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Target Audience
This activity has been designed to meet the educational needs of psychiatrists, advanced practice psychiatric nurses, and other mental healthcare professionals involved in the care of patients with mood disorders.

Statement of Need/Activity Overview
Worldwide, bipolar disorder is responsible for more loss of disability-adjusted life years than all forms of cancer or major neurologic conditions, such as epilepsy and Alzheimer's disease. Despite the prevalence of bipolar depression, these patients are often misdiagnosed with major depressive disorder (MDD). Patients with bipolar disorder frequently wait years for a correct diagnosis. The diagnosis of bipolar disorder is challenging because most patients seek treatment for depressive symptoms as the first episode of mood disturbance. Differentiation of bipolar disorder I and bipolar disorder II also can be challenging. The recent recognition of MDD with subsyndromal hypomania or mania as described in the DSM-5 presents new considerations for psychiatrists and other healthcare professionals in the differentiation of depressive disorders. Management of patients with bipolar disorder requires an accurate differential diagnosis to prevent inappropriate or ineffective pharmacotherapy. This activity includes a case-based learning opportunity to enhance healthcare providers' knowledge of the accurate diagnosis of bipolar disorder I, bipolar disorder II, and MDD with subsyndromal mania or hypomania. The authors review practical patient-centered strategies for the diagnosis and management of depression across the spectrum of mood disorders.

Learning Goal/Purpose
The goal of this activity is to educate healthcare providers on the latest information in the area of mood disorders.

Educational Objectives
After completing this activity, the participant should be better able to:
- Establish a differential diagnosis of bipolar depression and other depressive disorders
- Apply evidence-based clinical strategies for the management of patients with bipolar depression
- Discuss current evidence for the diagnosis and treatment of patients with major depressive disorder with subsyndromal hypomania or mania

CONTINUED ON PAGE S2

Depression Across the Spectrum of Mood Disorders: Advanced Strategies in Major Depressive Disorder and Bipolar Disorder

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Differentiating Major Depressive Disorder and Bipolar Depression

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CASE PRESENTATION

Amrita is a 28-year-old woman previously diagnosed with major depressive disorder (MDD). She has had several depressive episodes from ages 18 to 21 years. Amrita is currently employed as a loan officer at a community bank and has a 3-year-old daughter. She has been referred to your psychiatric practice by her primary care provider, who is concerned that her depression is nonresponsive to treatment. Amrita complains of feeling sad and "empty" on most days and reports anhedonia and insomnia. She describes "moving slowly" and has had difficulties working and caring for her daughter. She has a history of migraines and hypothyroidism managed with levothyroxine. She has had a partial response to sertraline but still reports being "down most days."

An important question for this patient with symptoms of depression is whether she has had episodes of feeling energetic and times when she was not her usual self. When asked, Amrita reports a 2-week period when her depression "improved"; this interval was characterized by high productivity and lack of need for sleep (sleeping only 3 or 4 hours per night).

Diagnosing Bipolar Depression

Diagnosing bipolar depression can be challenging, and it is probably the most misdiagnosed phase of the bipolar disorder spectrum. Many

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Method of Participation

There are no fees for participating in and receiving credit for this activity. During the period August 2017 through August 2018, participants must: 1) read the learning objectives and faculty disclosures, 2) study the educational activity, and 3) complete the posttest and evaluation at **https://MERdepression.cvent.com**. A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better.

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Journal supplement

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There is no fee for this educational activity.

patients with bipolar depression are initially diagnosed and treated for MDD.[1] The consequences of misdiagnosis and improper treatment of bipolar depression can be considerable. Patients misdiagnosed with MDD are usually treated with antidepressant monotherapy, which is not efficacious and may be associated with a risk of mood switching.[1,2]

The extent of misdiagnosis was highlighted by the results of a survey of 600 patients with bipolar disorder in the National Depressive and Manic-Depressive Association advocacy group.[3] Although more than one-third sought professional care within 1 year of symptom onset, 69% were misdiagnosed, principally with unipolar depression. Among those misdiagnosed, patients consulted an average of 4 psychiatrists before being correctly diagnosed. For one-third of patients, it took at least 10 years to receive an accurate diagnosis. Another study showed that among outpatients (n=649) receiving treatment for depression, 21% screened positive for bipolar disorder, most of whom had never been diagnosed.[4] In a study of 501 patients with bipolar disorder, the mean interval between the first episode and treatment was 9.6 years.[5] Longer duration of untreated bipolar depression was associated with more mood episodes and suicidal behavior,[5] and an increasing number of previous episodes was associated with poorer outcomes once treatment was started.[6,7]

Bipolar depression has a considerable impact on patients. Two long-term prospective studies that assessed the natural history of weekly symptom status in patients with bipolar disorder demonstrated the burden of depression in these patients.[8,9] In a study of 146 patients with bipolar I disorder, depressive symptoms were 3 times as frequent as manic/hypomanic symptoms (31.9% vs 8.9% of follow-up weeks) and 5 times more frequent than cycling/mixed symptoms (5.9% of follow-up weeks).[8] In a companion study of 86 patients with bipolar II disorder, depressive symptoms were even more predominant (50.3% of follow-up weeks), compared with hypomanic symptoms (1.3%) and cycling/mixed symptoms (2.3%).[9] Although bipolar I disorder is characterized by episodic mania, the severity of bipolar depression is greater in patients with bipolar II disorder (50.3% vs 31.9% of follow-up weeks).[8,9] Depressive symptoms are also more troublesome to social adjustment than are manic symptoms. In a survey of 593 patients with bipolar disorder, self-reported depressive symptoms were more frequent than manic symptoms and were associated with significantly greater disruption of occupational, social, and family functioning.[10] Further, an increasing body of evidence suggests that the predominant mood polarity is an important prognostic indicator in patients with bipolar disorder and may have implications for long-term treatment.[11-13] Recent research has shown that depressive-predominant bipolar disorder is associated with longer delay until diagnosis and a higher number of suicide attempts.[11,13]

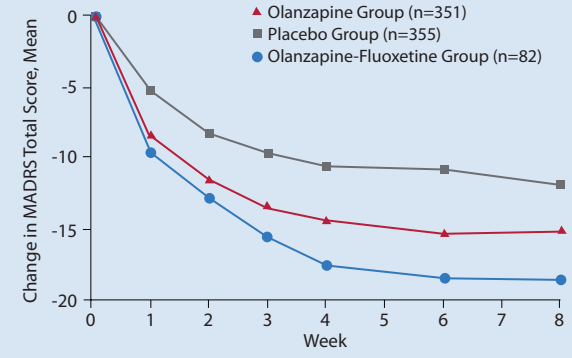
According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria, differentiating bipolar from unipolar depression requires documentation of a past episode of hypomania or mania.[14] However, patients frequently underreport previous hypomanic and manic episodes and/or may not perceive these periods as being outside of the ordinary. As shown in the case presentation, Amrita presented with a major complaint of depression, but only when probed for a hypomanic or manic history did she reveal an episode suggesting symptoms of mania. In the absence of pathognomonic characteristics of bipolar depression, it is possible to take a probabilistic approach to the diagnosis based on numerous patient characteristics associated with an increased likelihood of bipolar disorder.[15] Outside of a prior history of mania, one of the most informative questions that one can ask a patient is whether he or she has a family history of bipolar disorder.[16-18] Additional characteristics of the patient's history and clinical episodes may increase the likelihood of bipolar versus unipolar depression. In a study of 306 patients undergoing a major depressive episode, the most significant predictive factors for bipolar disorder were seasonality, number of past episodes, hospitalization for psychiatric disorders, mixed states, and mood reactivity.[19] Another study that examined diagnostic conversion from MDD to bipolar depression found that earlier age at onset and treatment-resistant depression were significantly associated with conversion.[20] Another presentation that is associated with bipolar depression is antidepressant-related emergent mania or hypomania.[21] The risk of antidepressant-emergent mania was much higher among patients with bipolar depression, compared with MDD (13.8% vs 1.24%).[21]

