

CHAPTER 1

Mood Disorders

- Description of mood disorders
- The bipolar spectrum
- Can unipolar depression be distinguished from bipolar depression?
- Are mood disorders progressive?
- Neurotransmitters and circuits in mood disorders
 - Noradrenergic neurons
 - Monoamine interactions: NE regulation of 5HT release
 - Monoamine interactions: 5HT regulation of NE and DA release
- The monoamine hypothesis of depression
- The monoamine hypothesis, monoamine receptors, and gene expression
- Symptoms and circuits in depression
- Symptoms and circuits in mania
- Genes and neuroimaging in mood disorders
- Summary

This chapter discusses disorders characterized by abnormalities of mood: namely, depression, mania, or both. Included are descriptions of a wide variety of mood disorders that occur over a broad clinical spectrum. Also included is an analysis of how abnormalities in regulation of the trimonoaminergic neurotransmitter system – comprising the three monoamine neurotransmitters norepinephrine (NE; also called norepinephrine, or NA), dopamine (DA), and serotonin (also called 5-hydroxytryptamine, or 5HT) – are hypothesized to explain the biological basis of mood disorders. 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 neurotransmitters within the trimonoaminergic neurotransmitter system. The genetic regulation and neuroimaging of these hypothetically malfunctioning brain circuits are also briefly mentioned. The discussion of symptoms and circuits 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 reviewed in the following two chapters (Chapters 2 and 3).

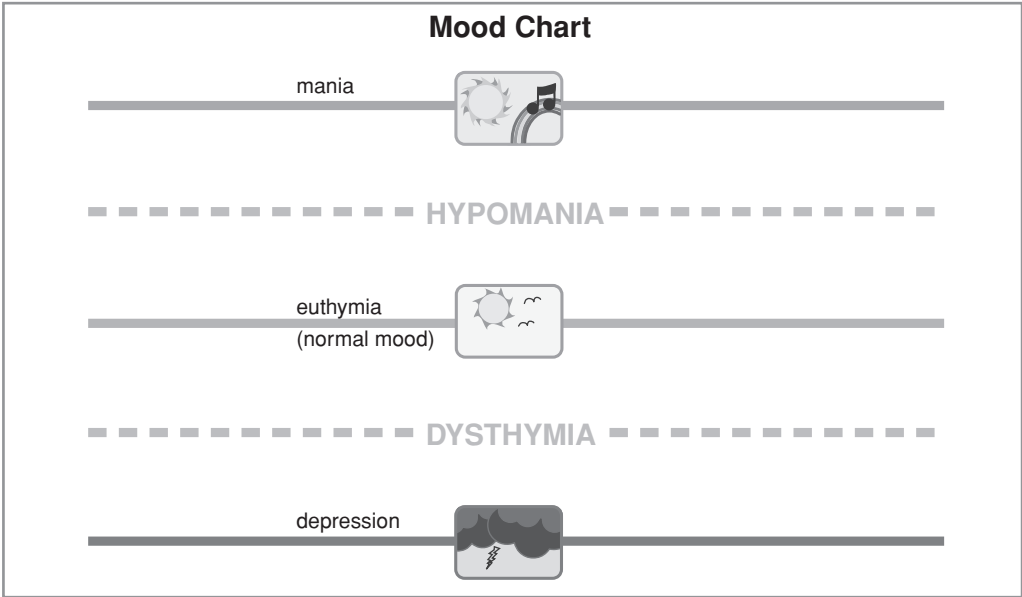


FIGURE 1-1 Mood chart. Disorders of mood can be mapped on a mood chart to track the course of illness, identify phase of illness, and aid in differential diagnosis. As shown in this chart, mood can range from mania at the top, to hypomania, to euthymia (normal mood) in the middle, and to dysthymia and depression at the bottom.

