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Exploring Diagnostic Strategies in the Assessment of Mixed Affective States

Andrew Troy Hodge, MD; Suporn Sukpraprut-Braaten, PhD

Depression has been well known to the medical community for multiple millennia. Through the ages, the understanding of depression and other affective disorders has undergone multiple revisions based on an evolving foundation of knowledge from contributing scientists and physicians (**Figure 1**). In 400 BCE, Hippocrates first used the terms *mania* and *melancholia* as a means of describing mental illness. Later, in the year 30 AD, Celsus, who was a physician in Rome, noticed that there was a relationship between depression and black bile, thus describing the term *melancholia* in his work *De re medicina*. As the understanding of mood disorders broadened over the centuries, clinicians began to notice the tendency for patients to fluctuate between mood states. In 1854, French psychiatrist Jean-Pierre Falret created the term *folie circulaire* to signify the alternating moods of depression and mania.[1] By 1889, the physician Emil Kraepelin described what he called a manic-depressive illness, using very similar criteria that are used today to diagnose bipolar I disorder. Kraepelin also noticed a differentiating factor between manic-depressive and psychotic illnesses, noting that the former did not have a deteriorating course.[1] Nevertheless, the definition of manic-depressive illness did not account for patients presenting with both depressive and manic symptoms simultaneously within a similar time frame.

Figure 1. A Historical Timeline

400 BCE	30 AD	1854	1889
Hippocrates uses the terms *mania* and *melancholia* as a means of describing mental illness	Celsus describes the term *melancholia* in his work *De re medicina*	Jean-Pierre Falret creates the term *folie circulaire* to signify the alternating moods of depression and mania	Emil Kraepelin describes *manic-depressive illness* to diagnose what we now call bipolar I disorder

ACTIVITY GOAL

The goal of this activity is to explore historical and current diagnostic approaches toward patients who present in mixed affective states.

LEARNING OBJECTIVES

1. Explore historical and current diagnostic approaches toward patients who present in mixed affective states.
2. Examine how current DSM nosology defines the proper method of assessing a mixed-episode patient and which diagnostic labels to give them based on their presenting symptomatology.

TARGET AUDIENCE

This accredited continuing education (CE) activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals seeking to improve the care of patients with mental health disorders.

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Although many diagnostic schemas have been created to define various mood states over the years, the intermixed presentation of depressed and manic symptoms has remained one presentation that has been difficult to define.[2] *Manic-depressive insanity* was a term used by Kraepelin, which he defined as containing all affective states; nevertheless, other psychiatrists (even at the time) were skeptical of such definitions.[3-5] Kraepelin stated later in his career that he believed that mixed episodes were the most common type of mood episodes.[3] He also observed that the frequency of mixed mood episodes were just as important as the polarity when diagnosing manic-depressive illness.[3] That is to say, repeated mood episodes of any polarity were diagnosed as manic-depressive illness as long as there were some mixed characteristics. This hints at the importance of detecting not only the content but also the frequency of mood episodes when diagnosing patients.[3]

Even in the contemporary era, it has been suggested that the difference between diagnosing bipolar disorder versus major depressive disorder should not be limited by the presence or absence of a history of manic or hypomanic episodes.[6] In cases where it is not possible to determine a patient's history of mania or hypomania, strategies have been researched to diagnose bipolar disorder from the characteristics of a patient's depressive episodes, which—compared with patients with only major depression—have more atypical features such as leaden paralysis, hypersomnia, or (and) hyperphagia.[6] Having broader, more dynamic diagnostic tools would increase clinicians' ability to diagnose and treat patients' affective conditions, even in circumstances where the presentation may not be as clear.

Looking for Answers

We performed a literature search on PubMed, an electronic database for the scientific literature on May 10, 2020, using the search phrase "depression with mixed features." Articles were restricted to publication dates between 1973 and 2020. No restrictions were placed on language or article type. Articles were selected for inclusion based on the relevance of their titles and abstracts to the topic of mixed affective states. Information from review articles, retrospective studies, and clinical trials was ultimately included. The studies' reference lists were also surveyed to discover additional pertinent articles. The cumulative history of mixed affective states was analyzed, and information from several of Kraepelin's publications was included, along with information from Kaplan and Saddock's *Synopsis of Psychiatry* in the historical context. Several versions of the DSM were included as references.

