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REVIEW ARTICLE

Mixed features: evolution of the concept, past and current definitions, and future prospects

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Mixed states address the relationships between episodes and the course of an illness, presenting significant clinical challenges. Recurrent affective disorders were described thousands of years ago as dimensional disturbances of the basic elements of behavior, combining the characteristics of what we would now consider manic and depressive episodes. It was recognized from the beginning that combinations of depressive and manic features are associated with a severe illness course, including increased suicide risk. Early descriptions of affective disorders formulated them as systemic illnesses, a concept supported by more recent data. Descriptions of affective disorders and their course, including mixed states, became more systematic during the 19th century. Structured criteria achieved importance with evidence that, in addition to early onset, frequent recurrence, and comorbid problems, mixed states had worse treatment outcomes than other episodes. In contrast to 2000 years of literature on recurrent affective episodes and mixed states, the unipolar–bipolar disorder distinction was formalized in the mid-20th century. Mixed-state criteria, initially developed for bipolar disorder, ranged from fully combined depression and mania to the DSM-5 criteria, no longer limited to bipolar disorder, of a primary depressive or manic episode with at least three symptoms of the other episode type. The challenges involved in understanding and identifying mixed states center largely on what drives them, including (1) their formulation as either categorical or dimensional constructs, (2) the specificity of their relationships to depressive or manic episodes, and (3) specificity for bipolar versus major depressive disorder. Their existence challenges the distinction between bipolar and major depressive disorders. The challenges involved in identifying the underlying physiological mechanisms go to the heart of these questions.

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Introduction: Episode and illness

> It appears to me that melancholy is the commencement and a part of mania.
>
> –Aretaeus[1]

Bipolar disorder is currently defined as the manifestation of depressive and manic episodes. The presence of manic episodes distinguishes it from major depressive disorder (MDD). These definitions and distinctions appear to be clear cut, but they have become increasingly open to question. Depression and mania were described in classical times and were defined as opposites, though combinations of depression and mania, or mixed states, were described from the outset. These early descriptions hinted at the possibility of lifetime recurrent or chronic conditions consisting of depression, mania, or both. The modern concept of bipolar disorder developed from these early descriptions, and it is still evolving. Focusing on mixed states, we will explore (1) the conceptual development of depression and mania, as well as the nature and extent of their specificity and combinations; (2) the transition from classical to modern psychiatry; (3) the evolution of the mixed-state concept; and (4) their synthesis, including alternative models of mixed states, their relationship to diagnosis, and the question of what drives mixed states.

The Ideas of Depression and Mania: From Aretaeus to Kraepelin

Symptoms, syndromes, and diseases

Symptoms related to mood disorders have been described for thousands of years. Aretaeus of Cappadocia[1] described manic and depressive behavior as manifestations of a

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common illness. His descriptions of "melancholia" and "mania" could meet the DSM-5 criteria for these conditions. Hippocrates and Plato described similar conditions. Plato believed that they stemmed from a disconnection between the rational soul in the brain and the irrational soul within the body,[2] analogous to Galen.[3,4] Hippocrates[5] and Aretaeus[1] emphasized physical causes. Since what we call depression and mania have probably not changed much over the centuries, it is not surprising that these descriptions of illness accord with subsequent work through modern times, though the proposed mechanisms of action have changed.

However, there was little progress toward understanding mental illness over the ensuing centuries, along with a retrogression in treatment methods, at least in Europe. This resulted from the idea that psychiatric symptoms were believed to be associated with evil or demonic possession instead of being the result of natural processes.[3]

