Diagnosis and Treatment Strategies for Mixed Episodes in Bipolar Disorder

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference series "Treatment Strategies for Mixed Episodes in Bipolar Disorder," which was held in May and June 2007. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Eli Lilly and Company.*

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Understanding the Complexity of Bipolar Mixed Episodes

Because many clinicians do not understand that depression and mania may simultaneously co-occur in the same individual, they do not recognize the complex presentations of bipolar mixed states, explained Susan L. McElroy, M.D. Although many people believe mania and depression to be polar-opposite states of bipolar illness, these states often can be present in the same patient at the same time.[1]

Definitions of Mixed States

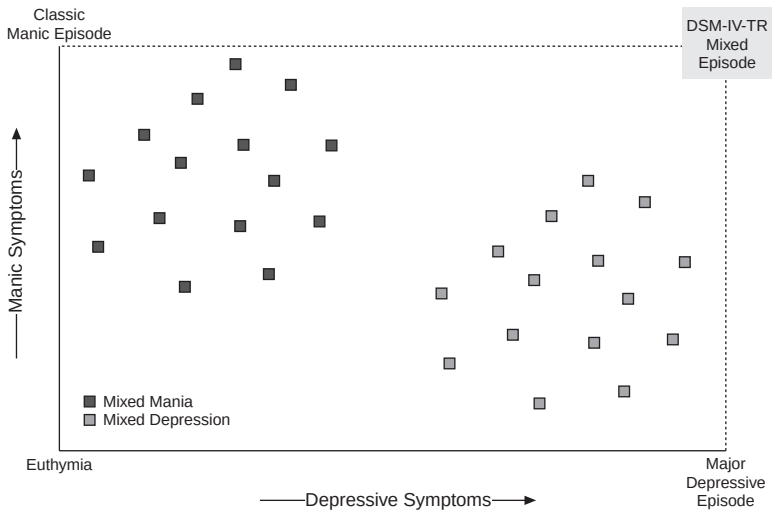
The terminology in the discourse of mixed episodes has not been strictly defined because a consensus has not been reached regarding many of the definitions. However, the term *mixed* in reference to bipolar episodes or states is generally defined as the combination of manic and depressive symptoms or occurrence of manic and depressive symptoms at the same time. The term *mixity* may be used for this co-occurrence.[2]

Bipolar disorder episodes have a high likelihood of coming back (or *recurring*),[3] and the tendency toward frequent recurrence has been called *cyclicity*.[4] Although patients have often been thought to cycle between mania and depression rather than experience both at the same time, the relationship between mixity and cyclicity is unclear. Cyclicity and mixity may be dichotomous conditions that may or may not be related, or they may represent a dimensional phenomenon in which mixity represents cycling that is so severe and rapid that the seemingly opposite symptoms actually occur at the same time. Dr. McElroy stressed that as the field develops a better understanding about the phenomenology of bipolar illness, the nomenclature may need to be altered because the current system of diagnosis and classification is inadequate to describe the complexities of the illness.

Dr. McElroy stated that the early descriptions of manic-depressive states presented in Emil Kraepelin's seminal 1921 book *Manic-Depressive Insanity and Paranoia* are still useful.[5] Kraepelin explained the complexity of mixed states by noting instances in which people can be, for example, both grandiose and suicidal, both depressed and hypersexual, both hyperactive and fatigued, or have racing thoughts but be depressed. Kraepelin identified *depressive or anxious mania* as full mania with a predominantly depressed or anxious mood. His term *excited depression* describes what today might be called *agitated depression*. He described *manic stupor* as euphoria without the overactivity characteristic of mania, and *depression with flight of ideas* as a type of depressive mixed state. Dr. McElroy stated that Kraepelin's descriptions of mixed states are much broader and encompass more presentations than most current operational definitions of mixed episodes, such as that in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR).[3]

The DSM-IV-TR criteria for a mixed episode require that the full criteria for a manic and a major depressive episode be met nearly every day for a 1-week period, and the patient must show marked impairment or psychosis or be hospitalized.[3] However, Dr. McElroy explained that this definition of a mixed episode represents only

Figure 1. Patterns of Mixed Mania and Depression Along the Spectrum of Mood States



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

a severe form of a mixed state; it does not reflect the numerous other combinations of manic and depressed symptoms that patients with bipolar disorder may have. The World Health Organization's (WHO) operational definition of mixed mania[6] is similarly narrow. The WHO states that the current episode must be characterized by a rapid alternation of hypomanic, manic, and depressive symptoms; the manic and depressive symptoms must be prominent for at least 2 weeks; and at least 1 authenticated hypomanic or manic, depressive, or mixed affective episode must have been experienced in the past. According to Dr. McElroy, the duration requirements of these 2 definitions seem arbitrary and do not reflect what happens in the natural clinical course of mixed states.

