the vast majority were in treatment with antidepressants, which was associated with worsening of clinical conditions, with overlapping symptoms of opposite polarity. It should be noted that the percentage of cases of mixed depression 'induced' by therapy was particularly high for those affected by bipolar II disorder; in 71% of cases the episode appeared after treatment with an antidepressant or other stimulants, compared to 48% of bipolar I cases and 50% of patients with unipolar depression. The latter aspect is clinically relevant, especially considering the fact that DSM-IV-TR criteria do not allow for identification of mixed depression, equating it to pure major depression with consequences for treatment that have given rise to doubts among clinicians and researchers.

Lastly, the fact that, at least in theory, mixed depression can be diagnosed as unipolar major depressive disorder leads to the concept that it might act as a 'bridge' between unipolar and bipolar disorders; furthermore, this is in agreement with the hypothesis of a 'spectrum' of bipolar disorders proposed by Akiskal³⁷⁻³⁹. According to this idea, among mood disorders there is a continuum in which the clinical states of pure depression and pure (hypo)mania are at the extremes; correlated disorders are then located along the continuum as follows: major depressive disorder, agitated depression, depression with flight of ideas, bipolar II disorder, bipolar I disorder^{19,40}.

The role of temperament

The most important studies on the role of temperament in bipolar disorder carried out during the last three decades revolve around Hagop Akiskal. Considering mixed states, this author built upon the concept already postulated by Kraepelin and developed an innovative classification system. According to this system, mixed states are not a mere overlap of depressive and manic elements, but rather the combination of an episode of affective alteration with a dominant temperament of opposing polarity. Akiskal proposed³¹ three types of mixed states depending on the type of interaction of temperament/affective interaction:

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

The presence of a dominant temperament is identified by the administration of specific psychometric scales.

According to this opinion, therefore, the presence of hyperthymic temperament would render manic episodes 'pure', while the manifestation of some aspects of such a temperament in the case of a major depressive episode would 'contaminate' it with mixed elements. A cyclothymic temperament is considered by the author to be a specific predictor of bipolarity in major depression, conferring mixed, strongly instable characteristics to the episode. The role of temperament has been documented in several studies in which Akiskal also benefited from Italian colleagues at the Pisa and French schools^{28,30,39,41-43}.

From a symptomatological/phenomenological point of view, type I mixed states I (type B-I) comprise psychotic episodes that are similar to the concept defined by the French school as "*bouffées délirantes*". These are characterized by productive, solid psychotic symptoms, and strong emotional perplexity with sudden mood swings that are almost indistinguishable from the acute phases of schizophrenia spectrum disorders.

Type II mixed states are generally non-psychotic and classically require the manifestation of a cyclothymic temperament in the context of inhibited depression. Thus, together with mood deflection, hyperphagia, hypersomnia and asthenia, other symptoms appear intermittently such as racing thoughts, excessive joking, fits of rage, emotional tension, restlessness, impulsivity, disinhibition and dramatic suicide attempts. The abuse of stimulants and sedatives is also particularly frequent^{39,43}.

The third type of mixed states manifests as major depressive episodes in the context of stabile hyperthymic temperament: according to the author³⁷, this type of mixed state is characterized by persistent dysphoria together with irritability, agitation, asthenia and marked racing of thoughts, panic attacks and insomnia, obsessive ideas of suicide associated with suicidal impulses and discomforting sexual hyperarousal. Substance abuse with alcohol or drugs is frequent. In the author's opinion, such a clinical picture is typically seen in hyperthymic patients who have suffered multiple major depressive episodes over a lifetime and undergone numerous antidepressant therapies. While such a condition may have been considered as 'unipolar', it should actually be considered as part of bipolar II disorder³⁹. Therefore, in this type of classification, while the first type of mixed state is similar to the idea of 'mixed episode' in the DSM-IV-TR, the other two types are identified as mixed states in the context of type II bipolar disorder or in 'pseudounipolar' patients, and in categorical terms comparable to the definition of mixed depression as described above.

Future considerations: DSM-5 and ICD-11

The inadequacy of the DSM-IV-TR and ICD-10 in identifying mixed states together with the results from recent studies has prompted investigators to re-evaluate criteria for mixed episodes, also considering the newly released and forthcoming additions. The DSM-5 was released during the APA's 2013 Annual Meeting in May 2013⁴⁴.

