

Bipolar Disorder: Diagnostic Challenges and Treatment Considerations

Dwight L. Evans, M.D.

A review of the criteria for the diagnosis of bipolar disorder identifies a number of complicating factors that historically have interfered with the accurate and precise diagnosis of patients. Patients with different subtypes of the disorder sometimes present with different symptoms, and the careful diagnostician must be aware of them. These include comorbidity of bipolar disorder and attention-deficit/hyperactivity disorder, comorbidity of bipolar disorder and substance abuse, and mania secondary to prescription drugs or physical illness, particularly in the elderly. As a result of these factors and others, bipolar disorder is significantly underdiagnosed. Accurate and precise diagnosis has a direct impact on the choice of treatment and will be easier for those clinicians who are aware of the several subtypes of mania and depression and are familiar with the relevant Expert Consensus Guidelines for treatment. (*J Clin Psychiatry* 2000;61[suppl 13]:26–31)

Bipolar disorder has been known to medicine since at least the time of Hippocrates, in 400 BC, when it was viewed as 2 separate biological disorders called mania and melancholia. By the 1950s, psychiatrists in the United States had come to view the condition as a psychosocial disorder arising out of life events; they called it manic depressive reaction, which represented an individual's behavioral response to his environment. The disorder was not considered a biological disease until the 1960s and 1970s. Since then, however, its position as a medical disease has been sufficiently established to the degree that we are now able to refine our system of classification to include discrete subtypes of bipolar disorder, each having its own associated treatment.

BACKGROUND

Bipolar disorder—or manic depressive illness, the name preferred as more descriptive by many patients and their families—is first and foremost a life-threatening medical illness. The rate of completed suicide is extremely high in this population and affects 10% to 15% of all patients. Many clinicians suspect that as many as 15% to 20% of untreated depressive and manic depressive patients eventually kill themselves,¹ an extraordinarily high

mortality rate for a medical disease. Bipolar disorder is also a lifelong disease: an episodic, long-term illness with a variable course.¹ While it is thought that early treatment may alter disease course, lifelong treatment will continue to be essential for the majority of patients. Another important consideration is that bipolar disorder often goes unrecognized; it is frequently misdiagnosed, and even when diagnosed, it is all too often inadequately treated.

According to the 1988 National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) survey^{2,3} and other surveys, the prevalence of bipolar disorder I in the United States ranges from about 0.4% to 1.6%, or somewhere between 1 million and 3.5 million people.^{1,3} Bipolar disorder II is found in at least another 0.5% of adults, or about 2 million people.¹ Unlike unipolar depression, which is 2 to 2.5 times more likely to afflict women than men, bipolar disorder I is found equally in men and women, whereas bipolar disorder II is more common in women.^{1,3}

Early Onset, Late Treatment

Bipolar disorder is noteworthy for the fact that it has an early onset but is generally treated much later. A survey sponsored by the National Depressive and Manic-Depressive Association (DMDA)⁴ of 500 patients with bipolar disorder determined that the peak age at onset was the mid- to late teens, somewhere between 15 and 19 years, and both the ECA¹ and the DMDA⁴ studies found the mean age of individuals with bipolar disorder to be 21 years. The mean age at which patients first receive treatment, however, is not until 5 years after onset: fully half of the patients interviewed for the DMDA study reported that they had received no treatment whatsoever for the 5 years following their first episodes of illness.⁴

From the Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia.

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Reprint requests to: Dwight L. Evans, M.D., University of Pennsylvania School of Medicine, 423 Guardian Dr., Philadelphia, PA 19104 (e-mail: psych@mail.med.upenn.edu).

The reason for the discrepancy between age at onset and age at first treatment is that the disease simply is not recognized early enough by patients, their families, or their health care providers: it has been estimated that as many as 60% of people with bipolar disorder did not receive a diagnosis within the 6 months following the initial episode. Some 35% of people with bipolar disorder fail to seek treatment for as much as 10 years after their initial episode, while among the patients who do go for treatment during their first episode, 34% are likely to receive another diagnosis. As the DMDA survey revealed, patients often see as many as 5 health care professionals before receiving an accurate diagnosis, usually from a psychiatrist.⁴ The DMDA survey also revealed another significant hindrance preventing patients from getting appropriate treatment: 13% of patients surveyed had no medical insurance whatsoever, and 15% had failed to take a prescribed medicine on at least 1 occasion, for financial reasons.⁴