The 18th and 19th centuries marked a return to attempts at naturalistic explanations of psychiatric symptoms. Gall championed the idea that specific brain structures are associated with bodily and emotional functions, a concept that led first to phrenology, but which, with scientific advances, now underlies much of neuroscience.[6] Kahlbaum synthesized the ideas reviewed above to develop a concept of "cyclic insanity" and the new emphasis on course and recurrence of illness.[3,7] In 1854, Falret described the concept of a *folie circulaire*, "a continuous cycle of depression, mania, and free intervals of varying length."[8] Kraepelin also separated recurrent affective disorders from schizophrenia, providing what is considered the classic modern description of depressive and manic states, formulated as part of a recurrent condition, and termed "manic-depressive insanity," implying, without explicitly requiring, that both states be potentially present in the same person, and emphasizing the importance of mixed states.[9] His student and colleague, Weygandt, wrote the first book on mixed states.[10] Allowing for cultural differences, these descriptions were analogous to those of Aretaeus[1] and described people who would be likely to meet the modern criteria for a recurrent affective disorder, though perhaps differently named.

Diagnosis and Biology

Historical descriptions of mood states were vivid but were not associated with specific structures for diagnosis or codified into diagnostic categories. Similarly, severity of illness was not systematically quantified. This may have been related to differences in biological models for affective disorders, as well as their treatment, as will be discussed below. Illnesses were formulated according to the system designed by Empedocles (490–430 BCE) based on four elements with corresponding qualities and humors (fire–heat–blood, earth–dryness–phlegm, water–moisture–yellow bile, and air–cold–black bile),[3] arguably the original dimensional model, spanning psychiatric and nonpsychiatric illness.

Early descriptions of affective disorders were, accordingly, based on detailed biological descriptions and implicit models, derived from observation but not experiment. Aretaeus employed Empedocles' general medical model of four elements and their corresponding qualities and humors. While Aretaeus considered one of the main origins of mood states to be the "head,"[1] he generally considered them to be systemic disorders, related to premorbid traits. Hippocrates[5] and Galen[11] put forward similar formulations. While later formulations posited a primary role for the brain in affective disorders, recent data suggest that they may be, at least in part, systemic illnesses.[12,13]

Specificity of Depressive and Manic States

Aretaeus wrote separate chapters for melancholy and mania, but he discussed both in each chapter.[1] He viewed them as related and often intermingled in the same episode; in fact, he considered these combinations to be their most basic form, emphasizing the manner in which disease-related substances or states could combine or change in a fluid manner in a susceptible patient.

Along similar lines, Kraepelin,[9] while not emphasizing pathophysiology, viewed mood episodes as combinations of three aspects of behavior (mood, action, and thought), any of which could be either depressive or manic. Therefore, some combination of manic and depressive features was the rule, rather than an exception, in his model. Despite his generally descriptive approach, he viewed the severity of mixed states, driven by increased arousal, as greater than pure depression or mania. He described, but provided no definition of, "manic" or "depressive" characteristics for any of the three behavioral constructs; they were not measured or recorded systematically. Kraepelin classified the behavior underlying affective disturbances dimensionally, like Aretaeus, but, unlike Aretaeus, his dimensions were behavioral rather than biological, and he conceptualized these disturbances as components of specific affective states. He looked systematically at components of observed behavior, while Aretaeus and his contemporaries looked at the consequences of proposed combinations of physiological factors.

Aretaeus[1] and Kraepelin[9] observed that there were people with an inherently high risk for mood episodes; Aretaeus, but not Kraepelin, characterized individuals susceptible to depression or mania. Both[1,9] implied a continuous range of susceptibility based on premorbid characteristics.

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Acute Episodes and the Course of Illness

Aretaeus wrote major works on both acute[14] and chronic[1] illnesses. It is noteworthy that he addressed melancholy and mania in his treatise on chronic illnesses. He emphasized that, while individuals could have relatively asymptomatic intervals, the pathological states were likely to recur and the severity of illness to increase. He recognized the risks of suicide and of harm to others in melancholy or mania and noted that premature death could occur as a result of health problems, suicide, or risky behavior. His humoral model implied that the characteristics of episodes would be consistent within individuals. Kraepelin also saw manic-depressive illness as a recurrent lifelong condition, associating severity of the course of the illness with prominence of mixed features.[9]

Summary and Future Prospects

Table 1 summarizes formulations of affective disorders. Psychiatric thinking, through to the time of Kraepelin, viewed mania and depression as being dimensional properties of mood states in general. Further, they recognized affective disorders as recurrent and potentially lifelong, with a course ranging from chronic to episodic. There was no differentiation between bipolar and unipolar disorders but recognition of a continuum of proneness to depressive or manic states. Each true to his era, Aretaeus (a general physician) viewed affective disorders as systemic illnesses, while Kraepelin (a psychiatrist) viewed them as brain disorders.

