

Mixed states: still a modern psychopathological syndrome?

A. Tortorella¹, U. Albert², A.M.A. Nivoli³, A. Erfurth⁴, F. Colom⁵, G. Maina⁶

¹ Department of Psychiatry, University of Naples SUN, Italy; ² Rita Levi Montalcini Department of Neuroscience, Anxiety and Mood Disorders Unit, University of Turin, Italy; ³ Psychiatric Clinic, Department of Experimental and Clinical Medicine, University of Sassari, Italy; ⁴ 6th Psychiatric Department, Otto Wagner Hospital, Wien, Austria; ⁵ Bipolar Disorder Unit, Hospital Clinic, IDIBAPS, CIBERSA, University of Barcelona, Spain; ⁶ Department of Mental Health, "San Luigi-Gonzaga" Hospital, University of Turin, Orbassano, Italy

Summary

Objectives

The aim of this review is to evaluate whether the DSM-5 concept of mixed features "specifier" provides a definition that reflects the richness and multiplicity of this psychopathological picture pointing out the historical development, clinical conceptualisation and proposed therapeutic approach to mixed states.

Methods

We review and discuss the recent evidence on the presence of mixed features during mania and depression and summarise findings on the conceptualisation of mixed states. Electronic searches of all English-language papers were performed in the MEDLINE and PUBMED database using and cross-listing key words: mixed state, mixed features, bipolar disorder, major depressive disorder, mania, hypomania, depression.

Results

The mixed categorical-dimensional concept used in the DSM-5 broadens the concept of mixed episodes, introducing substantial changes to the diagnosis of mixed states. This definition appears more appropriate for less severe forms of mixed states

Introduction

Mixed affective states are largely considered the simultaneous occurrence of manic and depressive features with a complex clinical presentation that frequently represents a real challenge for clinicians due to the evident difficulties in diagnosis, classification and treatment. The concept of mixed states introduced by Kraepelin was characterised by the presence of depressive and manic/hypomanic phases in manic-depressive patients and by the presence of a continuum between depressive and manic features. Though several authors had previously described the characteristics of mixed states, Kraepelin firstly provided a conceptualisation within a broader context, defining mixed states as the 'third polarity' of manic-depressive disorder and used this idea to consolidate his unified vision of this disorder. Through the years the concept of mixed states has

presenting clear and detectable mood symptoms with evident improvement compared to the DSM-IV, as the possibility of classifying depression "with mixed features".

Conclusion

The transition from the classical definition of mixed states to the one reported in the DSM-5 has determined a complex modification of the concept of mixed state. The DSM-IV-TR description, based on the co-presence of symptoms of opposite polarity, was extremely reductive and did not capture the sub-syndromal symptoms of the opposite pole experienced in bipolar and major depressive disorders. The DSM-5 definition of mixed features "specifier" represents a valid tool to improve the recognition and proper treatment of bipolar mixed patients, reducing misdiagnosis and mistreatment associated with chronic and repetitive exposure to antidepressants and sedatives, although the mixed categorical-dimensional concept does not adequately reflect some overlapping mood criteria, such as mood lability, irritability and psychomotor agitation.

Key words

Mixed state • Mixed features • Bipolar disorder • Major depressive disorder • Mania • Hypomania • Depression

been consolidated and the relevance of mixed states has been recognised, but the concept of a continuum between different affective states was excluded from the main psychiatric diagnostic systems (DSM and ICD). The failure of the DSM-IV-TR and ICD-10 in recognising mixed states together with the result of several studies on the topic encouraged many clinicians and researchers to reconsider the criteria for mixed episodes. In the DSM-5, the mixed episode as defined in DSM-IV-TR has been removed and sub-threshold non-overlapping symptoms of opposite polarity are identified using a mixed feature specifier to be applied to depression, mania and hypomania.

