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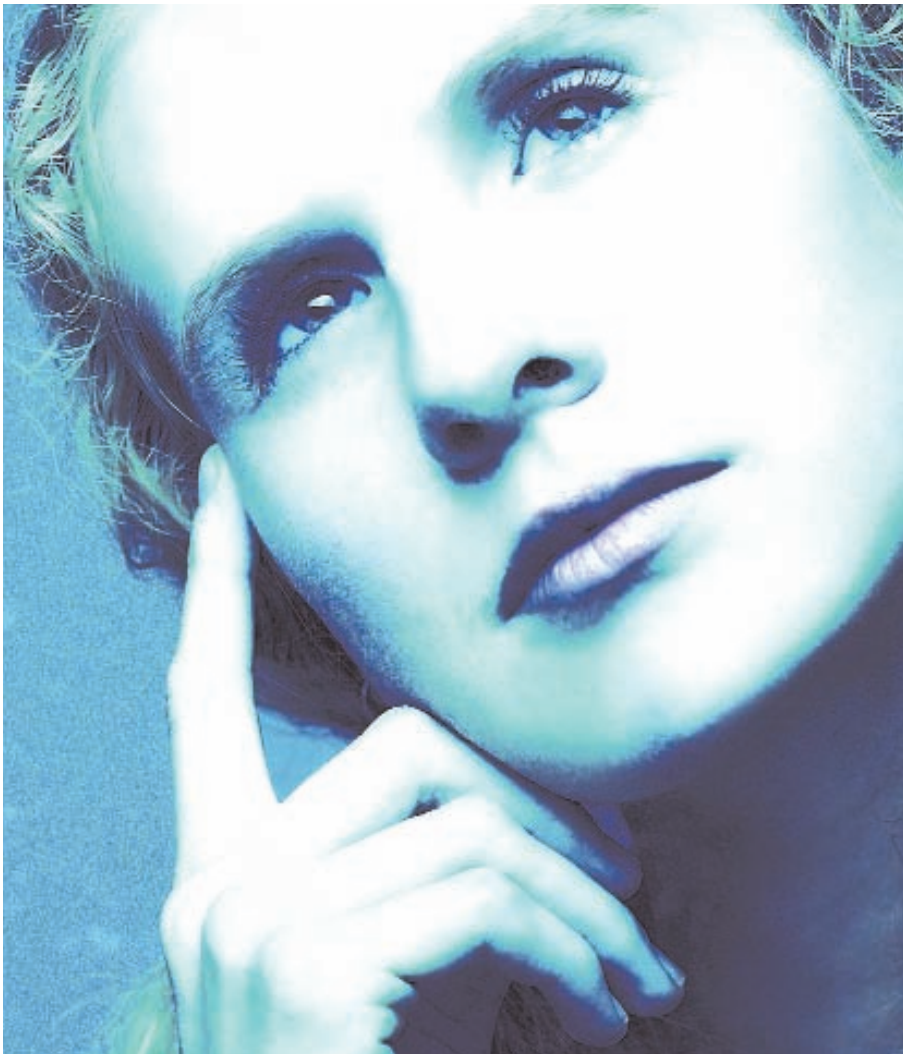
MISDIAGNOSIS *of Bipolar Disorder*

ABSTRACT

The objective of this article is to review the literature on one of the most complex topics in contemporary psychiatry—the diagnosis of bipolar disorder. Bipolar disorder is a disabling psychiatric illness that is often misdiagnosed, especially on initial presentation. Misdiagnosis results in ineffective treatment, which further worsens the outcome. Major contributors toward misdiagnosis include lapses in history-taking, presence of psychiatric and medical comorbidities, and limitations in diagnostic criteria. Careful screening for symptoms of hypomania/mania and clinical features suggestive of bipolarity as well as use of collateral history and screening instruments, such as mood questionnaires, might help in limiting the rate of misdiagnosis.