The idea that systemic factors play an important role in affective disorders, espoused by Aretaeus and his contemporaries, is supported by recent data.[12] Similarly, the humoral theories of his time were consistent with the more modern concepts of temperament in affective disorders, in that constitutional interepisode characteristics, expressed as temperament or as dominant polarity, were important during the course of illness.[15–17] Unlike when these ideas were originally formulated, we are now in a position to understand them better in terms of physiology and treatment.

Transition to Modern Psychiatry

Episode definitions and specificity

After a long and relatively dormant period, the late 19th and early 20th century saw advances in systematic medical observation, neurobiology, and pharmacology that altered classical models of illness-associated mood states.

Episode specificity

Increasingly, depression and mania were viewed as distinct. As potential treatments were discovered, rating scales and operationalizable criteria for depressive or manic states were developed to identify potential candidates for treatment. Because treatments were generally found serendipitously, specific descriptions of episodes were utilized to search for potentially mechanism-based treatments specific for depression or mania. Depression and mania were viewed as distinct and specific entities, and mixed states were relatively ignored. As Schneider insisted, "We do not believe in mixed states."[18]

The reemergence of mixed states was accelerated by findings that manic episodes with depressive features appeared to not respond well to lithium[19] and were associated with a severe general course of illness.[20,21] Contrary to earlier thinking, mixed states were considered paradoxical because they combined two presumably opposite states.

Illness specificity

The idea of bipolar disorder and major depressive disorder as distinct entities emerged during the 1950s and 1960s, partially because of family history and/or genetic differences.[22] Clinically, it can be difficult to distinguish bipolar from unipolar depressive episodes,

TABLE 1. Formulations of affective disorders

	Aretaeus	Kahlbaum	Kraepelin	DSM–III/IV	DSM–5
Episodes	Dimensional, mania, melancholy	Cyclic insanity; affective and psychotic	Categorical; three aspects of mania or depressions	Categorical	Categorical
Course	Recurrent-chronic	Recurrent-chronic	Recurrent-chronic	Recurrent-chronic	Recurrent-chronic
Physiology	Dimensional: element–quality–humor	Specific brain structures (Gall)[6]	—	—	—
Classified	General	Affective or psychotic	Affective	Unipolar–bipolar	Unipolar–bipolar
Susceptibility	Premorbid	—	Premorbid	—	—
Reference	1,3	7	9	38, 39	42

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and treatment responses (at least in the short term) overlap. Illness course in bipolar disorder appears more recurrent and complicated than that in major depressive disorder, with earlier onset[23] and more frequent episodes,[24,25] but patients with both disorders cover an overlapping spectrum of illness courses, leading to the suggestion that illness can be classified by course rather than by "polarity."[26]

Course of illness

The discovery of potential episode-based treatments led to an emphasis on identification and treatment of episodes. Strategies for preventing episodes generally consisted of continued treatment with the agents found to be effective in treating episodes.[27]

Summary

After Kraepelin, advances in the neurosciences and largely serendipitous discoveries of episode-based treatments resulted in a more analytical approach to affective episodes. This led to categorical and mutually exclusive diagnostic criteria for depressive and manic episodes, an emphasis on the specificity of depression versus mania and bipolar versus major depressive disorders, a view of affective disorders focusing on brain-centered, rather than systemic, mechanisms, and an emphasis on episodic characteristics, rather than on the course of the illness, all of which departed from the classical view of affective episodes and mixed states, as shown in Table 1.

