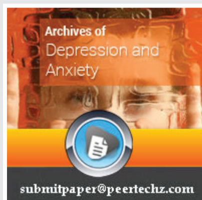

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Archives of Depression and Anxiety — Open Access Journal

ISSN: 2455-5460 DOI: https://dx.doi.org/10.17352/ada

Research Article

Mixed states in bipolar disorder: The DSM-5 dilemma

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Received: 22 January, 2024
Accepted: 31 January, 2024
Published: 01 February, 2024

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Keywords: Bipolar disorders; Depression; Mania; Mixed states; DSM5; ICD11

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Abstract

Although clinical descriptions of mixed states date from the beginning of the 19th century, the first use of the term mixed state dates back to French nosological descriptions by Falret in 1861, who thus described "predominant ideas often of a sad nature, in the middle of a state of excitement simulating true mania", but also "inverse states, an extreme confusion of ideas which is combined with the calm of movements and the appearance of reason". It is rather in Germany that the mixed state will be integrated into a homogeneous conception of a psychiatric disorder, similar to our modern conception. Kraepelin describes it more completely in the seventh edition of his treatise. Weygandt, a student of Kraepelin, contributed to the description of mixed states and wrote a treatise specifically on this subject. Kraepelin's conception will be expanded by differentiating on the one hand the transitional forms (the mixed state being a form of passage between the manic and depressive poles) and the autonomous forms (with a worse prognosis). Akiskal offers an interesting enrichment of Kraepelinian and Hamburgers in mixed states. To do this, he uses his work on temperaments. Some clarification therefore seems necessary on the notions of temperament, character, and personality before delving deeper into this data. A decisive synthesis work is carried out by McElroy, et al. whose objective is then to establish an exhaustive review concerning the clinical characteristics, demographic, evolutionary, biological, familial, comorbidity, or response therapy of mixed states. Mixed states appear today in international classifications and are defined there as the summation of manic and major depressive episodes, both complete. Considering these definitions as too restrictive, some authors propose other broader and very variable criteria.

Introduction

Bipolar disorder is characterized by the alternation of "high" phases and "low" phases but it is also characterized by the mixture of "high" and "low" elements which are called "mixed states" [1]. The DSM-5 defines a mixed state as a manic or depressive episode with at least three symptoms of the other polarity, during the majority of the days of the episode, excluding "non-specific symptoms": agitation, irritability, distractibility, considered to be symptoms of depression in their own right [2]. In practice, these three symptoms are very often present in mixed depression and entirely suggestive of "contamination" by hypomania. Their exclusion creates confusion and does not allow mixed depression to be properly identified.

The coexistence of manic and depressive symptoms results in clinical pictures of great diversity, evoking various psychiatric disorders. Mixed state diagnosis remains little or poorly known to clinicians, and seems to be insufficiently focused or to excess [3]. Beyond this confusion on the diagnostic level, uncertainties persist about the therapeutic particularities of mixed states.

What can data from the literature tell us about this concept of mixed state? Are they able to overcome these difficulties encountered in practice? What can they also teach us about the nature of mixed states?

Mixed depression corresponds to a depressive syndrome with elements of psychomotor activation, of the hypomanic lineage. Patients with mixed depression are particularly at risk of suicidal behavior, substance abuse, and especially therapeutic resistance [4]. However, this pathological situation remains little identified and little studied despite its high frequency. Its low recognition was probably linked to the absence of this concept in international classifications. The DSM-5, recently published in its final version, proposed an

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overhaul of the definition of mixed states, going beyond a particularly restrictive conception in the DSM-IV [5]. "Mixed features" may serve as a specifier for a mood disorder episode, depressive or manic. Depression with mixed characteristics is defined by the presence of three symptoms of the manic lineage associated with depression, excluding agitation, distractibility, or irritability. In this article, we discuss the clinical relevance of this concept. It is shown that the DSM-5 diagnostic criteria lack clinical consistency, are difficult to apply, and do not make it possible to identify the majority of mixed depressions. These risks slow down the progress of research into mixed depression, the therapeutic strategies of which remain little systematically studied, and the epidemiology and risk factors of which are still only partially known [6]. The innovative approach of the DSM-5 ultimately led to a modest advance, the scientific basis of which remains debated. The goal of this paper is to clarify the notion of a mixed state through the history of the concept.

Historical evolution of mixed state concept

Antiquity: Mania and melancholy are among the disorders described earliest in history. These states of pathological depression and exaltation are known to physicians and professional philosophers of the pre-Hippocratic era. Certain poems of the period are used by ancient Greek physicians, including Hippocrates (460-337 BC) who established the first classification of mental disorders including melancholy, mania, and paranoia [7]. These concepts of mania and melancholy, much broader than those today, included certain types of schizophrenia, organic disorders, as well as schizoaffective disorder.