Clinical descriptions and criteria for the diagnosis of disorders of mood are mentioned only in passing. The reader should consult standard reference sources for this material. Here we discuss how the discovery of various neurotransmitters and brain circuits has influenced the understanding of symptoms in mood disorders. The goal of this chapter is to outline current ideas about the clinical and biological aspects of mood disorders in order to prepare the reader to understand the various treatments for these disorders discussed in later chapters.

Description of mood disorders

Disorders of mood are often called affective disorders, since affect is the external display of mood or emotion which is, however, 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., as in patients who just experience the *down* or depressed pole) and “bipolar” [i.e., as in patients who at different times experience either the *up* (manic) pole or the *down* (depressed) pole]. In practice, however, depression and mania may occur simultaneously, in which case a “mixed” mood state exists. Mania may also occur in lesser degrees, known as “hypomania”; or a patient may switch so quickly between mania and depression that it is called “rapid cycling.”

Mood disorders can be usefully visualized not only to distinguish different mood disorders from one another but also to summarize the course of illness for individual patients by showing them their disorders 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 1-1). Mood abnormalities for the major diagnostic entities are summarized in Figure 1-2 and shown in more detail in Figures 1-3 through 1-29.

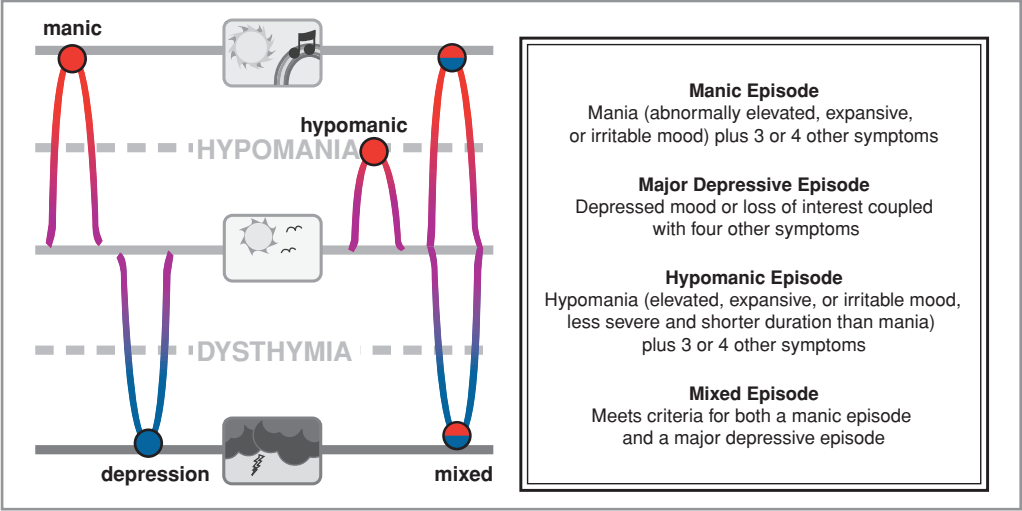


FIGURE 1-2 Mood episodes. Bipolar disorder is generally characterized by four types of illness episodes: manic, major depressive, hypomanic, and mixed. A patient may have any combination of these episodes over the course of illness; subsyndromal manic or depressive episodes also occur during the course 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.

