Practical Clues to Early Recognition of Bipolar Disorder: A Primary Care Approach

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Early treatment can favorably impact the course of bipolar disorder, a lifelong illness. Because bipolar disorder can masquerade as various mental and physical illnesses—primarily major depressive disorder—patients with this condition frequently go unrecognized for years. During this recognition lag, such patients may present to their primary care physician on multiple occasions. Accordingly, primary care physicians would benefit from knowing the "clues" to early recognition of the disorder, because early recognition and management can reduce disability, improve social and employment stability, and result in improved functional outcomes. This review describes 3 pathways to the diagnosis of bipolar disorder relevant to the primary care setting: detection of mania or hypomania, differential diagnosis of recurrent depressive episodes, and identification of interepisode disorder and its comorbidities. We summarize these pathways in terms of a practical tool that a primary care physician can use to trigger further evaluation or referral.

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Bipolar disorder is a lifelong illness. Longitudinal studies show that the course of illness tends to worsen with time but that early intervention can improve long-term outcome.[1] The first step in effective treatment, accurate diagnosis, requires the identification of episodes of mania or hypomania. These conditions are often missed, however, since they may not be recalled as illnesses.[2] The illness usually starts with depression rather than mania, so even when mania is detected accurately, the onset of bipolar disorder may be missed.[1,3] Increasing recognition of these problems has led to potential improvements in identifying bipolar disorder and its antecedents.

The onset of impairment from bipolar disorder may precede that of recognizable manic episodes. Table 1 summarizes characteristics that suggest risk for bipolar disorder. When prominent affective symptoms occur in someone with any of these characteristics, bipolar disorder should be strongly suspected and ruled out before a patient is treated with either antidepressants or stimulants without concomitant mood-stabilizing treatments. We will discuss 3 pathways to the recognition of bipolar disorder: detection of mania, differential diagnosis of recurrent depressive episodes, and identification of interepisode bipolar disorder and its comorbidities.

PATHWAYS TO DIAGNOSIS OF BIPOLAR DISORDER

Unrecognized Mania or Hypomania

Detection of mania, or at least of brief hypomania, is required for diagnosis of bipolar disorder. This diagnosis is often missed or not remembered as an illness.[2,4] People close to the patient may recall episodes, however, and patients who do not remember episodes of affective disturbance may recall their consequences.

Diagnostic criteria for hypomania with adequate specificity and sensitivity require suitable definition of the manic syndrome and of the minimal duration of symptoms. DSM-IV criteria for hypomania require that the syndrome be present for at least 4 days, but recurrent briefer hypomania appears to be a more useful criterion.[5] Subthreshold mania may be an adequate marker for bi-

Table 1. Characteristics Suggesting Bipolar Disorder in Patients With Recurrent Depression

Onset of behavioral or psychiatric difficulties during or before adolescence
Frequent relapses of mood or other psychiatric problems
Periods of increased energy and activity with decreased need for sleep, which may not be recognized as an illness even if they caused problems
Susceptibility to problems related to abnormal regulation of arousal, motivation, or impulsivity, including attention deficit disorders, substance abuse, and anxiety disorders
Development of hypomania or abnormal activation during treatment with an antidepressant
Lack of response to antidepressants
A family history of bipolar disorder in first-degree relatives, or of any affective disorder in multiple generations

Table 2. Evidence Suggesting Past Manic Episodes[a]

Recurrent brief periods of hypomania, or clusters of hypomanic symptoms
Consequences of mania
Recurrent interpersonal conflicts
Extreme extroversion that leads to problems
Legal problems, sexual promiscuity, or other events possibly related to episodic impulsivity
Sudden or frequent job or career changes
Severe and/or recurrent financial reverses or indiscretions

[a]This evidence should be taken together with other historical and current clues before making a diagnosis of bipolar disorder.