Evolution of the Mixed-States Concept

Emergent properties of mixed states

Research since 1970 has revealed the characteristics of depression and mania that are relevant to mixed states:

Mixed depression is common and is associated with a recurrent, complicated illness course.[28–30]

A succession of studies, many by Benazzi and his coworkers, investigated the characteristics of patients with depressive episodes that were related to mania symptom counts. An increasing number of manic symptoms during depressive episodes was associated with early onset, frequent episodes, comorbidities, suicide-attempt history, and family history of bipolar disorder.[31,32] Depressive symptoms during mania conferred similar properties.[33] In terms of possible mixed state criteria, two manic symptoms appeared too sensitive, while three manic symptoms appeared too restrictive.[30] Perhaps most important, Akiskal and Benazzi[30,34] studied individuals who only experienced hypomania when they were depressed. These patients resembled people with bipolar disorder who had freestanding manic or hypomanic episodes in terms of early onset, frequent episodes, and family history of bipolar disorder. While intradepressive hypomania was more common in bipolar depression, it followed a uniform distribution across bipolar disorder and MDD,[35] as did behavioral activation.[36] Further, patients whose hypomanic episodes had only occurred during depression were likely to eventually develop freestanding hypomanic or manic episodes.[37]

Mixed features may be a dimensional property of mood episodes

In bipolar depressed patients, we found a wide range of mania severity, not significantly correlated with severity of depression. As mania rating scale scores increased, there was a gradual increase in the likelihood of a history of suicide attempts, substance-use disorder, early onset, and impulsivity. Receiver operant curve analysis showed an inflection at a mania score of 6, compared to the score of 12 often considered a threshold for hypomania.[38] Studies comparing individuals diagnosed with bipolar and major depressive disorders have generally found a dimensional, or "dose–response," relationship between mixed symptoms and properties associated with bipolar disorder.[39]

Manic episodes similarly develop "mixed" properties, including anxiety, unstable illness course, and suicide attempt history, with 1–3 depressive symptoms. Relative resistance to lithium treatment emerged with two depressive symptoms.[40] A study across depression and mania showed, regardless of primary episode type, that increased anxiety, frequent recurrence, and suicide attempt history emerged with 1–3 opposite-polarity symptoms.[41]

To study mixed states across depression and mania, we developed an index of the degree of mixed features, consisting basically of the product of normalized depression and mania scores. This "mixed state index" was associated with an unstable illness course and suicide attempt history, and correlated with impulsivity.[41] Pacchiarotti *et al.*[42] identified a "mixity" factor, with similar clinical characteristics and independent of depression- and mania-related factors, in a factor-analytic study across inpatients with bipolar I disorder.[42]

Individuals with mixed states, regardless of whether they were predominately depressive or manic, were significantly more likely than not to have subsequent mixed states, of similar polarity.[43,44]

In mixed mania, hypothalamic–pituitary–adrenocortical axis function is increased similarly to depressive episodes,[45] and CSF cortisol correlates with depression score.[45,46] Increased peripheral and central measures of catecholamine function are increased in mania, but are almost 50% higher in mixed than in nonmixed mania,[46] compatible with the driven state hypothesized by Kraepelin.[9] Consistent with

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this, Henry *et al.*[47] developed a dimensional approach to mixed states based on emotional reactivity.

These data show that, in agreement with Kraepelin and Aretaeus, depressive and manic features combine across episodes, and, regardless of the "primary" episode type, mixed features confer similar properties, including a more severe illness course. They raise the possibility that mixed features may be associated with similar treatment responses across episodes, and that episodes can be primarily mixed rather than either depressive or manic.