These are the descriptions of the Cappadocian Order (first century BC) which contain the first traces of the possible coexistence of manic and depressive symptoms. He does not consider mania and melancholy as two distinct disorders but as two different presentations of the same disease. Mania is the most severe stage for him, melancholy as evidenced by these extracts from his book: "I think that melancholy is only the beginning and only part of the mania", then "The onset of mania represents a worsening of the melancholic illness more than any other illness" [8]. We find in this same book the modern concept of irritable, dysphoric, or furious mania: "In some patients, mania manifests itself as euphoria... This form of mania does not cause little concern to the patient's loved ones. Other patients, however, present a furious rage, tear their clothes to shreds, and willingly attack people who take care of them, some even going so far as to commit suicide". The work also contains a description of what Kraepelin would later call agitated depression: "...melancholic people often express only sadness. But he is possible to enter states of rage and thus spend a large part of their life in a madness pushing them to terrible and humiliating acts". Without clearly delimiting and individualizing mixed states, these concepts of mania and melancholy persisted until the 19th century.

State of science in the 19th century: Most pre-Kraepelinian authors describe forms of mixed states. From the start of the eighteenth century, certain forms of melancholy that can be linked to diversity are described by Boissier de Sauvages and William Cullen: the "melancholia enthusiastica", "melancholia furens", "melancholia moria", "melancholia saltans" and "melancholia errabunda" [8]. Lorry even described "mania-melancholica" in 1765. The first classification of individualizing mixed states is that of Heinroth in 1818 in his book (Disorders of Mental Life or Mental Disorders) where he divides mental disorders into three categories: states of exaltation (hyperthymia), depression (asthenia), and states mixed then called "mixture of exaltation and depression" [9]. This last category is itself broken down into three parts: "mixed mental disorders", "mixed mood disorders" and "mixed willpower disorders".

The French school of the 19th century: The further we advance in the 19th century; the more attention is drawn to this cyclicality of a part mood disorders. Wilhem Griesinger was one of the first to describe it in 1845 and his observations will prove decisive in the development of the concept of circular madness of the French school [10]. Jacquelin Dubuisson already testified also in 1812 in his Dissertation on the Mania of the close relationships between diversity and cyclicity in two observations: "melancholy complicated by manic attacks which return every two days" and "melancholy complicated by manic attacks which return every night." His description of a "mania caused by deep sorrows" is a remarkable observation of melancholy, highlighting the possible instability of the symptoms: "..., the face is pale and sad, the look is dark and worried, the insane person seeks solitude. He keeps a dull and obstinate silence, or else it complains, it groans deeply, it pours out in violent imprecations. It is in vain that we try to tear him away from his dark ideas, from his dark reveries; all attempts in this regard made by even the dearest people, torment and irritate this unfortunate person, and often give rise to odious reproaches and violent impatience..."[11].

It was in 1851 that Falret, a student of Esquirol, published his fourteen lines entitled "Of Madness circular or form of mental illness characterized by the regular alternation of mania and melancholy." He then describes a mental disorder that he calls "circular madness". Characterized by a continuous cycle linking depression, mania, and free intervals. He will complete his concept over the following three years with a publication: "Clinical Lessons in Mental Medicine Given at the Salpêtrière Hospice" [12] and a memoir presented to the Academy of Medicine under the title: "Memoir on Circular Madness, a form of mental illness characterized by successive reproduction and regular pattern of the manic state, the melancholic state and a more or less lucid interval prolonged". Baillarger's concept of "Double Form Madness" presented three years later, and which is greatly inspired by the observations of J.R. Jacquelin Dubuisson, is quite similar, apart from the lesser importance given to the free interval [10]. The two rivals and "fathers" of the concept of bipolar disorder are at the origin a major advance in the field of psychiatry. These concepts of "circular madness" and "double-form madness" already raise some questions about mixed states. Could they therefore only be forms of transitional mood disorders?

Kraepelin and Weygandt

The birth of the concept: Kraepelin is the creator of the concept of mixed state in the sense that he manages to clarify

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and systematize the various works of the authors preceding him in order to establish with his student Weygandt, which remains the greatest advance in the field to this day. The roles of the two men remain difficult to distinguish other than by the analysis of their publications [13].

First of all, it is appropriate to clarify Kraepelin's conception of psychic life: he breaks it down into three distinct parts: mood, thought, and will (or activity). These three domains oscillate too intensely between two extremes in manic depressive illness: mood between euphoria and depressive mood thought between tachypsychia and bradypsychia, and the activity between psychomotor excitation and slowing down or even inhibition psychomotor. The evolution of these three areas is consistent and synchronous, towards both classic forms of mood episodes. Depression then manifests itself through mood depression, bradypsychia, psychomotor slowing, and mania through euphoria, tachypsychia and psychomotor excitation.

