Strategies to Reduce Misdiagnosis of Bipolar Depression

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Research over the past decade indicates that the prevalence of bipolar disorder is similar to that of major depression. The author discusses complexities in the diagnosis of bipolar disorder, especially in distinguishing bipolar from unipolar depression. Bipolar depression is associated with more mood lability, more motor retardation, and greater time spent sleeping. Early age of onset, a high frequency of depressive episodes, a greater percentage of time ill, and a relatively acute onset or offset of symptoms are suggestive of bipolar disorder rather than major depression. Because *DSM-IV* criteria require a manic or hypomanic episode for a diagnosis of bipolar disorder, many patients are initially diagnosed and treated as having major depression. Treatment of bipolar disorder with antidepressants alone is not efficacious and may exacerbate hypomania, mania, or cycling. It is important that clinicians be alert to any hint of bipolarity developing in the course of antidepressant therapy, especially among patients with first-episode major depression. (*Psychiatric Services* 52:51–55, 2001)

Beginning with this issue, *Psychiatric Services* initiates a monthly series of informal articles by experts in the study of depressive disorders. As the editor of this series, I have solicited papers with the aim of transmitting research-based information to the journal's readers in terms that they may be able to apply in their day-to-day work with patients. Some readers of the journal have the expertise to prepare future articles in the series. If you have a perspective that may be unique, please contact me and I will respond promptly to your idea.

My objective is to take manageable bits of data and summarize them in clinically relevant terms. The articles will cover major depression, bipolar depression, mania, and dysthymia. Bipolar disorder will receive substantial attention. This particular focus stems from a sharp increase over the past decade in research on bipolar depression and bipolar disorder in general and evidence that the prevalence of major depression and bipolar disorder are relatively similar (1,2).

The series starts with a review of the evidence that some patients initially diagnosed as having major depressive disorder, schizophrenia, or anxiety disorders have illnesses that fundamentally reflect bipolar disorder pathophysiology.

Complexities in the diagnosis of bipolar depression

Diagnosing bipolar depression is not always difficult. In an evaluation of a patient who has had an unequivocal manic episode, the diagnosis is relatively simple. However, several factors combine to complicate the diagnosis in a large proportion of patients. The younger the age of onset—bipolar disorder starts in childhood or early adulthood in most patients—the more likely the first episode or two are to be depression. Because *DSM-IV* requires a manic or hypomanic episode to make a diagnosis of bipolar disorder, many patients are initially diagnosed and treated as having major depression.

The consequences of such misdiagnosis can be serious. Treatment of bipolar disorder with antidepressants alone is not efficacious. With misdiagnosis, not only is efficacious treatment with mood stabilizers and appropriate counseling specific to bipolar disorder delayed, but also when such treatment is initiated for patients who have had several episodes of illness, it may be less effective (3). Recent evidence from a double-blind, placebo-controlled study indicates that patients who had three or more depressive episodes were less likely to respond to lithium in the treatment of mania (4).

Additional difficulties are posed by patients' underreporting of illness-defining hypomanic or manic episodes. In the structured setting of a hospital or professional office, a patient's behavior may be more organized than during the course of the patient's usual activities. The durational requirements for a manic or hypomanic episode in the *DSM-IV* criteria are longer than the actual duration of such syndromal symptoms in many patients. In addition, course of illness is not considered in the *DSM-IV* criteria.

Initial diagnosis as major depression

Ghaemi and associates (5) recently reported that 40 percent of a group of patients with bipolar disorder had previously received an incorrect diagnosis of major depression. A French study applied *DSM-IV* criteria to 250 patients with major depressive episodes (6). When the cri-

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teria were used, 72 percent of the patients were identified as having major depressive disorder and 28 percent as having bipolar disorder. A second diagnostic assessment of the same patients using systematic structured interviews to assess carefully for evidence of bipolar disorder and stricter criteria for unipolar depression found that only 45 percent met criteria for unipolar depression, whereas 55 percent met criteria for bipolar disorder (6).

The National Institute of Mental Health Clinical Collaborative Depression Study followed 559 patients initially diagnosed as having major depression for an 11-year period (7). Despite careful application of research diagnostic criteria at the initial assessment, 3.9 percent were subsequently found to have developed bipolar I disorder and 8.6 percent to have developed bipolar II disorder. Lewinsohn and colleagues (8) conducted an epidemiological study of youths in Oregon. The rate of bipolar I and II disorder was 5.7 percent when symptomatic criteria were applied and durational criteria deleted; an additional 1 percent met both symptomatic and durational criteria. These bipolar youths were more than ten times more likely to have had an initial mood episode of depression than of mania.