The history of the concept of mixed states

The first descriptions of a clinical condition that we currently would consider a mixed state appeared in the nine-

Correspondence

Alfonso Tortorella, Department of Psychiatry, University of Naples SUN, largo Madonna delle Grazie, 80138 Naples, Italy • Tel. +39 081 5666517 • Fax +39 081 5666523 • E-mail: alfonsotortorella@gmail.com

teenth century (Table I); however, traces of what is considered to be a “mixed state” are present in antique medical textbooks (especially Aretaeus of Cappadocia) and in some treatises on psychopathology in the 1700s¹. Heinroth, in his treatise entitled *Disturbances of Mental Life or Mental Disturbances*², was one of the first psychiatrists to explore mixed states in detail; he used a German term (*Mischungen*) translatable as “mix or mixture” to define psychopathological conditions in which discordant elements coexisted. Another German psychiatrist, Griesinger³, described states of mental alteration in which melancholic and manic elements coexisted (as in Heinroth’s descriptions), as well as forms that would be currently defined as rapidly cycling affective disorders. He defined such psychopathological conditions as “mid-forms” (*Mittelformen*), “in which a change from depression to the manic exaltation occurs”, and described “Melancholia with destructive impulses” and “Melancholia with long-lasting exaltations of volition”. In his view, then, mixed states could be often transitional forms.

In addition to the above authors, other European psychiatrists before Kraepelin described psychopathological conditions that had similarities to mixed states. For example, Jules Falret in 1861 described what he termed *État Mixte*, a condition characterized by “predominant ideas, often of sad nature, in the middle of an excitation state, simulating true mania”. However, none of the cited authors provided a precise categorisation of psychopathological conditions in the manic-depressive area, including mixed states, which first appeared with the works of Wilhelm Weygandt and Emil Kraepelin. These two authors first conferred nosographic autonomy to mixed states in the context of Manic-Depressive Insanity.

Emil Kraepelin first used the term “mixed states” (*Mischzustände*) (Table II) starting from the 5th edition of his *Textbook of Psychiatry*⁴, and maintained this term in the revised editions of the text^{5,6}. He recognised as a significant contribution to his categorisation the work of his apprentice Wilhelm Weygandt, author of a pioneering monograph on the subject, the first book in the psychiatric literature on mixed states. Weygandt first described three conditions under the term *Mischzustände* (Table I), and recognised that these mixed states had a favourable outcome compared to schizophrenia (*Dementia Praecox*) (“when we deal with manic stupor, agitated depression, and unproductive mania, we can foresee a highly favourable outcome”)⁷. Kraepelin, however, first provided a conceptualisation of mixed states within a broader context: he viewed mixed states as a ‘third polarity’ of manic-depressive disorder, and used this idea to consolidate his unified vision of this disorder (*The inner relationship of the apparently opposing conditions becomes most clear through the experience that there are fits of circular insanity in which excitement and depression are mixing in an inextricable way*)⁶. The possible co-occurrence 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 and Weygandt opinion, were involved in manic-depressive illness. The three domains consisted of mood (emotion), ideation (intellect, or thought) and motor activity (volition or *psychomobility* in Weygandt terminology). Each domain can fluctuate

TABLE I.
The development of the concept of mixed states (before Kraepelin).

Author	Definition
Heinroth, 1818	MISCHUNGEN (mixtures) – hypo/asthenias
Griesinger, 1845	MITTELFORMEN (middle forms) “in which a change from depression to the manic exaltation occurs”: <ul style="list-style-type: none"> • melancholia with destructive drives • melancholia with long-lasting exaltation of volition
Falret, 1861	ÉTAT MIXTE (mixed state) “predominant ideas, often of sad nature, in the middle of an excitation state, simulating true mania”
Weygandt, 1899	MISCHZUSTÄNDE (mixed states): <ul style="list-style-type: none"> • manic stupor (elevated mood with psychomotor inhibition and decreased ideation) • agitated depression (depression with flight of ideas and agitation) • unproductive mania (elated mood with increased motor activity and inhibition of thinking) <p>“When we deal with manic stupor, agitated depression, and unproductive mania, we can foresee a highly favourable outcome”</p>

TABLE II.
Kraepelinian view of mixed states.