It is quite different for states mixed in which the oscillation of the three domains is discordant. The origin of Kraepelinian theory probably lies in the fourth edition of his book of psychiatry in 1893 where he characterizes and describes stuporous mania which he describes as “mixed” without yet using the term “mixed state” [14]. He considered a few years later this stuporous mania as the most common type of mixed state. More “convincing”. The term "mixed state" is first mentioned in 1896 in the fifth edition of his book but the first evolution of his classification is located in the sixth edition in 1899. He then divided them into two categories: manic states with inhibition and states depressed with excitement. It is interesting to note that many modern authors retained this dichotomous vision of mixed mania and depression in their work after more than a century. This already underlines the precursory nature of the Kraepelinian theory then even though it is only in its infancy.

First student and then a colleague of Kraepelin, Weygandt also contributed to the evolution of the mixed state concept. He published, in the same year 1899, after the publication of the sixth edition of Kraepelin's book, the first psychiatry book on mixed states (On Mixed States of Illness Manic depression).

Weygandt explains in particular that the manifestation of diversity is due to the fact that both manic (euphoria, excitability, and flight of ideas) and depressive symptom lines (depressed mood, psychomotor, and ideational inhibition) are not stable in any way uniform. Lability is possible for him in each of the three areas of mood thinking and psychomotor skills, independently. The mixture of symptoms of these three domains results in a mixed state that individualizes three types which are the most common: stuporous mania, agitated depression, and unproductive mania. He devotes two-thirds of his book to describing these mixed states whose evolution is according to him more chronic than that of “pure” episodes but whose prognosis is not different.

Mixed states according to Kraepelin: According to Kraepelin, the three domains of psychic life: mood, thought and activity, can therefore oscillate in a shifted manner in the evolution of manic-depressive illness. The mixed states thus manifested are then mainly transitional forms of mood disorders, intermediate between mania and depression. These intermediate forms are then for him the sign of the close relationship between mania and melancholy and indicate the probable uniqueness of the pathological process [15]. However, he also notes stable and autonomous forms of mixed states, less frequent, which he considers to be forms of manic-depressive illness in the most pejorative prognosis. Certain data such as female predominance, the unfavorable prognosis of these mixed states, the longer evolution, and the tendency to chronicize will be confirmed a century later by several studies. Kraepelin and Weygandt also noted that two-thirds of manic-depressive patients present or one or more mixed states are presented, most of which are transitional, which is not very far from current data (between 5% and 70%) [13].

Mixed manias: In 1913 in the eighth edition of his book, Kraepelin described six types of mixed states. The first three are individualized from his category of inhibited manias (1896) and can be considered mixed manias: depressive mania, inhibited mania, and mania poor in thought. All three are based on the basic symptoms of mania, but each is characterized by the presence of an opposite polarity symptom in one of the three domains of psychic life. In depressive mania, euphoria is replaced by a depressed mood, in thought-poor mania, the flight of ideas is replaced by an inhibition of thought, and finally, in inhibited mania, excitement psychomotor is replaced by inhibition [16].

Mixed depressions: The other three types of mixed states come from excited depressions. They then constitute mixed depressions: agitated depression, depression with leaked ideas, and stuporous mania. The basic symptoms are those of depression, but each type presents one of the domains of opposite polarity. The agitated depression is characterized by psychomotor excitation instead of inhibition, in depression with flight of ideas, the inhibition of thought is replaced by a flight of ideas, and finally, the stuporous mania is characterized by euphoria replacing depressed mood [17].

Post-Kraepelinian theories

The German school: The second quarter of the twentieth century is considered a period of less interest concerning mixed states. The explanation lies mainly in a massive rejection of Kraepelinian theories on manic-depressive illness by most schools of German and psychoanalytics. This opposition, started and led by Carl Wernicke, challenges the unitary nature of this concept. He and his successors then conceived the disease manic-depressive rather and only in the manner of Falret and Baillarger as a repetition of episodes alternating between mania and melancholy. Recurrent mania and depression are considered separately. The complexity of these German concepts is reflected logically in multiple classifications and distinctions. Wernicke, for example, suggested already in 1900 five types of melancholy: affective, depressive, agitated, hypochondriacal, and atonic [9]. The complexity of these concepts and classifications compared to those of Kraepelin will make their acceptance difficult. Some of

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these works are nevertheless of capital importance, such as the distinction between affective disorders unipolar and bipolar by Karl Kleist, a student and then colleague of Wernicke [10].