A survey of members of the National Depressive and Manic-Depressive Association also found that depressive symptoms were the single most frequent initial symptom of the illness; such symptoms contributed to initial misdiagnosis as unipolar depression for 33 percent of respondents (9). Every systematic study of this issue finds similar results, regardless of methodology. A large proportion of patients with fundamental bipolar disorders receive a diagnosis of major depressive disorder. It is useful to look at the factors that contribute to this problem.

DSM-IV criteria

DSM-IV criteria assume the same phenomenology for major depression and bipolar depression. The minimum duration of four days required by *DSM-IV* criteria for hypomanic symptoms exceeds the actual average duration of hypomania (10). These factors can make it difficult for clinicians to make a diagnosis of bipolar disorder even when the evidence so inclines them. However, significant differences in symptom expression and course of illness between major depression and bipolar depression can aid in earlier recognition of bipolar disorder, permitting safer, more effective treatment. Early age of onset, a high frequency of depressive episodes, and a greater proportion of time ill are each suggestive of bipolar disorder rather than major depression. A relatively acute onset or abatement of symptoms also characterizes bipolar depression more than unipolar depression (11).

The focus on bipolar disorder stems from recent research indicating that the prevalence of major depression and bipolar disorder are relatively similar.

Symptomatic differences

Compared with unipolar depression, bipolar depression is associated with more mood lability during the episode (12), more motor retardation (13), and greater time spent sleeping (14,15), whereas major depression is often accompanied by insomnia. Also, weight loss (16) and agitation (17,18) occur less than with unipolar depression. Because of the overlap of symptoms in the two conditions, no single or specific constellation of these symptomatic presentations allows unequivocal diagnosis of unipolar or bipolar depression.

Psychometric differences

Psychometric studies complement the evidence of symptomatic studies on differences between patients with unipolar and bipolar depression (19). Patients with bipolar depression and bipolar manic patients had much higher scores than patients with unipolar depression on extraversion, novelty seeking, and being less judgmental. The results indicate that some of the key behaviors that differentiate bipolar depressed patients from unipolar depressed patients are enduring characteristics of bipolar disorder and appear in all phases of the illness.

Other features besides illness course and symptoms can be used to improve diagnostic accuracy. Depression—and indeed all mood episodes—in the postpartum period are more likely to reflect an underlying bipolar disorder (20,21). Depression occurring on a seasonal basis is more likely to be within the bipolar spectrum. A family history of relatively many members with mood disorders is associated with bipolar disorder (22).

Bipolar II disorder

Bipolar II disorder poses a particular problem in diagnostic characterization. *DSM-IV* criteria for hypomania are overly restrictive, requiring the full symptomatic picture of mania and a duration of at least four days. However, the modal duration of a hypomanic state is one to three days (23). In addition, many persons with bipolar II disorders who seek treatment while depressed either do not recall hypomanic episodes or view past hypomanic episodes as within the range of normal, even desired, function. The consequence of these interacting factors is that many patients with bipolar II or similar mild forms of bipolar disorder are temporarily or permanently seen as having unipolar depression.

Improving diagnostic differentiation

Clinicians can improve their accuracy in diagnosing bipolar II disorder by asking patients whether they have

noted hypomanic symptoms immediately before or after a period of depression. Also, asking the patient whether friends or relatives have noticed or commented on symptoms within the manic spectrum can be useful; a patient's denial of such symptoms does not necessarily represent an unwillingness to acknowledge them but is likely to reflect an inability to perceive behaviors as linked to illness. Questioning the patient about moment-to-moment mood lability can also help uncover underlying bipolar disorder.

However, questioning the patient is of limited value in investigating some core aspects of bipolar disorder. Impulsivity is less sensitive to inquiry than to observation of actual behavior in an ordinary environment, without the structuring context of an office or hospital unit. For these reasons, speaking with a close family member is recommended. Involvement of a family member is helpful during both initial assessment and continuing treatment, although such involvement may be less important in the latter phase if the patient develops improved self-awareness of symptoms and related function.

