Chapter 6

Mood disorders

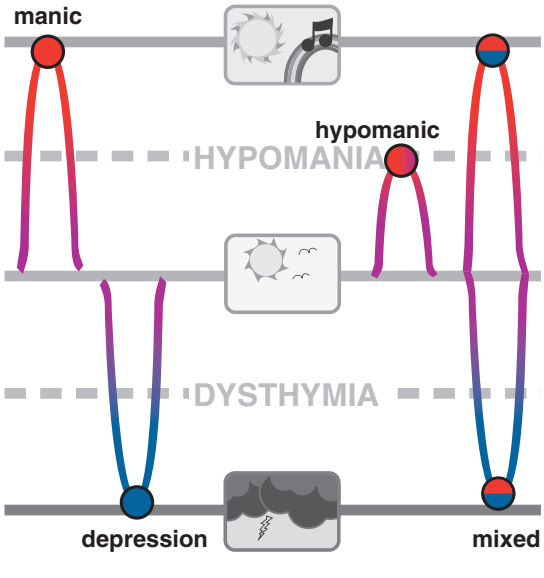
This chapter discusses disorders characterized by abnormalities of mood: namely, depression, mania, or both. Included here are descriptions of a wide variety of mood disorders that occur over a broad clinical spectrum. Also included in this chapter is an analysis of how monoamine neurotransmitter systems are hypothetically linked to the biological basis of mood disorders. The three principal monoamine neurotransmitters are norepinephrine (NE; also called noradrenaline or NA), discussed in this chapter, dopamine (DA), discussed in Chapter 4, and serotonin (also called 5-hydroxytryptamine or 5HT), discussed in Chapter 5.

The approach taken here is to deconstruct each mood disorder into its component symptoms, followed by matching each symptom to hypothetically malfunctioning brain circuits, each regulated by one or more of the monoamine neurotransmitters. Genetic regulation and neuroimaging of these hypothetically malfunctioning brain circuits are also discussed. Coverage of symptoms and circuits of mood disorders in this chapter is intended to set the stage for understanding the pharmacological concepts underlying the mechanisms of action and use of antidepressants and mood stabilizing drugs, which will be reviewed in the following two chapters (Chapters 7 and 8).

Clinical descriptions and criteria for how to diagnose disorders of mood will only be mentioned in passing. The reader should consult standard reference sources for this material.

Description of mood disorders

Disorders of mood are often called affective disorders, since affect is the external display of mood, an emotion that is felt internally. Depression and mania are often seen as opposite ends of an affective or mood spectrum. Classically, mania and depression are "poles" apart, thus generating the terms *unipolar* depression (i.e., patients who just experience the *down* or depressed pole) and *bipolar* (i.e., patients who at different times experience either the *up* [i.e., manic] pole or the *down* [i.e., depressed] pole). Depression and mania may even occur simultaneously, which is called a *mixed* mood state. Mania may also occur in lesser degrees, known as *hypomania*, or switch so



Manic Episode
Mania (abnormally elevated, expansive, or irritable mood) plus 3 or 4 other symptoms

Major Depressive Episode
Depressed mood or loss of interest coupled with four other symptoms

Hypomanic Episode
Hypomania (elevated, expansive, or irritable mood, less severe and shorter duration than mania) plus 3 or 4 other symptoms

Mixed Episode
Meets criteria for both a manic episode and a major depressive episode

Figure 6-1. Mood episodes. Bipolar disorder is generally characterized by four types of illness episodes: manic, major depressive, hypomanic, and mixed. A patient may have any combination of these episodes over the course of illness; subsyndromal manic or depressive episodes also occur during the course of illness, in which case there are not enough symptoms or the symptoms are not severe enough to meet the diagnostic criteria for one of these episodes. Thus the presentation of mood disorders can vary widely.

fast between mania and depression that it is called *rapid cycling*.

Mood disorders can be usefully visualized not only to contrast different mood disorders from one another, but also to summarize the course of illness for individual patients by showing them mapped onto a mood chart. Thus, mood ranges from hypomania to mania at the top, to euthymia (or normal mood) in the middle, to dysthymia and depression at the bottom (Figure 6-1). The most common and readily recognized mood disorder is major depressive disorder (Figure 6-2), with single or recurrent episodes. Dysthymia is a less severe but long-lasting form of depression (Figure 6-3). Patients with a major depressive episode who have poor inter-episode recovery, only to the level of dysthymia, followed by another episode of major depression are sometimes said to have "double depression," alternating between major depression and dysthymia, but not remitting (Figure 6-4).

Patients with bipolar I disorder have full-blown manic episodes or mixed episodes of mania plus depression, often followed by a depressive episode (Figure 6-5). When mania recurs at least four times a year, it is called rapid cycling (Figure 6-6A). Patients with bipolar I disorder can also have rapid switches from mania to depression and back (Figure 6-6B). By definition, this occurs at least four times a year, but can occur much more frequently than that.

Bipolar II disorder is characterized by at least one hypomanic episode that follows a depressive episode (Figure 6-7). Cyclothymic disorder is characterized by mood swings that are not as severe as full mania and full depression, but still wax and wane above and below the boundaries of normal mood (Figure 6-8). There may be lesser degrees of variation from normal mood that are stable and persistent, including both depressive temperament (below normal mood but not a mood disorder) and hyperthymic temperament (above normal mood but also not a mood disorder) (Figure 6-9). Temperaments are personality styles of responding to environmental stimuli that can be heritable patterns present early in life and persisting throughout a lifetime; temperaments include such independent personality dimensions as novelty seeking, harm avoidance, and conscientiousness. Some patients may have mood-related temperaments, and these may render them vulnerable to mood disorders, especially bipolar spectrum disorders, later in life.

