Three issues of current concern in bipolar II disorder include: diagnostic criteria for hypomania, diagnosis of mixed depression, and management of mixed depression.

Prevalence of BP II

A recent series of studies has found that BP II is much more common than the 0.5% community prevalence reported by DSM-IV: the current estimate of community prevalence is about 5%.[2-4] However, clinical studies in different settings have found a much higher prevalence of BP II among depressed outpatients, reporting an equal number with major depressive disorder (MDD) in a ratio of 1:1.[5-13] In comparison to previous studies,[4,8,10-15] the much higher prevalence of BP II found in these studies is related to the following methodologic advances:

- Use of semistructured interviews by trained clinicians.
- A minimum duration of hypomania of 2 or more days.
- Bypassing the stem question of DSM-IV to assess the history of hypomania.
- Focusing the probing for history of hypomania on overactivity.

The use of fully structured interviews by lay interviewers, which used yes/no questions and did not provide for clinical evaluation, often led to underdiagnosis of BP II or misdiagnosis of BP II as MDD. The use of semistructured interviews by trained clinicians provides a clearer diagnostic perspective and consequently, a smaller margin of error.

Using the criteria of a minimum duration of hypomania of 2 or more days rather than the DSM-IV 4-day cutoff may increase accurate diagnosis. Unlike the 4-day cutoff, the 2-day cutoff is based on data that show no difference on bipolar measures such as family history, age at onset, and number of recurrences. When DSM-IV criteria are strictly followed, BP II is often (at least 30% of the time) misdiagnosed as MDD.

Because the DSM-IV stem question requires remembering periods of elevated or irritable mood, the response to this question by patients with BP II is frequently "no," since these periods may be seen as normal mood fluctuations. If the wording of the question includes "much more than usual," this may be perceived as a sign of a severe mental disorder, and is often denied. Bypassing the stem question of DSM-IV to assess the history of hypomania can provide a more accurate diagnosis.

Overactivity (increased goal-directed activities) is an observable behavior, easier to remember than the mood state required by DSM-IV. During the initial interview, relatives and friends can report on mood changes that are more easily recalled after remembering a period of overactivity.
has been found to be the core feature of hypomania, and it can have at least the same priority as mood changes for the diagnosis of BP II.\textsuperscript{4,11,13,16}

Factor analysis studies and clinical studies have supported the upgrading of overactivity. Factor analysis studies have shown that “activation” is the core feature of hypomania. Many DSM-IV symptoms of hypomania (7 of 9) could be considered to be the result of an activation/excitement state of the brain: increased goal-directed activity, psychomotor agitation, decreased need for sleep, more talkativeness, racing thoughts, distractibility, and excessive involvement in risky activities.

In 1913, Kraepelin\textsuperscript{17} described 3 basic domains of mania/hypomania and depression: excitement or inhibition of mood, thinking, and behavior. He did not set any priority among them, but stated that “increased busyness,” ie, overactivity, was “the most striking feature” of hypomania. His predecessors, Falret (1854) and Hecker (1898) noted the diagnostic utility of behavioral activation for the diagnosis of disorders similar to BP II, ie, “cyclothymia” and “circular insanity.”\textsuperscript{18,19} Actually, in Kraepelin’s view, there could be a manic state even without an elevated mood, as in the mixed state “depressive or anxious mania.”\textsuperscript{17} According to DSM-IV, elevated mood is the prototypical symptom of hypomania. This may mislead clinicians into believing that the basic feature of hypomania is elevated mood and that the other symptoms are secondary and less important.

The major depressive episodes of BP II, and not uncommonly those of MDD, may have concurrent hypomanic symptoms but cannot include elevated mood and the related inflated self-esteem. These mixed depressions thus become “missed” depressions. Mixed depression misdiagnosis impacts negatively on the treatment of depression. Clinical studies have shown that BP II diagnosed by setting overactivity, and not mood changes, as the priority symptom of hypomania is similar on diagnostic measures to DSM-IV BP II, which requires mood changes for the diagnosis of hypomania. Diagnosing hypomania by requiring overactivity does not lead to overdiagnosis of BP II, and most DSM-IV BP II (approximately 80%) is included.

The Structured Clinical Interview for DSM-IV (SCID)\textsuperscript{20} has the disadvantage of having the stem question for hypomania based on mood changes, if the response is negative, assessment must move to nonbipolar disorders. Another important disadvantage of the SCID is that it does not assess hypomania/hypomanic symptoms in a major depressive episode, leading to missing mixed depressions, especially in outpatients.