Spectrum of Mood States

Recent research[7–11] suggests that the psychiatric field is moving toward the concept that mood disorders lie on a dimensional spectrum and away from the idea that bipolar and unipolar disorders are categorically distinct. Dr. McElroy said that this shift allows for countless combinations of manic and depressive symptoms (Figure 1). Euthymia would fall on the graph where the fewest manic and depressive symptoms occur, and a full-blown DSM-IV mixed episode would fall at the point where the highest degrees of both manic and depressive symptoms occur. Inside the axes of this frequency distribution are innumerable degrees of mixity.

Dr. McElroy stated that the concept of a mood spectrum has led to the emergence of contemporary criteria for different types of mixed states. These new criteria reflect the clinical reality of individuals with bipolar disorders better than the current operational criteria do, allowing that people can have various combinations of mania and depression. For example, those who have predominantly depressive symptoms with a mild degree of manic symptoms such as restlessness, racing thoughts, and anxiety are said to have *agitated* or *mixed depression*.[12–14] *Mixed depression* has been defined as syndromal major depression with 3 or more intraepisode hypomanic symptoms that do not meet the DSM-IV criteria for full hypomanic or manic episodes.[11,15] Prevailing mania with at least a mild degree of depressive symptoms may be termed *dysphoric* or *mixed mania*.[2]

Dr. McElroy and colleagues[16] proposed operational criteria for the diagnosis of dysphoric mania or hypomania: the presence of 3 or more symptoms of major depression imposed on a full manic or hypomanic episode. Because the DSM-IV-TR does not recognize subthreshold mixed states, mixed mania is likely to be categorized as mania, while mixed depression is often categorized as depression. Moreover, soft mixed states such as combined hypomania and dysthymia are often overlooked, diagnosed as depressive disorder, or diagnosed as conditions other than mood disorders.[7,17]

Dr. McElroy noted that mixed depression and mixed mania are prevalent states. One study[11] reported mixed depression in 58% of patients with bipolar II disorder and 23% of patients with unipolar depression, and Dr. McElroy and colleagues[16] reported a prevalence of dysphoric mania of about 31% across reviewed studies of patients with bipolar disorder. Among the general population, bipolar disorder has been estimated at 5%, and about 40% of these individuals may experience mixed states in their lifetimes.[8] As criteria for various types of mixed states become validated, prevalence rates can be better established.

Comorbidity and Differential Diagnosis

Bipolar disorder frequently cooccurs with other conditions such as anxiety disorders, substance use disorder (SUD), eating disorders, attention-deficit/hyperactivity disorder (ADHD), Axis II disorders, and medical disorders.[18] If a comorbid disorder is present, a mixed presentation may be more likely than a pure mood state. As reviewed by Frye and Salloum,[19] comorbid alcohol abuse or dependence increased rates of dysphoric or mixed mania in patients with bipolar disorder, and Minnai et al.[20] found that SUDs were more likely to be diagnosed in patients admitted to the hospital with mixed bipolar episodes than in patients admitted with major depression or mania.

In the differential diagnosis of bipolar mixed states, clinicians should particularly consider SUD,[3] Cluster B personality disorders such as borderline personality disorder,[21,22] rapid and ultrarapid cycling,[4,7] treatment-resistant depression,[23] and posttraumatic stress disorder (PTSD).[19,20,24] Antidepressant-resistant depression should be evaluated closely to determine whether a mood stabilizer may be more beneficial than an antidepressant, which could be perpetuating a bipolar mixed state masquerading as a treatment-resistant unipolar depression.[25] Individuals with bipolar disorder seem to be vulnerable to developing PTSD, especially if they have depressive and hypomanic symptomatology.[24] For women with biplolar disorder and PTSD, this comorbidity may be associated with higher rates of alcohol use disorders.[26]

Mixed-state symptoms may be masked by a comorbid disorder,[8] which complicates diagnosis. Dr. McElroy recommended being extremely sensitive when looking for mixed episodes and their numerous presentations, because patients will often seek help for their comorbid disorders but not necessarily their bipolar disorder. For example, a patient who is obese, grandiose, and suicidal may seek help for his obesity, or a patient who is binge eating, depressed, and irritable may seek help for her binge eating and not realize that the binge eating is related to her having a subtle mixed state. Similarly, patients with anxiety disorders, ADHD, or SUD, upon closer evaluation, may have mixed state symptoms as well. Dr. McElroy stressed the importance of remembering that comorbidity in bipolar disorder is highly common and may mask the presentation of mixed state symptoms.

Screening for and Assessing Mixed States

Understanding mixed states is an important aspect of assessing patient symptoms in the clinical setting, especially if a patient's mood symptoms do not fall neatly into a particular diagnostic category. Patients often understand and are responsive to screening questions regarding their manic and depressive symptoms. For example, asking if they have ever felt "hyper" and tired at the same time, felt sad and "high" at the same time, or had racing thoughts and depression at the same time may elicit responses that lead to a mixed-state diagnosis. Making the patient aware of his or her symptomatology and the fact that mania and depression may co-occur is an important psychoeducational aspect of effective treatment. Many patients have simply never been asked if they have had co-occurring manic and depressive symptoms and are often unaware that this is even a possibility.