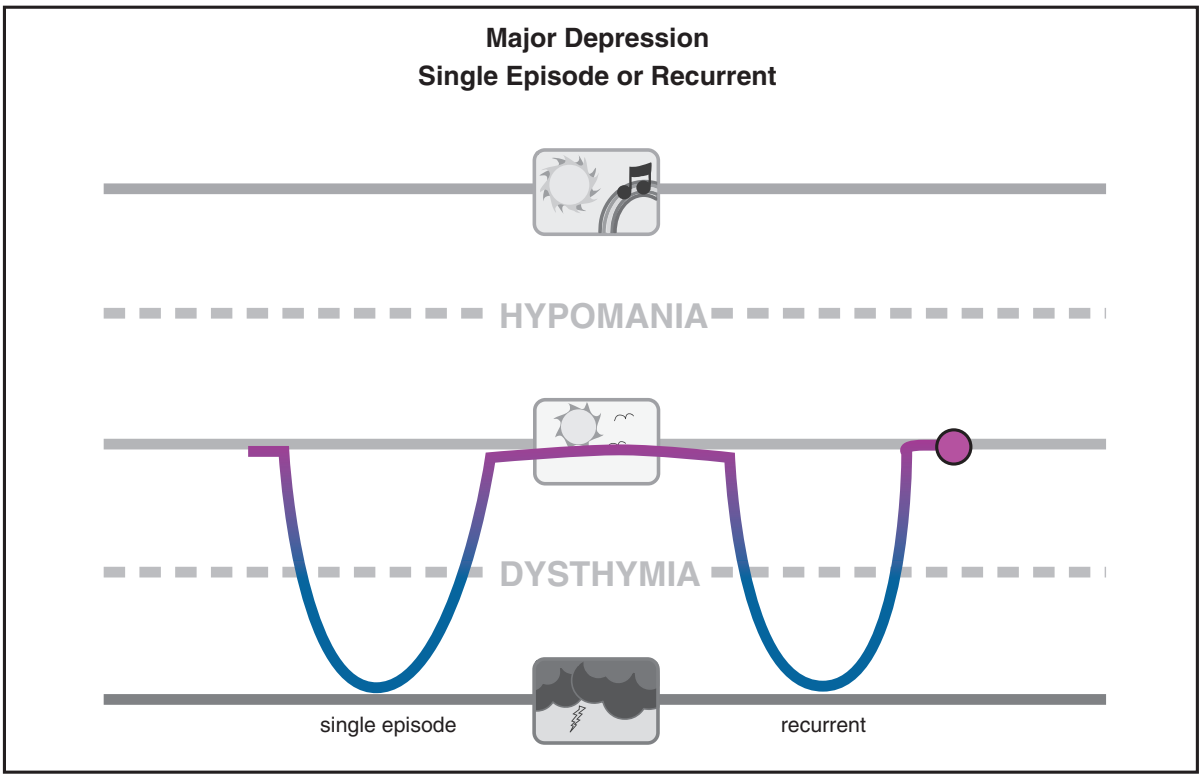


Figure 6-2. Major depression. Major depression is the most common mood disorder and is defined by the occurrence of at least a single major depressive episode, although most patients will experience recurrent episodes.

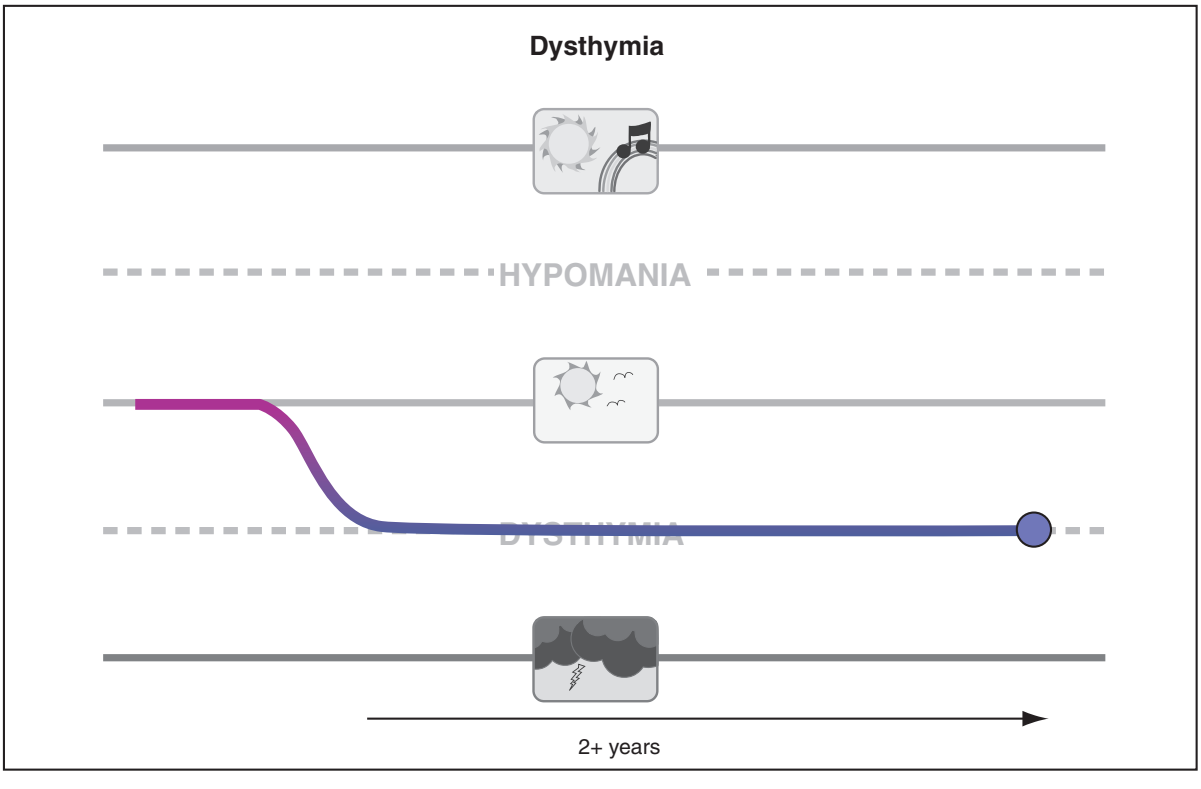


Figure 6-3. Dysthymia. Dysthymia is a less severe form of depression than major depression, but long-lasting (over 2 years in duration) and often unremitting.

