Diagnosing bipolar disorder: how can we do it better?

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ABSTRACT

- Accurate diagnosis of bipolar disorder is essential for effective treatment.
- The diagnosis of bipolar disorder is particularly complex, resulting in lengthy delays between first presentation and initiation of appropriate therapy. Inappropriate therapy destabilises the course and outcome of the disease.
- Although the defining features of bipolar disorder are manic or hypomanic episodes, patients typically present for treatment of depression and commonly deny symptoms of mood elevation.
- A correct diagnosis can easily be masked by comorbidities, personality issues and complex phenomenology.
- A diagnosis of bipolar disorder can be assisted by:
  - asking about symptoms of mania or hypomania in every patient presenting with symptoms of depression.
  - recognising mixed states in which manic and depressive symptoms occur simultaneously.
  - identifying the features of bipolar depression that distinguish it from unipolar depression.
- There is a risk of over-diagnosis of bipolar disorder among patients who are histrionic, show abnormal illness behaviour and/or have issues of secondary gain.

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Difficulties and delay in the diagnosis of bipolar disorder impede effective treatment and amplify the burden of illness on the individual, the family and society.[1] The 2000 National Depressive and Manic-Depressive Association survey[2] estimated the prevalence of bipolar I and II disorder in the United States to be 3.4%. Of people with bipolar disorder, almost a third (31%) had been incorrectly diagnosed as suffering from unipolar depression and, in nearly half (49%), the condition was both unrecognised and undiagnosed. Remarkably, just over a third (35%) of these individuals had been symptomatic for more than 10 years before the correct diagnosis was made.

The 2003 Access Economics report for SANE Australia on the costs of bipolar disorder in Australia[1] confirmed that a 10-year gap before correct diagnosis is not uncommon. The SANE report found that over two-thirds (69%) of people with bipolar disorder were misdiagnosed (on average, three to four times) before receiving the correct diagnosis. The most common alternative diagnoses included depression (60%), anxiety disorder (26%), schizophrenia (18%) and borderline or antisocial personality disorders (17%).[1] Not surprisingly, a number of studies involving extended periods of follow-up[3] have illustrated that there is a substantial switch in diagnosis from unipolar to bipolar disorder over time.[4]

We believe that correct diagnosis of bipolar disorder and appropriate early intervention is possible and likely to enhance long-term patient outcomes (Box 1). We can increase the detection of bipolar disorder, and thus improve outcomes, by asking and answering further questions about factors that may contribute to problems in diagnosis. For example:

- Is bipolar disorder too rigidly and narrowly defined, with many sufferers not meeting the full criteria for diagnosis until they have endured many years of illness?
- Are clinicians insufficiently aware of the importance of prior episodes of mania or hypomania in establishing an accurate diagnosis of bipolar disorder?
- Do we need to consider depression as having a wider differential diagnosis, which includes bipolar disorder?

We hope that our discussion of issues related to these questions will assist clinicians to diagnose bipolar disorder earlier and more accurately.

Diagnostic systems

There is no definitive diagnostic system for bipolar disorder. Significant differences between definitions of "bipolar disorder" in the American Psychiatric Association's DSM-IV[17] and the World Health Organization's ICD-10[18] disease classifications mean that some patients will be diagnosed with bipolar disorder under one system but not the other. There are also a number of controversial areas within the DSM system (Box 2). Additionally, inability to confirm a diagnosis of bipolar disorder may be unavoidable, as neither diagnostic system allows the diagnosis of bipolar disorder until a full episode of mania or hypomania has occurred, yet many patients will commence their illness with an episode of depression, and may have had hypomanic symptoms that, for example, did not meet criteria for duration of symptoms. Therefore, there is intrinsic diagnostic delay.

Basic diagnostic indicators

Despite the difficulty presented by current diagnostic systems, we believe that good clinical practice requires that when a patient presents with a depressive episode the clinician should have an index of suspicion that the episode may be part of bipolar disorder. Careful evaluation and constant vigilance, coupled with knowledge of potential indicators of bipolarity, are likely to improve diagnosis.

A number of authors have attempted to identify clinical indicators suggestive of bipolarity in individuals presenting with depression (Box 3). These include strong indicators, such as family history, and suggestive features, such as postpartum onset and a seasonal pattern. Simple screening questionnaires such as the Mood Disorder Questionnaire may be useful in suggesting an appropriate diagnosis of bipolarity, particularly in primary care settings.[19] Furthermore, an awareness of the multiple factors that can obfuscate diagnosis of bipolar disorder (eg, complex phenomenology, age at onset, comorbidity and the heterogeneity of bipolar disorder presentations) can help in correct diagnosis. Early intervention with appropriate treatment is likely to enhance long-term outcomes.