Development of Operational Criteria

The DSM system initially paid little attention to mixed states. The DSM-III adopted the Leonhard model of separate bipolar and unipolar disorders[22] rather than the Kraepelinian model that combined them,[48] so that mixed states were associated with bipolar disorder and were regarded as rare and paradoxical. A range of criteria was developed by investigators in affective disorders, from stringent criteria requiring full syndromal depression and mania (DSM-III and DSM-IV) to definitions requiring only a few mixed symptoms. The Vienna Research Criteria employed a model based on affective drives[49] that resembled Kraepelin's approach and was applicable to either depressive or manic mixed episodes.[50] Partially because of interest engendered by lithium resistance,[40,51] initial criteria for mixed episodes were otherwise generally limited to episodes meeting full manic criteria. Probably most widely used were the Cincinnati Criteria,[52] requiring mania plus three nonoverlapping depressive symptoms.

The DSM-III and DSM-IV essentially required mania plus full criteria for a major depressive episode for at least one week.[53,54] These highly specific criteria had significant drawbacks, including: (1) they applied only to manic episodes, not addressing mixed depressions, which are common;[55] and (2) they excluded people who clearly did not resemble "pure" mania. This was regarded as a potential attempt to eliminate the "inconvenient truth" of mixed states.[48] Indeed, in his own clinic, Weygandt found more than 60% of mood-disorder patients to be in (Kraepelinian) mixed states (in a population including what would now be considered both bipolar disorder and MDD),[10] while it was estimated that about 10% of patients with bipolar disorder met revised DSM-III criteria for mixed states.[56]

These problems contributed to the development of new criteria for mixed states in the DSM-5.[57] In short, the DSM-5 criteria were based on a mixed specifier rather than a separate episode type, and applied symmetrically to either depressive or manic episodes. The mixed specifier required at least three symptoms of the opposite polarity of the primary episode, excluding a set of symptoms with the potential to overlap between depression and mania. This addressed many of the criticisms of the DSM-IV, especially the earlier restriction to manic episodes, but remained controversial, partially because of its treatment of anxiety and agitation, "overlapping symptoms" between depression and mania that were excluded from the mixed-features specifier.[48]

DSM-5 "overlapping symptoms" and mixed states

Anxiety and agitation can overlap between depression and mania, a potentially confounding factor in attempts to identify mixed states in terms of opposite-pole symptoms. Both, however, are not only potentially useful in assessing and identifying mixed states, but they may be more closely related to its pathophysiology than conventional mood symptoms are. **Anxiety** is prominent in depression[58] and is associated with mixed, but not with non-mixed, mania.[51] Its association with mixed states is prominent across episode types; anxiety correlates with depression severity in manic episodes, with mania severity in depressive episodes, and with mixed-state index scores across all episodes.[41]

Agitation is present in depression and mania, but in different forms: increased, disinhibited goal-directed activity in mania, and severe inner tension, resulting in increased activity that is generally not goal-directed in depression. Both forms are generally present in mixed states.[59]

The dilemma of overlapping symptoms in identifying and understanding mixed states

As noted above, agitation and anxiety are prominent in mixed states and appear related to its pathophysiology. As pointed out by Koukopoulos, "mixed states are nothing but overlapping symptoms."[60] Unlike the case with mood-based diagnostic criteria, if one is trying to understand the pathophysiology and treatment of mixed states, these symptoms are basic to mixed states. Ignoring them may lead to underdiagnosis. Further, studies of relationships between specific "depressive" or "manic" symptoms and mixed states have found many or even most "mood-specific" symptoms to have only weak associations with mixed states.[42,61]

Summary and Future Prospects

Characteristics associated with mixed states–including early onset, severe recurrence, bipolar disorder family history, severe anxiety, and poor treatment outcomes–emerge with increasing symptoms of the secondary episode type, or increased mixed symptoms in general across depressive and manic episodes. Table 2 shows the changing clinical specificity of mixed states. Diagnostic criteria are generally based on depressive or manic episodes with symptoms of the opposite type. Mixed states, however,

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TABLE 2. Formulations of mixed states