Kraepelin, 1893-1913	
Tripartite model: 1. affect 2. psychomotor activity 3. associative processes	MISCHZUSTÄNDE (mixed states) or MISCHLFORMEN (mixed forms): 6 types
Two general classes of mixed states	1. <i>Transitional forms</i> : a stage 2. in between, when depression changes to mania and vice versa
	3. <i>Autonomous forms</i> : mixed disorder on its own

around baseline in two directions: overall increase and decrease, giving rise to 2 states characterised by all 3 domains being in the same phase (classic mania and depression), and 6 mixed states, uniquely defined by asynchronous phase shifting of the 3 domains. Thus, he described the different mixed states of a) “manic depression or anxiety” (depressed mood, flight of ideas and hyperactivity), b) “excited depression” (depressed mood, inhibition of thought and hyperactivity), c) “unproductive mania” (euphoria, inhibition of thought and hyperactivity), d) “manic stupor” (euphoria, inhibition of thought and apathy), e) “depression with flight of ideas” (depressed mood, flight of ideas and apathy) and f) “inhibited mania” (euphoria, flight of ideas and apathy) (Table III).

The subsequent revisions of Kraepelin and Weygandt of the concept of mixed states partially overcame this tripartite model of the psyche, favouring a dimensional approach that involved a broadening of the concept to the

infinite possibilities that a mixture of manic and depressive elements could manifest in the same patient⁸. In their opinion, apart from multiform phenomenal appearances, the essential point for diagnosis of a mixed state was the co-occurrence of manic and depressive elements/symptoms/signs in a patient with clinical features that reflected manic-depressive disorder, and in particular a previous history of manic and depressive episodes (according to Kraepelin, cyclicity – recurrent episodes – defines the illness, irrespective of polarity).

Beyond the six subtypes of mixed states, Kraepelin distinguished between two general classes of mixed states: “transitional” forms, i.e. clinical pictures that frequently arise in the transition from mania to depression and vice versa (reflecting Giesinger’s vision of mixed states), and “autonomous” forms, i.e. those that appear and manifest as such (Table II). According to Kraepelin, these “autonomous” mixed states were the most unfavourable ones, presenting with a longer course and the tendency to become chronic⁹.

The concept of Kraepelinian mixed states was the object of harsh criticism by other prominent European psychiatrists: Karl Jaspers¹⁰, for example, refused the concept of a mixed state from a methodological standpoint, and Kurt Schneider¹¹ 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. These are only two examples of the general lack of interest in mixed states that manifested after 1920s, defined by Marneros⁹ as the “period of ignorance”, evidenced by the dramatic decrease in the number of publications on the subject.

One of the few exceptions was a monograph by the German psychiatrist Mentzos, who utilised some con-

TABLE III.
Kraepelinian Mixed States (1913).

	Mood	Motor activity	Ideation
1. Depressive or anxious mania (<i>depressive oder angstliche Manie</i>)	-	+	+
2. Excited depression (<i>erregte Depression</i>)	-	+	-
3. Unproductive mania or Mania with thought poverty (<i>ideenarme Manie</i>)	+	+	-
4. Manic stupor (<i>manischer Stupor</i>)	+	-	-
5. Depression with flight of ideas (<i>ideenfluchtige Depression</i>)	-	-	+
6. Inhibited mania (<i>gehemmte Manie</i>)	+	-	+

cepts 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 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 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 “colours” thoughts of consciousness. In this model, mania and depression are seen as concordant alterations of boost and mood (increased energy and euphoric mood vs. decreased energy and depressed mood), while mixed states are viewed as discordant alterations (e.g. increased energy and depressed mood). 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 (unstable). 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 in the international nomenclature¹².