Table 3. Clinical Characteristics of Bipolar Versus Unipolar Depression

Episode characteristics of bipolar depression
More motor slowing
More atypical or reversed neurovegetative features: severe slowing, rejection sensitivity, hypersomnia, increased appetite and/or weight
Mixed (depressive) episodes: 3 or more manic symptoms during a depressive episode
Poor response, or loss of initial response, to antidepressive agents
Course characteristics of bipolar disorder
More relatives with affective, especially bipolar, disorder
Earlier onset
More frequent episodes
Susceptibility to behavioral activation or mood lability during antidepressant or other pharmacologic treatment

polar disorder if it can be reliably detected.[6] Table 2 lists clues that a manic episode may have occurred. Patients may recall behavioral changes or symptoms better than discrete episodes of illness. For example, distorted interpersonal behavior, including lack of respect for interpersonal boundaries or appropriate social limits, can be a destructive characteristic of manic episodes.[7] Patients should therefore be asked about situations that would have been consequences of the interpersonal problems, impulsivity, or poor judgment that can accompany manic episodes.

The Mood Disorder Questionnaire was developed to screen for the possibility of bipolar disorder by eliciting a history of any of the symptoms that make up the diagnostic criteria for mania.[8] Individuals who are able to recall at least 7 of these are reported as likely to have bipolar disorder.[9]

Delusions and formal thought disorder are common in manic episodes. Mood-incongruent delusions usually reflect more severe psychosocial impairment. First manic episodes may be especially likely to have psychotic features, resulting in a presentation resembling schizophreniform disorder.[10,11] The incidence of psychosis appears not to be as high in later manic episodes, though it remains at around 50%.[11]

Detection of Bipolar Depression

Most episodes of bipolar disorder, including the first, are usually depressive.[1,3] In some of these cases, previous manic episodes may have been missed. Nevertheless, depression appears to account for most of the morbidity of bipolar disorder.[12,13] This section will discuss predictors of diagnostic change to bipolar disorder in patients originally thought to have recurrent depressive illness and differences between bipolar depression and unipolar depression (termed *major depressive disorder* in DSM-IV).

Predictors of bipolar disorder in adults with no known history of mania or hypomania. Because depression is often the first episode of bipolar disorder and early hypomanic episodes are often missed, the diagnosis of patients initially believed to have major depressive disorder may change to bipolar disorder. Table 3 summarizes characteristics of bipolar depression. A naturalistic chart review study found 37% of patients with bipolar disorder to have been initially misdiagnosed as having major depressive disorder.[14] Two studies[15,16] compared patients whose diagnosis changed from unipolar to bipolar with those of similar age whose diagnosis remained stable. Those who were subsequently diagnosed with bipolar disorder had more previous depressive episodes, more mood lability, earlier onset of illness, and greater variability of associated psychiatric problems, described as "pleomorphic" pathology.

A retrospective study of 320 patients with bipolar disorder found that more than 50% reported depression for the initial episode. Patients whose first episode was depression had more episodes of illness, more rapid cycling, and more suicidal behavior than patients whose first episode was manic.[3] It is not clear whether patients whose illness began with depression were more severely ill or were treated for years with antidepressants without mood-stabilizing treatments, worsening their natural course of illness.

Characterizing the course of illness that precedes the first manic episode is important to understanding bipolar disorder. A retrospective study revealed early onset of illness and multiple depressive episodes, noting that in over 50% of patients with bipolar disorder there were at least 3 depressive episodes before the first manic episode was

detected.[17] In 74 patients (mean age of about 23 years) hospitalized for major depressive disorder, at 15-year follow-up 46% had experienced mania or hypomania.[18] Similarly, a poll conducted by the National Depressive and Manic Depressive Association of its members found that 59% of respondents had onset during or before adolescence, that the most common presenting symptom was depression, and that there was a delay of over 8 years between onset of psychiatric problems and accurate diagnosis.[1] These studies suggest that the onset of bipolar disorder is often depressive, though each is subject to the criticism that manic or hypomanic episodes may have been missed.