The diagnosis of bipolar disorder can be difficult to make under the best of circumstances. First, symptoms overlap with those of other psychiatric disorders, including schizophrenia, schizoaffective disorder, unipolar depression, and attention-deficit/hyperactivity disorder (ADHD).⁵ Second, substance abuse and alcoholism are very often comorbid in the patient with bipolar disorder. The ECA study³ found that comorbidity, in general, was more extensive among the mentally ill than had previously been recognized, particularly substance abuse. Third, bipolar disorder can easily be confused with secondary mania, particularly in the elderly. Manias secondary to such conditions as head trauma, stroke, and disorders of the thyroid and exposure to toxins, neurotoxins, and certain medications, especially steroids, are seen quite often in patients with no previous history of bipolar disorder.

SECONDARY MANIA

The concept of mania as a phenomenon occurring as a consequence of concurrent medical conditions was described in 1978 by Krauthammer and Klerman,⁶ who reported that mania not only occurred in manic depressive disease but also appeared in patients who had experienced organic dysfunction attributable to disease or exposure to toxic compounds, including medications. By reviewing the relevant medical literature, the authors found reports of mania in patients who had taken steroids, isoniazid, procarbazine, levodopa, or bromide. They also found reports of patients who had experienced manic episodes during hemodialysis and after surgery, in addition to reports of mania associated with infection, neoplasm, and epilepsy.

To differentiate secondary from primary mania, Krauthammer and Klerman⁶ noted that most cases of secondary mania were of later onset and affected patients whose families had no history of affective disorders.

Accordingly, the authors recommended that clinicians evaluate such patients by screening for drug ingestion, medications, or recent infection; by performing electroencephalography (EEG) and radiography of the skull, toxic screening, and neurologic examinations; and by looking particularly for focal signs.

Writing in 1978, Krauthammer and Klerman⁶ pointed out that the appropriate treatment for secondary mania may differ from that for primary mania, although the therapeutic options available at that time were very limited. In most cases of secondary mania, all that the authors could suggest were short courses of lithium carbonate or neuroleptics. Today, we are fortunate to have a much greater variety of medications from which to choose to treat secondary mania, including anticonvulsants, whose mood-stabilizing properties had not yet been identified in 1978. As a general rule, mania associated with central nervous system (CNS) structural disease responds best to anticonvulsants such as valproate or carbamazepine; moreover, the anticonvulsants topiramate, lamotrigine, and gabapentin may hold promise as well, although they have not been adequately studied to date. Mania secondary to renal disease is often best treated with valproate or carbamazepine, whereas mania associated with liver disease is often best treated with lithium.

SUBSTANCE ABUSE

According to the NIMH ECA study, the Axis I diagnosis most often associated with substance abuse is bipolar disorder. The ECA study determined that among the bipolar disorder I group, over 60% had a substance abuse disorder as well; additionally, fully 46% had an alcohol diagnosis, while 40.7% had a drug abuse or dependence diagnosis.⁷ Approximately half the patients with bipolar disorder II were found to abuse various substances: 38% used alcohol alone, 12% used a combination of alcohol and drugs, and 9% used drugs alone.⁸

The interplay between substance abuse and bipolar disorder adds significantly to the challenge confronting the clinician by compounding some symptoms and obscuring others, just as it adds to management problems. Substance abuse by a patient with bipolar disorder tends to make the disorder more severe, and the course of the disease appears worsened by the complications associated with substance abuse. The relatively large subpopulation of patients with bipolar disorder can therefore be very difficult to diagnose and treat, and they may have a generally more intractable disease. Mixed symptoms, including rapid cycling, are common among substance abusers; such individuals can take longer to recover from affective episodes, and as Brady and others^{7,8} have reported, they have considerably more lifetime hospitalization. Fortunately, anticonvulsant agents such as divalproex sodium appear to be particularly useful in this population, more so than lith-

ium.⁸ The utility of other anticonvulsants, such as topiramate, lamotrigine, gabapentin, and carbamazepine, awaits controlled study.