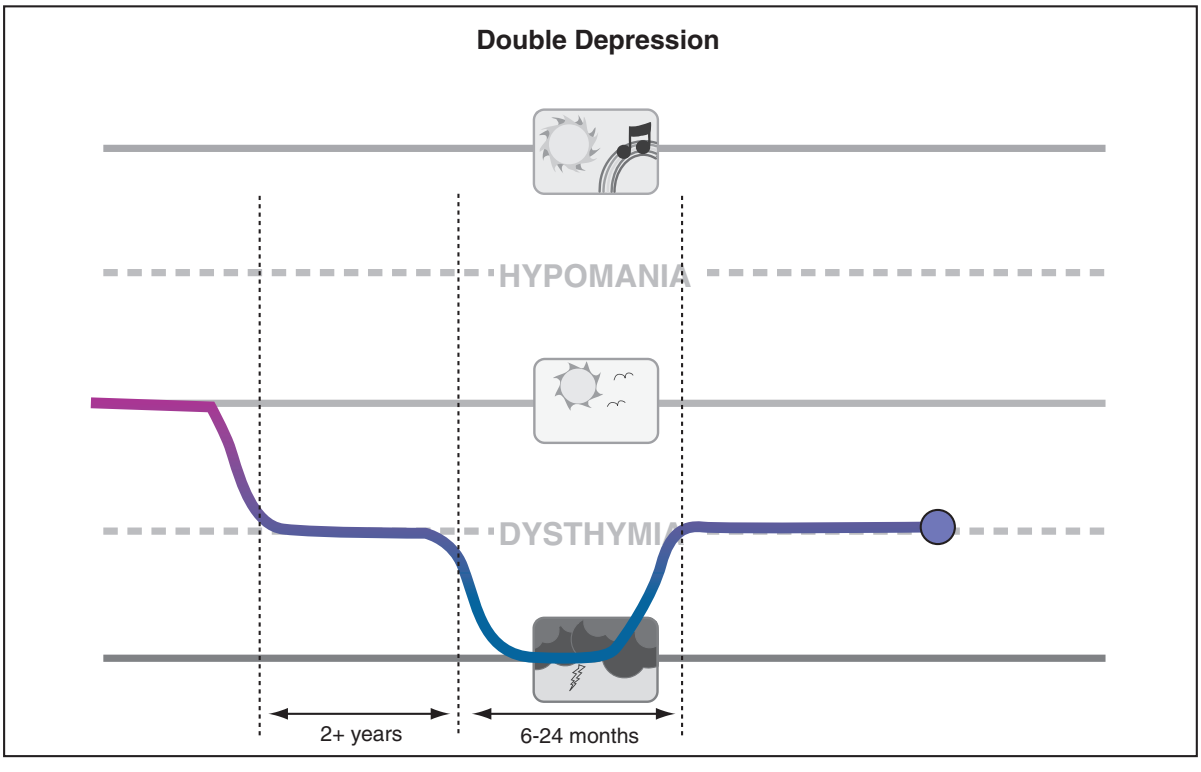


Figure 6-4. Double depression. Patients with unremitting dysthymia who also experience the superimposition of one or more major depressive episodes are described as having double depression. This is also a form of recurrent major depressive episodes with poor inter-episode recovery.

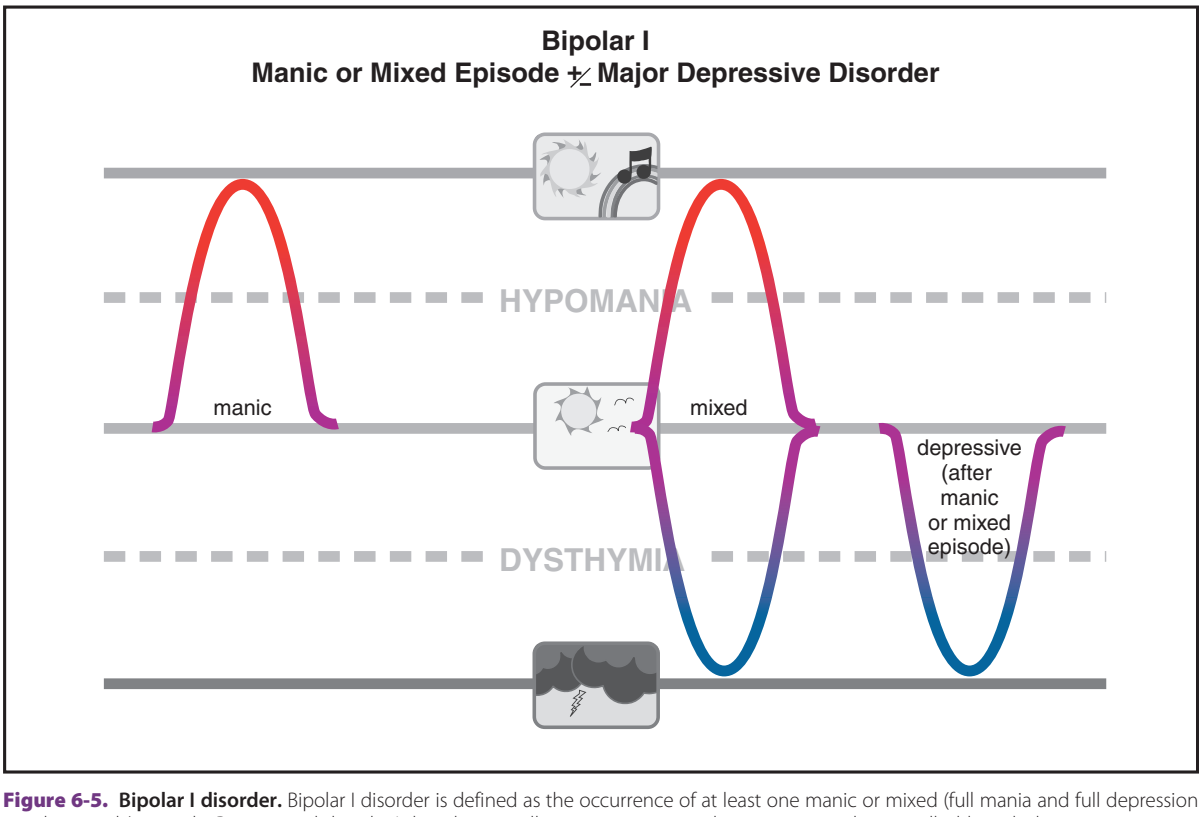


Figure 6-5. Bipolar I disorder. Bipolar I disorder is defined as the occurrence of at least one manic or mixed (full mania and full depression simultaneously) episode. Patients with bipolar I disorder typically experience major depressive episodes as well, although this is not necessary for the bipolar I diagnosis.