Conclusion

Dr. McElroy concluded that understanding the spectrum of bipolar mixed states is a fundamental aspect of effectively treating patients with bipolar illness. Mixed states have complex presentations, compounded by inadequate diagnostic criteria and a high incidence of comorbidity. However, once the characteristics of mixed states become familiar to the clinician, screening for bipolar mixed states can be relatively easy.

Diagnostic Dilemmas and Clinical Correlates in Mixed States

Mixed states were, until recently, an understudied aspect of bipolar illness, said Mark A. Frye, M.D. However, as Dr. McElroy noted, research has confirmed that when bipolar patients are symptomatically ill, they frequently have varying degrees of mixed states rather than pure mood episodes. Numerous patterns of manic and depressive symptoms do not fit the current operationalized criteria. The lack of formal criteria for many types of mixed states poses diagnostic dilemmas for the clinician. Mixed states are also associated with several clinical correlates that complicate diagnosis and treatment, including suicidal ideation, gender differences in presentation, and slow recovery.

Diagnostic Dilemmas

As Dr. McElroy discussed, differences between the DSM-IV-TR definition of a mixed episode and the WHO criteria for mixed mania create diagnostic dilemmas. These differences need to be resolved to establish more useful criteria for spectrum bipolar states.

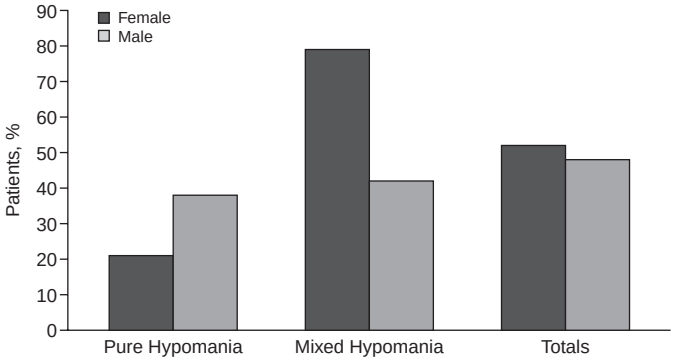
Researchers are recognizing the importance of creating quantitative criteria to diagnose mixed states that do not meet current operationalized criteria but are clinically recognized as mixed bipolar states. For example, Dr. Frye cited a recent study by Benazzi and Akiskal[15] that isolated the most discriminant symptoms of a depressive mixed state. They found that irritability and psychomotor agitation serve as signs that clinicians should probe further to assess whether a patient with major depressive episodes is experiencing depressive mixed states. The identification of specific hypomanic symptoms that occur during depressive mixed states may help clinicians to more accurately diagnose patients with depressive mixed states.

Clinical Correlates

Dr. Frye explained that, despite diagnostic controversy, mixed states are associated with a number of clinically relevant correlates, such as gender differences, suicidality, and slow treatment response.

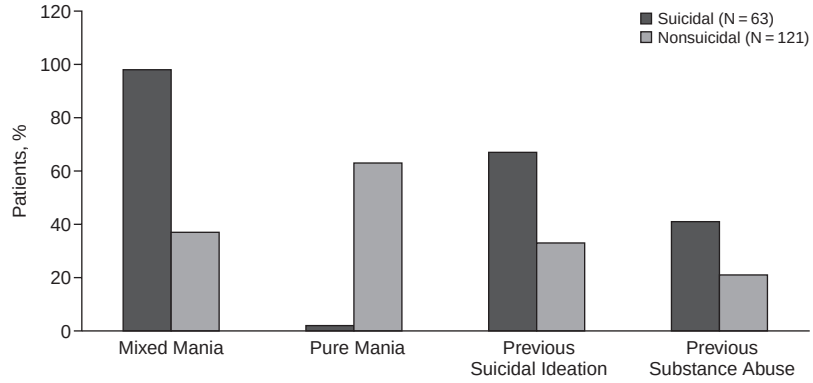
Gender differences. Recent research has evaluated gender differences in the presentation of bipolar spectrum mixed states. McElroy et al.[16] reviewed evidence on dysphoric mania and found that it was more likely to occur in women than men. Grant et al.[27] found that, among individuals with bipolar I disorder, women were more likely to have mixed and major depressive episodes, while men were

Figure 2. Patients With Pure Hypomania Versus Mixed Hypomania by Gender[a]



[a]Data from Suppes et al.[28]

Figure 3. Mixed States, Suicidality, and Substance Abuse in Bipolar Patients Who Were or Were Not Suicidal During Index Episode[a]



[a]Data from Goldberg et al.[29]

significantly more likely to have unipolar mania ($p < .05$). Suppes et al.[28] evaluated 908 patients with mixed hypomania by gender and found that, during almost 2 years, more women than men experienced mixed hypomania (Figure 2). Furthermore, mixed hypomania was experienced differently by men and women. Men primarily had irritability and agitation, whereas women exhibited symptoms across all depressive symptom domains. Women had a significantly higher probability ($p < .001$) of experiencing depressive symptoms during hypomania than men.