Depression with Psychosis

Depression with psychotic features is a subtype of MDD in the DSM-5.[14] However, researchers have proposed that psychotic depression may be a distinct diagnostic classification based on biologic, clinical, therapeutic, and prognostic differences between psychotic and nonpsychotic depression.[22] Unipolar psychotic depression is closely related to bipolar disorder[22]; for example, psychotic symptoms are more common in bipolar depression than in unipolar depression.[23] Psychotic features of depression are predictive of a bipolar disorder diagnosis and are associated with emergent mania in depressed patients.[24,25] In a meta-analysis of prospective studies, patients with major depression and psychotic symptoms were almost 5 times more likely to transition to bipolar disorder than those without psychotic symptoms (odds ratio [OR], 4.76; 95% confidence interval [CI], 1.79-12.66).[26] Additionally, bipolar disorder was more prevalent among those with a family history of psychotic depression than those with a family history of nonpsychotic depression.[27] The presence of psychosis in bipolar disorder is associated with neurocognitive impairment and poorer prognosis.[28]

FIGURE 1

Mean changes in MADRS scores in an 8-week study. Reductions in MADRS scores with the use of olanzapine and olanzapine-fluoxetine were significantly greater than with placebo throughout the study.[30]



Abbreviation: MADRS, Montgomery-Åsberg Depression Rating Scale.

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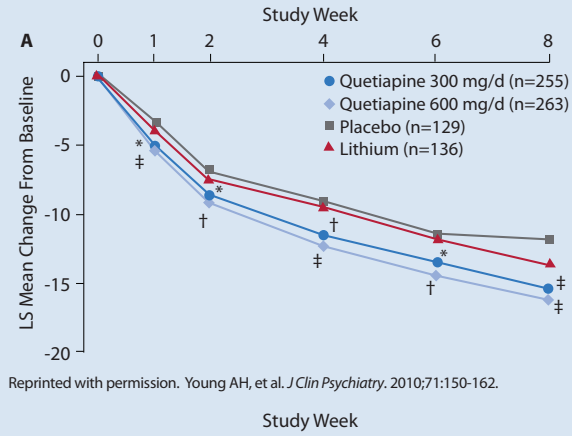
FIGURE 2

Mean changes in MADRS scores in an 8-week study comparing (A) placebo versus quetiapine and lithium (EMBOLDEN I) and versus (B) quetiapine and paroxetine (EMBOLDEN II).[33,34]



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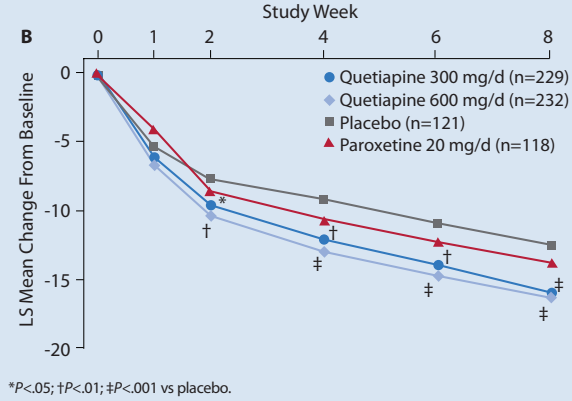

*P<.05; †P<.01; ‡P<.001 vs placebo.

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

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One of the outstanding questions in treating patients with psychotic depression is diagnostic stability. A study monitored 49 patients with a first episode of MDD and psychotic features to determine rates of remission and recovery and to evaluate diagnostic stability.[29] After being followed for ≥2 years from first hospitalization, 41% of patients had a different diagnosis. Of those with a new diagnosis, 70% of the new diagnoses were bipolar disorder and 30% were schizoaffective disorder. Notably, those patients with psychotic depression and a change in diagnosis had a 2.4-fold higher baseline score on the Young Mania Rating Scale than patients without a diagnostic change (score of 5.05 vs 2.12; OR, 1.18; 95% CI, 1.01-1.38; P=.036), and the presence of manic symptoms predicted a switch to bipolar disorder. Of those retaining the initial diagnosis of psychotic depression for 2 years, 42% remained symptomatic.

Pharmacotherapy for Bipolar Depression

Four treatments for bipolar depression are currently approved by the US Food and Drug Administration (FDA): olanzapine/fluoxetine combination, quetiapine, lurasidone monotherapy, and lurasidone adjunctive to lithium or valproate. Although there have been no direct head-to-head comparisons to date, studies have shown that these medications appear to have comparable efficacy with different adverse effects.

The efficacy of olanzapine and olanzapine-fluoxetine combination was evaluated in a randomized, double-blind, 8-week trial.[30] The study enrolled 833 adults with bipolar I depression and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of at least 20. Patients received placebo (n=377), olanzapine 5-20 mg/d (n=370), or daily olanzapine-fluoxetine 6 mg/25 mg, 6 mg/50 mg, or 12 mg/50 mg (n=86). The olanzapine and olanzapine-fluoxetine groups demonstrated significantly better improvement in depressive symptoms compared with the placebo group in each of the 8 weeks (P<.001 for all) (***Figure 1***).[30] Compared with olanzapine, the combination olanzapine-fluoxetine group showed significantly greater improvement at Weeks 4 through 8 (P<.02). A significantly higher percentage of patients had potentially clinically significant weight gain (greater than 7% from baseline) with olanzapine (18.7%) and olanzapine-fluoxetine (19.5%) compared with placebo (0.3%; P<.001 for all).

FDA approval of quetiapine monotherapy for bipolar depression was based on efficacy and tolerability in 2 trials: BOLDER I and II.[31,32] These two 8-week studies showed that quetiapine 300 mg/d or 600 mg/d significantly improved symptoms of depression according to a decrease in MADRS scores compared with placebo. Head-to-head comparisons between established and newer treatments were evaluated in the EMBOLDEN I and II studies.[33,34] EMBOLDEN I was a double-blind, placebo-controlled study to evaluate quetiapine or lithium monotherapy

in 802 adult patients with bipolar disorder and recent depression (499 with bipolar I and 303 with bipolar II).[33] Patients were randomly assigned to quetiapine 300 mg/d (n=265), quetiapine 600 mg/d (n=268), lithium 600-1800 mg/d (n=136), or placebo (n=133) for 8 weeks. From Week 1 through Week 8, both doses of quetiapine were significantly more effective than placebo based on decreases in MADRS scores ($P<.05$) (***Figure 2A***).[33] The improvement in MADRS score in patients receiving lithium was not statistically significant compared with placebo. The most commonly reported adverse events with quetiapine were somnolence, dry mouth, and dizziness; for example, dizziness occurred in 18.1% and 17.6% for quetiapine 300 mg/d and 600 mg/d, respectively, compared with 8.8% for lithium and 3.8% for placebo.