In the DSM-5, the new criteria have eliminated the category "*mixed episode*" and replaced it with the specification "*with mixed features*", which should be applied to individual episodes of major depression, either hypomanic or manic, together with or in close juxtaposition with at least three symptoms with opposite polarity among those listed. Whenever a patient presents with symptoms that satisfy criteria for both mania and depression (which according to the DSM-IV-TR is defined as a mixed episode), this is now considered "*mania with mixed features*", thus favouring the greatest functional compromise and clinical severity of mania over depression. For diagnosis of major depressive episodes with mixed aspects, this is possible in the context of bipolar disorders (I, II and NOS) and in unipolar major depressive disorder. It is evident that

these new criteria have introduced considerable changes to the diagnosis of mixed states, which are in agreement with many of the aforementioned studies.

The ICD-11⁴⁵ criteria are substantially similar to those in the DSM-5, with the difference that the term "*mixed episode*" is maintained, which is further divided into six subtypes depending on the current predominant episode and presence of psychotic symptoms. For example, the possible diagnoses are "actual mixed episode, current mania with depressive symptoms, psychotic (or non-psychotic)"; a similar scheme is used for hypomanic and depressive episodes. In our opinion, it would also be useful to maintain the nosographic category for mixed episodes: firstly to allow greater diagnostic sensitivity and favour research on mixed states, and secondly since a distinct diagnosis would facilitate specific treatment decisions for mixed states, which would otherwise be influenced by the "dominant" episode.

Conclusions

In the present review, the complex problem of diagnosis of mixed states was examined in detail. Beyond psychopathological considerations, which in itself represent an interesting stimulus for further research in this area, identification of reliable and valid criteria for diagnosis of mixed states would have important clinical implications, in terms of both prognosis and therapy. Consider the classic example of mixed depression, which cannot be diagnosed with the DSM-IV-TR: in this case, what difference would correct identification make for the overall psychopathological picture? If one thinks about the fact that several lines of evidence indicate that, in similar cases, antidepressant therapy is likely to be without any clinical benefit or even dangerous due to the increased risk of suicide⁴⁶, the advantage is enormous. In the case of mixed mania, the possible consequences of diagnosis are perhaps less evident, but nonetheless important from a clinical standpoint. For example, it has been reported that the presence of depressive symptoms during the course of mania (which would be the definition of mixed mania) is a negative predictor for response to lithium, which in these cases is inferior to valproate, and thus would be considered as first-line treatment⁴⁷.

What appears obvious is that, following a historical phase in which clinicians and researchers progressively lost interest in the concept of a mixed state, over the last three decades this tendency has been reversed, with a recovery of classic ideas (and especially those of Kraepelin) to extend knowledge on the subject with the goal of improving diagnostic sensitivity and specificity. Mixed states have now gained increased attention, and it should be kept in mind that they are relevant for the clinical practice of every psychiatrist.

Following the publication of the most frequently used psychiatric diagnostic manuals (DSM-IV-TR and ICD-10), it can be confirmed that, in the area of mixed states, the vast majority of criticisms were centred around the fact that that diagnostic criteria for mixed states were inadequate since they were too rigid. As a consequence, new proposals focus on more inclusive diagnostic models. In this regard, clinical studies appear to confirm the fact that compared to more traditional models the use of broader criteria is more adequate for correct identification of mixed states. Moreover, the available data support the utility of differentiating between manic mixed states and mixed depressive states, or at any rate to acknowledge the existence of a plurality of different types of mixed states instead of the single diagnostic entity in the ICD-10 and DSM-IV-TR. Nonetheless, it should be kept in mind that while such a distinction may appear useful to increase diagnostic sensitivity, there is a still large overlap between manic and depressive mixed states with regards to course of disease, prognosis and response to treatment²⁰; this would suggest that it is useful to consider mixed states as a single clinical entity, regardless of their phenomenological polymorphism.

Herein, we have focused our attention on diagnostic models in the area of mixed states that can help the clinical psychiatrist from a practical standpoint. For this reason, we have given preference to categorical diagnostic models, which are not widely adopted in clinical practice. It is obvious that this leads to some limitations, and one may have the impression that correct diagnosis depends only on an uninteresting summary of conflicting symptoms. By understanding such limits, the application of these models is fundamental to promote the use of universally accepted and clear terminology that does not refer to theoretical models, but rather provides a broad synopsis. Moreover, a categorical approach can always be integrated with a dimensional approach, which will further help the clinician in diagnosis; in this regard, it should be mentioned that there are several reports in the literature proposing dimensional models that be applied to mixed states^{22,48}. In conclusion, mixed states are now a research area of primary importance in bipolar disorder. Undoubtedly, genetic and neurophysiological studies of mixed states will be fundamental in further delineating diagnostic criteria and new therapies.

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