The Kraepelinian conception of mixed states then gradually drowns in this complexity as well as in the anthropophenomenological and psychodynamic approaches of the time. They are gradually reconsidered as a sort of crossroads of different psychoses, having a variable and unpredictable evolution, which clearly reduces the interest of the concept [18]. The German classifications of the time, initiated by Wernicke and continued by his successors left little room for them. The latest versions completed by Karl Leonhard distinguish "partial states" from "mixed states". The first, very frequent, are characterized by the presence of an incomplete manic or depressive syndrome. They are opposed to the second, much rarer, and presented as the mixed states of Kraepelin.

Mentzos and unstable mixed states: The only German school continuing the tradition of mixed states during these decades of fierce opposition is that of Hamburg. This is largely due to the arrival of Weygandt who settled there and exerted his influence there at the beginning of the twentieth century. Kraepelin's theories are therefore explored in depth.

The three types of mixed states according to Mentzos: The second monograph on mixed states (Mischzustaende und Mischbildhafte Phasische Psychosen, 1967) appeared 68 years after Weygandt's [19]. It is the work of Stavros Mentzos who individualizes three different forms of diversity: mixed states stable ("Mischzustaende"), mixed psychoses ("Mischpsychosen"), and mixed states unstable ("Mischbild" translating into English as "mixed-picture"). The first is the forms described by Kraepelin, superpositions of manic symptoms and depression by a dissociation between mood and activity. The latter represents a large part of what we could today call schizoaffective disorders. The last category is individualized for the first time by Mentzos and defined as a rapid, desynchronized alternation of manic and depressive symptoms [20].

The concept of unstable mixed state: Manic-depressive illness is then considered a cyclical evolution and more or less congruent with the different domains of psychic life (mood, thought, and will). They can therefore progress in a concordant and stable manner towards manic episodes and "pure" depressives, but can also evolve in a way that is out of sync with each other. In this case, if the mood, the thought, and the will keep the same speed oscillation, a mixed Kraepelinian state manifests itself. Mentzos then qualifies these mixed states as "stable" due to this synchronized oscillation. On the other hand, in certain patients, mood, thought and will oscillate completely desynchronized and chaotic. In this type of mixed condition, symptoms may then alternate extremely quickly, sometimes within a few minutes or a few hours. These mixed states called "unstable" by Mentzos then seem better to take into account the frequent lability of symptoms already observed previously by Weygandt. Compared to stable forms, these predominate in young women and seem to be correlated with certain biological factors, bringing them closer to the concept of rapid cycles which would be defined a few years later in 1974 [21].

A controversial entity: Mentzos frequently observes manifestations during these unstable mixed states of delusional, hallucinatory, catatonic, and confusional, to the point that he suspects this instability causes these psychotic manifestations. At the time, he considered that the forms stable and unstable were manifestations of different severity of the same process pathological making the transition from one to the other entirely possible [22]. This point of view is not really shared by contemporary authors of Mentzos. If the stable mixed states seem to belong to manic-depressive illness, mixed states-unstable could, according to them, come closer to a possible crossroads between bipolar disorders and schizophrenia [23]. This notion remains ignored by a large part of current psychiatry. North American nosology, little fond of trans-nosological considerations, does not retain this conception of unstable mixed states in the latest versions of the DSM. These clinical presentations can therefore today inspire diagnoses as varied as those of schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or even bipolar disorder with incongruent psychotic features.

Berner and the vienna school: Mixed stable and unstable states are nevertheless adopted by the Vienna school which deepens fifteen years later by introducing a third possible disturbance to the level of mood: dysphoria, then considered equivalent to irritable mood [24]. Berner, inspired by Janzarik's model, therefore considers dysphoria as a third pole in mood disorders [25]. He ultimately adapts this vision to mixed states as conceptualized by Mentzos. During stable mixed states, mood can then evolve towards one of the three poles depressed, euphoric, or irritable. This can lead to the manifestation of associations between anhedonia/activation and euphoria/inhibition, but also the association of mood dysphoria with manic activation or depressive inhibition [26].

During unstable mixed states, however, mood oscillates rapidly and is anarchic between these three poles of mood, but in a desynchronized way compared to the oscillations of activity. When the instability is slight, the picture can easily evoke an anxiety disorder, a conversive disorder, or a personality disorder of the histrionic type or borderline. On the other hand, at high levels of instability, the picture is different and impressive and can lead to the appearance of psychotic symptoms. This loss of contact with reality could be explained by the incessant oscillations of the threshold of emotional reactivity and perceptual thresholds to different stimuli [21].