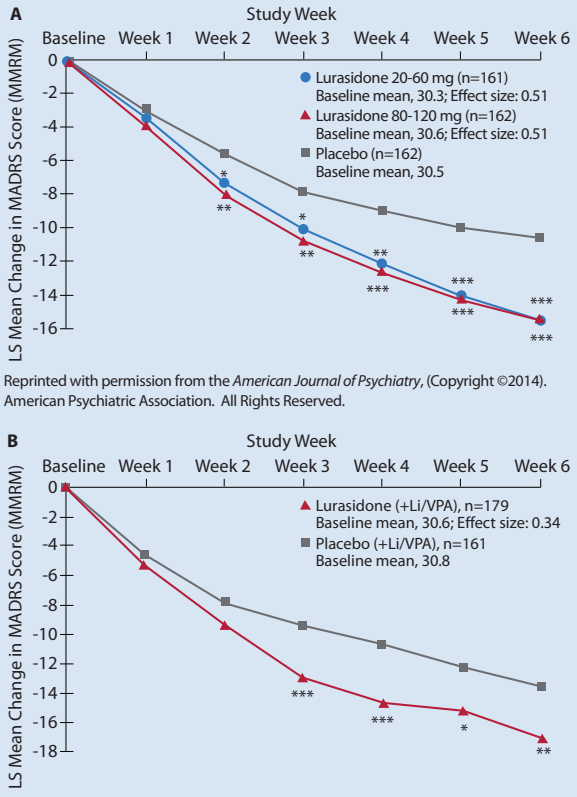
EMBOLDEN II compared the efficacy and tolerability of quetiapine and paroxetine monotherapy with placebo in an 8-week, double-blind trial in patients with bipolar depression.[34] A total of 740 patients (478 with bipolar I and 262 with bipolar II) were randomized to quetiapine 300 mg/d (n=245), quetiapine 600 mg/d (n=247), paroxetine 20 mg/d (n=122), or placebo (n=126) for 8 weeks. Improvement in MADRS scores from baseline was significantly greater for quetiapine-treated patients at both doses compared with placebo, but was not significant for those receiving paroxetine (***Figure 2B***).[34] Adverse events were comparable to those in EMBOLDEN I; the most common adverse events in patients receiving quetiapine were dry mouth, somnolence, sedation, and dizziness.

Lurasidone was approved by the FDA in June 2013 as monotherapy or adjunctive therapy (with lithium or valproate) for adults with bipolar I disorder. Efficacy and safety of lurasidone in patients with depression associated with bipolar I disorder were studied in 2 PREVAIL trials. The primary end point of the studies was reduction in depressive symptoms as indicated by changes from baseline in MADRS score.[35,36] In the lurasidone monotherapy trial (PREVAIL 2), 505 patients with bipolar disorder who were currently experiencing a major depressive episode were randomized to 6 weeks of double-blind treatment with lurasidone 20-60 mg/d (n=166), 80-120 mg/d (n=169), or placebo (n=170).[35] Both dose groups showed a significantly greater improvement on the MADRS total score compared with placebo (***Figure 3A***).[35] The effect size was 0.51 for both lurasidone dose groups. The most common adverse events in patients receiving lurasidone were nausea, headache, akathisia, and somnolence. There were no clinically significant differences in metabolic parameters or body weight between lurasidone and placebo.

In the PREVAIL 1 adjunctive therapy trial, patients were randomized to 6 weeks of double-blind treatment with lurasidone 20-120 mg/d (n=183) or placebo (n=165) as add-on therapy to mood stabilizers (lithium or valproate).[36] Compared with placebo, lurasidone achieved a significantly lower mean MADRS total score at 6 weeks,

FIGURE 3

Mean changes in MADRS scores in a 6-week study comparing (A) placebo with lurasidone monotherapy (PREVAIL 2) or comparing (B) placebo with lurasidone adjunctive to lithium or valproate (PREVAIL 1). [35,36]



*$P<.05$; **$P<.01$; ***$P<.001$

Abbreviations: LI, lithium; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model for repeated measure; VPA, valproate

with an effect size of 0.34 (***Figure 3B***).[36] The most commonly reported adverse effects were nausea, somnolence, tremor, akathisia, and insomnia, while minimal changes were noted in body weight and metabolic parameters.

The adverse-event profiles of FDA-approved pharmacotherapies for bipolar depression are summarized in ***Table 1.***[37-39]

Conclusion

Bipolar depression is often undiagnosed or misdiagnosed. Depression is frequently the presenting mood state for patients with bipolar disorder, so screening for hypomania or mania is essential in patients with depression. It is important to remember that patients may be reluctant to disclose symptoms of hypomania or mania, or may find these episodes unremarkable. Several additional cues may point to bipolar depression, such as early onset of depression, family history, treatment-resistant depression, and number of past episodes. Psychotic

TABLE 1 Adverse Effects With Antipsychotics That Are FDA-Approved for Bipolar Depression[37-39]

Adverse Effect	Olanzapine	Quetiapine	Lurasidone
Metabolic			
Weight gain	+++	++	+/0
Dyslipidemia	+++	+	0
Glucose dysregulation	++	+	0
Neurologic			
Somnolence/ sedation	+++	+++	+/0
EPS	+	0	+/0
Cardiovascular			
Myocarditis/ cardiomyopathy	0	0	0
QTc prolongation	+/0	+	0
Hormonal			
Prolactin elevation	+/0	0	0

Abbreviations: EPS, extrapyramidal symptoms; FDA, US Food and Drug Administration.

Data from: McIntyre RS, Konarski JZ. *J Clin Psychiatry.* 2005;66(Suppl 3):28-36. Cha DS, McIntyre RS. *Expert Opin Pharmacother.* 2012;13:1587-1598.

features of depression may herald future transition to bipolar disorder. There are currently 3 FDA-approved antipsychotic agents for treatment of bipolar depression. While comparable in efficacy, they vary in their adverse-event profiles.

CASE PRESENTATION: CONCLUSION

Amrita was diagnosed with bipolar depression. She currently has symptoms of MDD. Her depression was preceded by a manic episode that lasted approximately 2 weeks, during which she demonstrated flight of ideas, pressured speech, lack of need for sleep, and increased goal-directed activity. Her young age at onset and number of depressive episodes are further clues to her diagnosis of bipolar depression.

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Current PSYCHIATRY

Distinctions Between Bipolar I and Bipolar II Depression

Claudia Baldassano, MD

CASE PRESENTATION

Matthew is a 28-year-old man who has experienced numerous depressive episodes on and off for about 10 years. He is an unmarried freelance information-technology specialist. During depressive periods he often misses work, sometimes staying in bed most of the day. In recent months, he has experienced sad or depressed moods on most days. He reports a loss of appetite, weight loss, loss of interest in work and personal pursuits, and social isolation. Matthew has been undergoing cognitive-behavioral therapy and previously received fluoxetine, but switched to venlafaxine because of lack of efficacy. Matthew was referred by his primary care physician for depression unresponsive to an antidepressant. His psychiatrist asked whether he ever had a period of time that was characterized by more energy and that he may have considered unusual. Matthew reported that shortly after changing medications to venlafaxine, for approximately 3 or 4 days "I was finding myself a lot more outgoing and talkative than usual."