Two recent studies have reported on mixed hypomania, which is a combination of hypomania and depressive symptoms or a major depressive episode.\textsuperscript{21,22} This diagnosis also will be missed by the SCID. Patients with BP II may not seek treatment for hypomania, because it is frequently seen as a period of improved functioning. Impairment in hypomania, when it occurs, is mild, and is seen more often by relatives and friends than by patients with hypomaniac BP II.

**Basic data support distinction between BP I and BP II**

The basic data supporting a distinction between BP I and BP II\textsuperscript{23,24} are presented in the Table. In comparison to BP I, there are many fewer studies of BP II and there is little evidence to support the treatment guidelines. Compared with BP I, patients with BP II are more prone to episodes of depression, higher Axis I comorbidity (especially panic disorder), a higher suicide risk, and a high incidence of substance abuse.\textsuperscript{9,25-28}

<table>
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<tr>
<th>Characteristic</th>
<th>BP I</th>
<th>BP II</th>
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<tr>
<td>Diagnostic stability\textsuperscript{23}</td>
<td>Long-term</td>
<td>Long-term</td>
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<tr>
<td>Bipolar family history\textsuperscript{24}</td>
<td>More BP I relatives than BP II relatives</td>
<td>More BP II relatives than BP I relatives</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Equal in</td>
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People with BP II plus concurrent cyclothymic temperament (high instability of mood, thinking, and behavior) are more common in tertiary care settings (around 50% of these patients), have more Axis I comorbidity, and are at higher risk for suicide and substance abuse. Because of the negative impact that this concurrent temperament has on the course of BP II, this subgroup is referred to as “dark”; without the concurrent condition the subgroup is called “sunny,” because there are often periods of improved functioning.

The DSM-IV boundary between hypomania and mania is based on marked impairment of functioning in mania, but its definition is unclear and may lead to misdiagnosis. However, it helps that hypomanic episodes often have improved functioning, especially in nontertiary-care settings. It is unknown whether mood-stabilizing agents should be given long-term to patients with BP II. The risk of switching to hypomania with antidepressants is lower in BP II than in BP I, but because BP II is highly recurrent (especially depression), understanding how to prevent future episodes of depression is imperative. Depression associated with BP II is often mixed and atypical; and its treatment needs to be the focus of future studies.

Many episodes of depression (major depressive episodes) in BP II are mixed. Mixed depression (depressive mixed state) has been defined as the combination of depression and hypomanic symptoms (usually not reaching the minimum number required by DSM-IV for the diagnosis of hypomania). Hypomanic symptoms start during the depression (ie, these are not the tail of a recent hypomanic episode), and are not induced by antidepressants (ie, have a spontaneous onset), although antidepressants can induce and worsen these symptoms.

Very few studies have included samples of untreated BP II that would allow the study of spontaneous-onset intradepression hypomanic symptoms. Several definitions of mixed depression have been suggested and tested. Some require 2 or 3 hypomanic symptoms, others require 3 specific symptoms such as psychomotor agitation. The most validated definition to date requires a cutoff of 3 hypomanic symptoms. Its validation is based on stronger associations with bipolar validators, such as family history, age at onset, and BP II. This mixed depression has a positive predictive value of more than 70% for BP II.

The diagnostic validity of agitated depression has been tested in outpatients. Most agitated depressions are mixed (they have many intradepression hypomanic symptoms), and most are related to BP II. Inpatients with agitated depressions often have many severe manic symptoms, including psychosis (uncommon in outpatients with agitated depression). In a BP II and MDD sample, agitated depression was different on bipolar validators from nonagitated depression only when it was mixed (it was often mixed). This finding suggests that it is not psychomotor agitation alone that makes agitated depression different from nonagitated depression, which brings into question the diagnostic validity of agitated depression.

The frequency of mixed depression in BP II has ranged between 20% and 70%. Its frequency is related to the setting (eg, tertiary care vs nontertiary care, inpatients vs outpatients), the interview methods, the BP I and BP II ratio versus MDD, the study of treated samples (as mood-stabilizing treatment suppresses manic/hypomanic symptoms), and the definition used. It is more common in BP I and BP II than in MDD, but it is not uncommon in MDD (around 30% in outpatients). Mixed depression in MDD has been found to be closer to that of BP I and BP II, on bipolar family history and age at onset, than to that of nonmixed MDD.