The resulting visual, coenesthetic, or auditory disturbances can range from simple strangeness to hallucinations, including derealization, depersonalization, or catatonia. It is therefore necessary to emphasize once again the trans-nosological nature of this concept of unstable mixed state which seems to concern mood disorders as much as mental psychotic disorders. The deepening of Kraepelin's theory of mixed states does not benefit ultimately not of a considerable impact. The enrichment is nevertheless present but the redirection towards a trans-nosological concept clearly reduces the interest in the

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states mixed. However, certain aspects of the work of Mentzos and Berner remain important currently in the study of the relationship between mixed states, bipolar disorders, and schizophrenia [27].

Mixed states today

Entry into international classifications: The first diagnostic criteria for mixed conditions come from the diagnostic criteria for research [28], wanting to be free from any etiopathogenic a priori that will inspire the development of the first version of the DSM (Diagnostic and Statistical Manual of Mental Disorders). According to this classification, mixed-state diagnosis requires validation criteria for a manic episode and those for a depressive episode.

Mixed states appear in the DSM in its third revised version in 1987 (DSM III-R). Their definition then reflects a certain hesitation, attempting a sort of consensus between numerous perspectives [29]. Thus, these criteria are strict as to the degree of associated depression since the complete criteria of a major depressive episode. On the other hand, the criterion of minimum duration of symptoms of depressive symptoms is reduced to one day while manic symptoms must be present for at least two weeks. Regarding the temporal relationship between manic symptoms and depression, the simultaneous presence and rapid alternation (a few days apart) are accepted which does not distinguish unstable forms from stable forms. Mixed states then appear to be considered a subtype of mania with one or more irruptions of depression for which stability is not obligatory. They also already suggest some differential diagnostic problems with, on the one hand, the thymic lability of the manic state, and on the other hand rapid cycles.

It is precisely to overcome these problems that the DSM-IV clearly restricts the definition. Only the simultaneous association of the two disorders is then retained, and this during the least a week practically every day. Episodes induced by antidepressants are now considered separately as a "mood disorder induced by a substance, with mixed characteristics", but the symptoms that have a mixed appearance occurring during pharmacological treatment of a manic state are not eliminated [30].

Emphasis is also placed on the severity of access without taking into account the forms of incomplete symptoms such as mixed hypomania or episodes borrowing symptoms of manic and depression without meeting the criteria for both syndromes. However, the biggest limitation of this classification system is the lack of consideration of symptoms common to mania and depression. Indeed, out of the nine items, five of which are necessary to establish the diagnosis of a major depressive episode, four are possibly encountered in mania: weight change, sleep disturbances, disturbances psychomotor disorders, and reduced ability to think or concentrate. It is therefore enough to bring together a single specific criterion for a major depressive episode in a patient with a manic state to meet mixed state criteria. This definition is retained for the latest revised version of the DSM: DSM-IV-TR.

The international classification of diseases includes for the first time mixed states in its tenth version. The mixed episode is then characterized by the presence of hypomanic, manic, and depressive symptoms, intertwined or rapidly alternating (within a few hours), these symptoms persist for at least two weeks, ICD-10 and DSM-IV are therefore divergent, both in terms of duration (one week versus two) and the co-occurrence of disorders. The ICD-10 retains the rapid alternation of the DSM-III-R but the scale of a few hours which makes the distinction even more difficult with the lability of mood, which is frequently present in mixed states. On the other hand, the advantage in relation to the DSM-IV is the consideration of mixed hypomania and mixed episodes of less intensity [31].

The contribution of scientific work: Since the end of the seventies, two types of work have contributed to renewing interest in mixed states: semiological studies, showing the frequency of the association of manic and depressive symptoms in acute mood episodes, and studies evaluating the therapeutic effectiveness of antidepressants and mood stabilizers, thus showing their limits in these cases [32].

Goodwin and Jamison, summarizing studies over seventy years, concluded in 1990 that depression and irritability are more common than euphoria in manic patients [33]. These results agree with those of Prien, et al. [34], who, on a series of 103 maniacs, found only 33% of purely euphoric mania, the rest being manias presenting a more or less high number of depressive symptoms on the Hamilton scale. All of these studies highlight increased therapeutic difficulties in cases of diversity, in particular, less effective lithium than in pure mania.

About ten years later, Koukopoulos is interested in certain forms of episodes depressive characterized by the presence of hypomanic symptoms, for which the prescription of antidepressants would prove harmful, worsening the clinical picture [35]. He opens thus the path to several semiological studies on depression: Benazzi noted in 2001 on a cohort of bipolar II and unipolar depressed patients the presence of at least one hypomanic symptom in 90% of cases and the presence of at least three symptoms in 48.7% of patients [36]. These results are confirmed by Perugi and Akiskal on a population of bipolar I patients depressed in the same year [37]. A poor response to treatment antidepressants is also often observed in these forms of mood episodes including symptomatology seems rather improved by mood stabilizers or electroconvulsive therapy [38].