The idea that some patients with recurrent depressive episodes may have bipolar disorder is consistent with a prescient observation by Kupfer 30 years ago that there were "two types of unipolar depression."[19] One type had family history and personality characteristics similar to bipolar disorder, with good response to lithium and relatively poor response to antidepressants. More recently, a series of patients with recurrent unipolar depressive episodes who repeatedly lost response to antidepressant treatments was reported to have good response to mood stabilizers without antidepressants.[20] Recurrent depressive episodes with poor or inconsistent responses to antidepressive treatments may therefore represent bipolar disorder.

Comparison of unipolar and bipolar depression. Table 3 shows that, while the associated "melancholic" syndrome may be similar in unipolar and bipolar depression,[21] bipolar depressive episodes have more motor slowing[22,23] and are more likely to have atypical features, like hypersomnia and increased appetite.[23,24]

Depressive mixed states, with at least 3 manic symptoms, were reported in 46.6% of bipolar patients versus only 7.1% of unipolar depression patients.[25] The most common manic symptoms were aggression, irritability, pressured speech, and flight of ideas or racing thoughts.[26] One study found that 22% of an initial sample of depressed patients met diagnostic criteria for bipolar disorder, but that at follow-up 40% of the patients had bipolar disorder. Characteristics that predicted change to a diagnosis of bipolar disorder included mixed episodes, frequency of episodes, and severe suicidality.[27]

Precursors of Bipolar Disorder: Clues From the History

Patients with bipolar disorder may experience other psychiatric morbidity even before the first recognizable bipolar episode. Early symptoms can appear nonspecific, at least until the history of depressive or manic symptoms is elicited. As summarized in Table 4, bipolar disorder should be suspected if prominent behavior problems, anxiety, and substance abuse were present during childhood in someone with recurrent depression and a family history of affective disorders. It can be a useful diagnostic clue if any of the patient's children have similar difficulties.

Table 4. Possible Precursors of Bipolar Disorder

- Attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders
  - Almost ubiquitous in childhood mania and commonly predate mania
  - Manic symptoms and ADHD symptoms are each like the uncomplicated disorder
  - Treatment with stimulants alone may in some children worsen the course or hasten onset of bipolar disorder. Many patients may therefore benefit from the combination of stimulant and mood-stabilizer treatments
  - Anxiety may be prominent in early-onset bipolar disorder and may predate affective symptoms, but may also be an early manifestation of major depressive disorder
  - Consider in triad of prominent behavior problems, anxiety, and substance abuse
- Psychosis
  - Delusions are more prominent in adolescent mania than in later episodes
  - Mood incongruence is more likely than in later episodes and may be associated with worse outcome
  - Psychotic episodes with family history of bipolar disorder or history of previous depressive episodes are indicators of bipolar disorder

Early depressive episodes. A history of prepubertal major depressive disorder, even without attention deficit disorders or other complications, strongly suggests bipolar disorder. In a group of 6- to 12-year-old children (mean age = 10 years) with major depressive disorder, at a mean age of 20 (10-year follow-up), 48.6% had a diagnosis of bipolar disorder, versus 33% with major depressive disorder; positive family history predicted emergence of bipolar disorder.[28] This finding was impressive because children with attention-deficit/hyperactivity disorder (ADHD) or delusional depressions, both of which are associated with increased risk for subsequent development of bipolar disorder, were excluded. Combined with data described above,[18] this finding suggests that every 10 to 15 years, at least during young adulthood, half of patients meeting criteria for major depressive disorder will develop a manic or hypomanic episode.

Attention deficit and disruptive behavior disorders. Disruptive behavior disorders in childhood are associated with eventual emergence of bipolar disorder or major depressive disorder.[29] In ADHD, severely disturbed behavior or a family history of bipolar disorder suggests a bipolar disorder.[30] There is a strong link between these disorders, substance abuse, and family history of bipolar disorder.[31,32] In general, the symptoms of ADHD[33,34] and conduct disorder[35] resemble the symptoms of these disorders in patients who do not develop bipolar disorder.