	Aretaeus	Kraepelin–Weygandt	Cincinnati–McElroy	DSM–III, IV	DSM–5
Model	Dimensional	Categorical: depression-mania mismatch across three elements	Categorical: mania plus >2 depressive scale items	Categorical: full mania plus full symptomatic depression (shorter duration)	Categorical: depression or mania plus >2 "mixed" symptoms
Episode diagnosis	Any episode, madness, melancholy, mania	Any affective episode	Mania, bipolar	Mania, bipolar	Mania or depression, any affective disorder
Proposed physiology	Characteristics from combined elements–qualities–humors	Driven, hyperarousal	Defined clinically, reported with increased catecholamine and HPA	Defined clinically, reported with increased catecholamine and HPA	Previous work suggests increased catecholamine as well as HPA
Susceptibility	Premorbid	Premorbid, continuum	Comorbidities*	Comorbidities*	
Course	Severe	Severe	Severe	Severe	Severe
Reference	1	8, 9	37	38, 39	42

* Could be cause or effect. HPA = hypothalamic–pituitary–adrenocortical axis.

cannot be understood merely in terms of combined symptoms. Course of illness and neurobiological evidence suggest that the underlying mechanism that drives mixed states is related to hyperarousal,[46] resulting in the anxiety and agitation that characterize these states.[42,61] Factor analyses show that depressive and manic symptoms are independent of these core mixed features and may be regarded as epiphenomena. Yet, the DSM-5 criteria call for either a depressive or manic episode plus at least three symptoms of the opposite episode type, excluding "overlapping" symptoms of agitation and anxiety. By incorporating both depressive and manic episodes and not requiring full syndromal "opposite-pole" symptoms, the DSM-5 criteria are an improvement over earlier criteria. However, the exclusion of so-called "overlapping" criteria that strongly characterize mixed states, and the requirement for a linked depressive or manic episode, are still problematic.[62]

Future Prospects and Current Dilemmas: What Drives Mixed States?

The development of the ideas of mixed states and of the underlying mood disorders leads to questions with important implications.

Definitions of mixed states

Categorical versus dimensional

This distinction is important and sometimes controversial in psychiatry.[63] Categorical definitions are useful for classifying episodes or selecting treatments. A categorical definition of mixed states implies that depressive and manic characteristics are discrete and that their combination accounts for the properties of mixed states. A truly dimensional definition implies a continuously variable characteristic, neither depression nor mania, producing susceptibility to their combination, with clinical features characterizing mixed states. Even a dimensional pathophysiological model can be operationalized, using clinical manifestations, to a categorical approximation useful in identifying patients. For example, Kraepelin's model was categorical, but the hypothesized mechanism was dimensional.[9] Empirical descriptions of mixed states support dimensional models, whether based on symptoms[39] or behavior.[47]

Relationship to depression or mania

Current definitions of mixed states require primary manic or depressive episodes. Similarly, bipolar disorder can be usefully classified in terms of dominant episode "polarity."[64] However, individuals could have periods with three nonoverlapping depressive and manic symptoms without meeting criteria for depressive or manic episodes,[41] possibly as the dominant episode type. This number would increase if the "overlapping" symptoms of anxiety and agitation, markers for mixed states in general,[65] were included in the criteria. In fact, recent factor analyses revealed that most mixed episodes were not predominately depressive or manic,[66] and that, across affective states, a factor was specifically related to "mixity" and independent of specific affective symptoms of depression or mania.[42]

Specificity of relationship to "bipolar disorder" or "major depressive disorder."

The original definitions of mixed states were developed before bipolar disorder and MDD were distinguished. Both manic and depressive episodes can be mixed. Behavioral activation[36] and intradepressive hypomania[35] are distributed across bipolar and unipolar depressions and associated with increased episode recurrence and comorbidity. Similarly, it can be debatable whether agitated depression without freestanding hypomania or mania is part of

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unipolar or bipolar disorder; it could be misdiagnosed as non-mixed according to DSM-5.[60] There are two possibilities. First, we could assume that lifetime mania or hypomania means bipolar disorder. In that case, hypomania occurring only during depression would have to be considered bipolar disorder,[30,34] especially given these subjects' high prevalence for a family history of bipolar disorder, a recurrent bipolar disorder-like course, and, most important, a high incidence of "conversion" to bipolar disorder by eventually having freestanding manic episodes.[37] Alternatively, these individuals may be considered to have MDD, since they have had no freestanding hypomanic or manic episodes. In that case, one could argue strongly that "bipolar" and "major depressive" disorders are the same illness, with course (recurrence, mixed features) determined by a dimensional characteristic, such as susceptibility to behavioral sensitization,[65] cutting across apparent diagnoses.

