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Is it possible to distinguish bipolar depression from unipolar depression?

Clinical features can help determine whether a patient's depressive episode is more likely to be unipolar depression or a presentation of bipolar disorder. The likely diagnosis influences the treatment decisions made.

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The hallmark characteristic of bipolar disorder is pathologically elevated mood but depression is now recognised to comprise the predominant affect over time, and to make a major contribution to the disability related to this condition.

A depressive episode is the first manifestation of bipolar disorder in at least half of patients with the condition and most studies report that the majority of patients first present to medical practitioners in this phase of the illness. There are currently no accepted diagnostic criteria for bipolar depression for either research or clinical purposes, and depressed patients with bipolar disorder are often misdiagnosed as having unipolar depression (major depressive disorder). There is, however, growing recognition that there are clinical features that are more common in bipolar depression than in unipolar depression, and vice versa.[1-3] These features have the potential for use in determining whether a depression is more likely to be unipolar depression or a presentation of bipolar disorder. This is important to know because the treatments of unipolar depression and bipolar depression differ, with treatment of bipolar depression being complex and involving the use of various combinations of antipsychotics, lithium, antidepressants

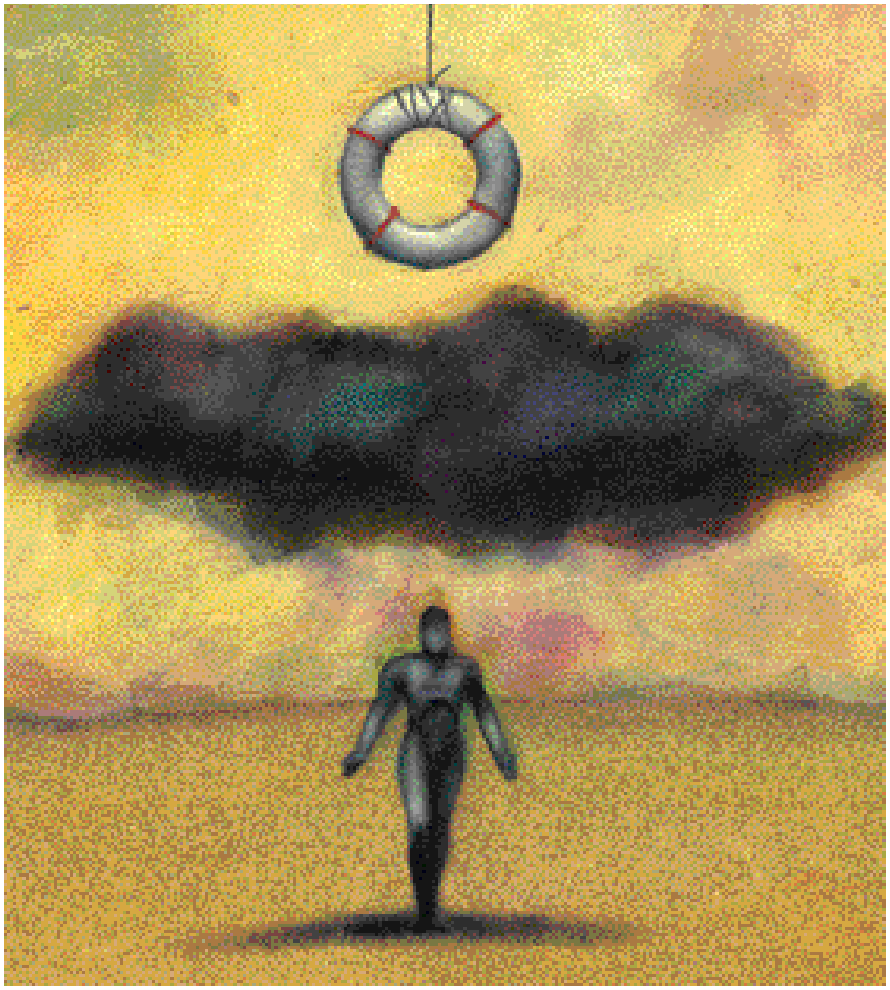
IN SUMMARY

- **Knowing whether a depression is more likely to be unipolar depression or a presentation of bipolar disorder is important because the treatments of unipolar depression and bipolar depression differ.**
- **There are currently no accepted diagnostic criteria for bipolar depression and depressed patients with bipolar disorder are often misdiagnosed as having unipolar depression (major depressive disorder).**
- **Diagnostic uncertainty is likely in depressed patients with ambiguous past histories of hypomania or mania or family histories of bipolar disorder and in young patients presenting only with recurrent depressive episodes.**
- **Certain clinical features (signs or symptoms and various characteristics of illness course and family history) are more common in bipolar depression than in unipolar depression, and vice versa.**
- **A 'probabilistic' approach is suggested to the diagnosis of bipolar I depression in a patient with a major depressive episode and no clear prior episodes of hypomania or mania, based on the differential likelihood of specific depressive clinical features being experienced.**

and other medications rather than antidepressants alone. Also, suicidal thoughts and attempts are more common in patients with bipolar disorder-associated depression than in patients with unipolar depression, occurring at about twice the rate.[5]

Clinical scenarios in which there may be diagnostic uncertainty include depressed patients with an ambiguous past history of episodes of hypomania or mania or a family history of bipolar disorder and young patients presenting only with recurrent depressive episodes.

