Discriminating Between Bipolar Disorder and Major Depressive Disorder

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• Diagnosis • Nosology • Misdiagnosis • Bipolar disorder • Major depressive disorder • Irritability

KEY POINTS

- During depressive episodes, bipolar disorder (BD) and major depressive disorder may be difficult to distinguish.
- Misdiagnosis may lead to delay in effective treatment and to exposure to ineffective treatment.
- Illness features more often observed in BD may include psychomotor slowing or agitation, cognitive impairment, mood lability, psychosis, onset in the peripartum period, and early age at illness onset, among others, but none is sufficient to warrant a bipolar diagnosis.
- Only a careful, systematic assessment for current or past manic or hypomanic symptoms allows accurate diagnosis.
- Biomarkers useful in distinguishing the 2 mood disorders have not yet been established.

Despite decades of effort, psychiatry still lacks a reliable biological marker to distinguish the 2 depressive disorders, major depressive disorder (MDD) and bipolar disorder (BD), whose phenomenology can be extremely similar. There remain 2 commonly held assumptions about these 2 disorders. The first assumption is that MDD and BD are clear-cut and easily separable diagnostic conditions, requiring only careful assessment to distinguish. The second assumption is that there is no true difference in the clinical phenomenology of unipolar depression (UD) versus bipolar depression, and that, at least in the midst of a depressive episode, the 2 disorders cannot be distinguished. Unfortunately, both assumptions likely oversimplify the evidence base and tend to inhibit rigorous investigation by introducing biased assessment. The oft-cited observation

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that approximately one-third of individuals may wait 10 years or more for an accurate diagnosis can be challenged on numerous levels, but the fundamental point that patients are ill-served by the current diagnostic system is hard to dispute.

Despite the fact that MDD and BP are both included in the same group of conditions called mood disorders, clinical distinctions between them have been recognized for many decades.[1] Although clinically distinct, bipolar depression, and more specifically, the depressive phase of bipolar type II (BPII), has proven especially difficult to differentiate from MDD. Both have been defined mainly by the presence of depressive symptoms, and Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 continues the approach of prior editions in defining criteria for depressive episodes that are identical across these 2 disorders.[2] Furthermore, as most patients with BPII present for treatment when depressed rather than hypomanic, it is not surprising that it is difficult to differentiate cross-sectionally between BPII and UD.[3]

MOTIVATION FOR DISCRIMINATING BIPOLAR DISORDER FROM MAJOR DEPRESSIVE DISORDER

If the presentations are so similar, why bother to differentiate? Could this represent an example of the much-maligned notion of pseudo-specificity, carving biology at joints that do not necessarily even exist? For some clinicians and health systems, the drive to distinguish is administrative: billing requires a diagnostic code, either MDD or BD, which may account for the striking frequency of "not otherwise specified" diagnoses. However, at the core, there are 2 key reasons it might be worthwhile to distinguish BD from MDD, and importantly, they suggest potentially different solutions. To begin with, the diagnosis may have predictive validity: it may convey important information about prospective course. In particular, it may convey information about probable treatment response: interventions for the 2 disorders may be almost totally different. Generally speaking, BD requires attention to treating and preventing manic/hypomanic episodes (and to not inadvertently worsening or precipitating such episodes), whereas MDD treatment can focus solely on depressive symptoms and prevention of depressions. A second, less commonly appreciated reason is the need to draw such a distinction to facilitate biological investigation. That is, distinguishing the 2 disorders more effectively would facilitate the identification of associated biology, whereas high rates of misclassification might make such studies infeasible.

Absence of Antidepressant Efficacy

There is solid if not entirely consistent evidence suggesting lack of efficacy, or at least more modest efficacy, for antidepressants (the most common drug used in both conditions[4]), specifically in bipolar depression. Recently, new evidence supporting this small effect has emerged: 2 randomized clinical trials (RCT), double-blinded, testing "modern" antidepressants added to mood stabilizers, compared with placebo, showed neither acute nor long-term efficacy for bipolar patients suffering from a depressive episode.[5,6] In addition, a meta-analysis included these already mentioned 2 RCT along with 4 more RCT (around 1300 patients total) and showed an acute modest effect of antidepressants when added to mood stabilizers or atypical antipsychotics, but greater risk for manic episodes over a year of follow-up.[7]

On the other hand, there is robust evidence suggesting antidepressants' efficacy for MDD. Large, well-developed, and funded by National Institutes of Health, clinical trials, such as STAR-D, have found that almost two-thirds of UD patients have reached clinical remission in a year period of treatment.[8] In addition, a recent reanalysis of a