The identification of early-onset bipolar disorder is a controversial diagnostic challenge.[36] Confusion has resulted from attempts to apply adult-derived diagnostic criteria to children without allowance for developmental differences and from use of excessively inclusive signs, such as hyperactivity and irritability, rather than specific

Table 5. Characteristics That May Be Seen in Interepisode Bipolar Disorder (between frank episodes)

Even when individuals are not in an episode, bipolar disorder exceeds major depressive disorder in terms of the following:
Attentional and executive function impairment
Decreased sense of well-being and more intrusiveness of illness
Personality traits associated with bipolar disorder include the following:
Novelty seeking
Impulsivity
Bipolar disorder has overlap with these disturbances of impulsivity and arousal:
Substance abuse
Anxiety disorders
Family history characteristics include the following:
Increased incidence of bipolar disorder or major depressive disorder in first-degree relatives
Incidence in relatives is more marked in patients with early-onset disorder

symptoms of mania, leading to overdiagnosis.[37,38] The extent to which children with manic episodes go on to develop bipolar disorder as adults is not established.[39]

Anxiety disorders. Bipolar disorder and panic disorder can coexist, with additive symptoms. Suicide attempts and psychosis are more likely in patients with the combination than in those with either disorder alone.[40] Prepubertal fearful panic attacks are associated with later emergence of an affective disorder, with an odds ratio of 3 for major depressive disorder and 7.9 for bipolar disorder.[41] In adolescents with bipolar disorder, 88% had psychiatric comorbidity, including an anxiety disorder in 75%.[42] The combination of the disorders results in severe illness, with an association between anxiety, bipolar disorder, and suicide attempts among adolescents.[43]

Early psychotic episodes. Nearly 50% of adults with mania were previously diagnosed as schizophrenic.[44] The first manic episode is the most likely to be delusional.[10,11,45] Psychotic symptoms are more likely to be mood incongruent than is the case with mania later in life, with one study finding mood-incongruent psychosis in 77% of adolescents having their first manic episodes,[46] increasing the likelihood of misdiagnosis.[47,48] Mood-incongruent symptoms in the first episode were associated with increased chronicity and worse overall outcome,[49] a marker of severe illness but not of a distinct clinical type.[50] Comorbid disturbances were reported in 69% of psychotic first episodes, with 80% of these predating the psychotic episode.[51] Impairment is prolonged, with syndromal recovery requiring less than 3 months but functional recovery taking longer than 6 months.[52]

Comorbidities and Interepisode Bipolar Disorder in Adults

Between episodes of bipolar disorder, patients may experience residual affective symptoms or other problems including cognitive impairments or impulsivity. People with bipolar disorder are also more likely than others to have anxiety or substance abuse disorders even when they are not experiencing depressive or manic episodes. Characteristics of personality or temperament may also distinguish euthymic or interepisode patients with bipolar disorder from others without the illness. Table 5 summarizes characteristics of interepisode bipolar disorder.

Characteristics of "euthymic" patients. Bipolar disorder is associated with symptomatic impairment even without an active mood episode. For example, well-being was less in euthymic patients with bipolar disorder than in major depression patients or controls.[53] "Intrusiveness" of illness in these patients was increased compared with that in major depression patients and controls, especially if patients had been depressed within the previous year.[54] In patients with bipolar I disorder, symptoms occurred in 47.3% of weeks over a 2.8-year period, with depression almost 4 times as frequent as mania; there were an average of 6 symptom switches and 3 polarity switches per year.[55] Increased mood variation or lability was also reported in adolescents with bipolar disorder.[56]

Executive function was impaired during remission, but not as severely as in patients with schizophrenia.[57] Attention, including fine motor function and reaction time, can also be impaired in remitted bipolar disorder.[58]

Personality characteristics. Patients with interepisode bipolar disorder have been reported to have increased novelty seeking compared with controls.[59,60] Studies of temperament have detected cyclothymic or hyperthymic temperaments in remitted bipolar disorder.[4,61,62] Residual symptoms may be associated with interpersonal distortions resembling those reported with manic episodes.[7] The potential for impulsivity in interepisode bipolar disorder patients appears greater than in controls,[63] perhaps increasing their susceptibility for substance abuse and other comorbidities.[64]

