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Diagnosing and Managing Depressive Episodes in the *DSM-5* Era

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CME Information
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Overview
This article provides a review of the particular challenges related to diagnosing bipolar and major depression disorders with mixed features and discusses the importance of accurate assessment of the mixed features qualifier in order to provide optimal treatment for patients. Moreover, the differences between management of bipolar disorder with mixed features and major depressive disorder with mixed features will be addressed.

Target Audience
This activity has been designed to meet the educational needs of psychiatrists and mental health researchers who manage patients with depressive episodes.

Educational Objectives
After participating in this educational initiative, the participant should be better able to:
- Integrate mechanisms for distinguishing unipolar and bipolar depression into the diagnosis of patients with depressive symptoms, including with the mixed features specifier
- Incorporate appropriate use of current evidence-based treatments for depression with manic and hypomanic symptoms, taking into account data that support their use, efficacy, and safety
- Translate the available evidence for the appropriate management of the different types of depression into clinical practice

Faculty
Roger S. McIntyre, MD, FRCPC
Professor of Psychiatry and Pharmacology
University of Toronto
Head, Mood Disorders
Psychopharmacology Unit
University Health Network
Toronto, ON, Canada

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The premise of the newly introduced mixed features specifier in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) is similar to what was proposed approximately a century ago as part of the "manic depression" unification hypothesis. German psychiatrist Emil Kraepelin (1856–1926) originally conceptualized affective states as a continuum, wherein an individual's diagnosis was arrived at via a confluence of contemporaneous disturbances in mood, thought processes, and volition (behavior). His original description was agnostic insofar as it lacked the 2 categorical constructs, bipolar disorder and major depressive disorder—terms that eventually appeared in the *DSM*. Kraepelin described a total of 6 types of mixed states (depressive or anxious mania, excited depression, mania with thought poverty, manic stupor, depression with flight of ideas, and inhibited mania) and pure depression. The phenotypic variation of states that Kraepelin described (***Figure 1***) are similar, but not identical, to the phenotypic heterogeneity of mixed states subsumed under the mixed features specifier in the *DSM-5*.[1]

Applying the mixed features specifier

The definition of mixed features specifier during a major depressive episode would be identical in persons whose categorical diagnosis is either bipolar disorder or major depressive disorder. The presence of the mixed features specifier during a major depressive episode in an adult with major depressive disorder heuristically bridges bipolar disorder and major depressive disorder and is a tacit endorsement of an affective continuum (***Figure 2***).[2-4] The mixed features specifier in *DSM-5* supplants the previous diagnosis of mixed states, which was defined as the syndromal presence of a manic and depressive episode.[3] The specifier "with mixed features" can be applied to an episode of hypomania/mania if 3 or more prespecified depressive features are present, as well as a major depressive episode if 3 or more prespecified hypomanic features are present.[3] ***Figure 2*** presents and juxtaposes the conceptual framework of *DSM-IV-TR* and *DSM-5*. As can be seen in the figure, for a diagnosis of mania with mixed features, at least 3 core manic symptoms and at least 3 core depressive symptoms need to be present. For a diagnosis of depression with mixed features, at least 3 core manic symptoms and at least 5 depressive symptoms need to be present.[3]

Several core and nonoverlapping symptoms exist in depression with mixed features. Symptoms that are core (ie, allowed) include diminished interest or pleasure, slowed physical and emotional reac-

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tion, fatigue or loss of energy, and recurrent thoughts of death. Several symptoms that are nonoverlapping (ie, not allowed) include anxiety, distractibility, irritability, indecision, insomnia, or agitation.[3]

Based on this conceptualization, there is a phenomenological and diagnostic overlap between bipolar disorder and major depressive disorder with mixed features. Notwithstanding the dimensional characterization of mood disorders in *DSM-5*, major depressive disorder and bipolar disorder remain as discrete entities with respect to illness "validators" (eg, pattern of comorbidity, age at onset, course of illness, suicide risk, response to psychotropic agents, and family history).