The role of temperaments according to Akiskal: Akiskal (1992) offers an interesting enrichment of Kraepelinian and Hamburgers on mixed states [39]. To do this, he uses his work on temperaments emotional [40]. Some clarification therefore seems necessary on the notions of temperament, character, and personality before delving deeper into this data. On this innate organic disposition is grafted the character, which is an imprint on him. It designates all the events and exchanges that the subject performs with its environment [41]. The ongoing interactions between temperament and character appear to modify in return this natural expression of genes. The subject

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elaborates therefore secondarily his personality in a later time of development, by a composition between his temperament and the acquired characteristics of his character.

At the thymic level, Akiskal takes up the idea of fundamental states initiated by Griesinger in 1845 and adapted by Kraepelin in 1913 and therefore isolates four affective temperaments: hyperthymic, cyclothymic, dysthymic (or depressive), and irritable. They can then be considered as a factor of vulnerability to thymic pathologies, which can influence their course, as prodromes or premorbid states, but also as attenuated forms of mood disorders [42].

Proposals for new definitions

Dysphoric mania according to McElroy: The relevance and adequacy of international classification systems with practice clinical are discussed by certain authors. Indeed, the wrong response of a manic state to traditional treatment with lithium seems linked to the presence of depressive symptoms rather than the presence of a complete depressive syndrome.

A decisive synthesis work is carried out by McElroy, et al. whose objective is then to establish an exhaustive review concerning the clinical characteristics, demographic, evolutionary, biological, familial, comorbidity, or response therapy of mixed states. This general review concerns seventeen studies published between 1969 and 1992 bringing together a total of 981 manic patients. It appears from these analyses that 50% of manic patients are resistant to lithium treatment. These patients usually have depressive symptoms and are particularly vulnerable to suicide [43].

The course of bipolar illness seems unfavorable in the event of a first mixed episode and the association with alcoholism, substance abuse and neuropsychiatric abnormalities (migraine, epilepsy, brain tumors, and neurological diseases) is common in cases of mixed. Finally, these states often seem to be induced by antidepressants [44]. In her conclusion, McElroy questions the relevance of the distinction between mixed state and pure mania [45]. Indeed, some data seem to distinguish them, but others suggest mixed states such as a particular form of mania or a transitional state between depression and mania. McElroy, on the other hand, argues for the excessive variety of definitions and their unsuitability for practice. It therefore proposes new criteria in order to standardize the type of patients included in this diagnostic category which she calls "dysphoric mania" of which the prevalence is then 31% among all; the term "mania" rather than "state" reflects the author's ambivalence regarding the need for distinction between mixed states of mania. This definition, however, has the merit of erasing certain shortcomings of those of the DSM, starting with taking into account certain forms of lesser intensity [46]. Indeed, it is no longer necessary to meet the criteria complete manic episode or major depressive disorder. It is enough to bring together a minimum of those of the hypomanic episode and at least three depressive symptoms to validate the diagnosis of dysphoric mania [47]. Furthermore, these depressive symptoms exclude those encountered in mania (insomnia, decreased appetite, agitation psychomotor, and reduced power of concentration). McElroy's criteria seem then much more representative of the tables observed in practice. On the other hand, the problem of temporality is not resolved since, despite the necessary simultaneity of manic and depressive symptoms for at least twenty-four hours, their alternation in a few minutes is accepted. Here again, the distinction with the ability of the mood of manic states is far from obvious. The term "dysphoric mania" also suffers from the variability in the meaning of the term "dysphoria" depending on the different schools [30]. These diagnostic criteria from the University of Cincinnati still remain an advance important in developing the definition of mixed states.