Suicidality. In a study by Goldberg et al.,[29] mixed mania was significantly associated with suicidality. In this study, previous suicide attempts were more common among patients with mixed mania than among patients with pure mania (36.7% vs. 8.2%, $p < .001$), and 57.9% of the patients with mixed mania versus 1.3% of patients with pure mania were suicidal ($p < .001$). Dilsaver et al.[30] found that 2.0% of patients with pure mania were suicidal, but 54.5% of patients with depressive mania were suicidal.

Suicidality has also been associated with patient histories of substance abuse or dependence in those with dysphoric mania.[19,31] Among inpatients with an index bipolar episode, suicidal patients were more likely to have past substance abuse, past suicidal ideation, and mixed mania than nonsuicidal patients (Figure 3).[29] A better understanding of patients with the triad of mixed mania, substance abuse, and suicidal ideation could aid clinicians in stabilizing these patients and optimizing their treatment outcomes.

Slow recovery. Dr. Frye stressed that mixed states are associated with slower recovery from acute episodes and more chronicity than pure mood states. According to a study by Goldberg et al.,[29] multiple suicide attempts were a factor in nonremission from mixed manic episodes; for every suicide attempt prior to the index manic episode, a 49% decline in the probability of remission occurred. In one study,[32] after 8 weeks of treatment for an acute episode, recovery rates were 61% for patients with mania, 44% for patients with depression, and 33% for patients with mixed or cycling episodes. At a median follow-up of 18 months,[33] the probability of patients remaining ill was 7% for patients with pure mania at baseline, 22% for patients with pure depression, and 32% for patients with mixed states. A 5-year prospective follow-up[34] found that median recovery rates were 6 weeks for patients with pure mania, 11 weeks for patients with pure depression, and 17 weeks for patients with mixed or cycling episodes. Patients with mixed or cycling episodes were also quickest to relapse after recovery from the index episode.

Conclusion

Dr. Frye concluded that inconsistent formal diagnostic criteria for mixed bipolar states create diagnostic dilemmas for clinicians. The existence of mixed state presentations that do not fit the current formal criteria for diagnosis and potential gender differences in the presentation of mixed states further complicate diagnosis. However, accurate diagnosis is crucial in minimizing clinical correlates of mixed episodes, such as suicidality, substance abuse, and delayed treatment response. Further study of mixed presentations is needed to improve diagnosis and identify optimal treatment options.

Bipolar Mixed Episodes: Costs, Characteristics, and Comorbidities

Costs of Bipolar Mixed Episodes

Joseph F. Goldberg, M.D., reported that mixed episodes of bipolar illness are associated with serious societal costs and longitudinal consequences. The projected total lifetime cost (including the direct and indirect costs of treatment) of treating an individual whose index episode of bipolar disorder is mixed is about 20% more than the cost of treating an individual whose index episode is purely manic.[35] However, costs differ between patients who respond to initial treatment and remain fairly stable and those who have chronic nonresponse. If an initial mixed episode is treated to remission, the lifetime direct mental health cost may be reduced by 95% of that of a patient with chronic nonresponse (Figure 4).[35] While mixed states are difficult to treat and may have greater societal and/or economic costs than pure manic or depressed episodes, Dr. Goldberg stressed that if the treatment of an initial mixed episode leads to a stable response, the lifetime direct costs are even less than those of an initial pure manic or pure depressive episode.

Characteristics of Bipolar Mixed Episodes

Dr. Goldberg described the characteristics and consequences of mixed states. One characteristic of mixed states, as noted by Dr. Frye, is the risk for suicidality.[29] Other characteristics or potential consequences of mixed states are cycling into depression, recurring mixed episodes, impaired quality of life, and cognitive complaints.

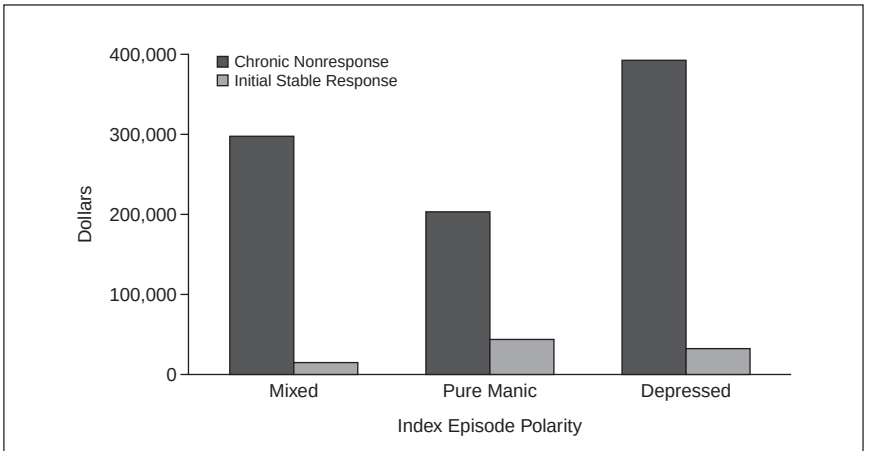
Subsequent episodes. Longitudinal data,[36] have shown that a greater number of patients in mixed states may be at risk for cycling into a depressed phase of illness than patients in pure manic states, explained Dr. Goldberg. In one study,[36] about 43% of patients cycled into pure depression without recovery from an initial mixed episode, compared with about 24% of patients who had a pure manic index episode.

