Mixed Depression: The Importance of Rediscovering Subtypes of Mixed Mood States

Mixed depressions—that is, major depressive episodes accompanied by subsyndromal manic or hypomanic symptoms—have been recognized for more than a century, but only recently have they provoked interest given their implications for course and treatment. Both Emil Kraepelin and his mentee Wilhelm Weygandt recognized and described an entire spectrum of mixed states. Kraepelin, adapting Weygandt's work to his own, theorized that varying depressive and manic symptoms could combine to produce no fewer than *six* mixed states, depending on how affect (euphoria versus depression), psychomotor activity (excitement versus retardation), and thought process (flight of ideas versus thought blocking) combined in any given patient (1–3). Indeed, over the last century, terms such as "melancholia activa," "melancholia agitata," "irritable-hostile depression," "agitated depression," and "mixed depression" have all been employed in an attempt to categorize the phenomenon in which depressed mood predominates but activation and agitation are present.

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In contrast to such complex categorization, DSM-IV defines only one mixed state: the simultaneous occurrence of full manic and depressive symptoms lasting at least 1 week. Because mania is a requirement for the diagnosis, mixed states are by definition restricted to patients with bipolar I disorder. Such narrow criteria belie the evolving notion of bipolar disorder as a dimensional illness, and they ignore the host of subsyndromal manic and hypomanic symptoms that clinicians working with bipolar depressed patients observe all too commonly. Contemporary researchers, including Koukopoulos (4), Akiskal (5), Benazzi (6), and others, have investigated the frequency and significance of co-occurring manic and depressive symptoms, noting their presence not only in bipolar I and II patients but also in a subset of unipolar patients. Indeed, the presence of subsyndromal manic or hypomanic symptoms in unipolar depression has raised questions as to whether such patients might be considered along a bipolar spectrum and treated with mood-stabilizing agents rather than antidepressants.

In this issue of the *Journal,* two studies continue to extend the conceptual model of mixed states beyond mixed mania. Both studies challenge our existing bipolar nosology while imparting important clinical insight into the assessment and treatment of depressed bipolar patients.

Goldberg and colleagues report on the frequency, nature, and extent of manic symptoms in 1,380 patients diagnosed with bipolar depression (7). In this large, cross-sectional study from the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), more than one-half of patients with bipolar depression had concomitant subthreshold manic symptoms. Full mixed symptoms were observed in only 15% of the patients, while "pure" bipolar depressions, that is, depressive symptoms without co-occurring manic symptoms, were observed in fewer than one-third of the patients upon study entry. Thus, the majority of bipolar depressed patients had elements of manic symptoms yet would be classified as having "pure" depression accord-

ing to strict DSM-IV criteria. An important finding is that these patients were more likely to be male, have bipolar II disorder, and have histories of more complex psychopathology (earlier onset, recent rapid cycling, greater likelihood of past suicide attempts) than those without concurrent manic symptoms. In addition, the authors found a lower mean number of manic symptoms among patients taking antidepressants than among those who did not, suggesting that concomitant manic symptoms were not an artifact of antidepressant treatment but, instead, an independent component of their depressive presentation.

The study by Frye et al., while numerically more modest, presents the first prospective and controlled data suggesting that patients with bipolar depression who have concomitant minimal manic symptoms are at heightened risk for developing treatment-emergent mania when given antidepressants (8). Their 10-week study, in which moderately to severely depressed bipolar patients received both mood stabilizers and antidepressants (sertraline, bupropion, or venlafaxine), highlights the risks of giving antidepressants to patients with even minimal manic symptoms. Unlike the study of Goldberg and colleagues, this investigation did not identify any demographic variables that were of help in identifying patients at risk for developing treatment-emergent mania. Instead, levels of minimal manic symptoms at the time of antidepressant initiation distinguished those patients who went on to develop treatment-emergent mania from those who did not. Not only did higher baseline scores on the Young Mania Rating Scale (YMRS) predict treatment-emergent mania, but particular clusters of symptoms—specifically increased motor activity, speech, and thought content—were the individual YMRS items that held greatest predictive value.

Evidence against use of antidepressants in bipolar depression continues to mount. Studies have demonstrated that the addition of antidepressants may provide no more benefit than treatment with mood stabilizers alone (9), may worsen manic symptoms in patients with mixed depressive symptoms (10), and may significantly increase the frequency of suicidal ideation (11). In addition, antidepressants may cause the frequency of mood cycling to increase, even for rates below the threshold for rapid cycling (12).

While some may argue how many manic symptoms should be counted to define mixed depression, there should be little argument regarding the relevance of mixed depression as a concept and the idea that mixed states themselves constitute a behavioral continuum. The present studies of Goldberg, Frye, and their colleagues complement the extensive work of Koukopoulos (4), Benazzi (6), Akiskal (5), Bottlender (13), and others, showing the frequency with which depressive and manic symptoms intertwine. Work by Suppes and colleagues (14) also demonstrated that depressive symptoms can co-occur with full hypomanias, in a state the authors designated "mixed hypomania." In that study, nearly 60% of patients with hypomania had significant co-occurring depressive symptoms, with mixed hypomanias especially common in women. Studies such as these continue to reveal the complexity of bipolar disorder and point out the inadequacies of our current nosological system.

How can patients benefit from such findings? Because depressive mood predominates in bipolar disorders (15, 16) and self-reports of hypomanic episodes are often unreliable, bipolar depressions continue to be misdiagnosed as unipolar depressions, often with adverse consequences. As Goldberg and associates point out, distinctions between unipolar and bipolar depressive episodes have traditionally focused on qualitative differences in depressive symptoms. Hypersomnia, hyperphagia, mood reactivity, and leaden paralysis have often been considered clues to the presence of bipolar depression when no clear hypomanic or manic episodes are reported. By reemphasizing the importance of evaluating racing thoughts, distractibility, psychomotor agitation, irritability, and pressured speech, clinicians may be able to better predict which patients have an underlying bipolar diathesis and thereby *avoid* giving them antidepressants.

Recently, I evaluated three consecutive patients who presented nearly identical histories of long-standing refractory depression. All had been taking multiple antidepressants for many years, and all complained of irritability, crowded thoughts, and varying degrees of agitation. None had a history of clear hypomania or mania, with or without antidepressants, and none had a family history of bipolar disorder. The practitioners' dilemma is apparent: are these cases of refractory unipolar depression that require more aggressive antidepressant treatment, or are there sufficient bipolar symptoms to introduce a mood stabilizer? Studies such as the two published this month help clarify these fundamental decisions. In light of the present findings, I was more inclined to consider my patients' symptoms consistent with mixed depression, taper their antidepressants, and initiate treatment with mood stabilizers. Future controlled trials examining the efficacy of mood stabilizers in mixed versus nonmixed depression will further support or refute such treatment strategies.

In addition, the findings from the Goldberg and Frye studies reemphasize the need to improve our current categorization of bipolar disorder, perhaps by including pure depression, mixed depression, mixed hypomania, mixed mania, and pure mania. Should such classification ultimately prove to have long-standing utility and validity, it not only will enhance our care and treatment of patients but will be yet another acknowledgment of the remarkable insights of Kraepelin and his contemporaries more than a century ago.

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