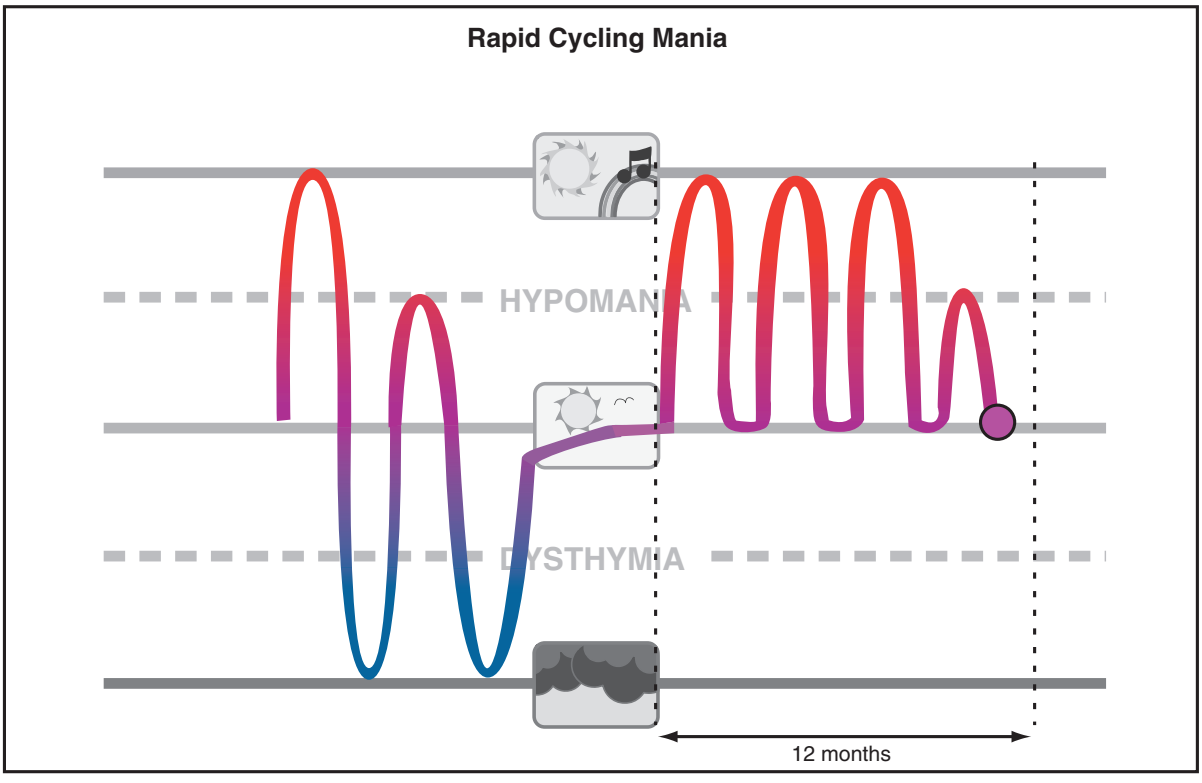


Figure 6-6A. Rapid cycling mania. The course of bipolar disorder can be rapid cycling, which means that at least four episodes occur within a 1-year period. This can manifest itself as four distinct manic episodes, as shown here. Many patients with this form of mood disorder experience switches much more frequently than four times a year.

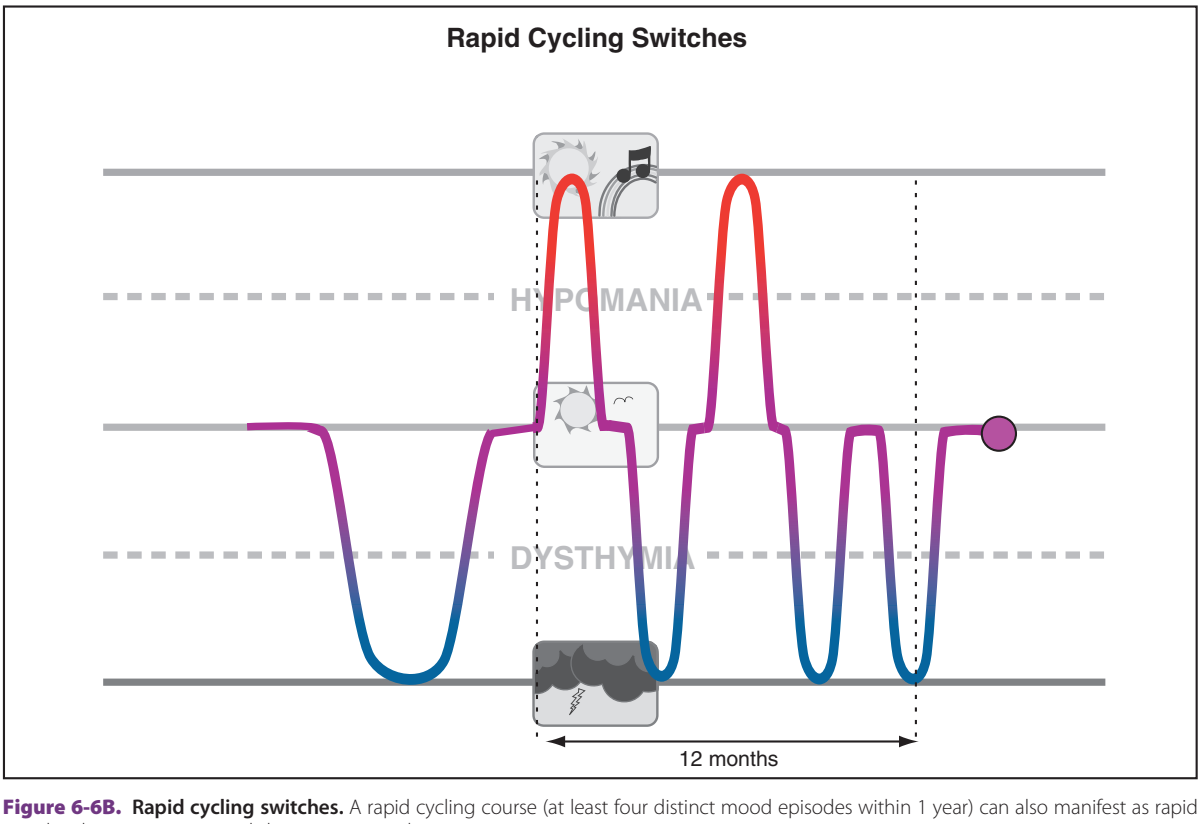


Figure 6-6B. Rapid cycling switches. A rapid cycling course (at least four distinct mood episodes within 1 year) can also manifest as rapid switches between manic and depressive episodes.