Some patients with bipolar II disorder have even milder manic excursions than described above. These persons generally have hyperthymic temperaments, evidenced by high energy, remarkable capacity for productive work, impatience, and a tendency to be easily annoyed. Possessing these characteristics would not qualify a person for a diagnosis of bipolar II disorder or of cyclothymia, but the characteristics appear to be associated with a bipolar-spectrum form of mood disorder (24).

If some of these associated features, such as early onset of illness and a family history of depression, are present but no hypomanic episode can be documented, the clinician has a dilemma. I generally tell the patient about the evidence supporting a diagnosis of bipolar depression and indicate the rationale for starting treatment with a standard antidepressant compared with the rationale for initial use of a mood stabilizer or lamotrigine. I also discuss with the patient and family member what signs to look for as evidence of bipolar disorder in the course of treatment.

The American Psychiatric Association work group on bipolar disorders has begun the process of review that will lead to the next revision of *DSM*. It is likely that several of the limitations of *DSM-IV* regarding bipolar disorder will be modified, on the basis of evidence, in *DSM-V*. However, the task force for *DSM-IV* recognized the limitations of the strictly categorical approach taken and specifically reminded users of the manual to use clinical judgment: "The specific diagnostic criteria included in *DSM-IV* are meant to serve as guidelines to be informed by clinical judgment and are not meant to be used in a cookbook fashion. For example, the exercise of clinical judgment may justify giving a certain diagnosis to an individual even though the clinical presentation falls just short of meeting the full criteria for the diagnosis as long as the symptoms that are present are persistent and severe" (25).

If a patient's depressive episode is treated with antidepressants and the patient subsequently develops mood lability, cycling phenomena, hypomania, or mania, *DSM-IV* criteria require a diagnosis of a manic episode secondary to a general medical condition, a diagnosis that is not within the spectrum of bipolar disorder. However, the evidence is conclusive that such states are indicative of bipolar-spectrum conditions (26,27). The problem here is less with the clinician than with the patient. Almost all psychiatrists who prescribe antidepressants have seen unequivocal instances of increased mood lability, cycling, and frank mania with all currently approved antidepressants. However, it can be difficult to persuade many patients that their treatment course will be better with addition of a mood stabilizer when the official diagnostic nomenclature argues against a bipolar designation.

Some authorities have expressed concern about broadening the concept of bipolar disorder to the point that the specificity so important to understanding genetics, pathophysiology, illness course, and treatment response is lost (28). I agree in general with such concerns. However, the evidence summarized here comes almost strictly from studies of patients assessed in structured research interviews and is based on use of rigorous diagnostic criteria. It is important to note that bipolar II disorder is associated with functional impairment and illness sequelae as great as bipolar I disorder (29). Recent treatment research on bipolar II disorder, which is characterized by full depressive symptomatology, suggests that it may have a more unsatisfactory naturalistic course than does bipolar I disorder (30).

Consequences of misdiagnosis

Depression is not the only disorder that is erroneously diagnosed in patients with fundamental bipolar disorder, but it occupies an especially important place among the frequently misdiagnosed entities because of the consequences of misdiagnosis. The standard treatment for major depression is an antidepressant medication. Only meager data are available from controlled studies of use of antidepressants in treating bipolar depression. However, all appear to support an association between antidepressants and an elevated risk of hypomania, mania, and cycling. This risk is compounded by the standard practice, which is supported by research, of continuing antidepressants for a year or longer after recovery from a major depressive episode. Longer duration of treatment increases the risk of cycling in fundamentally bipolar patients.

Some aspects of antidepressant-induced hypomania or cycling can easily be misconstrued by the patient, or even an astute psychiatrist, as a worsening of the depression. A logical response would be to increase the dosage of the antidepressant, which then increases the risk of mood destabilization.

As a result of better understanding of the risks posed by antidepressants, authorities recommend shorter periods of treatment for uncomplicated bipolar depressive episodes (31). However, when bipolar disorder is not recognized, the clinician has no impetus to discontinue medication after a relatively brief intervention.

In addition, there is evidence that patients who have had three to eight

lifetime episodes of illness are much less likely to benefit from lithium, either for treatment of acute mania or in prophylaxis (3,32). The lack of response suggests the possibility that medications used inappropriately to treat depressive states in persons with bipolar disorder could be altering neuronal systems toward a state permanently refractory to lithium. In the one published study comparing lithium and divalproex, patients treated with divalproex had equivalent responses regardless of the lifetime number of episodes (3). There may be other explanations for the link between number of episodes and lithium response. Patients who have many episodes may have a form of bipolar disorder that is inherently less responsive to lithium.