Mixed depression: However, McElroy's criteria do not yet take into account all states' mixed conditions observed in the clinic. Indeed, most studies of the time are interested in the presence of depressive symptoms during manic states [48]. But from observations and the work of Koukopoulos, the question of manic symptoms (or hypomanic) during depressive states will gradually arouse more and more interest. From 1992, based on several cases, he described a state that he considered mixed and which he named "excited anxious depression" in 1995. For him, it is a major depressive episode with signs of excitement without psychomotor slowing and with the presence of a high emotional expressiveness that does not meet the DSM mixed condition diagnosis [49]. These cases are described from subjects presenting major depression worsening under antidepressant treatment and improving with neuroleptics, lithium, anticonvulsants, or benzodiazepines but also electroconvulsive therapy. These subjects are according to Koukopoulos often considered "histrionic" or presenting another personality disorder with secondary depression [50]. The associated suicidal risk would be high and this common picture: 30% of female depressions and 16% of male depressions. Several works will follow, revealing the high frequency of manic symptoms and hypomanic in depression, equivalent to that of depressive symptoms in mania. However, the manic or hypomanic syndrome is rarely complete, not validating therefore not the diversity criteria of the DSM. Yet the recognition of these states seems capital in order to avoid the prescription of antidepressants. Benazzi proposed on several occasions in 2001 and 2003 a definition of mixed depression as a major depressive state with at least Benazir three hypomanic symptoms [51,52]. This mixed depression thus defined then represents a sort of mirror with the mixed mania defined by McElroy [53]. This concept, however, clashes still today to the difficulty of attributing these symptoms of excitation. Uncertainty remains in fact about their anxious or manic origin and the diagnosis differential of anxious depression often remains difficult to eliminate.

Mixed states according to Perugi: The tendency then is to divide mixed states into mixed manias and mixed depressions, depending on the dominant polarity, Perugi, et al. (1997) conducted a study with the aim of testing the validity of a new unifying definition of mixed states. These criteria particularly emphasize a state of emotional instability in which symptoms depressive and manic appear simultaneously or alternate. This emotional instability prolonged for at least two weeks would

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DOI: https://dx.doi.org/10.17352/2455-5460.000089

lead to fluctuation of symptoms, lability, irritability, and diurnal variations, and would be the clinical expression of dysregulation neurophysiology underlying bipolar disorders. The mixed states could then be considered the most eloquent expression of this dysregulation. In this study [54], 143 patients meeting the mixed state criteria according to Perugi are compared to 118 manic patients. Among the 143 mixed patients, only 54% meet the criteria for mixed status according to the DSM-IV, the remainder being distributed between major depressive episodes (17%) and manic episodes (26%). These three subgroups do not differ in evolutionary or temperamental characteristics. On the other hand, differences were found between the 143 patients and the 118 maniacs. Mixed subjects according to this new definition would present longer but fewer episodes than those of manic patients, with a less cyclical course and an interictal period of poorer quality. They also often begin the illness with an episode mixed. Temperaments would be especially hyperthymic in the group of patient maniacs while the group of mixed patients would include an equivalent proportion of depressive and hyperthymic temperaments. These data then seem to go in the direction of Akiskal's theory formulated five years earlier on the occurrence of a mixed state when the mood episode and temperament are of opposite polarity. These new criteria proposed are clearly inspired by the Kraepelinian vision of mixed states. We find in effect in criterion A the three domains of psychic life individualized a hundred years earlier (mood, thought, activity), the symptoms having to alternate between the two extremes of these three areas. Criterion B includes the notions of irritability and impulsivity but does not escape the catalog phenomenon that is neither practical nor convincing and the question of the alternation of symptoms facing thymic lability is still not resolved [55]. In total, this definition is all the same a good synthesis of the different currents and opinions on mixed states from Kraepelin via Mentzos, McElroy, and Akiskal [56].

Mixed states according to Dayer: Dayer was inspired by Berner's theories to propose a definition in 2000 originally including dysphoria as a syndrome as important for diagnosis as manic and depressive syndromes [57]. This dysphoric syndrome is first of all defined in the German way, that is to say, solely articulated around the notion of irritability by excluding any depressive element. Three types of mixed states are then proposed (paintings.). The first corresponds to the mixed state as defined by the DSM-IV, i.e. by the presence of complete manic and depressive syndromes. Type II-M requires the presence of a complete manic syndrome, at least three depressive symptoms (except psychomotor agitation), and a dysphoric syndrome, all of which must be present at least twenty-four hours. Type II-D represents a major depressive state with at least one hypomanic symptom (apart from psychomotor agitation and irritability) and a syndrome dysphoric, all this simultaneously for at least twenty-four hours. The alternation of symptoms in terms of a few minutes is still accepted. It is clear that this definition, more syndromic than physiological, contributes little to the level of understanding of the concept as highlighted by Swann [58]. However, the individualization of irritability versus mania and depression provides an interesting pattern, given its frequent manifestation in mixed states.

Discussion

From international classifications to the criteria proposed by certain authors, the objective remains above all the standardization of data, in order to be able to compare studies with each other in avoiding basing oneself on a theoretical presupposition [59,60]. There are, however, numerous limitations to start with the absence of specific diagnostic criteria and the systematic summation of different syndromes or symptoms, which is also what its name implies. The concept of mixed states therefore still remains to be clarified which will probably not be possible only with the contribution of biology and genetics. At present, diversity remains a source of discrepancies, questions, and confusion [61].