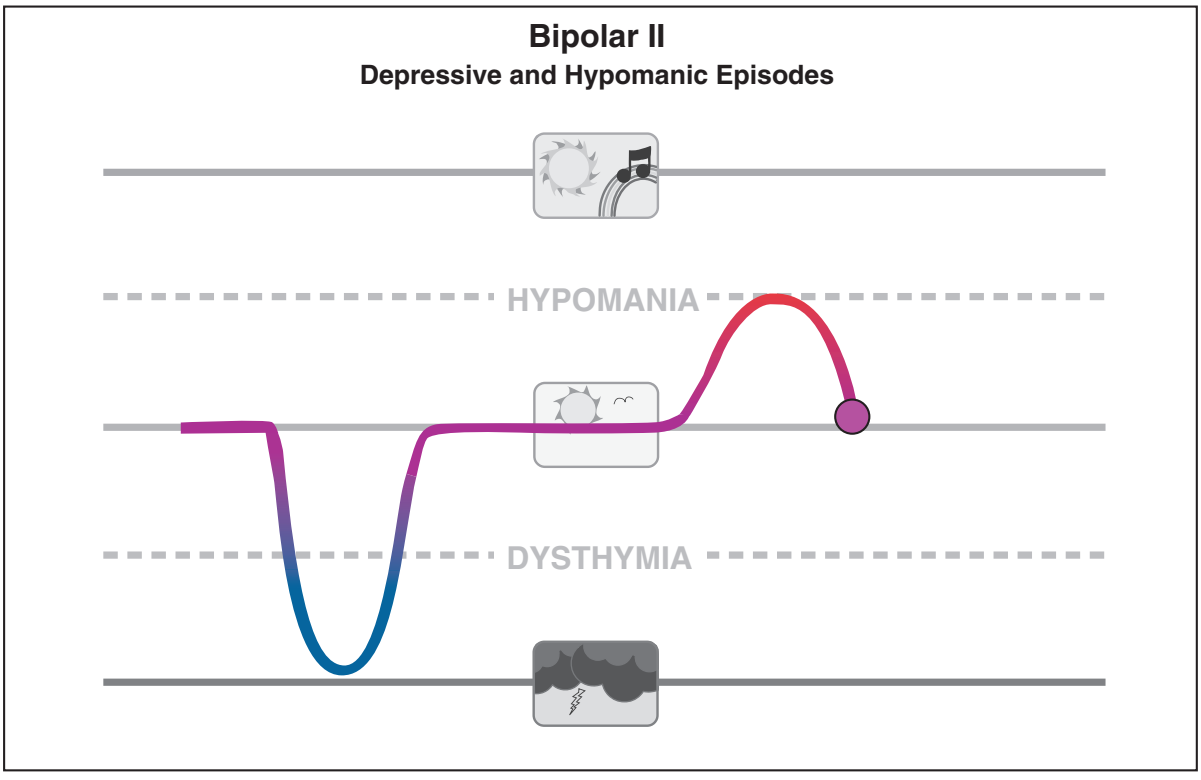


Figure 6-7. Bipolar II disorder. Bipolar II disorder is defined as an illness course consisting of one or more major depressive episodes and at least one hypomanic episode.

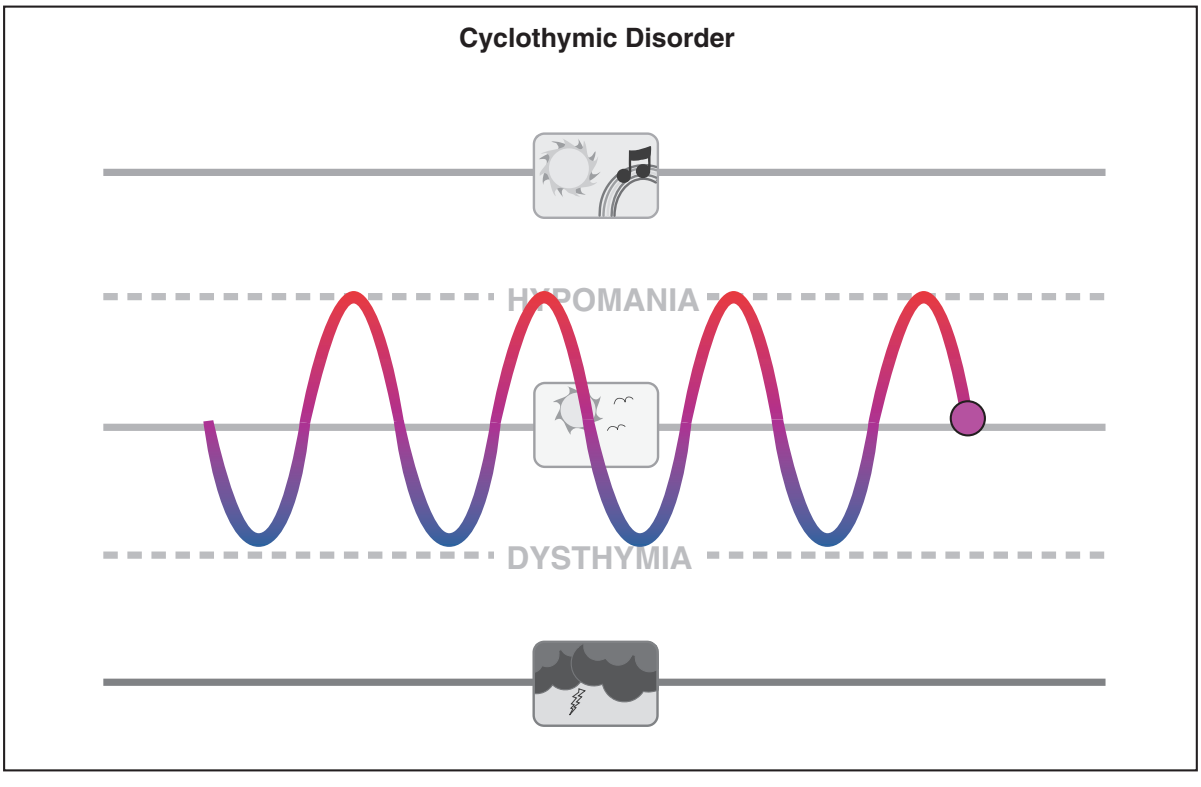


Figure 6-8. Cyclothymic disorder. Cyclothymic disorder is characterized by mood swings between hypomania and dysthymia but without any full manic or major depressive episodes.