Resulting Information

Since the topic of manic-depressive illness was popularized by Kraepelin, there has been debate regarding the proper diagnostic segmentation of affective states. Eventually, in the early 20th century, 2 polar archetypes including major depression and bipolar disorder were clinically defined and accepted.[7] Nevertheless, many noticed that some affective states appeared to remain intermediate between depression and mania.[8] DSM-IV (**Tables 1** and **2**) first formally acknowledged this state as a third major affective syndrome and labeled it as a mixed episode, which simultaneously met the diagnostic criteria for both major depressive and manic episodes nearly every day for at least a week.[9] Later, in DSM-5 (**Table 3**), it was decided to include a less stringent mixed feature specifier, instead of an entirely separate diagnosis, to modify and describe individual manic and depressive episodes to account for subthreshold affective symptoms when assessing patients on either end of the mood spectrum.[10,11] Exploring DSM-5's mixed features designation further, it is apparent that symptoms, including distractibility, irritability, and psychomotor agitation, as criteria were left out completely.[10] Nevertheless, many clinicians have argued that use of the mixed features specified in depression is compelling enough to alter diagnostic and treatment strategies because a patient may be at risk for having underlying bipolar disorder.[11]

Table 1. DSM-IV Criteria for a Major Depressive Episode[9]

Major depressive episode
Five (or more) symptoms have been present during 2-week period and at least 1 is either depressed mood or less of interest or pleasure
1. Depressed mood
2. Markedly diminished interest or pleasure
3. Significant weight change when not dieting or change in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or inappropriate guilt
8. Diminished ability to think or concentrate
9. Recurrent thoughts of suicide or death

Table 2. DSM-IV Criteria for a Manic Episode[9]

Manic episode
A distinct period of abnormally elevated, expansive, or irritable mood lasting at least 1 week with 3 (or more) symptoms (4 if the mood is only irritable)
1. Inflated self-esteem or grandiosity
2. Decreased need for sleep
3. More talkative than usual or pressured speech
4. Flight or ideas or racing thoughts
5. Distractibility
6. Increase in goal-directed activity or psychomotor agitation
7. Excessive involvement in pleasurable activities that have high potential for painful consequences

By eliminating the more rigid mood disorders section in the previous edition and placing bipolar and depressive disorders in separate chapters with their own unique modifiers, the DSM-5 seems to be attempting to transition from a categorical approach to a more multidimensional one when diagnosing mood disorders.[2] However, it must be stated that the aforementioned symptoms of distractibility, irritability, and psychomotor agitation were left out of the mixed features specifier criteria in the DSM-5.[10] Nevertheless, the aforementioned overlapping features that have been omitted in the mixed features specifier symptom list of the DSM-5 do occur often during mood episodes. One study found that among patients diagnosed with an active major depressive episode, irritable mood was present in 32.6%, distractibility was present in 24.4%, and psychomotor agitation was present in 16.1%.[12] Ultimately, the exclusion of these overlapping symptoms may serve to limit the practitioner from using the mixed features specifier, which may be detrimental to the patient, as many see the mixed affective state as a unique and commonly occurring syndrome in its own regard, with unique prognostic and therapeutic properties.[13]

The DSM-5 workgroup decided to exclude these 3 overlapping symptoms—distractibility, irritability, and agitation (DIP)—because they lack the specificity to differentiate between depression and mania.[14] Emerging evidence suggests, however, that having mixed episodes represents a unique syndrome with its own novel mechanism of pathogenesis.[14] As a result, certain researchers have suggested a return to a Kraepelinian approach by reintegrating DIP symptoms into the mixed features classification system in a more inclusive manner.[14] Others have gone so far as to say that mixed affective states need their own diagnostic category instead of a specifier due to the spectrum of state models proposed by Kraepelin in the 19th century.[15] It seems the exclusion of DIP symptoms from the diagnosis of mixed features per DSM-5 will likely serve to alter the methods clinicians use to diagnose the condition and change the direction of future research.[16] However, there have always been many interpretations and subcategorizations of mixed affective states based on the type and strength of the patient's presenting symptoms.