This article presents a suggested 'probabilistic' approach to the diagnosis of bipolar I depression based on the differential likelihood of a patient experiencing various clinical features.[6] Although the immediate definitive diagnosis of bipolar I disorder on the basis of this approach is not recommended, practitioners are encouraged to consider such a diagnosis, particularly if patients develop hypomanic or manic episodes when taking antidepressants, or respond poorly to standard antidepressant therapies. Articles published in the August and September 2009 issues of *Medicine Today* focused on the manic and depressive phases of bipolar disorder, and a future article will focus on maintenance therapy for the condition.[4,7]



Issues in diagnosis

Patients with bipolar disorder report that delays in diagnosis and incorrect diagnoses are common. A study of participants in a bipolar disorder support group revealed that more than one-third of these patients had sought professional help within a year of the onset of symptoms, but 69% were misdiagnosed, most frequently with unipolar depression.[8] Other frequently reported misdiagnoses were anxiety disorder, schizophrenia, borderline or antisocial personality disorder, alcohol or substance misuse and/or dependence, and schizoaffective disorder. Over a third of the patients who were misdiagnosed waited 10 years or more before receiving an accurate diagnosis. Notably, respondents rarely reported all their manic symptoms to a doctor; for example, less than one-third admitted symptoms such as reckless behaviour, excessive spending and increased sexual interest or activity.

The results of the described study would suggest two reasons for the original common 'misdiagnosis' of unipolar depression: firstly, many patients with bipolar disorder might not have experienced an episode of hypomania or mania by the time of 'misdiagnosis'; and secondly, for some patients with bipolar disorder, the occurrence of hypomanic or manic symptoms was either not elicited by clinicians or not acknowledged by the patients. Mania and hypomania may have overt and subtle presentations, and some patients with hypomania may not view them as abnormal, rather perhaps perceiving them as normal or even desirable (especially the feelings of being energised and needing less sleep).[7]

Clinical differences between bipolar depression and unipolar depression

The age of onset of the first depressive episode and the numbers of depressive episodes experienced are generally different for patients with bipolar depression and those with unipolar depression.

Table. A probabilistic approach to the diagnosis of bipolar I depression*

Clinical features more common with bipolar I depression	Clinical features more common with unipolar depression
Symptoms and signs	
Increased sleep and/or increased daytime napping	Initial insomnia/reduced sleep
Increased appetite and/or weight gain	Decrease appetite and/or weight loss
'Leaden paralysis' (sensation of heavy limbs)	–
Psychomotor retardation (physical and mental slowing)	Normal or increased activity levels
Psychotic features and/or pathologically excessive guilt	Somatic / hypochondriacal complaints
Lability of mood, manic symptoms	–
Course of illness	
Early onset of first depression	Later onset of first depression
Multiple prior episodes of depression	Long duration of episodes
Family history	
Positive family history of bipolar disorder	Negative family history of bipolar disorder

* Premised on a current major depressive episode in patients with no clear prior episodes of hypomania or mania.

The age of onset of the first depressive episode in bipolar disorder has been found in many studies to be earlier than that found in unipolar depression, and patients with bipolar disorder tend to experience more depressive episodes over a lifetime than those with unipolar depression. There does not, however, appear to be any significant difference in the severities of the depressions.

Bipolar I depression versus unipolar depression

There have now been a relatively large number of studies comparing the clinical characteristics of bipolar I depression (depression occurring during bipolar I disorder) and unipolar depression.[6] Features with potential clinical utility for diagnosing bipolar depression have been suggested by various studies, including Australian research reports such as those of Mitchell and colleagues and Parker and colleagues.[1,9] These features are:

- signs of psychomotor retardation
- melancholic symptoms such as worthlessness, unvarying mood and marked anhedonia
- 'atypical' depressive symptoms such as hypersomnia and leaden paralysis
- a past history of psychotic depression
- the absence of anxiety, initial insomnia, tearfulness and tendency to blame others.

Mitchell and colleagues acknowledged that these features reflected differing group means and were not pathognomonic of bipolar depression.[1]

The studies of Mitchell and Parker suggest that bipolar I depression is characterised by an admixture of melancholic, atypical and (less commonly) psychotic features.[1,9] This pattern suggests that the clinical presentation of bipolar I depression is distinct from the 'pure' atypical depression of, for example, seasonal affective disorder or the 'pure' melancholic presentation of some patients with severe unipolar depression.