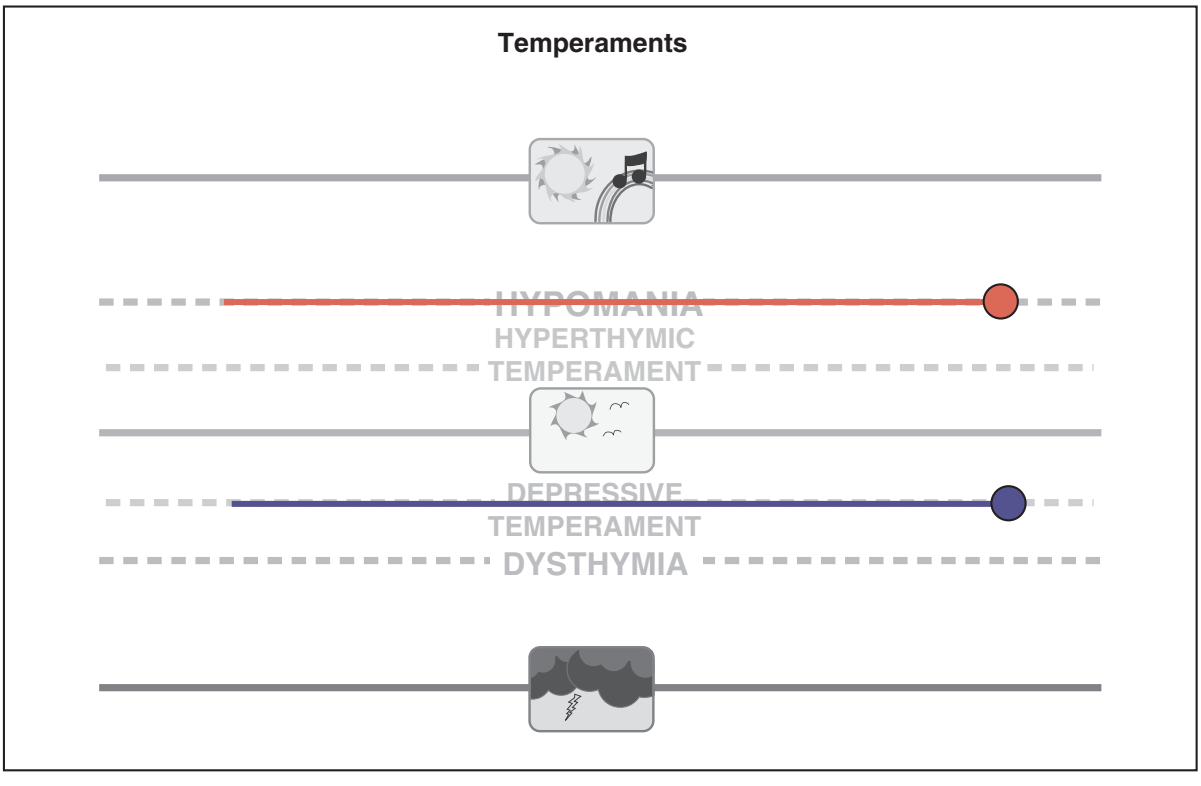


Figure 6-9. Temperaments. Not all mood variations are pathological. Individuals with depressive temperament may be consistently sad or apathetic but do not meet the criteria for dysthymia and do not necessarily experience any functional impairment. However, individuals with depressive temperament may be at greater risk for the development of a mood disorder later in life. Hyperthymic temperament, in which mood is above normal but not pathological, includes stable characteristics such as extroversion, optimism, exuberance, impulsiveness, overconfidence, grandiosity, and lack of inhibition. Individuals with hyperthymic temperament may be at greater risk for the development of a mood disorder later in life.

The bipolar spectrum

From a strict diagnostic point of view, our discussion of mood disorders could now be mostly complete. However, there is the growing recognition that many patients seen in clinical practice have a mood disorder not well described by the above categories. Formally, they would be called "not otherwise specified" or "NOS," but this creates a huge single category for many patients that belies the richness and complexity of their symptoms. Increasingly, such patients are seen as belonging in general to the "bipolar spectrum" (Figure 6-10), and in particular to one of several additional descriptive categories that have been proposed by experts such as Hagop Akiskal (Figures 6-10 through 6-20).

Bipolar ¼ (0.25)

One mood disorder often considered to be "not quite bipolar" and sometimes called bipolar ¼ (or 0.25) designates an unstable form of unipolar depression that responds sometimes rapidly but in an unsustained manner to antidepressants, the latter sometimes called antidepressant "poop-out" (Figure 6-11). These patients have unstable mood but not a formal bipolar disorder, yet can benefit from mood-stabilizing treatments added to robust antidepressant treatments.

Bipolar ½ (0.5) and schizoaffective disorder

Another type of mood disorder is called different things by different experts, from bipolar ½ (or 0.5) to "schizobipolar disorder" to "schizoaffective disorder" (Figure 6-12). For over a century, experts have debated whether psychotic disorders are dichotomous from mood disorders (Figure 6-13A) or are part of a continuous disease spectrum from psychosis to mood (Figure 6-13B).

The dichotomous disease model is in the tradition of Kraepelin and proposes that schizophrenia is a chronic unremitting illness with poor outcome and decline in