Prevalence of mixed features in bipolar and major depressive disorders

Prevalence rates for mixed features in individuals with bipolar disorder or major depressive disorder have been variably reported, influenced by the definitions employed. For example, reported rates for mixed features across bipolar and unipolar populations have varied from 20% to 70%.[5] According to one community-based study, 41.4% of those who met *DSM-IV* criteria for major depression experienced mixed features (defined as subthreshold hypomania with 4 or fewer symptoms) but did not meet *DSM-IV* criteria for hypomania, based on the Munich-Composite International Diagnostic Interview.[6]

The International Mood Disorders Collaborative Project reported that 11% to 54% of those with major depressive disorder had mixed features, depending on the threshold number of manic symptoms required for the diagnosis.[7-9] The International Mood Disorders Collaborative Project was a post hoc analysis of participants who met criteria for a current mood episode as part of bipolar disorder (bipolar I disorder: n = 216, bipolar II disorder: n = 130) or major depressive disorder (n = 506). The *DSM-5* mixed features specifier in this study was proxied by operationalizing a score of ≥1 on at least 3 select items on the Young Mania Rating Scale (YMRS) or ≥1 on at least 3 select items of the Montgomery-Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D17) during an index major depressive episode or hypomanic/manic episode, respectively. Taken together, 26% of individuals with major depressive disorder met criteria for the mixed features specifier, as did 34% of those with bipolar I disorder and 33.8% of those with bipolar II disorder. The mixed features specifier during a hypomanic/manic episode was identified in 20.4% (n = 52) and 5.1% (n = 8) of bipolar I disorder and bipolar II disorder participants, respectively (***Table***).[9]

In the multicenter, multinational study Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX, of 2811 adult patients with a current major depressive episode, 212 (7.5%) met the *DSM-5* criteria for depression with mixed features, but considerably more (818, or 29.1%) demonstrated mixed features if more inclusive research-based diagnostic criteria were used.[10] Specific mixed features included irritable mood (32.6%), emotional/mood lability (29.8%), distractibility (24.4%), psychomotor agitation (16.1%), impulsivity (14.5%), aggression (14.2%), racing thoughts (11.8%), and pressure to keep talking (11.4%).[10] Euphoria (4.6%), grandiosity (3.7%), and hypersexuality (2.6%) were less frequently observed.

The mixed features specifier was not applied to *DSM-IV* or *DSM-IV-TR*.[5] Using a proxied approach, however, it appears that mixed features in prior studies were common. A majority of those with *DSM-IV* bipolar depression were estimated as having mixed features in 2 clinical trials of an olanzapine/fluoxetine combination if 1 or 2 manic symptoms were present at study baseline; when 3 or more manic symptoms were present at study baseline, 31% had mixed features.[11]

Mixed features symptoms and *DSM-5*

The diagnosis of major depressive disorder with mixed features requires that predominant depression be present with evidence of subsyndromal manic or hypomanic symptoms. These can include elevated mood, inflated self-esteem, decreased need for sleep, an increase in energy, or goal-directed activity. At least 3 of these symptoms must be present nearly every day during the most recent 2 weeks of the major depressive episode for mixed features to be present.[12] Symptoms of mixed features in bipolar disorder and major depressive disorder can present in a broad variety of ways beyond what is described in *DSM-5*. Symptoms can include dysphoric mood, emotional lability, psychic and/or motor agitation, talkativeness, crowded and/or racing thoughts, rumination, initial or middle insomnia, impulsive suicidal attempts, incessant complaints, and irritability. Occasionally, verbal outbursts, physical aggression, or hypersexuality can also be present.[13]