To summarize, these findings about bipolar depression erroneously diagnosed and treated as major depression have two major clinical implications. First, attention to indicators of bipolar pathophysiology is important and can be achieved by going beyond the cross-sectional, ahistorical criteria of the *DSM-IV.* Second, the current limitations of our diagnostic schema and resources mean that many patients will be treated with antidepressants without the benefit of mood stabilizers. Therefore, it is important that clinicians be alert to any hint of bipolarity developing in the course of antidepressant therapy, especially among patients with first-episode major depression. In addition, patients may be apprised of such a risk, thereby helping them recognize any untoward effects of the antidepressant that may suggest bipolarity.

Finally, consideration should be given to treatments of depression that do not pose risks of destabilization of bipolar disorder. Evidence from randomized, double-blind, placebo-controlled trials supports the efficacy of only one medication—lamotrigine—for treating depression without inducing cycling or mania; studies of this drug in the treatment of mood disorders are ongoing (33-35). Other agents with putative antidepressant effects and mood-stabilizing properties exist, such as risperidone, olanzapine, and omega-3 fatty acids, but only slight, indirect evidence of efficacy has been found for any such compound. Psychotherapy may also be efficacious; however, to date no controlled studies have demonstrated efficacy for patients with bipolar depression (36).

Diagnosis of nondepressive disorders

Other psychiatric diagnoses are often made for patients with fundamental bipolar disorders. In some instances, misdiagnosis is a function of symptom overlap; in others, the patient may have a comorbid psychiatric disorder. In the past, bipolar disorder was often misdiagnosed as schizophrenia (37). This problem has diminished in recent years with the recognition that psychosis is common in both disorders rather than specific to schizophrenia. Also, *DSM-IV* criteria for schizophrenia yield greater reliability and specificity than earlier, poorly demarcated criteria.

Anxiety disorders often co-occur with bipolar disorder (38) and, when prominent, can mask evidence of bipolar disorder. Anxiety is an intrinsic symptom of manic states. Bipolar disorder with onset in childhood is often associated with attention-deficit hyperactivity disorder and conduct disorders. The relatively low reliability of criteria for the latter diagnoses, coupled with atypicality of the symptoms of bipolar disorder among youths, makes diagnosis difficult (39). Persons with bipolar disorder also have high rates of comorbid substance use disorders (40), and early-onset bipolar disorder may be a risk factor for substance use disorder (41).

Although bipolar disorder may be mistaken for each of the groups of disorders described above, the consequences are generally less ominous than for the misdiagnosis of depression. Most treatments for the other disorders do not worsen bipolar disorder, and some may help lessen a portion of the symptoms of bipolar disorder. Indeed, concurrent treatment of bipolar disorder and comorbid conditions is often desirable. Furthermore, systematic, structured diagnostic assessments will generally identify evidence of some features of bipolar disorder, and treatment for both conditions can be implemented.

Conclusions

Evidence indicating the misdiagnosis or incomplete diagnosis of bipolar disorder is now extensive and compelling. Understandably, much of it was not incorporated into the *DSM-IV* criteria, which are now a decade old. However, much of this evidence can be incorporated into sophisticated, sensitive assessments of our patients who have disorders that share some features with bipolar depression or that may co-occur with bipolar disorder. Any one of us may be wrong in our diagnostic assessments cross-sectionally. However, if we endeavor to reconsider diagnoses in the overlapping areas of bipolar depression, major depression, anxiety disorders, substance abuse, and schizophrenia, we are likely to arrive at the correct diagnosis early in the course of illness. For bipolar disorder, early diagnosis requires attention both to the specific features of the depression and the evidence for current or past manic or hypomanic symptomatology. ♦

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Psychiatric Services to Focus on Treatment of Anxiety in 2001

This year *Psychiatric Services* will publish a series of articles on the treatment of anxiety. The editor of the series, Kimberly A. Yonkers, M.D., of the Yale School of Medicine in New Haven, Connecticut, invites contributions that address anxiety disorders, including panic disorder, agoraphobia, obsessive-compulsive disorder, social phobia, posttraumatic stress disorder, and generalized anxiety disorder. Papers should focus on integrating new information that is clinically relevant and that has the potential of improving some aspect of diagnosis or treatment of one or more of these conditions.

Please contact Dr. Yonkers for more information about appropriate topic areas.

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