The revival of mixed states (what Marneros calls “the renaissance” of mixed states) started from the beginning

of the 1980s, the initial stages of which can be seen in the “Vienna Criteria”¹³, 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 unstable, and proposed precise diagnostic criteria for the identification of both (Table IV). These criteria were based on a well-defined psychopathological model known as Janzarik’s concept of structural-dynamic coherence¹⁴. According to this model, similar to the idea of Mentzos, mixed states were perceived as the product of unstable alteration of the “dynamic”. The term dynamic referred to the mixture of two components that normally form the individual’s personality: one that constitutes the functional substrate of the temperament and a “structural” form that encodes both innate and acquired behavioural patterns. A strict adherence to this model, which is provocative and challenging, limited the use of the Vienna Criteria to research purposes. Nonetheless, these criteria represented a turning point that influenced and stimulated research in the forthcoming years, giving rise to a large number of publications, especially in the US and Europe. Among these, Akiskal in the US and Koukopoulos in Italy, greatly contributed to the so-called renaissance or revival of mixed states¹⁵. Akiskal postulated that mixed states are not a mere overlap of depressive and manic opposite symptoms, but rather that they arise from the combination of an affective episode with a dominant temperament of opposite polarity; mixed states may arise: 1. when a temperament intrudes into an affective

TABLE IV.

Vienna school criteria for stable and unstable mixed states (from Berner et al., 1983, modified).

Unstable mixed states	
A.	Appearance of at least one of the following rapidly cycling changes following a period of normal functioning: <ol style="list-style-type: none"> 1. mood changes rapidly cycling from 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* <ol style="list-style-type: none"> 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): <ol style="list-style-type: none"> 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* <ol style="list-style-type: none"> 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.	

episode of opposite polarity (e.g., depressive temperament into mania or hyperthymic temperament into major depression), or 2. when the instability of a cyclothymic temperament transforms a major depression into a mixed picture¹⁶. Koukopoulos, on the other side, contributed to the understanding of agitated depression as a mixed state, and challenged the notion of polarity as the basic criterion for bipolar disorder¹⁷. He defined “mixed depression” a depression occurring with excitation, meaning manic symptoms (like flight of ideas or talkativeness), but also agitation, irritability and rage, marked anxiety and suicidal impulsivity. Koukopoulos considered this highly agitated and tense depressive state as the opposite of melancholia, which is markedly psychomotor retarded and not irritable or rageful. Unfortunately, Koukopoulos’ view was not fully endorsed in tge DSM-5.

Mixed states in DSM-IV-TR

Mixed Mania

In the scientific literature there is no univocal definition for mixed mania, also known as depression during mania or dysphoric mania, and the clinical presentation has been described in several different ways. The classic definition includes the presence of a complete manic syndrome together with the presence of at least three depressive symptoms, but, using a more unrestricted approach based on the presence of two depressive symptoms, the frequency of the diagnosis of mixed mania significant increases. Compared to non-mixed episodes, the symptomatology of mixed manic episodes includes the presence of a greater mood lability and irritability, dysphoric mood, anxiety, suicidality and cognitive impairment. On the other hand, these patients report less severe typical manic symptoms, such as euphoria, grandiosity, decreased need for sleep and involvement in pleasant activities. Frequently, the most severe forms are characterised by the presence of psychotic symptoms, such as delusions, hallucinations and motor disturbances that make it difficult to differentiate these forms from schizophrenia and other psychoses¹⁸.

Mixed depression

In the same way, a consistent number of depressed patients show manic symptoms, without a clear, univocal definition for this condition called mixed depression, also known as agitated depression or dysphoric depression. The frequency of this form is variable ranging between 20 and 70%, and this wide fluctuation mainly depends on the different tools used for the assessment of affective symptomatology. The classic definition includes the presence of a complete depressive syndrome together with the presence of a minimum of two or three

manic/hypomanic symptoms. Psychomotor agitation is required for the diagnosis of agitated depression. Compared to non-mixed episodes, the symptomatology of mixed depressive episodes includes the presence of a greater irritability and mood lability associated with mental and psychomotor overactivity, restless agitation and increased suicidality¹⁹.