Faced with problems concerning the diagnosis of mixed states, an evaluation scale was developed in 2009. This novel scale appears to capture the key features of mixed states. The two-factor solution fits well with previous models of bipolar disorder and concurs with the view that mixed states may be more than the sum of their parts [62].

Another self-administered rating scale "G.T. MSRS" has been designed to improve the clinical effectiveness of clinician psychiatrists, by enabling them to make an early "general" diagnosis of mixed states. Mixed episodes are difficult to diagnose and very painful for the individual [63]. This scale of 11 items:

1) Hyperactivity (euphoria) quickly alternating with periods of ....

psychomotor retardation (apathy)?

If Yes, for how many days/weeks? ....

2) Depressed mood together with irritability and/or ....

internal tenseness?

If Yes, for how many days/weeks? ....

3) Substance abuse (alcohol and/ or drugs)? ....

If Yes, for how many days/weeks? ....

4) Disorders of appetite? ....

If Yes, for how many days/weeks? ....

5) A sense of despair and suicidal ideation? ....

6) Anhedonia and widespread apathy? ....

7) Delusions and hallucinations? ....

8) Hyper or hypo-sexual activity? ....

If Yes, for how many days/weeks? ....

9) Insomnia (or sleep fragmentation) or hypersomnia? ....

If Yes, for how many days/weeks? ...

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10) Reduced ability to concentrate and mental overactivity? ....

If Yes, for how many days/weeks? ...

11) Gastrointestinal disorders (colitis, gastritis), headaches, and

various somatic symptoms (muscular tenseness; tachycardia)? ....

If Yes, for how many days/weeks, and what of those symptoms? ...

It could be useful to precise the diagnosis of mixed states. It is now available and validated in three languages Russian, English, and Italian [64]. The scale was also used in a retrospective manner [65]. Unfortunately, the use of such scales is not very popular, indeed many psychiatrists are still reluctant to diagnose a mixed condition." Unipolar depression" is not dead, although it is often punctuated by mixed states [66].

Mixed states appear today in international classifications and are defined there as the summation of manic and major depressive episodes, both complete. Considering these definitions as too restrictive, some authors propose other broader and very variable criteria. Recent data mainly concerns mixed states meeting the criteria of the manic episode. Epidemiological, clinical, therapeutic, and evolutionary data according to different studies do not favor a distinct category of mania. The particularities of this subtype of mania seem to be limited to a female predominance, increased suicidal risk, and decreased response to lithium. Certain hypotheses raised about the nature of these mixed states are not verified: that of a transitional manifestation, of a superposition of two thymic episodes, of an ultra-rapid alternation between two thymic poles, or even an extremely severe form or late mood episode.

Current definitions of mixed states are numerous and not very specific. The help provided to clinicians is therefore insufficient to deal with the numerous differential diagnoses which do not generate the same therapeutic approaches. The need for consensus on a categorical definition of mixed states currently encounters insufficient explanatory data on their nature and occurrence. Genetic, biological, and imaging studies could in the future provide some answers. In the meantime, it seems preferable for the clinician to refer to the vision Kraepelinian of mixed states, which combines dimensional and categorical considerations of mixed states.

Conclusion

Probably the most disturbing episodes are those including both symptoms of mania and depression, symptoms occurring at the same time or alternating quickly during the day. The people are excitable or agitated as in mania but also feel irritable and depressed. They are often difficult to diagnose. Due to the combination of high energy and depression, mixed episodes pose the greatest risk of suicide. In a given person, one type of episode often begins with the same type of symptoms called prodromes for example a reduction in sleep time or fatigue. It is important to know your own prodromes in order to take charge of the episode as quickly as possible before the table is complete.

Mixed depression is a clinical concept that deserves to be known to clinicians because the clinical and therapeutic implications are important. It corresponds to a picture straddling classic bipolar disorder and forms on the borders of the bipolar spectrum. The DSM-5 introduces the notion of elements of mixedness, and proposes substantial changes for mixed states, allowing the consideration of mixed depression. If these changes seem interesting at first glance, unfortunately, the relevance of these criteria does not stand up to further examination. The creators of the DSM-5 were probably concerned with compensating for the inadequacies of the DSM-IV, to take into account the clinical importance of mixed states. The proposed criteria partly meet these objectives. But the reflection was not, in our opinion, pushed to the end, particularly, by avoiding an in-depth semiological analysis. Finally, the diagnostic criteria are not very clinically relevant, and in the perspective of progress in epidemiological and therapeutic knowledge of mixed depression, the change in the DSM-5 could be a step for nothing. Making the diagnosis remains unlikely from a rigorous scientific perspective, the criteria being not very suitable, and the consequence could be a halt to the development of this type of research.

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