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INTRODUCTION

In 1854, Jules Falret provided a description for a condition characterized by episodes of depression and heightened moods, which he termed *folie circulaire* (circular insanity).[1] A year later, his term was given the name *maniac depressive psychosis*.[1]

Controversy surrounding the diagnosis of bipolar disorder became apparent in the 1950s when Congress refused to recognize *maniac depression* as legitimate illness. It was only in the early 1970s that laws providing Social Security benefits to patients with bipolar illness were enacted, eventually leading to the formation of the National Association of Mental Health (NAMI) in 1979.[2]

The third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III)[3] in 1980 replaced the term *maniac-depressive disorder* with *bipolar disorder*. The fourth edition of the DSM[4] classified bipolar disorder as bipolar I, bipolar II, cyclothymia, and bipolar disorder, not otherwise specified (NOS). Bipolar I is characterized by one or more episodes of severe mania or mixed episodes and major depression, while in bipolar II disorder, patients experience one or more hypomanic episodes and major depression. Cyclothymia is characterized by recurrent episodes of hypomania or depressive symptoms (not meeting criteria of major depression), with the cycling occuring for at least one year in children and adolescents and occurring for two or more years in adults. Bipolar disorder NOS is used for a number of clinical symptoms that do not meet the full criteria of bipolar I or II or cyclothymia.

BURDEN OF BIPOLAR DISORDER

The lifetime prevalence range for bipolar disorder is 1.4 to 6.4 percent worldwide.[5–7] Bipolar disorder is considered both chronic and disabling,[8] with significant risk of mortality as the lifetime risk of suicide is 20 times that of the general population.[9] This illness also carries significant economic costs and was ranked as the sixth leading contributor to disability in 1990 World Health Organization figures.[10] One study reported a seven-fold increase in the likelihood of missed work in people diagnosed with bipolar disorder.[6] Another study concluded that when a woman is diagnosed with bipolar disorder at the age of 25, she might lose nine years of life, 12 years of normal health, and 14 years of effective functioning.[11]

MISDIAGNOSIS OF BIPOLAR DISORDER

Bipolar disorder is often misdiagnosed.[12] Two surveys, one taken in 1994 and one taken in 2000, reveal little change in the rate of misdiagnosis.[12,13]

As per the survey taken by the National Depressive and Manic-Depressive Association (DMDA), 69 percent of patients with bipolar disorder are misdiagnosed initially and more than one-third remained misdiagnosed for 10 years or more.[13] Similarly, a survey done in Europe on 1000 people with bipolar disorder found a mean time of 5.7 years from the initial misdiagnosis to the correct diagnosis,[14] while another study reported that on average patients remain misdiagnosed for 7.5 years.[15]

Diagnosis of patients with bipolar illness can be challenging as most of these patients seek treatment only for depressive symptoms,[17,18] and more often than not, the first episode of mood disturbance is depression rather than mania. Two studies in 1999 and 2000 concluded that almost 40 percent of bipolar disorder patients are initially diagnosed with unipolar depression.[15,16] By DSM-IV[4] criteria, patients need to have an episode of hypomania or mania and an episode of depression in order to be given the diagnosis of bipolar disorder I. The diagnosis of bipolar II disorder can be even more challenging as the criteria in DSM-IV can be overly restrictive, requiring a full symptomatic picture of mania with a duration of four days, while many experts believe that the average duration of the hypomanic state is 1 to 3 days.[20–22] Furthermore, in bipolar II, it can be difficult to elicit a past history of hypomanic episodes from the patients.[17] An episode of hypomania has a milder presentation than mania and can happen without impairment in

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functioning at work or in a patient's social life, which may be why hypomanic episodes are unreported by the patients. In other words, the increased energy and heightened activity often experienced during hypomanic episodes may not be considered negative events by the patients who experience them.[17]

High comorbidity of bipolar disorder with other psychiatric and medical diagnoses[23–30] also makes diagnosis difficult. A study that examined patients with bipolar disorder showed that 46 percent of the patients suffered from alcohol abuse or dependence and 41 percent had comorbid drug abuse and dependence.[23] Some studies have even reported rates of alcohol abuse up to 69 percent and rates of drug abuse as high as 60 percent in patients diagnosed with bipolar disorder.[26] Research also supports high comorbidity of bipolar disorder with panic disorder, obsessive compulsive disorder, social phobia, eating disorders, attention deficit hyperactivity disorder (ADHD), and axis II personality disorders.[24,25,27–30] Association of bipolar disorder with medical conditions like thyroid disease and multiple sclerosis can also complicate the diagnosis.[29]

Research supports frequent onset of bipolar illness prior to age 20.[31] Pediatric bipolar disorder, unlike in adults, has been reported to present as nonepisodic, chronic, and mostly mixed manic states.[32] The unique presentation of bipolar disorder in children and adolescents and its frequent comorbidity with ADHD, anxiety disorders, oppositional defiant disorder, and conduct disorder might be a significant contributor to the difficulties in accurate diagnosis.[33–35]

TABLE 1. Characteristics of bipolar depression and unipolar depression[8,9,16–19,29,43,67–70]