Specialized diagnostic methodologies exist in the literature to better dissect and interpret mixed affective traits, such as segmenting the mixed episode into either a mixed depressive state or a mixed manic state on the basis of psychomotor activity and energy levels and treating accordingly.[17] Nevertheless, an idea on which many

Table 3. DSM-5 Criteria for Mixed Depressive and Manic Episodes[10, 11]

With mixed features
At least 3 of the following manic/hypomanic symptoms are present nearly every day during the majority of days of a major depressive episode
1. Elevated, expansive mood
2. Inflated self-esteem or grandiosity
3. More talkative than usual or pressured speech
4. Flight or ideas or racing thoughts
5. Increase in energy or goal-directed activity
6. Excessive involvement in pleasurable activities that have high potential for painful consequences
7. Decreased need for sleep
Full criteria are met for a manic/hypomanic episode and at least 3 of the following symptoms are present nearly every day during the majority of days of a manic/hypomanic episode
1. Depressed mood
2. Markedly diminished interest or pleasure
3. Psychomotor retardation
4. Fatigue or loss of energy
5. Feelings of worthlessness or inappropriate guilt
6. Recurrent thoughts of suicide or death

researchers can agree is that the DSM-5 designation of mixed features is inadequate because it does not include the DIP symptoms in its criteria.[18] Although the DSM-5 definition of the mixed episode is broader than the DSM-IV definition, it fails to include a sufficient number of symptoms altogether.[19] This leaves a large number of cases undiagnosed and patients untreated as a result of the DSM-5's lack of diagnostic openness and clarity.[20]

Evidently, the DSM-5 chose to exclude these aforementioned core DIP symptoms from the mixed features specified for pragmatic purposes and to avoid the overdiagnosis of mixed symptoms.[20] However, recent studies may prove this to be an important oversight (**Figure 2**). For instance, a recent study found that many patients presented with distractibility (59.2%), irritability (57.3%), and psychomotor agitation (36.5%) in mixed depression, whereas only 18% and 6.6% presented with euphoria and grandiosity, respectively.[21] Furthermore, other studies have shown that psychomotor agitation was the symptom observed most frequently in patients with both bipolar disorder (59.8%) and major depressive disorder (48.8%) who presented in a major depressive episode.[22] Because of this, clinicians and researchers have created more inclusive ways to define mixed episodes that do include symptoms such as psychomotor agitation and irritability.[19]

Another major criticism that has been made against the new DSM-5 mixed features specifier is that the manic or hypomanic symptoms required during a major depressive episode were the least common symptoms that actually arise in depressive mixed states.[20] This notion was further reinforced by other researchers and clinicians who criticized the DSM-5 for including uncommon symptoms such as euphoria and grandiosity as mixed feature criteria in major depressive episodes.[23] Mixed depression does not respond to traditional antidepressant therapy, and these drugs may in fact worsen the clinical picture by further agitating them or causing mania.[24]

It has been shown that patients with mixed depression compared to typical depression have a higher rate of suicide attempts, greater use of mood stabilizers and antipsychotics, and higher overall treatment cost.[25] Fortunately, the clinical significance of patients who display mixed affective features is slowly being recognized, and future larger-scale studies are being conducted to investigate these patients and how to effectively treat them.[23]

Patients who have underlying bipolar disorder and experience major depressive episodes with mixed features have higher rates of substance and alcohol use compared to those without mixed features.[26] Additionally, patients with depression and bipolar disorder with mixed episodes were found to be more likely to have cardiovascular disease compared to patients who did not display mixed mood episodes, hinting at a distinctive pathologic origin of this condition.[26] Patients who experience bipolar depression with concurrent manic or hypomanic symptoms are also found to report a younger age of illness onset, more severe illness course, higher percentage of rapid cycling course, more frequent hospitalizations, longer time to achieve remission, and concurrent psychotic features compared to patients who do not experience mixed features.[27-30]

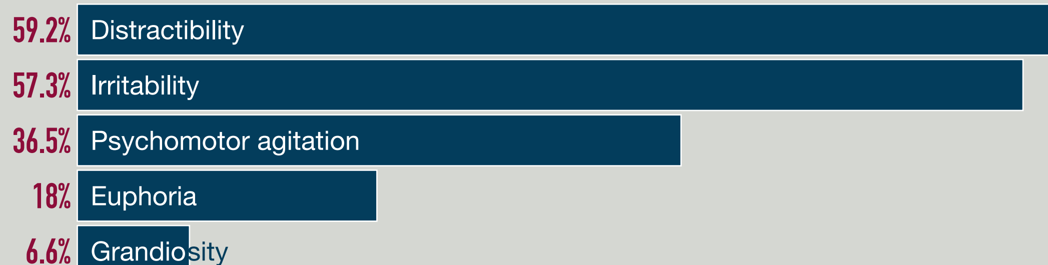
Thus, a more nuanced diagnostic approach is needed for patients who typically present with mixed episodes. Researchers have proposed alternate methods of assessing affective states in general, such as the ACE model, which considers 3 domains: activity, cognition, and emotion (thus, the name).[31] One proposed model of assessing mood states compared the use of the DSM-5 model of assessing mixed depression to a research-based diagnostic criteria (RBDC) model that included DIP symptoms and found that mixed depression was detected in 29.1% of patients using an RBDC model and only 7.5% of patients using the DSM-5 criteria model.[14]