Mixed states may also be likely to recur over time. Cassidy et al.[37] found that if an index episode was mixed, there was a 50% chance that the next episode would also be mixed. However, if an initial episode was manic, there was only an 8% chance that the next episode would be mixed. Sato et al.[38] reported that, among patients whose initial episode was a depressive mixed state, 58% had a depressive mixed second episode, but among patients who did not have an initial depressive mixed episode, only 16% had a depressive mixed second episode. Dr. Goldberg stressed that this confluence of manic and depressive symptoms may have trait stability, recurrence potential, and longitudinal endurance across episodes.

Quality of life and cognitive characteristics. Dr. Goldberg went on to explain that, in some respects, mixed presentations resemble manias more than depressions with regard to the potential for cycling, psychomotor acceleration, and impulsivity, but in other respects, mixed states tend to resemble depression. For example, quality of life scores for patients with mixed episodes were found to be more similar to those for patients who were depressed than those for patients who were manic, hypomanic, or euthymic (Figure 5).[39] Depressive aspects of the illness primarily determined quality of life for patients in mixed episodes.

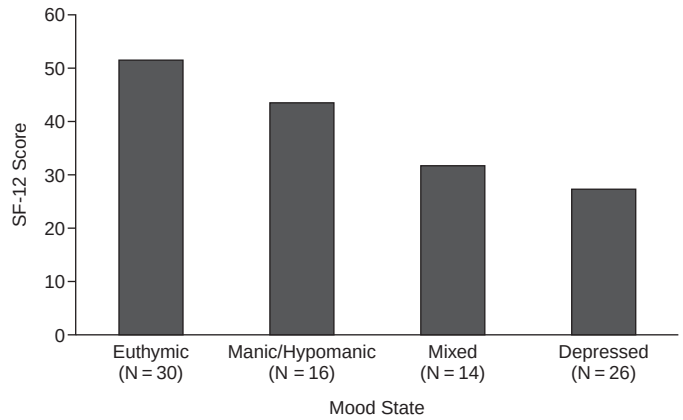
Similarities between mixed states and depression have also been found in patients' cognitive biases, which are thought patterns or beliefs about oneself and the world that become reinforced and ingrained over time. Beck et al.[40] reported that patients in the manic phase of bipolar illness scored highly on measures of excessive self-worth, grandiose beliefs about relationships, and unrealistic beliefs about activities, whereas scores of patients experiencing mixed states were much lower and were consistent with those found in patients with depression. Negative or pessimistic cognitive biases can be fruitful targets for psychotherapy in patients with depression or mixed states. Martinez-Aran et al.[41] reported that patients with bipolar disorder who had a greater number of mixed episodes had more subjective cognitive complaints ($p < .03$), and those with subjective cognitive complaints scored lower on measures of memory, attention, and executive function

Figure 4. Direct Mental Health Service Costs by Bipolar Group With Chronic Nonresponse and Initial Stable Response[a]



[a]Data from Begley et al.[35]

Figure 5. Mean Self-Reported SF-12 Mental Subscale Scores (Quality of Life) by Mood State[a]



[a]Data from Vojta et al.[39]
Abbreviation: SF = short form.

compared with control subjects. Thus, consequences of chronic mixed states may include negative cognitive biases as well as objective neurocognitive impairments.

Comorbidity With Bipolar Mixed Episodes

Psychiatric comorbidity. Dr. Goldberg cited several studies[20,42–44] that reported a greater degree of SUD in mixed states of bipolar illness than pure mood states, as Drs. McElroy and Frye noted. A history of SUD was found in 40% of patients with mixed episodes and in 23% of patients with pure mania, according to a study by Goldberg and colleagues ($p < .02$).[42] Dr. Goldberg observed that, when substance abuse and bipolar disorder are both present, the chronology of onset may affect the patient's prognosis. When bipolar illness precedes the onset of SUD, the prognosis may be poorer, the complexity of illness greater, and the persistence of mixed features much higher than if the SUD had an earlier onset. Strakowski et al.[44] found that if bipolar disorder was the initial diagnosis in patients who abused cannabis, the patients tended to spend more time in mixed states than if cannabis abuse was the initial diagnosis. An earlier study by Strakowski et al.[43] found a similar relationship between bipolar illness and alcohol abuse: less time was spent in mixed states if the onset of alcohol abuse preceded the onset of bipolar disorder than if bipolar disorder preceded the onset of alcohol abuse.