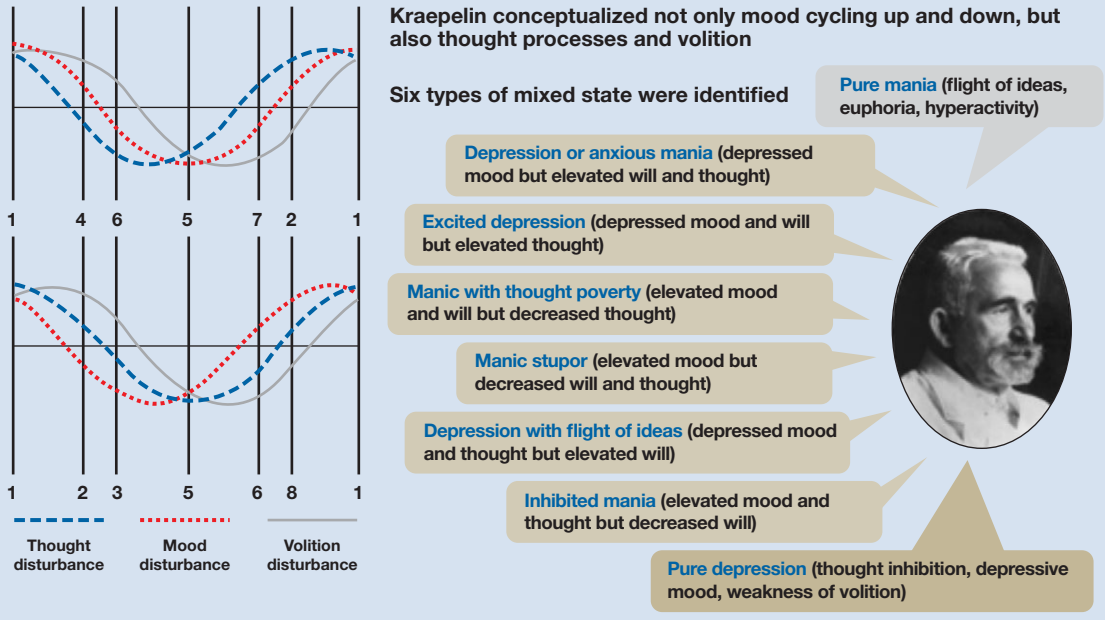
Implications of mixed features for illness severity, comorbidities, and treatment response

Recognition of mixed features in both bipolar disorder and major depressive disorder has significant clinical implications as individuals with mixed features are more likely to have a more severe illness, a greater number and complexity of comorbid conditions, and a lower likelihood of responding to conventional bipolar pharmacological therapies.

For example, results from the International Mood Disorders Collaborative Project indicate that individuals with a major depressive episode and mixed features as part of bipolar disorder or major depressive disorder exhibited a significantly more severe depressive pheno-

FIGURE 1

Kraepelin conceptualized affective states as a continuum[1]



type than those without mixed features (P = .0002 and P < .0002, respectively) and, in bipolar disorder, reported a higher rate of alcohol or substance use disorder (P = .002). Individuals with mixed features were more likely to have coexisting heart disease, with 37% of those with mixed features having heart disease compared with 14% of those with pure mania. In addition, mania with mixed features is associated with a higher unemployment rate compared with pure mania, with a 70% vs 44% unemployment rate, respectively.[9]

Bipolar disorder is more prevalent in patients with autoimmune disorders, cardiovascular disease, and metabolic dysfunction.[14] Likewise, people with bipolar disorder are differentially more likely to be obese or overweight and have metabolic syndrome.[15,16] This pattern of comorbidity has obvious implications for physical health, but it is particularly relevant for individuals with mixed features who have cardiac/metabolic comorbidity and exhibit a more "depression-prone" and possibly a "mixed features-prone" bipolar illness. The greater hazard of physical health abnormalities in adults with bipolar disorder further underscores the importance of preventive approaches and the avoidance of psychotropic agents with known adverse effects on physical health (eg, weight gain, metabolic disruption).