In contrast, many have argued that the DSM-5 system of assessing mixed states actually facilitates the inclusion of subthreshold symptoms of opposite polarity and is overall less restrictive than previous versions of the DSM.[32] This could help encourage diagnosis of mixed states on behalf of clinicians, thus possibly preventing the excessive prescription of antidepressant medications, which has been postulated to induce a type of hypomania in primarily depressive patients, referred to as bipolar III disorder.[33]

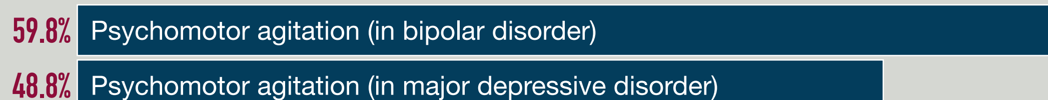
Although there is room for improvement, at least the new DSM-5 classification system has helped to identify more patients suffering from mixed states compared with previous nosology because of broadening the DSM-IV-TR criteria.[15] For example, in one study, patients previously diagnosed with bipolar disorder were examined when they were having a manic or hypomanic episode, and mixed features were detected in 20.4% during the episode using the DSM-5 criteria; however, using the DSM-IV-TR criteria, only 12.9% of the patients had a mixed episode, showing what appears to be a lower degree of sensitivity toward mixed affective states.[26] Another study found an approximately 3-fold-greater risk for a patient with bipolar disorder to be diagnosed as having mixed symptoms using DSM-5 criteria compared with using DSM-IV-TR criteria, concluding that additional patients identified with mixed features could have been underdiagnosed without the DSM-5 change.[29] There continues to be debate regarding the effectiveness of the current DSM system in capturing mixed affective symptoms.

Figure 2. Prevalence of Presenting Core DIP Symptoms

In mixed depression



Presented in a major depressive episode



Conclusions, Limitations, and Implications

Although there is some disagreement regarding how to diagnostically define a mixed affective state, it is evident that understanding their pathogenesis, epidemiology, and treatment is becoming increasingly important. A recent study of 36,309 US adults found that 10.4% experienced DSM-5–defined major depression in the past 12 months, and 20.6% of adults experienced DSM-5–defined major depression at least once in their lifetime.[34] Interestingly, the mixed features specifier criterion was met in 15.5% of the major depressive cases, showing that close to 1 in 5 patients experiencing depression may also be experiencing mixed symptoms.[34]

> **"Mixed depression does not respond to traditional antidepressant therapy, and these drugs may in fact worsen the clinical picture by further agitating them or causing mania."**

This increasing incidence of mixed affective presentations highlights the importance of recognizing mixed features of depression and mania early in the course of illness in order to tailor a specialized treatment plan. Although "mixed features" is only a specifier and not a diagnosis per DSM-5, novel drugs such as lurasidone (Latuda) or cariprazine (Vraylar) are already being suggested for the treatment of patients who specifically display DSM-5–defined mixed features, hinting at a growing trend toward proper identification of this subset of patients.[35,36]

There are a few limitations of this analysis. For instance, only PubMed was used to search for articles relevant to the topic. Similarly, the study only used the search phrase "depression with mixed features." "Mania with mixed features" was not used as a search term because "depression with mixed features" yielded a sufficient number of articles with information on mixed affective states of either polarity. Moreover, the amount of information available on patients who experience mixed affective states is relatively small compared to that on manic and depressed patients, which can create a publication bias. Ironically, the reason for limited data for patients with mixed episodes could be due in part to the dichotomous views that mental health professionals have toward mood states.

Moving forward, clinicians should keep a watchful eye on this subtype of depression and mania. Having a more clearly delineated understanding of the mood spectrum would certainly carry beneficial implications for patients with mixed episodes by improving treatment modalities, diagnostic methods, and, ultimately, clinical outcomes. More research is needed to better understand the root of mixed states pathology so that better treatment solutions can be offered to this patient population.

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