Diagnosis of Bipolar II Disorder

Patients with bipolar I and bipolar II depression have in common a current or previous major depressive episode. The necessary feature differentiating bipolar I from bipolar II disorders is a lifetime episode of mania versus hypomania. Bipolar II disorder is frequently undiagnosed in patients with depressive episodes because of the difficulty in differentiating the disorder from unipolar major depressive disorder (MDD) and the frequent lack of history or incomplete history of hypomania. According to data from the National Comorbidity Survey Replication, 12-month prevalence is estimated to be 0.6% for bipolar I disorder, 0.8% for bipolar II disorder, and 1.4% for subthreshold bipolar disorder.[1] In a reevaluation of data from the US National Epidemiologic Catchment Area study, the lifetime prevalence of bipolar spectrum disorders in the general population was found to be 6.4%.[2] This percentage included 0.8% for manic episode, 0.5% for hypomania, and 5.1% for subsyndromal but dysfunctional manic symptoms. Compared to patients without mental disorders, patients with any of these symptoms had significantly greater health care utilization, use of public assistance, and suicidal behavior.[2]

Many patients diagnosed with MDD are later found to have bipolar disorder. Among patients treated for unipolar depression in a primary care clinic, 21% screened positive for bipolar disorder.[3] Up to 45% of psychiatric outpatients diagnosed with depression have been found to have bipolar II disorder,[4] similar to the rate found in the French EPIDEP study (40%)[5] and a large study in Russia (35.9%).[4-6]

Evidence-based psychiatry depends on the empirical validation of symptom-based criteria, as reflected in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth edition* (DSM-5). Reliability of the DSM-5 criteria was assessed in the DSM Field Trials, which evaluated independent interviews by 2 different clinicians trained in the respective diagnoses; methods included a predetermined statistical approach.[7] Notably, the kappa statistic for interrater agreement was good for bipolar II disorder (κ=0.40), which was greater than that for MDD (κ=0.28) but lower than that for bipolar I disorder (κ=0.56).

The diagnosis of bipolar II disorder can be challenging for several reasons. Mood elevation is the least likely presentation of patients seeking treatment, and reliance on patients' self-report can be inadequate for identifying hypomania. Busy clinicians are often limited to a nonstructured interview, and screening may supplant a formal assessment. Common diagnostic confounders include unipolar depression, substance use disorder, borderline personality disorder, attention-deficit hyperactivity disorder, and anxiety disorders. Diagnosis of bipolar II disorder has important implications in terms of therapeutic interventions and prognosis. Suicidality risk is high in those with bipolar II disorder, and rates of suicide attempts are comparable to those in patients with bipolar I disorder (31.4% and 29.9%, respectively).[8] Compared with bipolar I disorder, patients with bipolar II disorder may experience more rapid cycling, depression recurrence, and psychiatric comorbidity.[9-11] An analysis of 493 patients showed that, compared with unipolar depression, bipolar II depression was associated with hypersomnia (vs insomnia), psychomotor activation (vs psychomotor retardation), guilt feelings, and suicidal thought.[12]

The duration of hypomania as a diagnostic criterion for bipolar II disorder has recently attracted much attention. Many patients have episodes of hypomania shorter than 4 days, the required duration using the DSM-5 diagnostic criteria. Currently, a diagnosis of bipolar II disorder requires that the patient have the requisite number of hypomanic symptoms present most of the day, nearly every day, for 4 days, and the symptoms must constitute a change from usual behavior.[13] An expert panel recommended reducing the required duration of 4 days for hypomania on the basis

of extensive evidence.[14] Research has shown that the usual course for hypomania episodes is 1 to 3 days and that those patients with hypomania of shorter duration do not differ substantially from those who have symptoms for 4 days.[15]

The DSM-5 includes a section called "Conditions for Further Study," which provides proposed criteria for conditions that are thought to be distinct from the clinical diagnoses of the DSM-5 but warrant further research and discussion.[13] Research criteria sets are established by expert consensus based on evidence from literature review and clinical trials. The syndrome of "depressive episodes with short-duration hypomania" is included in this section as a syndrome in which the frequency of episodes of hypomania is too short to qualify for a diagnosis of bipolar II disorder using the current criteria. This proposed condition is similar to that of bipolar II disorder and requires at least 1 major depressive episode but also requires "at least 2 lifetime episodes of hypomanic periods that involve the required criterion symptoms…but are of insufficient duration (at least 2 days but less than 4 consecutive days) to meet criteria for a hypomanic episode."[13]

Research supports the allowance for a shorter period of hypomania. In a study of 206 patients with bipolar II disorder and depression, a group of 140 patients with bipolar II disorder in remission, and 178 patients with MDD, participants were evaluated using the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)* Structured Clinical Interview, and short and long periods of hypomania were compared using bipolar validators.[16] Up to 30% of hypomania episodes lasted 2 to 3 days, and most (72%) lasted less than 4 weeks. Patients with bipolar II disorder with short hypomania versus longer hypomania were largely indistinguishable on bipolar validation characteristics such as early age at onset, depressive recurrence, mixed state, and family history. Indicators such as family history distinguished bipolar II disorder with brief hypomania from MDD. The authors estimated that the current 4-day threshold for symptom duration of hypomania would misclassify 1 of 3 patients with bipolar II disorder as having MDD.

An accurate and timely diagnosis of bipolar II disorder can be assisted by specific clinical strategies. For example, screening instruments can facilitate recognition of bipolar II disorder in patients with depression. The Mood Disorder Questionnaire (MDQ) is a widely used and well-studied self-report screening tool.[17] The MDQ takes about 5 minutes to complete. Of the 15 questions, the first 13 are designed to identify manic or hypomanic symptoms, and the last 2 questions evaluate symptom clusters and functional impairment. Another validated self-report screening instrument is the Hypomania Symptom Checklist (HCL-32).[18] HCL-32 has 2 introductory questions and another 32 questions that address specific symptoms of mania and hypomania. Studies have shown that systematic probing for a history of hypomanic symptoms improves the detection rate for bipolar II disorder.[19] In the multicenter study from France (EPIDEP), 250 patients diagnosed with major depressive episode were reevaluated for "soft" bipolar disorders.[5] A total of 48 psychiatrists were trained to use a common protocol for the diagnosis of hypomania, which was developed from several clinical instruments and used to validate the diagnosis in patients with MDD. The prevalence of bipolar II disorder was 22% at the first evaluation, and this nearly doubled to 40% with systematic evaluation (***Figure 1***).[5] This study demonstrated both the difficulty of diagnosing bipolar II disorder in patients with a major depressive episode and the importance of the clinical interview.

Treatment-Resistant Depression: Is it Bipolar Disorder?

Treatment-resistant depression (generally defined as insufficient response to 2 or more adequate trials of antidepressants) is prevalent in primary care and psychiatric outpatient settings. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which evaluated sequential medication regimens for patients with MDD, remission rates were 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment steps, respectively, indicating that multiple treatments have declining success rates.[20] Recently, it has been proposed that some patients with difficult-to-treat depression may actually have bipolar disorder. One study evaluated clinical characteristics and outcomes of 61 patients with resistant depression and an inadequate response to at least 2 antidepressants.[21] At the initial evaluation, 65% had MDD and 35% had bipolar disorder. At a reevaluation within 1 year, 43% had bipolar II disorder, 3% had bipolar I disorder, and 13% had bipolar disorder not otherwise specified. The results suggest that a considerable proportion of patients with unipolar treatment-resistant depression actually have a bipolar diathesis. Another study evaluated 602 patients from community practice settings with unipolar depression and nonresponse to at least 1 antidepressant trial.[22] Among these patients, 18.6% screened positive for bipolar disorder using the MDQ, regardless of the number of previous medication trials. These data suggest that clinicians should screen for bipolar disorder in patients with depression who have had an unsatisfactory response to an antidepressant.