Bipolar depression

1. Current or past history of episode of hypomania/mania
2. More withdrawn and retarded with tendency for hypersomnia
3. Agitation and weight loss less common
4. Relatively young age of onset of symptoms
5. Atypical symptoms of depression more common
6. Family history of bipolar disorder relatively more common
7. More recurrent pattern of illness and relatively brief episodes
8. Less response to antidepressant therapy
9. Postpartum onset and premenstrual syndrome more common
10. Psychotic features more common
11. Mood lability and seasonal pattern more common
12. Substance use and suicide attempt more common

Unipolar depression

1. No current or past history of episode of hypomania/mania
2. Anxiety symptoms, somatic complaints, and anger more common
3. Agitation and weight loss more common
4. Relatively older age of onset of symptoms
5. Atypical symptoms of depression less common
6. Family history of bipolar disorder relatively less common
7. Relatively less recurrence, but longer episodes of illness
8. More responsive to antidepressant therapy
9. Postpartum onset and premenstrual syndrome less common
10. Psychotic features less common
11. Mood lability and seasonal pattern less common
12. Substance use and suicide attempt relatively less common than bipolar depression

CONSEQUENCES OF MISDIAGNOSIS

Bipolar disorder is a complex illness to manage, and its misdiagnosis results in further treatment complications. Initial misdiagnosis results in delay of appropriate treatment, which in turn increases the risk of recurrence and chronicity of episodes.[17] As mentioned previously, the most common misdiagnosis for bipolar patients is unipolar depression.[17,18] An incorrect diagnosis of unipolar depression carries the risk of inappropriate treatment with antidepressants, which can result in manic episodes and trigger rapid cycling.[16,36–38] A study performed on bipolar patients who were previously diagnosed with unipolar depression reported that 55 percent of them developed mania and 23 percent became rapid cyclers.[16] Wehr, et al., performed a study on 51 patients with rapid cycling bipolar disorder and found that in 51 percent of the cases the use of antidepressants was associated with the continuation of cycling, and 73 percent of the rapid cyclers were taking antidepressants at the time of the onset of their cycling.[39] In the same study, investigators also found that bipolar patients who became rapid cyclers initially presented with depressive symptoms only, which most likely further increased their chances of being treated with monotherapy antidepressants.

Delay in start of mood stabilizers in bipolar disorder patients has been associated with

TABLE 2. Issues with current diagnostic systems

1. **To avoid diagnostic dilemma in bipolar disorder is almost impossible, as the diagnostic system does not allow the diagnosis without full episode of mania/hypomania, though it is well accepted that many patients start their illness with depression.**
2. **The diagnostic system requires at least four days of illness to meet criteria of hypomania, though many studies suggest that mean duration is just two days.**
3. **The diagnostic system uses the same set of symptoms for both unipolar and bipolar depression.**

increased healthcare costs,[40] which include increased suicide attempts and higher rates of hospital use.[41,42] Lifetime risk of suicide attempts in patients with bipolar disorder is between 25 and 50 percent[43] compared to 15 percent in patients with unipolar depression;[44] most suicides in patients with bipolar disorder have been reported to occur in the depressive phase.[43]

Economically, the misdiagnosis of bipolar illness has been reported to result not only in higher treatment costs but also in lost work days and productivity of these patients.[45,46] Misdiagnosed patients have been reported to lead disrupted lives, and with the onset of bipolar disorder being common in the adolescent years, this would have a negative effect on the development of interpersonal skills, education, and earning potential.[47]

HOW TO AVOID MISDIAGNOSIS

Lack of patient insight is one of the characteristic features of mania that contributes significantly to misdiagnosis.[48] Therefore, the use of collateral information from friends, family members, and significant others and taking a comprehensive longitudinal history of symptoms of each episode of depression, hypomania, and mania can help in improving the chances of accurate diagnosis of bipolar disorder.[18] Physical examination with relevant lab work is important, especially in cases with atypical presentation, to rule out any nonpsychiatric condition contributing toward the symptoms of bipolar illness.[49,50] There are several diagnostic instruments, but none of them have been found to replace careful diagnostic evaluation.[51]

After diagnostic evaluation, the instrument that has been reported to be most helpful in the diagnostic process of bipolar disorder is the Mood Disorder Questionnaire (MDQ).[52–54] The MDQ consists of a self report form with 13 questions used to assess any clustering of symptoms and functional impairment. Though this instrument is not sufficient to diagnose bipolar disorder by itself, it can serve as a useful screening tool and, if followed up with more detailed questions, increases the chances of reaching the correct diagnosis. The MDQ has been found to have good sensitivity (around 70%) and very good specificity (around 90%) for diagnosing bipolar disorder.[53,54] Some of the other scales that can be used for similar purpose include Bipolar Spectrum Diagnostic Scale[54] and Hypomanic Personality Scale.[56]