Dr. Goldberg stated that mixed states may also be highly comorbid with anxiety disorders and ADHD. For example, one study[45] found that significantly more patients meeting mixed criteria had comorbid obsessive-compulsive disorder (OCD) than patients with pure mania (21% vs. 4%, $p = .03$). OCD tended to cycle along with depressive features in patients in mixed states, i.e., when depression symptoms were more prominent in a mixed state, OCD symptoms tended to be more severe.[46] Other anxiety disorders, such as PTSD and generalized anxiety disorder, may be more common in mixed states than in pure depressive states.[47] Recent research[47] also suggests that ADHD may be more likely to occur in mixed presentations compared with pure depressed presentations.

Medical comorbidity. Conditions such as head trauma, stroke, epilepsy, and being HIV positive may predispose patients to secondary mania that often presents as irritability with mixed features rather than pure mania.[48] Dr. Goldberg stated that these secondary mixed states may be difficult to treat. Thompson et al.[49] found that a greater severity of baseline medical comorbidity among patients in mixed states was related to slower improvement in depression scores, even after controlling for baseline severity of depression.

Dr. Goldberg noted the importance of recognizing medical correlates of mixed states in bipolar illness. Cassidy et al.[50] found that, compared with patients with pure mania, patients with mixed mania had lower fasting serum cholesterol levels. Dr. Goldberg explained that this finding is clinically important because cholesterol is necessary for the myelination of nerve fibers and membrane stabilization. Data[51–56] have also suggested that suicidal features and complex psychopathology in patients with mood disorders may be associated with abnormally low serum cholesterol levels. Another study[57] found that adrenocortical dysfunction may be more common in mixed states than in pure mania. Patients diagnosed with mixed states had higher levels of cortisol than patients with mania. Hypercortisolemic states may be associated with increased stress levels, which may translate to adrenocortical dysfunction. Dr. Goldberg elaborated that high cortisol levels may have a neurotoxic effect on the hippocampus, accounting for some cognitive problems that arise in mixed states. Additionally, leukocytosis and hypoalbuminemia have been found in patients with mixed mania, suggesting an immune activation in mixed mania similar to that in depression.[58]

Dr. Goldberg cited a study[59] that found that patients with mixed mania had a mean thyroid stimulating hormone (TSH) level of 3.14 mU/mL, which was significantly higher ($p = .04$) than the TSH level found in patients with pure mania (1.16 mU/mL). Conversely, patients with mixed mania also had significantly lower ($p = .03$) thyroxine levels than

patients with pure mania. This study suggested that thyroid axis abnormalities are more common in patients with bipolar mixed states than with bipolar mania. Because subclinical hypothyroidism has been linked with rapid cycling, thyroid hormone supplementation to counteract clinical depression and mixed episode features may be beneficial to patients with mixed features of bipolar disorder.

Conclusion

Dr. Goldberg reiterated that mixed presentations of bipolar disorder are potentially recurrent phenomena associated with greater lifetime costs if initial treatment is unsuccessful in providing stable response. Mixed episodes tend to resemble depressive episodes more than manic episodes in terms of quality of life and cognitive styles and have been associated with suicidality and the potential to cycle into depression. Psychiatric and medical comorbidities that may slow recovery are also correlates of mixed presentations. Dr. Goldberg concluded that the clinical profile of mixed states is distinct from manic and depressive presentations not only in symptomatology but also in costs, characteristics, and comorbid psychopathology.

The Acute Treatment of the Patient With Bipolar Mixed Episodes

According to Roger S. McIntyre, M.D., F.R.C.P.C., a prevailing viewpoint in psychiatry is that mixed states in bipolar disorder are common clinical presentations that are associated with bipolar severity and poor treatment outcome. In his presentation, Dr. McIntyre described some general management principles for treating mixed states, reviewed the efficacy of available pharmaceutical treatments for mixed states, and advocated the use of a treatment algorithm when managing mixed states.

General Management Principles

In the acute treatment of patients with mixed states, the general management principles include establishing the diagnosis, screening for comorbidity, and clarifying the therapeutic targets.

Establish the diagnosis. When establishing the diagnosis, clinicians need to understand that mixed states overlap phenomenologically with many other disorders, particularly agitated depression, potentially complicating the diagnostic process.[60] Individuals with unipolar disorder must be differentiated from those with bipolar disorder, because the conventional pharmacotherapy for unipolar depression—treatment with a unimodal antidepressant—may worsen the clinical presentation, course, and outcome of bipolar disorder.[60,61] Therefore, an accurate diagnosis is essential for the patient to receive optimal therapy.

Screen for comorbidity. Mixed states are complicated phenotypes to begin with, but bipolar disorder is also commonly comorbid with other syndromes.[18] Medical and psychiatric comorbidities complicate the presentation of mixed states and pose a serious hazard to the overall course and outcome of bipolar disorder.