Comorbidities

Anxiety disorders. Anxiety disorders are common in patients with bipolar disorder. Panic disorder was reported in 20.8% of patients with bipolar disorder, compared with 10% of those with unipolar disorder, with earlier onset of bipolar disorder in such patients.[65] Similarly, obsessive-compulsive disorder was present in 21% of patients with bipolar disorder compared with 12% of those with unipolar disorder and 6% of controls in the Epidemiologic Catchment Area database; patients with bipolar and obsessive-compulsive disorder also had a higher rate of panic disorder (37% vs. 16% in bipolar patients without obsessive-compulsive disorder).[66] Fifteen percent of patients with obsessive-compulsive disorder had bipolar disorder, and more than half had cyclothymia.[67] A review of 17 studies of offspring of patients with bipolar disorder found that, while rates varied widely, mood and anxiety disorders were substantially more common than in controls of similar age and gender.[68]

Table 6. Patterns to Assist Early Identification of Bipolar Disorder

If You Observe	Then Inquire About	If Results Are Positive, Then
Depression	Family history of bipolar disorder	Only use antidepressants in combination with a mood stabilizer
Irritability	Behavioral problems in patient's children	
Mood lability	History of hypomania (full, brief, symptomatic, or pharmacologic)	Refer to a psychiatrist for evaluation
Problematic impulsivity	Childhood or adolescent onset of psychiatric symptoms	
	Frequency of recurrence	
	Previous treatment and loss of response	

Substance abuse disorders. Substance abuse disorders are the most prominent Axis I comorbidities of bipolar disorder[69] and are associated with earlier onset of illness.[39] Compared with patients who only have bipolar disorder, those with both bipolar disorder and substance abuse have earlier onset, more frequent episodes, higher risk for suicidal behavior, stronger family history of bipolar disorder, and higher prevalence of other Axis I or II disorders.

Personality disorders. Personality disorders may represent a pathologic adaptation to bipolar disorder or may represent a more chronic form of a similar behavioral disturbance. Their prevalence seems to increase with duration of illness, since a personality disorder was found in 33% of first-episode subjects but in 65% with multiple episodes.[70]

Familial pattern. Patients with bipolar disorder have an increased incidence of bipolar and unipolar disorders in their first-degree relatives.[71] This is especially pronounced if onset of bipolar disorder is early.[72,73] Most offspring of patients with bipolar disorder may have a major psychiatric diagnosis.[74] Obtaining a family history is a valuable and efficient diagnostic measure. Directly interviewing relatives is the most reliable method for obtaining a psychiatric family history,[75] but reliability for mania diagnoses was high using the Research Diagnostic Criteria-Family History method. As a preliminary screen, it is useful to ask about whether any relatives have the characteristics of bipolar disorder that are described in Tables 1 and 2. The Mood Disorder Questionnaire can be a useful screening tool for relatives of patients suspected to have bipolar disorder.

DETECTION OF BIPOLAR DISORDER IN PRIMARY CARE

Operationalized risk factors can be derived from the characteristics of bipolar disorder discussed here. The object is to detect patients who require further evaluation because bipolar disorder is likely, without overdiagnosing the illness. Table 6 gives a scheme to identify patients in whom bipolar disorder is likely.

Patients with characteristics suggesting bipolar disorder warrant further psychiatric evaluation. Antidepressants and stimulants should be used judiciously in patients with bipolar disorder,[76,77] since they can potentially destabilize mood.[78–80] Mood-stabilizing treatments should be used initially in these patients, since these treatments may themselves be effective for depression, and they can protect against pharmacologic mood destabilization although they do not eliminate it.[76,78] There are currently no biochemical or other objective tests that are practical for making the diagnosis of bipolar disorder. Measures such as those described in this article can potentially enhance clinical efficiency. Ultimately, there is no substitute for alert and accurate clinical diagnosis.

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