Mixed states in DSM-5 and ICD-10

Both the American Psychiatric Association classification system (the *Diagnostic and Statistical Manual for Mental Disorders* - DSM, now in its fifth edition)²⁰ and the World Health Organization (*International Classification of Diseases* - ICD-10)²¹ provide a definition of mixed states far from the richness and multiplicity of psychopathological descriptions reviewed in the previous paragraphs. The DSM classification, however, made significant changes in the description of mixed episode from DSM-IV-TR²² to the new “with mixed features” specifier in DSM-5.

According to DSM-IV-TR criteria, it was only possible to diagnose a mixed episode if the criteria for both a manic and a major depressive episode (except duration – only one week was required) were met. In the ICD-10, the term “mixed episode” indicates the co-occurrence or rapid cycling of prominent depressive and manic or hypomanic symptoms for at least 2 weeks. The 11th revision of the ICD will likely revise the concept of mixed episode following DSM revision. The two classification systems simplified the concept of “mixed states” and grouped them into a single diagnostic category (mixed episode); this simplification, however, brought 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 was excluded, contrary to common experience in clinical practice. Moreover, the definition of mixed episode as the coexistence of full depressive and manic episodes meant that the presence of few symptoms of opposite polarity in the context of predominant manic or depressive episode was not considered. A third limitation of the DSM-IV-TR criteria for mixed episode was the exclusion criterion C: “the symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication, or other treatment) or a general medical condition (e.g. hyperthyroidism)”; affective episodes temporally correlated with the use of substances (drug of abuse, antidepressants, somatic therapies) and with prominent mixed features are, on the contrary, very common in clinical

practice and could not be correctly recognised and diagnosed according to DSM-IV-TR criteria²³.

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 the diagnosis is not specified. A second limitation of ICD-10 criteria is the poor sensitivity relative to temporal criteria: ICD-10 requires a duration of two weeks, which is considered to be excessive²⁴.

In the DSM-5, a revision was made on criteria for mixed episodes: the new criteria have replaced the category "mixed episode" (extremely narrow definition of mixed states) with the specifier "with mixed features" (broad definition). The new classification will capture subthreshold, non-overlapping symptoms of the opposite pole using the new "with mixed features" specifier to be applied to manic episodes in bipolar I disorder (BDI), hypomanic and depressive episodes experienced in BDI, BD type II and major depressive disorder. In the new mixed categorical-dimensional concept used in the DSM-5, the mixed features specifier: 1) would apply not only to manic episodes (as in the DSM-IV), but also to hypomanic and major depressive episodes (even in a MDD longitudinal diagnosis), and 2) broadens the concept of mixed episodes as the threshold for the diagnosis is lowered to ≥ 3 symptoms of opposite polarity. 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 current DSM-5 definition replaced the diagnosis of "mixed episode" with a "mixed-features specifier" which should be applied to episodes of major depression, either hypomanic or manic, together with, or in close juxtaposition, with at least three symptoms of opposite polarity. The mixed features specifier may be considered when patients with manic or hypomanic symptoms show at least three depressive symptoms and, conversely, if a depressed patient shows manic or hypomanic symptoms. Patients meeting criteria for mania and depression (the mixed episode of DSM-IV-TR) in the DSM-5 satisfy the criteria for "mania with mixed features", highlighting the greatest functional compromise and clinical severity of mania over depression²⁰.

The ICD-11 criteria will be substantially similar to those of the DSM-5, with the difference that the term "mixed episode" will be maintained and further divided into six subtypes depending on the current predominant episode and presence of psychotic symptoms²⁵. For example, the possible diagnoses will be "actual mixed episode, current mania with depressive symptoms, psychotic (or non-psychotic)"; a similar scheme will be used for hypomanic and depressive episodes.