Identify therapeutic targets. Dr. McIntyre asserted that a key component in managing a patient with mixed states is the identification of the appropriate therapeutic targets. Clinicians do not simply treat mixed states; rather, they treat symptoms, or symptom clusters, that are a part of the larger phenotype called mixed states. In this phenotype, several common symptoms and symptom groups present in the clinical setting.[62] Depressive and manic symptoms are the hallmark features of mixed states, but psychotic features, catatonic symptoms, agitation, and anxiety are also common. Additionally, the patient's distress, often manifested as mood lability and/or suicidality, is a cardinal feature of mixed states. The combination of these symptoms comprises mixed states, and treatments are most likely differentially effective across these therapeutic targets.

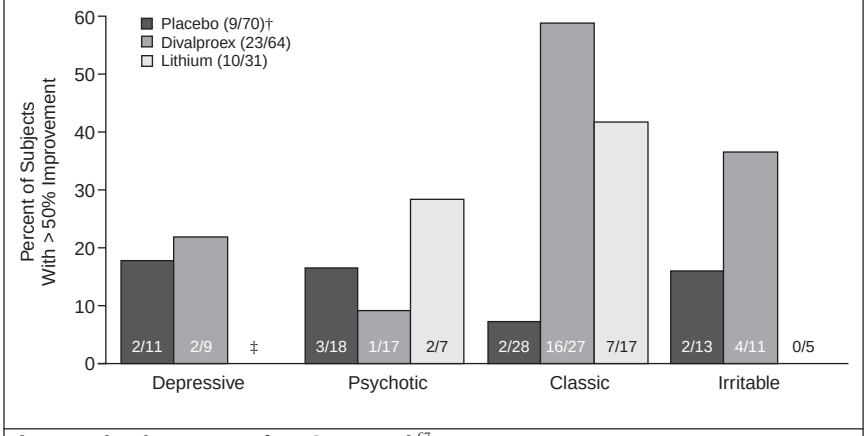
Pharmacologic Treatment Options

Dr. McIntyre summarized the available treatments for individuals who experience mixed states. First-line treatments for mixed states include divalproex, select atypical antipsychotics, or the combination of the 2. Conventional unimodal antidepressants are discouraged, and lithium is not considered a first-line treatment for mixed states.

Dr. McIntyre pointed out that, in studies attempting to evaluate the efficacy of putative antimanic drugs, subjects with mixed states are often a subgroup of a larger sample of individuals who usually have acute mania. No large studies have examined the efficacy of a drug exclusively in mixed states. Few controlled studies in mixed states exist,[63] and most of the studies are monotherapy trials. Also, because study participants have to give informed consent, most are not as severely ill as patients in clinical practice whose insight is too compromised to provide informed consent.

Mood stabilizers. Despite being well established as an efficacious treatment for mania, lithium is not indicated for mixed states.[64] People with mixed states are suboptimally responsive to lithium.[62,65,66] Increasing severity of depressive symptoms in mania seems to predict a decreased response to lithium and an increased response to divalproex. One study[67] examined divalproex and lithium in 4 naturalistic subtypes of mania: depressive, psychotic, classic, and irritable. Divalproex was superior to lithium in treating not only classic mania but also the irritable and depressive forms of mania (Figure 6). Dr. McIntyre stated that divalproex has been well established as particularly effective for mixed-state presentations and is

Figure 6. Efficacy* of Acute Treatment Across Manic Subtypes[a]



[a]Reprinted with permission from Swann et al.[67]
*Efficacy is defined as 50% improvement in Manic Syndrome score.
†Number of subjects with 50% improvement/total number of patients in the group.
‡Only 2 depressive patients were randomly assigned to lithium.

indicated for the treatment of mixed states.[68,69]

Carbamazepine is also indicated for the treatment of mixed states. Dr. McIntyre described a recent pooled analysis[70] showing that carbamazepine, unlike lithium, is just as effective for treating mixed states as it is for treating mania. In patients with mixed episodes, carbamazepine significantly reduced both depressive ($p < .05$) and manic ($p < .01$) symptoms.[70]

Atypical antipsychotics. Dr. McIntyre stated that, although some have been evaluated more than others, atypical antipsychotics are efficacious in mixed states. Most of the atypical antipsychotics are currently approved for the management of mixed states (olanzapine, risperidone, ziprasidone, and aripiprazole).[64] Ziprasidone[71,72] and aripiprazole[73,74] have been evaluated as monotherapy in placebo-controlled studies of mania with subgroups of patients with mixed states, and both drugs have shown favorable results in mixed-state patients. Risperidone has been evaluated extensively in acute mania[75,76] but not in mixed states.[63]

The atypical antipsychotic with the most evidence of efficacy in mixed states is olanzapine. As with carbamazepine, olanzapine appears to be efficacious in mixed states with no differential response across mania subtypes.[77,78] Two studies[79,80] comparing olanzapine with divalproex found that both agents were effective in reducing depressive symptoms as part of a manic episode, with no significant difference between the 2 medications.