Use of Antidepressants for Bipolar II Disorder

Guidelines often lack recommendations specific to the treatment of patients with bipolar II disorder. Depressive symptoms are more common than symptoms of hypomania in patients with bipolar II disor-

der, and these patients spend more time depressed than those with bipolar I disorder (reported as 50.3% vs 31.9% of follow-up weeks during about 13 years of monitoring).[23,24] Because depression is the predominant mood, the priority is to treat acute bipolar symptoms, prevent a relapse of depressive mood, and avoid inducing a switch into hypomania or mania.[25] The potential role of antidepressants in the management of patients with hypomania and mild mania has remained a controversial issue. There are few placebo-controlled, double-blind studies of antidepressant monotherapy in patients with bipolar II depression. Although there appear to be lower switch rates in depressed patients with bipolar II than bipolar I disorder who receive adjunctive antidepressants, less is known about antidepressant monotherapy in these patients.[26]

A 14-week, open-label study examined fluoxetine monotherapy in 148 patients with depression and bipolar II disorder.[27] There were 88 responders (59.5%) and 86 remitters (58.1%), and the mean time to remission was 64.4 days. Six patients had hypomania and 29 had subsyndromal hypomania, although there were no discontinuations in these patients. An additional open-label study of fluoxetine monotherapy in patients with bipolar II depression and rapid cycling course (n=42) versus those without rapid cycling course (n=124) found a greater decrease in depression scores for the patients with rapid cycling (P=.04).[28] Hypomania occurred in 5.4% of patients with rapid cycling, compared with 3.6% of those with nonrapid cycling. A randomized, double-blind study evaluated the efficacy of continuation antidepressant versus mood stabilizer monotherapy for the prevention of depressive relapse in 129 patients with bipolar II disorder and depression.[29] Venlafaxine was found to be similar to lithium with regard to relapse rate and time to relapse. Neither mania rating scores nor the frequency or duration of syndromal or subsyndromal hypomania showed any differences between the treatment groups. Repeated antidepressant use in bipolar II depression is associated with a stepwise loss in effectiveness, with a recent study reporting a 25% decrease in the likelihood of response with each increase in the number of previous antidepressant medications.[30]

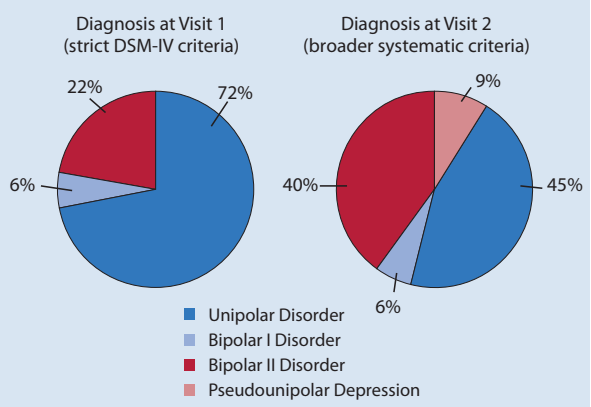
In a large randomized trial of antidepressants in patients with bipolar II disorder and depression, acute treatment was evaluated among 142 patients in a multicenter 16-week trial.[31] Patients enrolled in the study were randomized to receive lithium, sertraline, or a combination of both. Rapid cycling patients (42% overall) were evenly distributed among the treatment groups. The overall study dropout rate was 56%, and the rate was highest for the combination regimen (71%). The overall treatment response rate was 63%, and most patients who responded did so within 6 weeks (***Figure 2***).[31] Mood switch rates (14% overall) were comparable among the 3 groups after accounting for dropouts. No patient had mania or hospitalization for a switch. Response rates were comparable for all treatment groups among patients with a rapid cycling course. In contrast, those with a nonrapid cycling course had better response rates with either monotherapy than with combination therapy. In conclusion, lithium, sertraline, or a combination of both resulted in favorable response rates within 6 weeks in patients with bipolar II depression. Although switch rates were similar with monotherapy or combination therapy, there were more discontinuations in the combination therapy group.

Very few long-term data are available on antidepressant use in bipolar II disorder. One study to assess antidepressants in patients with bipolar disorder evaluated efficacy and safety in patients with bipolar I disorder (n=21) or bipolar II disorder (n=49) who were treated for acute major depressive episodes with antidepressants plus mood stabilizers until they achieved euthymia.[32] Patients were then randomized in an open-label phase to continue or discontinue antidepressants for up to 3 years. During a mean of 1.6 years of follow-up, patients with bipolar I depression had greater improvement than those with bipolar II depression. In addition, continuing antidepressants (vs discontinuing) resulted in a lower frequency of depressive recurrences in patients with bipolar II disorder (0.76 vs 0.97) and bipolar I disorder (0.59 vs 0.94); these differences were both statistically significant.

When treating with antidepressants in patients with bipolar II disorder, clinicians are always concerned

FIGURE 1

Increased recognition of hypomania in patients with major depressive episodes following implementation of systematic evaluation.[5]

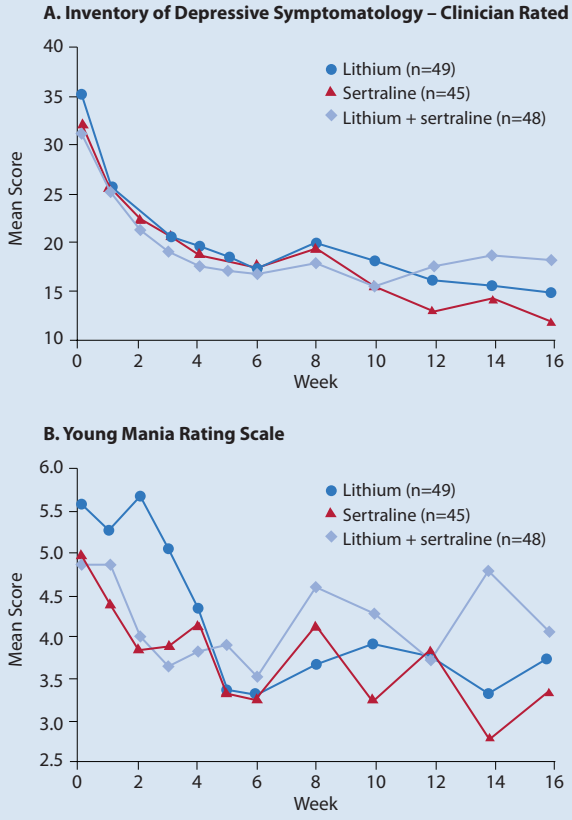


Abbrevation: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*

Reprinted from *Journal of Affective Disorders*, Vol 50(2-3), Hantouche EG, et al, Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study (EPIDEP), 163-73. Copyright ©1998, with permission from Elsevier.