It is widely acknowledged that the biggest challenge in avoiding misdiagnosis is to differentiate bipolar depression from unipolar depression. Apart from scales, research has found observed symptoms as helpful tools when evaluating a patient for bipolarity.[57] Some studies have supported the presence of hypersomnia[58,59] and motor retardation[60] during depression as symptoms suggestive of bipolar depression, while some have supported the reverse neurovegetative symptoms (excessive sleep and appetite),[8–10,61] irritability of mood,[62,63] and anger[64,65] as suggestive of bipolar depression. Perugi, et al., performed a study in Italy on patients with atypical features (mood reactivity, hypersomnia, weight gain, leaden paralysis,

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rejection sensitivity) of depression in an outpatient setting, and found that 72 percent of them met the criteria for bipolar spectrum.[61] Other features like earlier age of onset[31] and family history[17,18,52] of bipolar disorder have also been described as helpful in differentiating bipolar depression from unipolar depression. Genetic predisposition to bipolar illness has been reported to be based on family history of lithium responsiveness in a first-degree relative or simply the presence of bipolar history in family.[66]

Other features, such as history of multiple failed antidepressant trials, rapidly occurring episodes of recurrent depression, and history of prompt antidepressant response followed by sudden decline in response, have also been reported to suggest bipolarity.[57] Psychometric studies[67] have revealed that patients with bipolar disorder have higher scores of extraversion and novelty seeking and are less judgmental than patients with unipolar depression. Postpartum depression in women has also been linked with underlying bipolarity.[68,69] See Table 1 for a comparison of features of bipolar depression and unipolar depresion. Limitations include lack of diagnostic clarity (Table 2).

Many features suggestive of bipolarity, e.g., early onset, family history of bipolar disorder, atypical symptoms of depression (particularly hypersomnia), and psychomotor retardation, though helpful in diagnosis, can also be symptoms of unipolar depression.

OVERDIAGNOSIS OF BIPOLAR DISORDER

Though no significant empirical data exist to support overdiagnosis, we should not forget that patients can be incorrectly diagnosed with bipolar disorder, especially if DSM-IV criteria is loosely applied or simply because of overlap of symptoms between mania/hypomania and many psychiatric diagnoses. Racing thoughts can occur in mixed anxiety-depression, agitated depression, and mania/hypomania.[71] Affective instability, impulsivity, and episodic course of illness can also be part of borderline personality disorders. Grandiosity can also be characteristic of narcissistic personality disorders or related to substance use. An incorrect diagnosis of bipolar illness can have serious therapeutic implications with patients receiving mood stabilizers by exposing them to these drugs' side effects when unnecessary.

CONCLUSION

Bipolar disorder is a costly and disabling disease. Patients with bipolar disorder may be misdiagnosed with another illness in their initial presentation. Major challenges to accurate diagnosis include difficulties in differentiating bipolar depression from unipolar depression. Significant heterogeneity between different patients of bipolar disorder, such that they would report different symptoms, and high comorbidity of bipolar disorder with substance use and other psychiatric diagnoses makes accurate diagnosis even more difficult.

Some steps that might help in avoiding misdiagnosis include obtaining collateral information about the patient from friends, family members, and significant others, examining family history, looking for other distinct clinical features that might help in differentiation (Table 1), and use of screening instruments, like the MDQ.

Consequences of misdiagnosis can result in ineffective treatment, which might further worsen outcome. While consensus exists regarding prevention of misdiagnosis of bipolar illness, no consensus exists regarding treatment, especially bipolar II disorder. APA guidelines[72] for treatment of bipolar depression recommend against using antidepressant monotherapy (without mood stabilizer) but unfortunately makes no distinction between bipolar I and bipolar II depression. Some studies[73,74] endorse the use of antidepressant monotherapy in patients of bipolar II disorder with chronic depression and remote episode(s) of hypomania while some studies[75] suggest that even bipolar II patients carry risk of increased cycling if exposed to antidepressant monotherapy. Further research is needed to resolve the controversy.

Earlier age of onset[31] and family history[17,18,52] of bipolar disorder have also been described as helpful in differentiating bipolar depression from unipolar depression.

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