EARLY AND LATE ONSET

Adolescents

One of the biggest diagnostic challenges associated with bipolar disorder confronts the clinician treating an adolescent. Bipolar disorder is extremely hard to diagnose in adolescents. One problem facing the diagnostician is the fact that bipolar disorder shares symptoms with a number of other conditions when it presents in adolescence, as it does in perhaps the majority of cases. All too often, bipolar disorder in adolescents is misdiagnosed as schizophrenia, chiefly because overt mania in adolescents presents with a number of symptoms common to schizophrenia, such as delusions, incoherence, inappropriate flat affect, and hallucinations of various types. The fact that misdiagnosis is so common is particularly unfortunate, because early and vigorous treatment is important in early-onset bipolar disorder, when it can have deleterious effects on the adolescent's emerging sense of self and can interfere with fundamental developmental tasks of adolescence.

Another disorder commonly confused with bipolar disorder is ADHD in children and adolescents. In one study by Wozniak et al.,⁹ 16% of 301 patients under the age of 12 years who had been referred for evaluation met the diagnostic criteria for bipolar disorder, and all but one of them also met the diagnostic criteria for ADHD. The same group of researchers subsequently designed a longitudinal study¹⁰ in order to establish the rate at which bipolar disorder is comorbid with ADHD in children. They found that at initial assessment, 11% of children who had been diagnosed with ADHD also had bipolar disorder; moreover, at a 4-year follow-up, they reported that another 12% had been given the diagnosis of bipolar disorder. When both sets of data are aggregated, nearly a quarter of the children with ADHD also had bipolar disorder, a relatively high comorbidity.¹⁰ This quite likely represents the upper end of the comorbidity rate of bipolar disorder in children with ADHD, given the specialized nature of the tertiary referral center of these investigators.

Elderly

Secondary mania can be common among the elderly, although it is often unrecognized and therefore untreated. In this population, episodes can come quite close together, and suicide can be a major risk. Secondary mania in the elderly is associated with a variety of phenomena, including toxic factors, medications, metabolic factors such as thyroid disorders, head trauma, CNS lesions, stroke, and infections, including those associated with human immunodeficiency virus (HIV) and acquired immunodeficiency

syndrome (AIDS), which are becoming more prevalent, given the course of the AIDS epidemic.

A retrospective study¹¹ of 50 patients 65 years or older who presented with mania found 14 patients to be experiencing their first such episode; almost all of them (71%; N = 10) had a comorbid neurologic disorder. By comparison, only 28% (N = 10) of the 36 elderly patients who had had manic episodes earlier in life were found to have comorbid neurologic disorders. This finding points to the existence of secondary mania in the elderly and suggests that any assessment of a patient experiencing a first episode of mania at age 65 or older must include evaluation of the factors associated with secondary mania.

SUBTYPES OF BIPOLAR DISORDER

Diagnostic accuracy of all forms of bipolar disorder can be increased by taking comprehensive histories from the patient as well as from any available family members. Of paramount importance is the taking of a detailed medical history, including physical examination and laboratory testing, in order to rule out the many conditions associated with secondary mania. Another very useful diagnostic tool is a longitudinal assessment such as the life chart described by Roy-Byrne et al.,¹² which documents an individual patient's condition over time, highlighting manic episodes and periods of depression while correlating this information with the therapy or combination of therapies the patient was given at that time. The detailed observations made possible by this approach can thus be used to track the course of a patient's response to treatment, as well as to identify patterns of episodes of illness as they occur over time. The life chart approach is also useful to document a patient's response to different medication and psychosocial regimens; moreover, particular subtypes of the disorder may well emerge in the process of documenting the disease course.¹²

Bipolar disorder is a complex disorder, one that can and should be divided into various subtypes. Accurate diagnosis is easier when clinicians have precise guidelines they can trust to help differentiate among different presentations of the disorder. A careful assessment of bipolar disorder will take the relative severity of the disorder into consideration: severity may be a critical factor in determining treatment response, as is the presence or absence of psychotic symptoms. Other important factors that one should bear in mind when formulating the diagnosis are the concurrence of irritable or dysphoric mood with manic symptoms, and other psychiatric comorbidities such as substance abuse and ADHD. These considerations are among those determining the subtypes of bipolar disorder.

Manic States

There are 3 distinct manic states: pure mania, hypomania, and mixed mania.