FIGURE 2

Average weekly (A) depressive and (B) manic symptom scores among 142 patients treated for bipolar II disorder and depression.[31]



about the risk of switches to hypomania or mania. The risk of antidepressant-associated manic and hypomanic episodes in patients with bipolar I disorder, bipolar II disorder, or MDD was assessed in a large meta-analysis of acute (short-term) trials and maintenance studies.[33] In studies comparing patients with bipolar I and bipolar II disorders, mood elevations occurred in an average of 14.2% and 7.1%, respectively, during acute trials. In maintenance studies, the rates were higher, at 23.4% and 13.9% for bipolar I and bipolar II disorder, respectively. The relative risk (RR) of antidepressant-associated mood elevation was almost twice as high in bipolar I disorder than in bipolar II disorder (RR, 1.78; 95% confidence interval, 1.24-2.58; *P*=.002). In studies comparing patients with bipolar II disorder and MDD, mood elevation rates were 8.1% and 1.5%, respectively, in acute trials; and 16.5% and 6.0%, respectively, in maintenance trials. For patients with MDD and those with bipolar II disorder, most mood elevations were switches into hypomania, whereas patients with bipolar I disorder experienced hypomania and mania with comparable frequencies.

Overall, there is a lack of strong evidence to support a value for antidepressants in patients with bipolar disorder. Although some studies suggest that antidepressants may be helpful in some patients with bipolar II disorder, there is also evidence of potentially harmful mood elevation.

Conclusion

Significant psychosocial impairment is a characteristic of both bipolar I and bipolar II disorders. Bipolar disorder is difficult to diagnose, and bipolar II disorder can be especially challenging because most patients will present with a depressive episode and not mention previous hypomanic episodes. Patients with shorter durations of hypomania (1-3 days) may have clinical characteristics and outcomes similar to patients with bipolar II disorder despite not meeting the accepted criterion of a 4-day duration. Treatment with antidepressants may be just as ineffective for bipolar II as for bipolar I disorder, and there is a moderate risk of mood switching. For this reason, as well as to enhance prognostic information, it is crucial that clinicians distinguish bipolar II depression from unipolar depression.

CASE PRESENTATION: CONCLUSION

Matthew articulated some degree of mood elevation that was consistent with hypomania. Additional interviewing is appropriate to explore the level of dysfunction associated with Matthew's mood elevation. Patients seldom seek care when they are hypomanic, and patients presenting with depression will not always volunteer sufficient information about periods of mood elevation. During further questioning, Matthew reported a period of decreased need for sleep, pressured speech, flight of ideas, and involvement in activities with painful consequences. His symptoms occurred for "about 3 or 4 days" and shortly after starting venlafaxine. Although 1 or 2 symptoms such as irritation or edginess following antidepressant use are not sufficient for diagnosis of a hypomanic episode, Matthew's potential hypomania was more elaborate and may be associated with antidepressant use.

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Treatment of Major Depressive Disorder and Bipolar Mixed States

Vladimir Maletic, MD, MS

CASE PRESENTATION

Ramona is a 35-year-old unmarried woman who has recently relocated to the area and is seeking a psychiatrist. She works as a real estate attorney. Ramona describes herself as "depressed most of the time and manic." She reports having been depressed for 3 years. Over the last few months she has experienced depressed mood, loss of interest in personal pursuits such as piano and sculpting, and difficulty sleeping. When asked what she means by manic, she describes being physically "slowed down" but having a racing mind and pressure to keep talking to the point of disturbing others. Additionally, she describes periods of time when she is easily distracted. Ramona was initially treated with escitalopram, which her previous provider recently replaced with valproate.

Diagnosis of Bipolar Mixed States

Bipolar disorder may be at times difficult to diagnose. It is not uncommon for years to transpire between the emergence of symptoms and an accurate diagnosis.[1] One of the challenges in making a correct and timely diagnosis of bipolar disorder is the heterogeneity of its manifestations.[2] Patients often present with mixed states, such as manic or hypomanic states with mixed depressive features or a major depressive episode combined with subsyndromal hypomania or mania. Mixed states, manifested by coexistence of mania or hypomania and depression, can at times lead to misdiagnosis, with potentially negative consequences. For example, treatment of bipolar disorder with antidepressants may be ineffective or trigger mood elevations and lability.[3,4] Failure to detect the mixed nature of manic episodes may have dire implications. In a study of 184 patients, suicidality (past, current, or recurrent) was far more common in the presence of mixed mania (defined in the study as mania combined with 2 or more prominent depressive features) than in patients with pure mania (57.9% vs 1.3%; $P<.001$).[5]

Mixed states are increasingly appreciated in the context of a disorder spectrum, rather than as discrete categories of illness. This is reflected by changes in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) mixed features specifiers, compared with the earlier designation of mixed episode in the *DSM Fourth Edition, Text Revision* (DSM-IV-TR).[6] In the DSM-IV-TR, mixed state was defined as a week of concomitantly meeting full criteria for mania and full criteria for depression, accompanied by impaired functioning, psychosis, or hospitalization. In the DSM-5, a mixed categorical-dimensional approach is employed.[7] Three or more clinically significant subthreshold symptoms of the opposite pole are included in the DSM-5 mixed features specifier.[6] These changes have implications not only for diagnosis and treatment, but also for epidemiology, research, and education.[8] It remains unclear what the ramifications will be for clinicians, researchers, and patients from diagnosing and treating major depressive disorder (MDD) with mixed features.

Hypomania and Mania With Mixed Depressive Features

Although mixed manic states occur frequently in patients with bipolar disorder, estimates of prevalence vary widely because of the heterogeneity of criteria used to define the condition. In a cross-sectional study performed in 76 centers, 368 inpatients with bipolar disorder were assessed for mixed episodes using various criteria.[9] The estimated prevalence of mixed episodes of mania was 12.9% according to the DSM-IV-TR, 9% according to the International Classification of Diseases, Tenth Edition (ICD-10), and 23.2% based on clinical judgement. In a review of 17 studies (n=981), the overall rate of mixed states was 31% among acutely manic patients with bipolar disorder.[10] Relative to "pure" mania without mixed symptoms, mixed mania occurs more frequently in women than men, and those with mixed mania had a hospitalization at a younger age.[11,12]

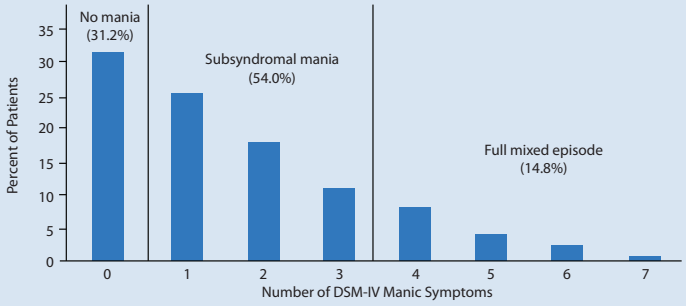
Mixed mania has a worse course and prognosis than pure mania.[13] Episodes tend to be more frequent and illness is of longer duration in patients with mixed mania.[11,14] Patients with mixed mania had an increased risk of subsequent depressive episodes and a much shorter interval until a new episode of depression than those with pure mania.[15] Further, patients who transitioned to a depressed episode without recovery from the index mania episode were more likely to have mixed mania than those who did not cycle into depression.[16] Mixed mania is also associated with more functional impairment, comorbid psychiatric disorder, substance use disorder, and suicidality.[5,12,17-19]