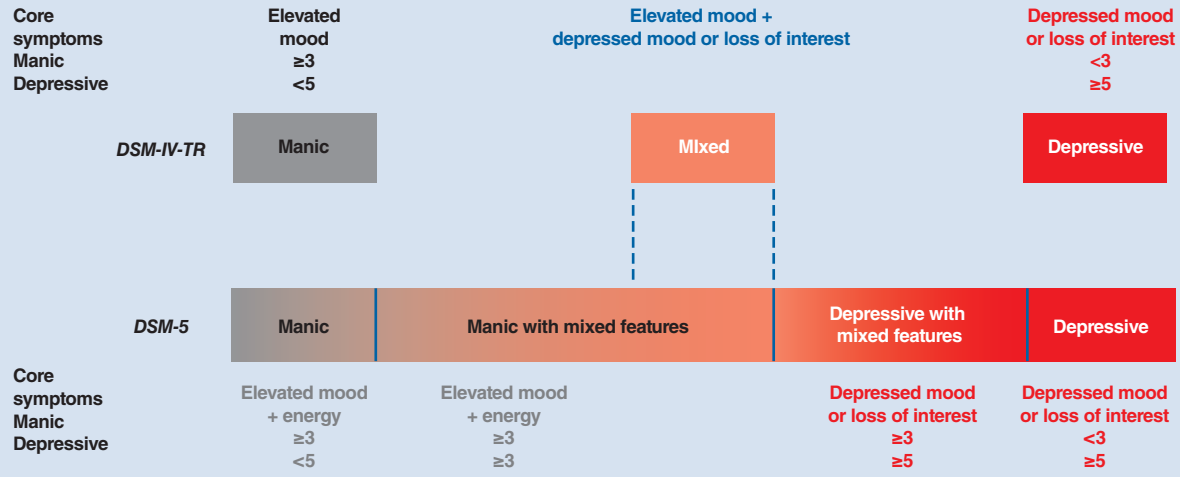
The greater number and percentage of current and lifetime comorbidities among individuals with mixed features, as well as the greater overall illness burden, provides an explanation for the consistent observation of a more complex clinical course and less robust response to treatment.[17,18] For example, in a study of 960 patients, depressive features were observed to be frequent in bipolar patients with manic episodes (34% mild, 18% moderate, and 4.3% severe).[19] With increasing baseline severity of depressive features in bipolar disorder with mixed features, treatment response was poorer with olanzapine and placebo but remained stable with asenapine.[19] A separate 10-week study of 176 outpatients found that bipolar depression with mixed features was associated with antidepressant treatment–emergent mania. The presence of minimal manic symptoms at baseline and bipolar depression was a predictor of treatment-induced mania or hypomania.[20]

The number of mixed symptoms may negatively impact a treatment response in an additive manner. For example, in a retrospective study of 158 inpatients with bipolar disorder, participants were examined with respect to mixed depressive features. The number of mixed depressive symptoms, including flight of ideas, racing thoughts, logorrhea, aggression, excessive social contact, increased drive, irritability, and distractibility, predicted switch during inpatient treatment.[21]

Poorer treatment outcomes and the need for multiple treatments and/or hospitalizations inevitably translate to increased health care costs for individuals with mixed

FIGURE 2

Conceptualization of pure and mixed states in *DSM-IV-TR* and *DSM-5*[2-4]



Source: Hu J, Mansur R, McIntyre RS. Mixed specifier for bipolar mania and depression: highlights of DSM-5 changes and implications for diagnosis and treatment in primary care. *Prim Care Companion CNS Disord*. 2014;16(2):pii. Copyright 2014, Physicians Postgraduate Press. Reprinted by permission.

features in both bipolar disorder and major depressive disorder. Overall, people with bipolar disorder and major depressive disorder with mixed features have increased comorbidities and increased health care costs when compared with those without mixed features. The foregoing multiple complications warrant careful appraisal of whether or not mixed features are present in individuals presenting with bipolar disorder and major depressive disorder, so that appropriate management approaches can be selected.