Combined treatment. Dr. McIntyre reiterated that the complexity and the frequent comorbidity of mixed states often create a need for combination treatment. While clinicians aim for simplicity in treating their patients, monotherapy for patients with mixed states may be unrealistic.[81] One study[82] evaluated olanzapine in combination with lithium or valproate in patients with dysphoric mania. This study found that the combination of olanzapine plus either valproate or lithium was superior to valproate or lithium alone in decreasing depressive symptoms, manic symptoms, and suicidality. Risperidone was also studied[83] in combination with lithium or divalproex, and the combination was more efficacious than the mood stabilizers alone in patients with manic episodes; efficacy of the combination was suggested in patients with mixed episodes, but the study lacked a metric for rating depression.

Perlis et al.[84] compared olanzapine and risperidone in the treatment of manic or mixed states in inpatients with bipolar I disorder. In this double-blind, multicenter study, results did not differ on the primary outcome measure, the Young Mania Rating Scale (YMRS). On secondary measures, results were similar for the Montgomery-Asberg Depression Rating Scale, but olanzapine-treated patients had greater improvement on the Hamilton Rating Scale for Depression and the Clinical Global Impressions-Bipolar Version scale.

Quetiapine has not been evaluated for mixed states in adults, but a study[85] of quetiapine augmentation with divalproex in adolescents with mania, many of whom had mixed state presentations, found that subjects had a superior response to the combination treatment. Dr. McIntyre stated that quetiapine is a potential treatment option for mixed states but requires more study.

Antidepressants. According to Dr. McIntyre, no subject in the field of bipolar disorder generates more controversy than the use of conventional unimodal antidepressants. An essential element of mixed states is the presence of depressive symptoms, so it stands to reason that many patients are prescribed an antidepressant to alleviate those symptoms. Unfortunately, antidepressants have not been reported to be efficacious in mixed states. Moreover, a growing body of literature indicates that mixed states, when treated with antidepressants, are, in fact, worsened.[60,86] Antidepressants pose a risk for mood destabilization and switching into mania, and the risks are greater if the patient has rapid cycling or comorbid substance abuse.[61,87]

One study[88] used the YMRS to examine the association between baseline mania severity and treatment-emergent mania during antidepressant treatment. The YMRS is scored between 0 and 60. Many investigators have defined hypomania as a score of 12 or greater and mania as 20 or greater. Yet, a low baseline score of 4 on the YMRS was associated with the emergence of mania in individuals who presented with depression and received an antidepressant. The clinical translation of these findings is that depression mixed with

even low-grade hypomanic symptoms at baseline (such as talkativeness, increased motor activity, and new interests) may be associated with the induction of hypomania or mania in patients who are exposed to antidepressants.

Aside from the risk of treatment-emergent mania posed by antidepressant treatment, evidence suggests that antidepressants do not increase the likelihood of recovery from mixed state bipolar disorder.[65,89] The emerging message is that insufficient evidence exists to support antidepressants as safe or efficacious treatments for bipolar disorder with mixed states.

Treatment Algorithms

As the number of agents indicated for use in bipolar disorder continues to rise, the need increases for clinicians to have an algorithm to aid in the selection and sequencing of medications. Treatment algorithms[90] have been shown to improve the cost-effectiveness, consistency, and overall quality and appropriateness of care for patients. Dr. McIntyre discussed the Texas Implementation of Medication Algorithms (TIMA) guideline for the treatment of bipolar disorder with mixed states.[91]

The TIMA algorithm categorizes divalproex and the antipsychotics aripiprazole, risperidone, and ziprasidone as first-line agents for patients with mixed states. Because of safety concerns, olanzapine and carbamazepine were listed as alternative monotherapy options in the case of nonresponse to the other first-line options. For patients who do not respond adequately to first-stage treatments, TIMA suggests drug combinations, but not 2 atypical antipsychotics. A combination of divalproex with one of the approved atypical antipsychotics, for example, would be reasonable. When polypharmacotherapy proves insufficient, Dr. McIntyre said that electroconvulsive therapy becomes a consideration. Failing all else, TIMA recommended the addition of clozapine to a patient's treatment regimen. Clozapine has not been sufficiently studied in mixed states, and clozapine is probably more effective as an antimanic drug than as an antidepressant in mixed states, but it should be considered, nonetheless.

Summary

Dr. McIntyre reiterated that the management of acute states begins with clarifying the diagnosis, screening for comorbidity, and establishing therapeutic targets. Patients should be educated as to the likelihood and duration of recovery, and it should be understood that for many patients, combination treatment will be required. Multiple drugs are approved for the treatment of mixed states. The largest body of evidence supports the efficacy of atypical antipsychotics and divalproex. Lithium is suboptimally effective in mixed states, and antidepressants should be avoided due to their unproven efficacy and their association with treatment-emergent mania. Finally, clinicians should consider the use of an algorithm or treatment guideline in order to organize and optimize the care of patients with mixed-state bipolar disorder.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril and others), divalproex (Depakote), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The chair has determined that, to the best of her knowledge, clozapine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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