Mixed mania states are often more severe and clinically complex than pure mania. The treatment of mixed mania is challenging because of the lack of prospective, randomized trials in homogeneous cohorts of patients with bipolar disorder and mixed manic episodes. The majority of evidence stems from subgroup or post hoc analyses. In general, patients with mixed manic episodes have a diminished response to pharmacologic therapy, in particular monotherapy, compared with patients with

pure mania episodes.[20] Most available evidence evaluates atypical antipsychotics and mood stabilizers.[20-22] In the absence of demonstrated superior efficacy in mixed mania, the selection of pharmacologic therapy is based on individual considerations and factors such as tolerability, safety, and long-term maintenance. One study of patients meeting criteria for DSM-IV-TR mixed episodes evaluated a mood stabilizer alone versus a mood stabilizer combined with an atypical antipsychotic.[23] Patients with inadequate response to divalproex were randomized to receive adjunctive olanzapine 5-20 mg/d (n=100) or placebo (n=101) for 6 weeks. Compared with placebo, adjunctive olanzapine achieved significantly greater decreases in mean scores on the Hamilton Depression Rating Scale (*P*=.02) and the Young Mania Rating Scale (YMRS; *P*<.001). Times to partial and full response were significantly shorter with adjunctive olanzapine. Increases in body weight, clinically significant weight gain (≥7% of total weight), and fasting plasma glucose were significantly greater with olanzapine than placebo.

FIGURE 1

Number of DSM-IV manic symptoms occurring during an index episode of bipolar depression in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (n=1380).[24]



Abbreviation: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*

Bipolar Depressive State With Mixed Mania

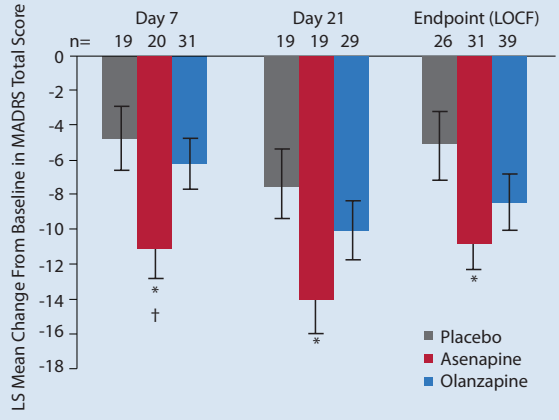
It has been recognized that the DSM-IV-TR criteria for mixed episode did not reflect the most common phenomenology of patients with bipolar depression and admixture of hypomania. The DSM-5 mixed features specifier addresses the idea that these symptoms are not necessarily divergent, but more often complementary. Therefore, it is important to appreciate mixed features because they have significant bearing on treatment decisions. Criteria for a major depressive episode did not change in the DSM-5. For patients with bipolar disorder, diagnosis of a major depressive episode with mixed features requires at least 3 manic or hypomanic symptoms during the majority of days of the current or most recent episode of depression.[6] In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, 1380 patients who met the criteria for bipolar I or II depression were evaluated for co-occurring manic symptoms.[24] Less than one-third of patients had no manic symptoms (31.2%). Approximately half (54.0%) had subsyndromal mania (1-3 symptoms of mania) and 14.8% had a full mixed episode according to DSM-IV criteria (***Figure 1***).[24] The most common (hypo)manic symptoms, folded into the context of depressive episode, were distractibility, flight of ideas, racing thoughts, and psychomotor agitation. In the STEP-BD study, patients with bipolar depressive episodes with mixed features of mania were more likely than those with pure depressive episodes to have an earlier age of onset, rapid cycling, bipolar I subtype, and history of suicide attempts.[24] As with patients with mixed mania, those with mixed depression are prone to more severe and frequent episodes of longer duration.[25,26]

Patients with bipolar depression and mixed features are often resistant to treatment; therefore, combination therapy with mood stabilizers and atypical antipsychotics has been recommended.[2,21] Although combination therapy may be needed, the role of antidepressants remains controversial. A recent review of the literature indicated that there is insufficient evidence to draw conclusions about safety and tolerability of antidepressants in patients with depressive mixed states.[27] Antidepressant monotherapy has limited efficacy but has the potential to worsen mixed depressive episodes.

Several atypical antipsychotics have been evaluated in patients with bipolar depression and mixed features, and a meta-analysis showed that treatment with atypical antipsychotics resulted in significant improvements in Montgomery-Åsberg Depression Rating Scale (MADRS) and YMRS scores versus placebo.[28] A post hoc study evaluated asenapine and olanzapine in a subgroup of patients with bipolar I disorder and moderate-to-severe mixed major depressive episodes who met DSM-IV-TR criteria for mixed episodes.[29] Data came from subgroup analyses of results from two 3-week, randomized, placebo-controlled trials (N=489 and N=488). Decreases in MADRS scores were significantly greater in the group randomized to asenapine compared with placebo, from baseline to study endpoint (***Figure 2***).[29] From baseline to Day 7, decreases in MADRS scores were significantly greater with asenapine than with olanzapine (*P*=.04). In another study, olanzapine monotherapy was evaluated in patients with bipolar I depression and mixed features using pooled data from 2 studies (N=1214).[30] The mean MADRS total scores were significantly decreased in patients with 0, 1-2, or ≥3 manic symptoms at baseline: –3.76 (*P*=.002), –3.20 (*P*<.001), and –3.44 (*P*=.002),

FIGURE 2

Improvement in depressive symptoms as assessed by mean changes from baseline in MADRS total scores in a study of asenapine and olanzapine versus placebo in patients with bipolar I disorder and mixed depression (n=98).[29]



*P<.05 vs placebo; †P<.05 vs olanzapine.

Abbreviations: LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale.

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respectively. Maintenance of response with olanzapine was studied in a post hoc analysis of 121 patients who achieved remission after a mixed episode and were then randomized to olanzapine or placebo.[31] Compared with placebo, olanzapine was associated with a longer time to symptomatic relapse (46 vs 15 days; P<.001). Another post hoc study evaluated the efficacy and safety of lurasidone monotherapy in patients with bipolar I depression who presented with mixed features (YMRS ≥4 at baseline).[32] Lurasidone was associated with a greater decrease in MADRS score at Week 6 versus placebo (–15.7 vs –10.9; P=.001) in the group with mixed features. The incidence rates of treatment-emergent hypomania and mania were similar for patients with and without mixed features in the placebo and lurasidone groups (0% to 3.4%).