Epidemiology

The diagnosis of mixed affective states represents a challenge for clinicians for the different definitions and the frequency of mixed and non-mixed manic subtypes, which are mainly dependent on setting, interview methods, assessment and criteria adopted. This problem is the main cause of the differences of prevalence rates found in the different studies. Akiskal²⁶ stated that mixed states are a common presentation of BD, but a careful evaluation highlights large differences among mixed manic or depressive states and a huge variability linked to the criteria used for the evaluation.

For mixed manic states, the prevalence rates are usually lower when adopting the ICD-10 and DSM-III/IV criteria, ranging from 19% (ICD 10, 33) to 6.7-28%^{27 28}. Prevalence rates of mixed depressive states are somewhat scarce and the variability for manic mixed state is similar to that found for mixed depressive states. Indeed, across studies, the differences fluctuate between 20 and 70%, and the frequency of mixed and non-mixed depressed subtypes is mainly dependent on setting, interview methods, assessment and criteria used²⁹. Data on gender generally demonstrate the presence of differences between subtypes, confirming the presence of a female predominance in the mixed manic state ranging from 63 to 69% and the absence of gender differences in the prevalence of mixed depression³⁰.

Treatment

The pharmacological treatment of mixed bipolar states remains a challenge for clinicians. Results from studies and clinical practice show that mixed presentations in bipolar disorder have a poorer pharmacological response compared with pure episodes, and combination therapy is often required^{31 32}. An additional challenge in the treatment of mixed states arises from the need to concurrently treat both manic and depressive symptoms: depressive-switch risk often may derive from an antipsychotic monotherapy centred on improving manic symptoms³³, particularly in the case of conventional antipsychotics and other drugs with a high polarity index³⁴. Conversely, antidepressants can induce a manic/mixed switch³⁵. The lack of standard definitions of mixed states, the low reliability of assessment measures and the DSM-IV-TR definition (considering mixed episodes as variants of mania) are further potential reasons for the lack of adequate research in this area. The majority of data is derived from post-hoc analyses of studies including manic patients and from a handful number of double-blind, placebo-controlled studies³⁶. Combinations of atypical antipsychotics and conventional mood stabilisers, particularly divalproate, have the most consistent evidence³⁷.

Even if most second generation antipsychotics (SGAs) have been approved for the treatment of mania, only a few guidelines make specific recommendations for managing mixed episodes, given the paucity of evidence-based data³². Available data show that asenapine, olanzapine and valproate have positive effects in patients with mixed mania in placebo-controlled trials³⁸⁻⁴⁰, and aripiprazole and ziprasidone show separation from placebo in pooled analyses⁴¹⁻⁴². There are a few positive data on the use of quetiapine in acute mixed states⁴³. Ziprasidone has been tested in depressive mixed states⁴⁴. Asenapine and olanzapine have shown positive effects in combination with valproate in patients with mixed mania. The guidelines of the *World Federation of Societies of Biological Psychiatry*⁴⁵ recommend lithium in pure euphoric mania rather than in mania with dysphoric or depressive symptoms, while carbamazepine is suggested for mixed states or dysphoric mania, and valproate for both manic/depressive dysphoric features during a manic episode. Among typical antipsychotics, haloperidol may exacerbate depressive and dysphoric symptoms in mixed mania. The guidelines of the *British Association for Psychopharmacology* (BAP)⁴⁶ recommend oral administration of antipsychotics or valproate as first-line treatments for severe mixed episodes, in patients not already on long-term treatment. The CANMAT and ISBD treatment guidelines⁴⁰ suggest aripiprazole, paliperidone ER, olanzapine and asenapine monotherapy as first-line choice in mixed mania. The NICE guidelines suggest that patients with mixed states should be treated as if they have an acute manic episode, and no antidepressants should be prescribed.

Data on the use of SGAs in the treatment of acute mixed episodes are limited, both in monotherapy and in combination. In one randomised trial of a mixed episode cohort, Houston et al.⁴⁷ reported earlier reduction of both manic and depressive symptoms of mixed episodes in patients treated with adjunct olanzapine over a 6 week period compared to adjunct placebo.