Table 1. Consensus Guidelines for the Treatment of Subtypes of Acute Mania^a

Mania Subtype	Treatment of Choice	First-Line Treatment	Second-Line Treatment
Pure mania	Lithium	Valproate	Carbamazepine or lithium plus valproate
Mixed mania	Valproate	Lithium or carbamazepine	Lithium plus valproate
Rapid cycling	Valproate	Carbamazepine	Lithium plus valproate or lithium or lithium plus carbamazepine

^aFrom Frances et al.^{13,14}**Table 2. Consensus Guidelines for the Treatment of Mania Plus Psychosis, Agitation, or Insomnia^a**

Mania Subtype	First-Line Treatment	Other Alternatives
Mania with psychosis	Mood stabilizer plus high- or medium-potency antipsychotic plus benzodiazepine	Switch to low-potency antipsychotic for added sedation
Severe mania without psychosis	Mood stabilizer plus benzodiazepine; no antipsychotic	Add high- or medium-potency antipsychotic
Hypomania without psychosis	Mood stabilizer plus benzodiazepine	Add high- or medium-potency antipsychotic (rarely needed)

^aFrom Frances et al.¹⁴

Pure mania. The pure manic state is the one most conceptualize when thinking about mania: the classic acute manic state characterized by grandiosity and euphoria, identified in DSM-IV⁵ as characteristic of bipolar disorder I. About half of all bipolar patients have episodes of pure mania. Pure mania typically responds well to treatment with lithium.

Hypomania. Hypomania is less severe than pure mania. It shares the clinical features of mania but does not cause marked impairment in functioning nor require hospitalization. This subtype corresponds to bipolar disorder II in DSM-IV.

Mixed mania. Mixed states include symptoms of depression and mania. Patients with mixed mania often present as manic, even though it becomes clear on examination that the content of their thinking may be almost entirely depressive in nature. About 40% of all bipolar patients have mixed mania.

Rapid Cycling

Rapid-cycling bipolar disorder, in which patients have at least 4 affective episodes per year, can occur in bipolar disorder I or II. This form of the disorder is not as responsive to lithium as pure mania.

Depression

The depressive states characteristic of bipolar disorder can be divided into 4 categories differentiated from one another by degree: mild, moderate, severe without psychosis, and severe with psychosis. DSM-IV makes a similar distinction by differentiating bipolar disorder I from bipolar disorder II, where bipolar disorder I refers to the combination of classic mania and classic depression,

while bipolar disorder II represents classic depression combined with less-severe mania or hypomania.

TREATMENT OPTIONS

Finding the best treatment choices for the subtypes of bipolar disorder was aided by the development of the Expert Consensus Guidelines in 1996.^{13,14} These guidelines were arrived at by aggregating the responses of 61 recognized expert clinical researchers to an 81-question survey about key decision points in the management of bipolar disorder. By applying the guidelines to the subtypes of bipolar disorder, we can readily identify preferential first-line treatment for each of the highly varied presentations characteristic of this complex disorder.¹³ The following examples of diagnostic subtypes of bipolar disorder will show how precise diagnosis can lead to preferred, specific, targeted therapies.

Treatment of Acute Manias

The experts were asked to select a mood stabilizer for the acute phase of mania, whether pure, hypomania, mixed, or rapid cycling. Table 1 shows the distinctions that are made with regard to subtypes of mania.^{13,14}

Treatment of Mania With Other Symptoms

The guideline for selecting adjunctive medication to treat symptoms of psychosis, agitation, and insomnia demonstrates that optimal treatment to control psychosis and/or induce sleep or sedation depends on the subtype of the disorder that is being presented by the patient.¹⁴ Table 2 shows how the experts differentiate among types of mania when other symptoms have to be addressed.

Treatment of Depressive Episodes

Following the guidelines for the treatment of depression can result in significant distinctions among treatment regimens, based on the subtype of bipolar disorder.¹⁴ Table 3 demonstrates how the choice of first-line treatment varies according to the subtype of depressive episodes found in patients with bipolar disorder I. Distinctions are made between depressive episodes in which psychosis is featured, those without psychotic features, and milder episodes. Table 4 shows the recommended treatment options for patients with bipolar disorder II, in which depressive episodes occur with or without psychotic features. Milder depressive episodes are also addressed.^{14,15} All 4 tables

make it clear that the choice of treatment depends on knowing which subtype of bipolar disorder is to be addressed.