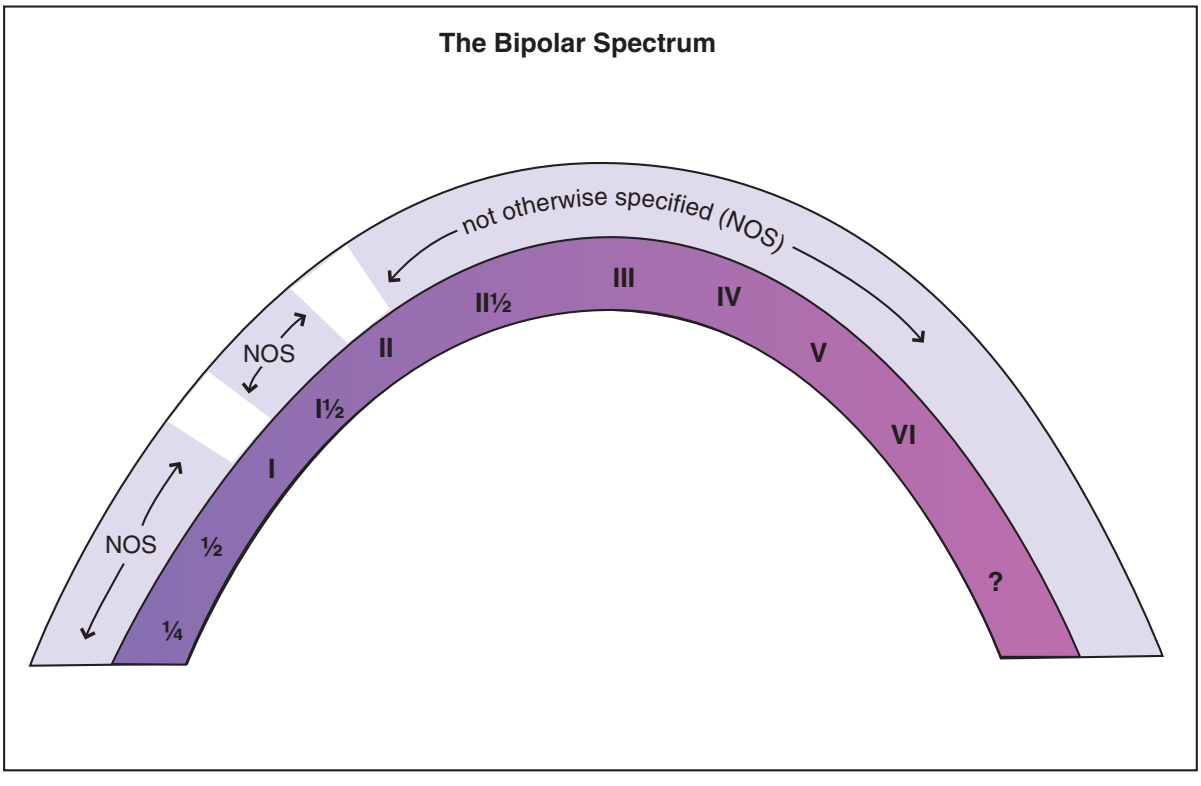


Figure 6-10. Bipolar spectrum. There is a huge variation in the presentation of patients with bipolar disorder. Historically, bipolar disorder has been categorized as I, II, or not otherwise specified (NOS). It may be more useful, instead, to think of these patients as belonging to a bipolar spectrum and to identify subcategories of presentations, as has been done by Akiskal and other experts and as illustrated in the next several figures.

function whereas bipolar disorder is a cyclical illness with a better outcome and good restoration of function between episodes. However, there is great debate as to how to define the borders between these two illnesses. One notion is that cases with overlapping symptoms and intermediate disease courses can be seen as a third illness, schizoaffective disorder. Today, many define this border with the idea that "even a trace of schizophrenia is schizophrenia." From this "schizophrenia-centered perspective," many overlapping cases of psychotic mania and psychotic depression might be considered either to be forms of schizophrenia, or to be schizoaffective disorder as a form of schizophrenia with affective symptoms. A competing point of view within the dichotomous model is that "even a trace of mood disturbance is a mood disorder." From this "mood-centered perspective," many overlapping cases of psychotic mania and psychotic depression might be considered either to be forms of a mood/bipolar disorder or to be schizoaffective disorder as a form of mood/bipolar disorder with psychotic symptoms. Where patients have a mixture of mood symptoms and psychosis, it can obviously be very difficult to tell whether they have a psychotic disorder such as schizophrenia, a mood disorder such as bipolar disorder, or a third condition, schizoaffective disorder. Some even want to eliminate the diagnosis of schizoaffective disorder entirely.

Proponents of the dichotomous model point out that treatments for schizophrenia differ from those for bipolar disorder, since lithium is rarely helpful in schizophrenia, and anticonvulsant mood stabilizers have limited efficacy for psychotic symptoms in schizophrenia, and perhaps only as augmenting agents. Treatments for schizoaffective disorder can include both treatments for schizophrenia and treatments for bipolar disorder. The current debate within the dichotomous model is: If you have bipolar disorder, do you have a good outcome? – but if you have schizophrenia, do you have a poor outcome? – and what genetic and biological markers rather than clinical symptoms can distinguish one dichotomous entity from the other?

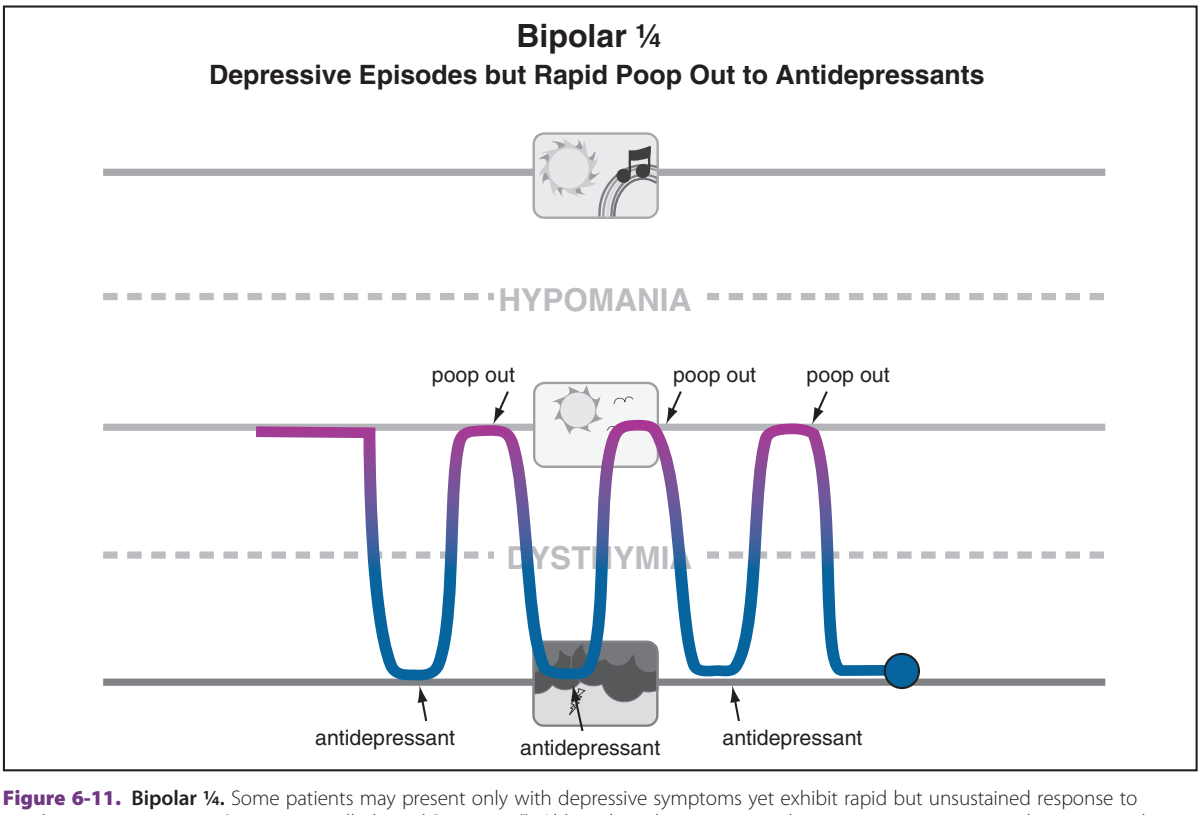


Figure 6-11. Bipolar ¼. Some patients may present only with depressive symptoms yet exhibit rapid but unsustained response to antidepressant treatment (sometimes called rapid "poop out"). Although such patients may have no spontaneous mood symptoms above normal, they potentially could benefit from mood-stabilizing treatment. This presentation may be termed bipolar ¼ (or bipolar 0.25).