Bipolar II depression versus unipolar depression

There have been relatively few studies of bipolar II depression (depression in bipolar II disorder). In one large study, the Italian researcher Benazzi reported on a comparison of the symptoms of depression in 379 outpatients with bipolar II depression and 271 outpatients with unipolar depression.[10] The features found in this study to be more common in the patients with bipolar II depression were weight gain, increased eating, hypersomnia, psychomotor agitation, worthlessness and a diminished ability to concentrate.

This small literature suggests that patients with bipolar II depression, like patients with bipolar I depression, manifest with 'atypical' features such as increased sleep and appetite, but unlike patients with bipolar I depression, do not have psychomotor slowing (rather they may be more likely to be agitated).

Clinical characteristics of 'converters' from unipolar depression to bipolar disorder

Another means of defining the characteristics of bipolar depression is by identifying apparent 'unipolar' patients who on long-term follow up 'convert' to bipolar I or II disorder. Angst and Preisig reported that about 1% of patients with unipolar depression initially identified while hospitalised convert from depression to bipolar I disorder each year.[11]

Akiskal and colleagues reported that the predictors of a later emergence of bipolar I disorder in patients with unipolar depression were onset of depression prior to age 25 years, hypersomnia and motor retardation, a family history of bipolar

disorder, medication-precipitated manic episodes and postpartum depression.[12] The NIMH Collaborative Programme on the Psychobiology of Depression 11-year prospective follow up found that 4% of participants 'converted' to bipolar I disorder and 9% to bipolar II disorder.[13] Those who switched to bipolar I disorder were more likely to have been psychotic or hospitalised at the index depressive assessment, compared with those who continued to have a diagnosis of major depressive disorder.[14] Mood lability in the depressive state was the most specific predictor of switching to bipolar II disorder.[13]

A proposed probabilistic approach to the diagnosis of bipolar I disorder

It is apparent that there are no pathognomonic characteristics of bipolar depression compared with unipolar depression. There are, however, replicated findings of clinical characteristics that are more common in patients with bipolar I depression than in those with unipolar depression, and vice versa, or that are observed in patients with unipolar depression who 'convert' to bipolar I disorder over time.

Drawing on the previously mentioned studies comparing the clinical characteristics of bipolar I depression and unipolar depression, the clinical features that have been most commonly and consistently reported to be more common in patients with bipolar I depression (or in unipolar-depressed 'converters' to bipolar I disorder) are:[6]

- course of illness: earlier age of onset, shorter duration of episodes and more prior episodes
- symptomatology: worthlessness, low self-esteem, social withdrawal, hypersomnia, hyperphagia/weight gain, 'atypical features' (such as leaden paralysis), lability of mood and psychotic features
- mental state signs: psychomotor retardation (lower activity levels)
- family history: positive for bipolar disorder.

Some other features of depression said to be indicative of the future development of bipolar disorder include induction of hypomania or mixed states by antidepressants, abrupt onset of depression, seasonal pattern, mixed presentations with hypomanic symptoms and postnatal onset.

Conversely, those clinical features that have been most commonly and consistently reported to be more common in patients with unipolar depression are:[6]

- course of illness: later age of onset, longer duration of episodes and fewer prior episodes
- symptomatology: initial insomnia,

appetite loss and/or weight loss, and somatic complaints
- mental state signs: normal or higher activity levels
- family history: negative for bipolar disorder.

Rather than proposing a categorical diagnostic distinction between bipolar I depression and unipolar depression, we have recommended a probabilistic (or likelihood) approach to the distinction.[4] There is no 'point of rarity' between the two presentations, but rather a differential likelihood of experiencing the symptoms and signs of depression listed above. As some of the features (such as worthlessness, low self-esteem and social withdrawal) are common in depression, we have considered these to be of low diagnostic specificity and have therefore not included these in the final probabilistic approach to the diagnosis of bipolar depression.

The suggested criteria for this probabilistic approach are detailed in the Table. We have utilised specific depressive clinical signs or symptoms (as well as characteristics of illness course and family history), rather than proposing a requirement for particular syndromal presentations of depression such as 'atypical' or 'melancholic' depression. This table is premised on a current major depressive episode in patients with no clear prior episodes of hypomania or mania. We specify features that indicate the greater likelihood of bipolar I depression or unipolar depression, respectively.

Conclusion

A probabilistic approach has been developed to assist clinicians in identifying depressed patients who have an increased likelihood of going on to develop bipolar I disorder. This approach is based on the differential likelihood of specific depressive clinical features being experienced by patients. As yet, there have been no formal treatment studies using the approach. At present, we do not recommend that clinicians immediately diagnose and treat depressed patients with these features as definitely having bipolar I disorder. However, we commend practitioners to seriously consider this possibility for such individuals as treatment progresses, particularly if patients develop hypomanic or manic episodes when taking antidepressants or respond poorly to standard antidepressant therapies. MT

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COMPETING INTERESTS: In the past three years, Professor Mitchell has received remuneration for advisory board membership from Eli Lilly and AstraZeneca, and consultative fees or lecture honoraria from AstraZeneca, Eli Lilly, Janssen-Cilag and Lundbeck. He is not currently a member of any pharmaceutical company advisory board.