Management strategies

The presence of mixed features invites the need for selecting treatment strategies to appropriately address illness severity, comorbidities, and poor treatment response. Currently, unfortunately, limited data support effective treatment of depression with mixed features. Conventional antidepressants have been associated with the induction of mania and rapid cycling in subpopulations with bipolar disorders.[22] Use of antidepressants in patients with mixed features may worsen symptoms; the hazard for antidepressant destabilization is greater in those with rapid cycling, mixed features, and bipolar I disorder and in individuals receiving antidepressant monotherapy.[23]

The notion that conventional antidepressants are anathema to treating mixed features was belied with results from the STAR*D study. Investigators from that study reported that among 2397 subjects with major depressive disorder, *DSM-5* mixed state features were associated with a greater likelihood of remission and were not associated with poorer antidepressant treatment outcomes.[24] A total of 449 subjects (18.7%) had at least 2 mixed symptoms. Mixed features were associated with a greater likelihood of remission across up to 4 sequential treatments. Two items, expansive mood and cheerfulness, were strongly associated with a greater likelihood of remission.

A consensus statement from a recent International Society for Bipolar Disorders Task Force report on antidepressant use in bipolar disorder was that non-antidepressant treatments should be considered as monotherapy before antidepressants to treat bipolar depression.[25] Therefore, an unanswered question remains regarding the role of conventional antidepressants in treating adults with major depressive disorder and the *DSM-5*–defined mixed features specifier, largely due to an absence of empirical studies.[24]

Psychosocial treatments are important to consider and implement in individuals with bipolar disorder and major depressive disorder with mixed features. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) demonstrated that adjunctive psychosocial treatments, but not adjunctive antidepressants, produced better outcomes than mood stabilizers alone. Treatments in this study included cognitive-behavioral therapy, family-focused therapy, interpersonal therapy, and social rhythm therapy.[26]

In addition to considering psychosocial interventions, management of comorbidities is an important focus of treatment. As part of general psychoeducation, a focus on the basic principles of a healthy lifestyle is warranted, including but not limited to appropriate food choices, regular exercise, and meticulous attention to appro-

TABLE The International Mood Disorders Collaborative Project: *DSM-5* mixed features specifier prevalence rate[9]

Mixed features specifier	Major depressive disorder	Bipolar II disorder	Bipolar I disorder
Depression with ≥1 on at least 3 YMRS items	26.0% (n = 149)	33.8% (n = 49)	34.0% (n = 65)
Mania/hypomania with ≥1 on at least 3 MADRS or HAM-D items	NA	5.1% (n = 8)	20.4% (n = 52)

HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; YMRS = Young Mania Rating Scale.

priate sleep hygiene and circadian rhythms. As previously mentioned, more severe depression, substance abuse, and cardiovascular disease are more prevalent in people with mixed features. Mixed features are, therefore, malignant, highly unstable, and perhaps one of the most dangerous phenotypes in all of psychiatry. Comorbidities should be screened for and treated in addition to the main presenting diagnosis.[9]

Efficacy studies in patients with mixed features

While few treatment options are currently available that focus specifically on mixed features in affective states, a recent post hoc analysis of lurasidone in patients with a *DSM-IV-TR* diagnosis of major depressive disorder associated with bipolar I disorder showed efficacy for the atypical antipsychotic.[12] Mixed features were found in 56% (272/485) of patients from the original clinical trial, 182/323 of those taking lurasidone and 90/162 of those on placebo. Participants had a MADRS score of ≥20 and a YMRS score of ≤12. Subjects were randomly assigned to 6 weeks of double-blind, once-daily treatment with either lurasidone (20 to 60 mg or 80 to 120 mg) or placebo. Mixed features were defined as a YMRS score of ≥4 at the beginning of the study. Efficacy analyses included a change in the MADRS total score from baseline to week 6. At week 6, lurasidone treatment produced significantly greater reductions in MADRS scores than placebo in both the mixed features group (-15.7 vs -10.9; $P = .001$) as well as the group without mixed features (-15.2 vs -10.8; $P = .002$) ***(Figure 3)***.[12] Lurasidone treatment was not associated with treatment-emergent mania.