Major Depressive Disorder With Subsyndromal Hypomania or Mania

The prevalence of mixed features in predominantly depressive patients was evaluated in the French EPIDEP study of 493 consecutive patients with MDD based on 2 semi-structured interviews. Mixed depression was identified in 23.8% of patients.[25] A study of nearly 600 patients with recurrent MDD and no family history of bipolar disorder evaluated the clinical outcomes of patients with subthreshold manic symptoms. Lifetime history of subthreshold symptoms of mania occurred in 9.6% of the sample.[33] Compared to those with MDD alone, patients with MDD and subthreshold mania were significantly more likely to have previous psychosis, poor response to antidepressants, more depressive episodes, and more hospitalizations. Other studies confirm that compared with patients with "pure" depression, those with subthreshold manic symptoms have more suicide attempts, more episodes, and more comorbidity (anxiety and substance use disorders).[33-37] Patients with MDD and mixed features have a greater likelihood of conversion to bipolar disorder. In the National Institute of Mental Health Collaborative Depression Study, 550 patients with MDD were screened for manic symptoms at baseline and monitored for a mean of 17.5 years.[38] The cumulative probability of developing hypomania or mania was 26.3%, resulting in a revised diagnosis of bipolar II disorder in 12.2% and bipolar I disorder in 7.5% of the patients. Clinical characteristics of MDD and subthreshold hypomania were evaluated among 211 participants in a large placebo-controlled trial.[39] The most common DSM-5-endorsed manic symptoms among patients with mixed major depression were flight of ideas or racing thoughts (66.8%), pressured speech (61.1%), and decreased need for sleep (40.8%). Also reported were distractibility (59.2%) and irritability (57.3%), although these symptoms are not specific for hypomania as they may occur within the context of a depressive episode. In another study, the composition of mood symptoms was compared in 117 patients with recurrent unipolar depression and 106 patients with bipolar I disorder.[40] In both groups, the number of hypomanic or manic symptoms reported was closely correlated with the number of depressive items reported.

Given the relatively recent incorporation of a mixed features specifier for subthreshold symptoms of hypomania or mania in patients with MDD, evidence for treatment is limited. In a claims analysis, patients with MDD and subthreshold hypomania were receiving antidepressants, mood stabilizers, and atypical antipsychotics; 72.1% received combination therapies with multiple drug classes.[37] Antidepressants are the most commonly used pharmacotherapy for MDD, but their efficacy and safety in patients with MDD and mixed features are not established. Antidepressants may not be efficacious in patients with depression and subthreshold symptoms of hypomania or mania, and they may be associated with treatment-emergent mood switching.[41,42] Therefore, although antidepressants remain the most common therapeutic choice for depression with mixed features, there are significant safety concerns associated with their use in these patients.[43]

A randomized, double-blind, placebo-controlled trial investigated the efficacy and safety of lurasidone in patients with MDD and mixed features.[44] Patients who met DSM-IV-TR criteria for MDD and had 2 or 3 manic symptoms were randomized to treatment with either lurasidone (20-60 mg/d, n=109) or placebo (n=100) for 6 weeks. For the primary endpoint of change from baseline in MADRS total score, the decrease was sig-

nificantly greater for lurasidone compared with placebo (–20.5 vs –13.0, respectively; *P*<.001; effect size=0.8) (***Figure 3***).[44] When endpoints were defined as treatment response (≥50% decline in MADRS score) and treatment remission (MADRS score ≤12), significantly greater proportions of patients randomized to lurasidone versus placebo met the criteria for response (64.8% vs 30.0%; number needed to treat [NNT]=3; *P*<.001) and remission (49.1% vs 23.0%; NNT=4; *P*<.001). The most common adverse events occurring in ≥5% of the lurasidone group were nausea and somnolence. At Week 6, change in weight was minimal for both the lurasidone and placebo groups (1.9% vs 1.0% for a ≥7% increase in weight).

A double-blind, placebo-controlled study evaluated patients with MDD or bipolar II disorder meeting DSM-IV criteria for a major depressive episode and 2 or 3 criteria for mania.[45] In this study, 73 patients were randomized to receive ziprasidone (40-160 mg/d) or placebo for 6 weeks. Decrease in MADRS score with ziprasidone was superior to placebo (*P*=.0038) (***Figure 4***).[45] Patients with bipolar II disorder had greater treatment efficacy than those with MDD and subthreshold mania. Adverse events reported in ≥5% of patients in the ziprasidone group were headache and drowsiness; weight change at 6 weeks was not significantly different between the ziprasidone and placebo groups (0.5 vs 0.6 lb).

Conclusion

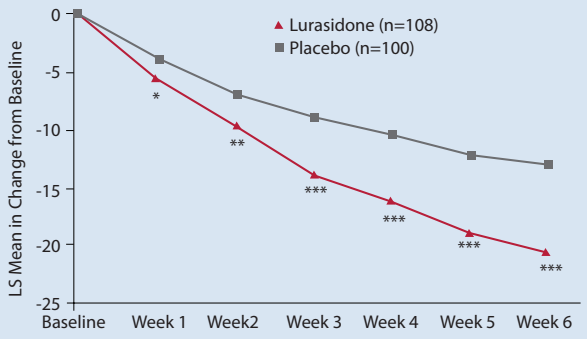
The diagnostic and clinical manifestations of mood disorders increasingly support a spectrum of disorders rather than discrete categories. Mixed episodes of mania or depression often portend worse outcomes and can be a challenge to treat. In particular, the role of antidepressants appears to be limited by lack of evidence for efficacy and concerns about safety. Patients with MDD and subthreshold hypomania or mania often have more severe illness than those with "pure" depression, and these patients may need different management approaches.

CASE PRESENTATION: CONCLUSION

Ramona could have bipolar I or bipolar II disorder with mixed states, or MDD with subsyndromal hypomania. If, in addition to her major depressive episodes, she has experienced a lifetime episode of mania, she would be diagnosed with bipolar I disorder; if she has had a lifetime episode of hypomania, but no mania, she would have bipolar II disorder. In the absence of an episode of hypomania or mania, her diagnosis would be MDD with mixed features based on the presence of subthreshold mania or hypomania. Notably, she reported pressured speech and racing thoughts, 2 prominent clinical characteristics of MDD with subsyndromal mania or hypomania. Additional clinical insights are needed. What is her specific sleep pattern? Does she have insomnia or a decreased need for sleep? It is important to determine the age at onset of her depression because older onset points toward unipolar depression. Duration of mood elevation and family history are also important elements of a diagnosis. Clarifying Ramona's diagnosis is crucial to treatment decision making.

FIGURE 3

Mean change from baseline in MADRS total score in a study of lurasidone versus placebo for treatment of major depressive disorder with mixed features (n=208).[44]

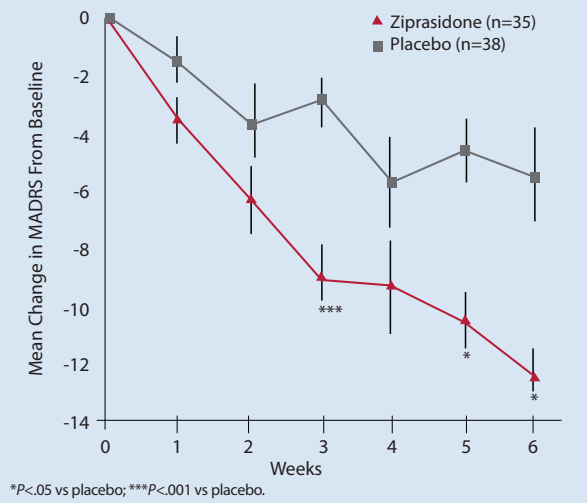


*P<.05; **P<.01; ***P<.001.

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

FIGURE 4

Mean change from baseline in MADRS scores in a study of ziprasidone versus placebo in patients with major depressive or bipolar II disorder and mixed features (n=73).[45]



*P<.05 vs placebo; ***P<.001 vs placebo.

Abbreviation: MADRS, Montgomery-Åsberg Depression Rating Scale.

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