The authors of the Expert Consensus Guidelines have pointed out that for the system of practice guidelines to have real value, the guidelines themselves will have to be updated at regular intervals, to make sure the experts' recommendations remain timely. Of particular importance to the designers of the guidelines is that expert practice wisdom must be updated to include newer pharmaceutical compounds that have had less time to establish themselves: "The more penetration [any] given medication has had into expert practice and the literature, the more likely that it will find favor with the experts."^{13(p305)} Keeping the Expert Consensus Guidelines updated and refined is an ongoing project, one that is intended to provide clinicians with treatment recommendations that are ever more precise and effective.

STIGMA

One reason that bipolar disorder is not diagnosed early enough, particularly in the case of adolescents, is that clinicians may try to avoid psychiatric labeling during childhood, especially when the disorder in question is likely to be one with a lifetime course. The fact is that the diagnosis of mania, depression, or bipolar disorder is still very stigmatizing in our society. At this moment, there is no cure for bipolar disorder. Treatment can, however, decrease mortality and morbidity by decreasing frequency, severity, and psychosocial consequences of disease episodes.

An overall goal in the clinical management of bipolar disorder is the improvement of psychosocial function between episodes, something that can only be accomplished by enhancing patient education and adherence to treatment. In this regard, many of us who deal with patients with bipolar disorder and their families have found it useful to point out that they are in very good company, for some of our most talented artists and public figures have suffered from serious depression and bipolar disorder.

LOOKING FORWARD

While it is true that mood disorders can be serious, life-threatening diseases, with complex morbidity and mortality, they are also diseases with an increasing range of treatment options and rational pharmacotherapies. Mood

Table 3. Consensus Guidelines for the Treatment of Subtypes of Depression in Bipolar Disorder I^a

Bipolar Subtype	First-Line Treatment	Second-Line Treatment
Bipolar I depression plus psychosis	ECT or mood stabilizer plus antidepressant plus antipsychotic	Mood stabilizer plus antidepressant or mood stabilizer plus antipsychotic
Severe bipolar I depression without psychosis	Mood stabilizer plus antidepressant	Add psychotherapy to the mood stabilizer plus antidepressant or give ECT
Milder bipolar I depression	Mood stabilizer plus antidepressant or mood stabilizer alone	Add psychotherapy to medication plan chosen

^aAbbreviation: ECT = electroconvulsive therapy. From Frances et al.¹⁴

Table 4. Consensus Guidelines for the Treatment of Depressive Episodes in Bipolar Disorder II^a

Depressive Subtype	First-Line Treatment	Second-Line Treatment	Occasional Options
Major depressive episode with psychotic features	Mood stabilizer plus antidepressant plus antipsychotic	ECT	...
Severe major depressive episode, nonpsychotic	Mood stabilizer plus antidepressant	Add psychotherapy to mood stabilizer plus antidepressant or administer ECT	Omit mood stabilizer; use antidepressant alone or with psychotherapy
Milder major depressive episode	Mood stabilizer plus antidepressant or add psychotherapy to the mood stabilizer plus antidepressant	Mood stabilizer alone or mood stabilizer plus psychotherapy	Omit mood stabilizer; use antidepressant alone or with psychotherapy

^aAbbreviation: ECT = electroconvulsive therapy. From Frances et al.¹⁴

stabilizers have long been the mainstay of the long-term prevention of both mania and depression. While lithium, valproate, and carbamazepine have been the staple mood stabilizers for some years now, newer products like lamotrigine, topiramate, and gabapentin may hold additional promise for the future. Antipsychotic medications have always played a role in the treatment of mania, despite their association with tardive dyskinesia. The newer atypical antipsychotics, such as olanzapine and risperidone, however, provide the advantages of neuroleptics without producing tardive dyskinesia or extrapyramidal symptoms,¹⁶ and they may also represent considerable promise for the future treatment of bipolar disorder.

Since this manuscript was accepted for publication, Bipolar Guidelines 2000 (Postgrad Med Special Report 2000[April]:1-104) has been published. Key comparisons with the 1995 survey include the following: ratings for divalproex have increased, ratings for lithium and carbamazepine remain stable, lamotrigine received positive ratings for the treatment of depression, and atypical antipsychotics are now rated ahead of conventional antipsychotics.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), gabapentin (Neurontin), isoniazid (Rifamate and others), lamotrigine (Lamictal), olanzapine (Zyprexa), procarbazine (Matulane), risperidone (Risperdal), topiramate (Topamax).

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