A separate study examined the efficacy of lurasidone in major depressive disorder with mixed features. This is the only study that has a priori sought to determine the effect of a therapeutic intervention in adults with *DSM-5*–defined major depressive disorder with mixed features as part of randomized, double-blind, parallel group placebo-controlled study.[27] In this study, patients (aged 18 to 75 years) were required to meet criteria for major depressive disorder plus 2 or 3 specified manic symptoms (occurring on most days over the last 2 weeks or longer). Manic symptoms included elevated, expansive mood; inflated self-esteem or grandiosity; being more talkative than usual or feeling pressure to keep talking; flight of ideas or subjective experience that thoughts are racing; increase in energy or goal-directed activity (either socially, at work or school, or sexually); increased or excessive involvement in activities that have a high potential for painful consequences (such as engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments), and decreased need for sleep (eg, feeling rested despite sleeping less than usual, in contrast with insomnia).

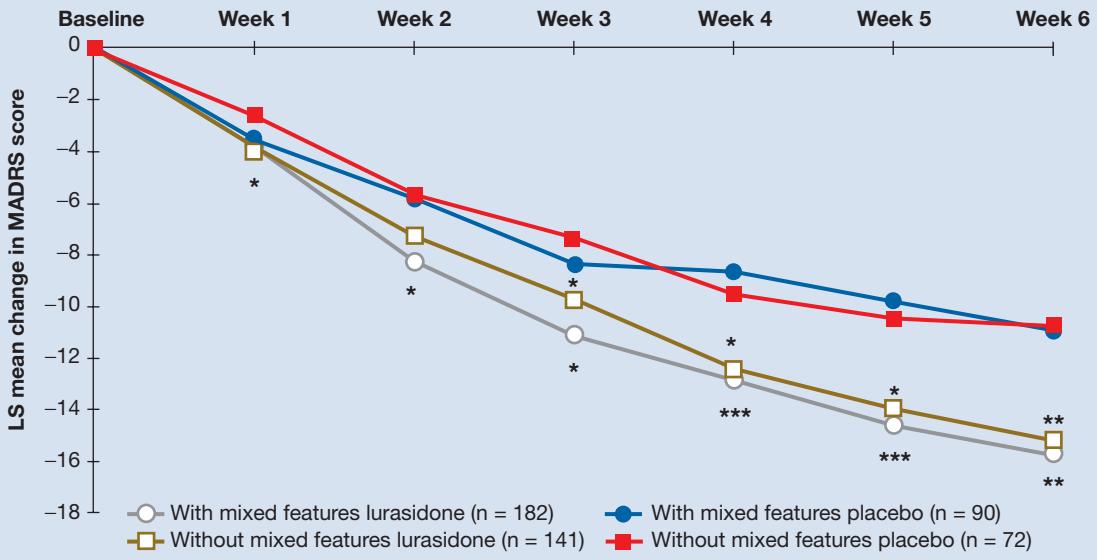
One-hundred participants per arm were included, with an initial 3 to 14 days of screening; one group took lurasidone 20 to 60 mg/day for 6 weeks and the other group took placebo. There was also a 12-week extension study. The mean change in MADRS score from baseline was significantly greater for the group taking lurasidone (-20.5) compared with the placebo group (-13.0), with an effect size of 0.8. In all, 64.8% of patients were responders with a 50% or greater reduction in MADRS total score at week 6 in the lurasidone group compared with 30% in the placebo group.[27] Mean reduction in Clinical Global Impression–Severity of Illness scale from baseline and the mean change from baseline in the Sheehan Disability Scale total score at 6 weeks were significant for lurasidone vs placebo.

Olanzapine, another antipsychotic, has been studied recently for the treatment of bipolar mania with mixed features, as defined by the *DSM-5*.[28] Data from 3 placebo-controlled olanzapine studies in patients with bipolar I disorder with manic/mixed episode were included (n = 228 olanzapine; n = 219 placebo) in this analysis. Mixed features were determined based on the number of baseline concurrent depressive symptoms, with 3 or greater defined as presence of mixed features. Depressive symptoms corresponded to 6 HAM-D17 items in the *DSM-5* definition of manic episode with mixed features. Efficacy was analyzed based on changes from baseline to 3-week YMRS total score. A total of 322 (72%) patients were found without mixed features and 125 (28%) were found with mixed features.