1 Bipolar disorder (BD): why does early diagnosis matter?

Disruption to daily life

People with undiagnosed BD frequently suffer continued chaotic existence. With the most common age of occurrence of illness being in adolescence or young adulthood, undiagnosed BD can disrupt the normal development of social skills and relationships and have a negative impact on education and earning potential.[5]

Benefits of early initiation of treatment

Emerging evidence suggests that the course and outcome of BD are worsened by persistent illness, whereas early intervention results in a more favourable outcome.[2] Studies of people with BD have shown that earlier initiation of lithium therapy is associated with greater response to the treatment.[6,7] BD is associated with neuropsychological impairment, and recent studies of mood stabilisers[7] and atypical antipsychotics[8] point to potential neuroprotective aspects of these treatments. Accurate diagnosis and appropriate treatment may also be protective against the functional impairment associated with BD.[9]

Harmful effects of inappropriate treatment

Optimal outcomes are contingent on appropriate therapy, and an inaccurate diagnosis is likely to lead to the initiation of inappropriate therapy. Ghaemi et al,[10] comparing people with BD and unipolar disorder, found that a higher proportion of those with BD failed to respond to antidepressant therapy, or had an initial response but subsequently lost response, or had a manic switch after initiation of antidepressant therapy. There is also a significant risk of inducing rapid cycling in people who are misdiagnosed as having unipolar depression and treated with antidepressants.[11] Recent long-term prospective studies examining the risk of switching into mania or hypomania after antidepressant treatment have shown far higher rates of switching than previously reported.[12]

Risk of suicide

There is an enduring risk of suicide in patients with BD, which may be higher than the risk for other mental disorders[13] and is 12 times higher than in the general population.[14] Studies have demonstrated the protective effects of appropriate lithium treatment on suicide risk.[15,16] ◆

Specific clinical issues

Emergence of symptoms

The emergence of symptoms of bipolar disorder may present a confusing picture for both clinician and patient. The onset of bipolar disorder is frequently insidious, with relatively minor, predominantly depressive, oscillations in mood, gradually giving way to episodes of depression. Features such as increased energy, elevated mood, disinhibition and racing thoughts are common antecedents to the emergence of a full-blown manic episode. Indeed, many patients who later develop bipolar illness present with a prodrome of behavioural mood problems long before an identified episode of illness. Equally, many patients experience major episodes of illness without a clear prodrome.[20] There may be substantial delay in seeking help because patients may not understand the nature of their symptoms, or may simply be embarrassed or fearful of potential stigma.[5] When help is sought, it is typically for depressive rather than manic or hypomanic symptoms, and yet it is the latter that serve as the signature of bipolar disorder. This creates a paradoxical situation in which the presenting symptoms of the illness are often not those needed to define or diagnose bipolar disorder.

2 Issues with current diagnostic systems

- The diagnostic criteria for unipolar depression tend to be broad, while those for bipolar disorder tend to be narrow.
- The DSM-IV classification[17] does not regard antidepressant-induced mania as part of bipolar disorder, but rather as a result of general medical factors.
- Subthreshold mixed states are clinically important but not part of the DSM-IV system. It is not clear what symptoms of depression and mania represent the minimum threshold for mixed states, but it is probably less than concurrent full symptoms of both mania and depression.
- The requirement for full-episode duration of depression and mania means that rapid and ultra-rapid cycling are not diagnosable using current criteria.
- While there are clinical features of bipolar depression (eg, atypical depression, abrupt onset and end, positive family history, highly recurrent pattern, early age of onset) that differ from those of unipolar depression, current systems use a single set of symptoms to define both sets of depression.
- The 4-day duration required for diagnosis of hypomania may be too long, and differs from community studies suggesting that the mean duration of hypomania is 2 days.
- Current diagnostic systems do not specify stage. Bipolar disorder spans an at-risk period, the prodrome, first episode, recurrence, and treatment resistance, all of which differ substantially in presentation and clinical needs. ◆

Comorbidity

The diagnosis of bipolar disorder is complicated by extensive comorbidity that may precede the onset of the illness. Especially common are substance misuse (in 42%–71% of patients) and anxiety disorders (in 42%–93% of patients).[21,22]

Family history

Family history is an important diagnostic indicator (Box 3). However, high rates of unipolar depression among individuals with a family history of bipolar disorder cause difficulty, as the index episode of bipolar disorder is typically depressive.

Age at onset

There are particular difficulties in diagnosing bipolar disorder in younger people, partly because of a low base rate and variability in clinical presentation, but also because of overlap in phenomenology with other disorders.[23] Particularly problematic is the boundary between bipolarity and attention deficit hyperactivity disorder, with comorbidity rates estimated to be as high as 87%.[24] In adolescents, the impact of development on symptom expression, resulting in subtly different phenomenology, is a further complication.[25] Clinical features in young people that may aid differentiation include higher rates of mixed mania (55%) and rapid cycling (87%).[24]

In children, the phenomenology is again somewhat different, with less discrete episodes of mania or depression and high rates of mixed states, dysphoria and rapid cycling.[26] Irritability persisting through episodes, with aggressive behaviour and temper outbursts, is common, with children frequently presenting as emotionally labile and explosive.