The continuum disease model proposes that psychotic and mood disorders are both manifestations of one complex set of disorders that is expressed across a spectrum, at one end schizophrenia (plus schizophreniform disorder, brief psychotic disorder, delusional disorder, shared psychotic disorder, subsyndromal/ultra-high-risk psychosis prodrome, schizotypal, paranoid, schizoid, and even avoidant personality disorders), and at the other end bipolar/mood disorders (mania, depression, mixed states, melancholic depression, atypical depression, catatonic depression, postpartum depression, psychotic depression, seasonal affective disorder), with schizoaffective disorder in the middle, combining features of positive symptoms of psychosis with manic, hypomanic, or depressive episodes (Figure 6-13B).

Modern genomics suggests that the spectrum is not a single disease, but a complex of hundreds if not thousands of different diseases, with overlapping genetic, epigenetic, and biomarkers as well as overlapping clinical symptoms and functional outcomes. Proponents of the continuum model point out that treatments for schizophrenia overlap greatly now with those for bipolar disorder, since second-generation atypical antipsychotics are effective in the positive symptoms of schizophrenia and in psychotic mania and psychotic depression, and are also effective in nonpsychotic mania and in bipolar depression and unipolar depression. These same second-generation atypical antipsychotics are effective for the spectrum of symptoms in schizoaffective disorder. From the continuum disease perspective, failure to give mood-stabilizing medications may lead to suboptimal symptom relief in patients with psychosis, even those whose prominent or eye-catching psychotic symptoms mask or distract clinicians from seeing underlying and perhaps more subtle mood symptoms. In the continuum disease model, schizophrenia can be seen as the extreme end of a spectrum of severity of mood disorders and not a disease unrelated to a mood disorder. Schizophrenia can therefore share with schizoaffective disorder severe psychotic symptoms that obscure mood symptoms, a chronic course that eliminates cycling, resistance to antipsychotic treatments, and prominent

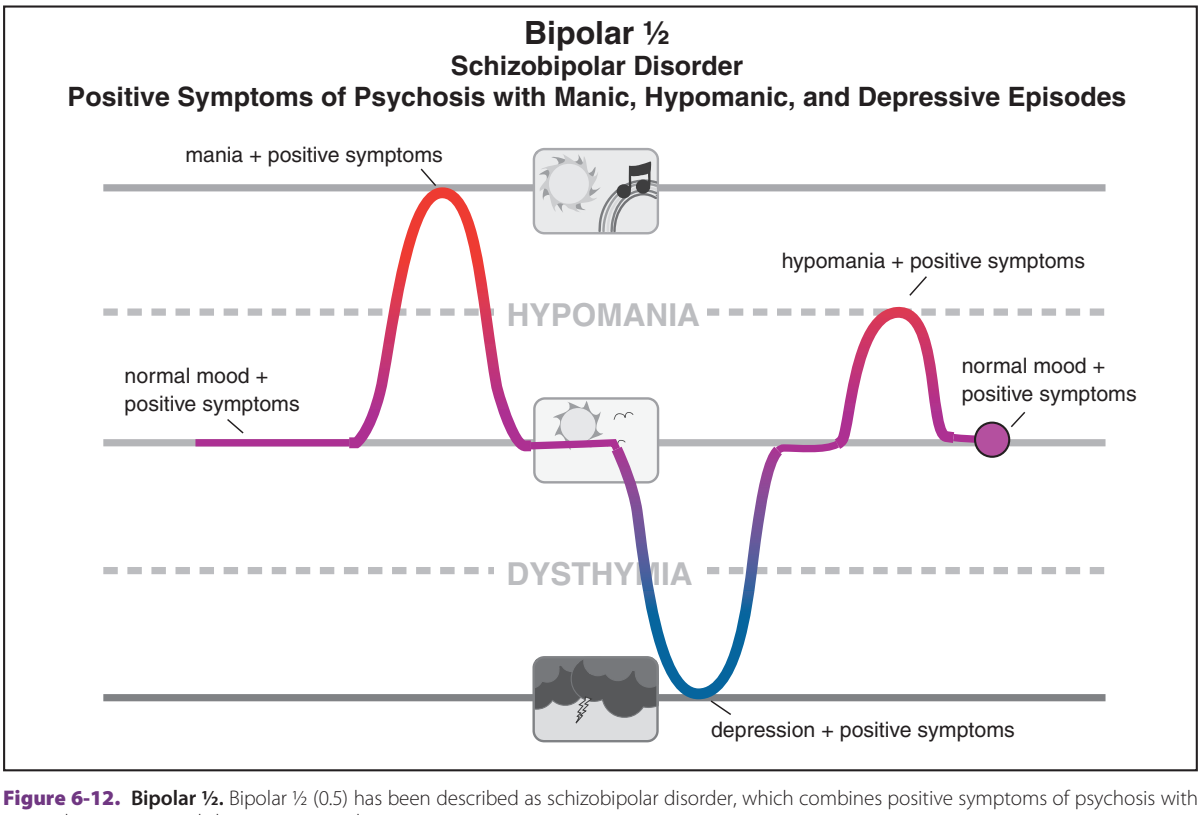


Figure 6-12. Bipolar ½. Bipolar ½ (0.5) has been described as schizobipolar disorder, which combines positive symptoms of psychosis with manic, hypomanic, and depressive episodes.

Schizophrenia and Bipolar Disorder

Dichotomous Disease Model

Schizophrenia	Schizoaffective Disorder	Bipolar Disorder
• psychosis	• psychosis	• mania
• chronic, unremitting	and	• mood disorder
• poor outcome	• mania	• cyclical
• "even a trace of schizophrenia is schizophrenia"	• mood disorder	• good outcome
		• "even a trace of a mood disturbance is a mood disorder"

Figure 6-13A. Schizophrenia and bipolar disorder: dichotomous disease model. Schizophrenia and bipolar disorder have been conceptualized both as dichotomous disorders and as belonging to a continuum. In the dichotomous disease model, schizophrenia consists of chronic, unremitting psychosis, with poor outcomes expected. Bipolar disorder consists of cyclical manic and other mood episodes and has better expected outcomes than schizophrenia. A third distinct disorder is schizoaffective disorder, characterized by psychosis and mania as well as other mood symptoms.