The average YMRS total score was 28.1 in those without mixed features and 27.8 in those with mixed features. Least-squares mean change of YMRS total scores in olanzapine vs placebo were -11.78 vs -6.86 (without

FIGURE 3

Change in baseline in MADRS score in patients with and without mixed features treated with lurasidone[12]



*P < .05.
**P < .01.
***P < .001.

Abbreviations: LS = least-squares; MADRS = Montgomery-Åsberg Depression Rating Scale.

Source: McIntyre RS, Cucchiaro J, Pikalov A, et al. Lurasidone in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features: post hoc analysis of a randomized placebo-controlled trial. *J Clin Psychiatry*. 2015;76(4):398-405. Copyright 2015, Physicians Postgraduate Press. Reprinted by permission.

mixed features) and -13.21 vs -4.72 (with mixed features). Patients in the olanzapine group compared with the placebo group experienced a greater decrease in YMRS total score, regardless of whether mixed features were present (P < .001). Olanzapine was therefore efficacious in individuals with bipolar I disorder mania, regardless of whether *DSM-5*–defined mixed features were present. More severe depressive symptoms, however, in those with mixed features appeared to diminish efficacy.[28] Unfortunately, a major limitation of olanzapine is that it presents a significant burden in terms of a patient's physical health, as olanzapine use is associated with weight gain and diabetes, with substantially increased risk for these problems relative to other atypical antipsychotics.[29,30]

The atypical antipsychotic asenapine was studied in a post hoc analysis of 2 clinical trials that primarily sought to determine asenapine's efficacy in acute mania. The analysis specifically focused on asenapine's effects on depressive symptoms in patients with bipolar I disorder who had significant depressive symptoms at study baseline and were experiencing an acute manic or mixed episode, rather than a depressive episode.[31] The original trials included 977 patients randomized to asenapine, placebo, or oral olanzapine. Three groups were identified using baseline depressive symptoms, based on a MADRS total score of ≥20 (n = 132), a Clinical Global Impression for Bipolar Disorder-Depression (CGI-BP-D) scale severity score of ≥4 (n = 170), and diagnosis of mixed episodes (n = 302). Overall, asenapine significantly and consistently reduced depressive symptoms in patients with mixed symptoms at baseline, whereas olanzapine also significantly reduced depressive symptoms vs placebo but was less consistent.

Asenapine may, therefore, be another option for the treatment of individuals with mixed symptoms, although further studies in bipolar disorder and initial studies in major depressive disorder are needed. Overall, these and other studies reinforce that major depressive disorder with mixed features requires more attention and more research since it is poorly understood and there are minimal data regarding treatment.

Mixed features: A complicated phenotype

The presence of mixed features in bipolar disorder and major depressive disorder represents a complicated

phenotype, one that requires mindfulness and appropriate assessment of the presence of mixed features as well as appropriate treatment decisions based on their presence. It is notable that the recent *DSM-5* mixed features qualifier emphasizes the relationship between bipolar disorder and major depressive disorder; however, it is also clear that the 2 conditions are distinct. Major depressive disorder with mixed features is not synonymous with bipolar disorder, as most persons with major depressive disorder and mixed features retain the major depressive disorder diagnosis after multiple years of follow-up.

Clinicians also need to recognize that bipolar disorder and major depressive disorder can be conceptualized along a spectrum and that it is a mistake to rely on a specific point in time to diagnose this type of patient because mixed features may present over time. While data are currently limited with regard to treatment of bipolar disorder and major depressive disorder with mixed features, it is critical that mental health care providers translate the available evidence for the appropriate recognition and management of depression with mixed features into clinical practice in order to achieve the best outcomes for these patients.

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