Inconsistency of information

Accurate diagnosis is also difficult because structured and clinical interviews often yield differing information. While structured

3 Clinical indicators of bipolar disorder

Strong indicators

- Family history of bipolar disorder in a first-degree relative
- History of antidepressant-induced mania or hypomania
- Hyperthymic personality* prior to onset of depression
- Early age at onset
- Highly recurrent pattern of illness
- Brief episodes of illness
- Atypical symptoms of depression (eg, hypersomnia,† hyperphagia, fatigue, sensitivity to rejection)

Suggestive features

- Postpartum onset
- Psychotic features
- Seasonal pattern
- Severe premenstrual syndrome
- Lack of response to antidepressant therapy
- Abrupt onset and end

* People with hyperthymic personality show persistent features similar to those of hypomania, with traits such as optimism, increased energy, reduced need for sleep, extroversion, promiscuity and overconfidence. † Hypersomnia is the most specific. ◆

interviews are regarded as being definitive diagnostically, there is a subgroup of patients who will claim the presence of symptoms that the clinician does not consider clinically salient. This includes patients who may be histrionic, have issues of secondary gain, or manifest abnormal illness behaviour. In such situations, there is a risk of over-diagnosing bipolar disorder. Equally, many patients deny or minimise symptoms that are evident to third parties. As a result of the global and universal nature of their negative cognition, patients suffering from depression may minimise or deny ever experiencing times when their mood was elevated.

Mania is commonly associated with a lack of insight that may impair self-report. In addition, for some people, mania is directly pleasurable. Many individuals report mania as the period when they are at their best, and reject any notion that the condition is abnormal. Indeed, in a subgroup of patients, direct "illness-seeking behaviour" may occur, such as deliberate discontinuation of treatment, use of stimulants, and creating a cycle of increasing psychosocial stimuli and rewards to drive manic and hypomanic symptoms.[27] It may be helpful in such instances to adopt conceptual models of substance misuse for diagnosis and intervention (eg, the use of motivational interviewing).[27]

A spectrum of disease

Few patients are "classically bipolar", alternating between episodes of "pure" mania and "pure" depression. Instead, an array of illness patterns occur, particularly mixed states, rapid cycling and diverse comorbidities. Moreover, bipolar disorder can be heterogeneous in severity. Mild variants such as cyclothymia can occur.

Bipolar spectrum

The concept of a "bipolar spectrum"[28] complicates the diagnosis of bipolar disorder. This pertains to a substantial group of individuals whose symptoms lie in a grey area between those of unipolar and bipolar disorder. The unclear diagnostic boundary between these groups limits the selection of appropriate therapeutic algorithms. Similarly, there is overlap among people presenting with psychotic symptoms, incorporating schizophrenia and bipolar I disorder. A further "spectral link" occurs between bipolar disorder and personality, with an overlap existing particularly with borderline personality disorder. The bipolar spectrum is particularly common in certain subgroups of patients, with rates of up to 72% in patients with atypical depression[29] and 50% in patients with treatment-resistant depression.[30] Within general practice, a quarter of patients with depression or anxiety have bipolarity.[31]

Mixed episodes

We believe one of the most common pitfalls in the diagnosis of bipolar disorder is that of mixed symptoms.[32] In a mixed episode, criteria are met for both manic and depressive episodes simultaneously. In practice, this manifests as the intrusion of depressive symptoms into a predominantly manic presentation or the intrusion of manic symptoms into what looks like a depressive presentation. Research suggests[33] that this delays diagnosis, perhaps because the predominant complaint is that of depressed or dysphoric mood, with key manic features (eg, increased motor drive, reduced sleep, crowded or racing thoughts) receding into the background. Mixed states have particularly high rates of comorbidity with anxiety, personality disorders and the use of antidepressants and substance misuse. An implication of this is that inappropriate diagnosis may drive inappropriate therapy, which can create clinical scenarios that are more difficult to recognise. One of the important differences between mixed and pure mania is that suicidality is a far greater risk in the former.[34]

Conclusion

Accurate diagnosis of bipolar disorder is prone to many pitfalls, especially when trying to make a diagnosis on the basis of a clinical interview in which the patient presents in a single phase of a complex illness. Extended follow-up and collateral information greatly assist in the diagnostic process. Making a correct diagnosis is essential so that a patient can be given the right treatment and obtain a good treatment outcome. There is considerable controversy over the boundaries of the diagnostic definition of bipolar disorder. Current research is focusing on defining these boundaries.

Competing interests

Michael Berk has received consultant fees, speaker fees and/or educational grants from various pharmaceutical companies, including AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Mayne Pharma, Novartis, Organon, Pfizer, Sanofi-Synthelabo, Servier, Solvay and Wyeth. Seetal Dodd has received consultant fees and travel assistance to attend meetings from Eli Lilly, and speaker fees and/or educational grants from Bristol-Myers Squibb, Eli Lilly, Mayne Pharma, Novartis, Organon and Servier.

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