Muralidharan et al.⁴⁸ published the first meta-analysis of all randomised double-blind placebo-controlled clinical trials on the efficacy of SGAs (as monotherapy or in combination with mood stabilisers) in treatment of mixed episodes, according to the DSM-IV criteria. The meta-analysis showed that SGAs in combination with mood stabiliser were superior to placebo plus mood stabiliser. The authors specified that SGAs were superior to placebo in the treatment of mixed episodes, particularly for manic symptoms, while moderately effective in reducing depressive mixed symptoms. Nonetheless, the interpretation of results should take into consideration that clinical trials included patients experiencing mixed episodes as defined in the DSM-IV, which considers mixed episodes

as a type of mania. The DSM-5 has eliminated mixed episodes as a category, while including mixed features as a course specifier for both manic and depressive episodes. The results of this meta-analysis suggest that SGAs are clearly effective in treating manic symptoms in mixed episode patients with syndromal mania and syndromal depression. However, findings on depression are limited and further studies are needed to establish the efficacy of SGAs in treating depressive symptoms in manic patients with mixed features.

Ouanes et al.⁴⁹ in a recent review demonstrated the overall efficacy of SGAs in mixed episodes. Antidepressant use is perhaps the most controversial issue in the treatment of bipolar disorder and the scientific literature is limited and controversial⁵⁰. Some studies support that the adjunctive use of antidepressants is not associated with an increased risk for switching to mania/hypomania or mixed episodes⁵¹, but others are at odds with these findings⁵², showing that antidepressants do not significantly increase the rate of enduring recovery from depression in bipolar I and II disorder. Nevertheless, there is a substantial consensus on avoiding antidepressant monotherapy in bipolar patients with mixed/cycling features or prior antidepressant-associated mania/hypomania⁵³. International guidelines give heterogeneous recommendation and take into consideration two potentially harmful effects of antidepressants, including the induction of hypomania/mania or mixed episodes and rapid cycling. However, a consensus exists in stopping the ongoing antidepressant medication during a mixed episode in both bipolar I and II patients⁵⁴.

Conclusions

Bipolar disorder has been the subject of significant revisions in the DSM-5. One of these major changes has been the removal of BD from the 'Mood Disorders' section and its inclusion in the new category of 'Bipolar and Related Disorders'. Another significant change concerns mixed states: the diagnosis of "mixed episode" has been replaced with a "mixed-features specifier" which should be applied to episodes of major depression, either hypomanic or manic, together with, or in close juxtaposition, at least three symptoms of opposite polarity. The mixed features specifier may be considered when patients with manic or hypomanic symptoms show at least three depressive symptoms and, conversely, when depressed patients show manic or hypomanic symptoms. Patients meeting criteria for mania and depression (the former mixed episode of DSM-IV-TR), will receive the DSM-5 diagnosis of "mania with mixed features", emphasising the greatest functional compromise and clinical severity of mania over depression.

The revival of the concept of mixed states will be hopefully fostered by changes in the DSM-5 definition, and is also a consequence of the renewed interest on this subtype of bipolar disorder. Of course, the current criteria of mixed states are not equivalent to the classical, Kraepelinian notion of mixed states and could have been improved. Both DSM-IV-TR definition of mixed states and the DSM-5 mixed features specifier show clear troubles, in particular in recognising severe mixed states, while the combinatorial model shows a greater sensitivity for the definition of less severe varieties of mixed states characterised by clearly identifiable symptoms. Moreover, the mixed categorical-dimensional concept used in the DSM-5 does not adequately reflect some overlapping mood criteria, such as mood lability, irritability and psychomotor agitation, considered among the most common features of mixed depression. The significant changes made in the DSM-5 will help researchers in studying the clinical characteristics of this subtype of bipolar disorder and in implementing effective treatment strategies. Guidelines for the treatment of mixed states, in fact, do not give clear indications for pharmacological or non-pharmacological treatments of mixed states, and the few available data are limited to post-hoc analyses and subanalyses performed in bipolar, mostly manic, patients.

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