The most common symptoms of mixed depression, which are more severe in BP I than BP II, are...
irritability, racing thoughts and distractibility (mental activation), psychomotor agitation (which is mild in outpatients), and talkativeness (behavioral activation). Factor analysis of these symptoms has found 2 factors: a mental activation and a behavioral activation factor. These factors closely match the factors found in the hypomania occurring outside the depression, supporting the hypomanic nature of these symptoms. In outpatients, symptoms such as irritability and racing (crowded) thoughts are often not spontaneously reported, and should be systematically assessed and psychomotor agitation is mild. Atypical depression is common in BP4,9,45 and studies have found that atypical depression is more likely than typical depression to be mixed. In this case, it is the mental activation of mixed depression that is present in atypical depression, making the combination of the 2 states possible.46

The bipolar nature of mixed depression is supported by several lines of evidence:

- Close association with BP I and BP II, and with bipolar family history.39-43
- Dose-response relationship between number of intradepression hypomanic symptoms and bipolar family history loading, ie, the higher the number of symptoms, the higher the bipolar family history loading.42
- Factor structure of the intradepression hypomanic symptoms similar to the factor structure of the hypomania occurring outside the depression.8,16,25,47
- Mixed depression in MDD showing a closer similarity to BP I and BP II on bipolar validators than to nonmixed MDD.39-42
- MDD shifting to bipolar disorder in the long run (around 40% to 50% of cases) is more likely to have mixed depression.48-50
- With antidepressant treatment, mixed depression, compared with nonmixed depression, is more likely to switch to mania/hypomania.51-5
- The distribution of the intradepression hypomanic symptoms between BP II and MDD is not bimodal.54,55

Two lines of evidence question the categoric definition of mixed depression,55 as reported above: (1) the distribution of the intradepression hypomanic symptoms between BP II and MDD is not bimodal, as it should have been in a categoric disorder;54 and (2) the dose-response relationship between number of intradepression hypomanic symptoms and bipolar family history loading, ie, the higher the number of symptoms, the higher the bipolar family history loading. A discontinuity, ie, no dose-response relationship, should have been found if mixed depression were a categoric disorder.42,55

The nonbimodal distribution of the cross-sectional intradepression hypomanic symptoms is complemented by a similar lack of bimodality in the lifetime manic/hypomanic symptoms in patients with BP I and MDD.56

From a clinical practice point of view, there are several important considerations regarding mixed depression. Depressed patients should be systematically assessed for concurrent hypomanic symptoms, which, if present, should lead to a careful probing for a history of hypomania, supplemented by information from key informants. Antidepressants should be used with care in the treatment of mixed depression, since antidepressants alone (ie, without protection by mood-stabilizing agents) could worsen the concurrent hypomanic symptoms, sometimes leading to suicidal behavior.36 Irritability, psychomotor agitation, and bipolarity are possible precursors to suicidality that may be related to the effects of antidepressants.57

Studies of mixed depression have shown that cross-sectionally assessed psychomotor agitation and racing/ crowded thoughts are independent predictors of suicidal ideas,58,59 and that mixed depression is often present before suicide attempts.60 It would thus appear that it is not antidepressants that induce suicidality, but their incorrect use.58-60 In mixed depression it seems logical to first control the hypomanic symptoms with mood-stabilizing drugs and then to add an antidepressant.35 Sometimes, when a patient with mixed depression has concurrent full hypomania (ie, irritability and at least 4 symptoms), quickly treating the hypomania also resolves the depression.

Controlled studies are needed, but, because of the FDA warning, cannot be undertaken. The FDA does not allow studies on antidepressants in subjects with depression who have symptoms/features (such as psychomotor agitation, irritability, hypomanic symptoms, impulsivity, bipolar depression, and bipolar family history) that may be precursors to suicidality. Therefore, retrospective studies and naturalistic studies are the only source of information about the treatment of mixed depression.

Conclusion
Diagnostic criteria for hypomania, mixed depression, and the treatment of mixed depression, are the current hot topics in connection with BP II. All 3 of these may have an important impact on the treatment of BP II disorder. Franco Benazzi, MD, PhD, is director of the Hecker Psychiatry Research Center at Forli, Italy, a University of California at San Diego (USA) Collaborating Center. The focus of his research is bipolar II disorder, atypical depression, and mixed depression. He has published numerous articles on these subjects in international peer-reviewed journals. He reports that he has no conflicts of interest concerning the subject matter of this article.

References

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