Treatment Considerations

Consequences of misdiagnosis

As discussed above, our current classification system for affective disorders was strongly influenced by the development of episode-based treatments. These were not necessarily specific for any diagnosis. There is broad evidence that so-called "antidepressive" treatments are less effective in bipolar than in unipolar depression,[67] may cause mood destabilization in bipolar disorder,[68,69] and may lack prophylactic efficacy in bipolar disorder.[70,71] Further, in people who are susceptible to pharmacological activation, such as those with bipolar disorder, antidepressants can cause activated depressions.[69,72] This can increase the risk for suicidal behavior.[34] There is strong evidence that individuals who have combined depression and hypomania have a course resembling that of bipolar disorder[34,61] and are susceptible to antidepressant-induced activation.[69] Therefore, it is important to identify individuals who are experiencing, or are susceptible to, mixed depressions, and to adjust their treatment strategy accordingly.

Specific treatments for mixed states?

The idea that mixed states were associated with a pathologically driven state, beyond simple depression or mania, has been extant since Aretaeus and was reinforced by Kraepelin. It is likely that the pathophysiology of mixed states is related to mechanisms involved in the course of the illness[65] and, as implied by classical descriptions and by more recent factor analyses, is distinct from that of depressive or manic symptoms themselves[42,47,66] and related to combined depression and activation.[46,47] Since nearly all treatments were developed primarily to treat acute episodes of depression or mania, it is not surprising that mixed states are difficult to treat and require more treatments. A better understanding of the neurobiology of mixed states will be required to facilitate development of more effective treatments.

Conclusions

Descriptions of mood disorders go back at least 2,000 years. The classical descriptions of mood disorders held that they were basically chronic, largely systemic disorders, without a systematic distinction between depressive and manic episodes. These descriptions were written by general physicians. Current understanding of mixed states incorporates the same concepts, within a different scientific framework. During the 19th century, disorders and episodes were described more systematically, with the distinction between nonaffective and affective recurrent, potentially psychotic, disorders, and the concept that mood disorders were related to specific brain structures. Episodes were described in terms of basic behavioral dimensions, each of which could be depressive or manic. Therefore, as in the case with classical descriptions, mixed states were the rule, with a continuous transition between mixed and non-mixed mood states. During the 20th century, the development of pharmacological treatments led to systematic structures for depressive and manic episodes, and mixed states were increasingly seen as anomalies. However, observations that mixed states responded poorly to treatments and had a severe course of illness led to increased efforts to define them according to structured criteria. These ranged from requirements for combined full syndromal depressive and manic episodes to combinations of a depressive or manic episode with two or three symptoms from the other type. Problems with these criteria, exemplified by the problem of what to do with symptoms that overlap between depression and mania, are exacerbated by the fact that the requirement to attach mixed states to depression or mania appears artificial. These distinctions, as well as the need for early predictors of or risk for mixed states, are clinically important because of their relationship to treatment resistance, severe course of illness, and risk for suicide.

We currently face three basic issues regarding mixed states: (1) defining the most parsimonious clinical model; (2) understanding the specificity of their relationship to bipolar versus unipolar affective disorders or to the possibility that bipolar and unipolar disorders are related; and (3) the question of treatments that are at least relatively effective and specific. These issues, especially the third, cannot be answered by argument. Solutions can be implied by careful clinical and epidemiological studies and obtained by neurobiological research on the processes underlying susceptibility to mixed states.

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