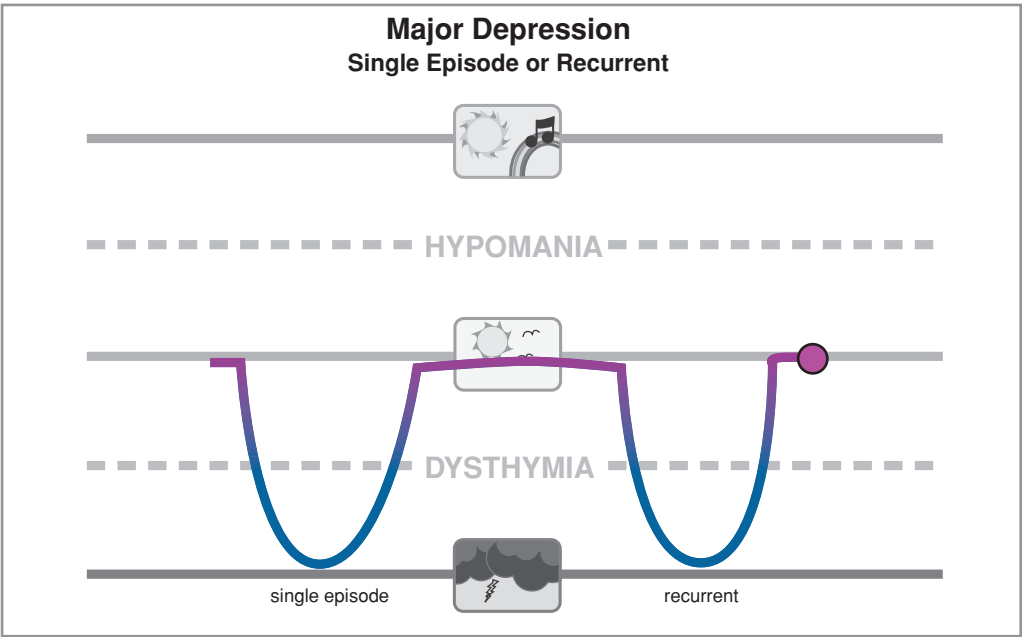


FIGURE 1-3 Major depression. Major depression is the most common mood disorder and is defined by the occurrence of at least a single major depressive episode, although most patients will experience recurrent episodes.

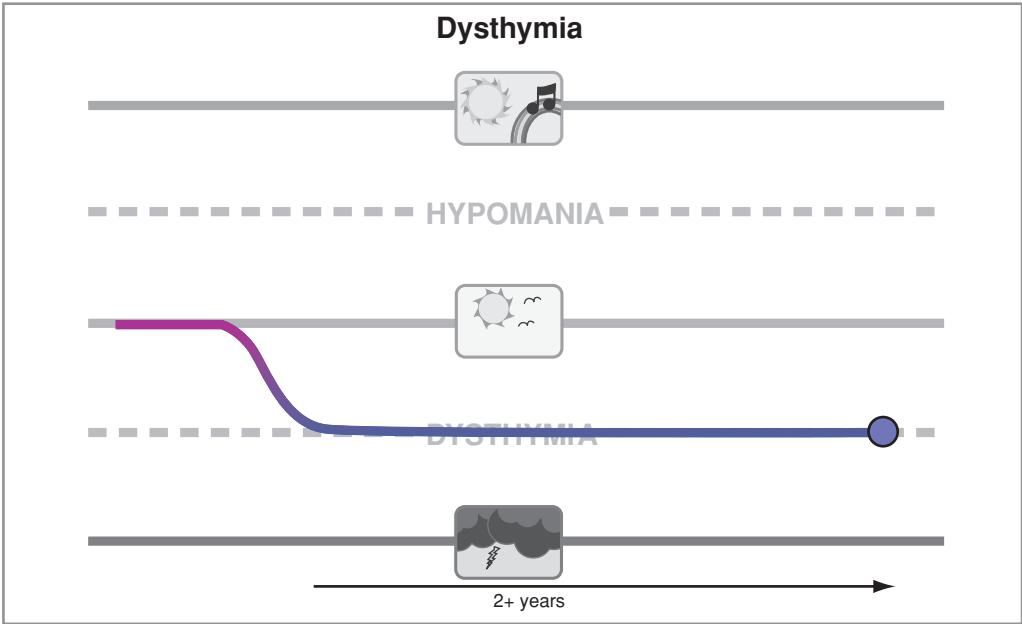


FIGURE 1-4 Dysthymia. Dysthymia is a less severe form of depression than major depression but long-lasting (over two years in duration) and is often unremitting.

The most common and readily recognized mood disorder is major depression (Figure 1-3) as a single episode or recurrent episodes. Dysthymia is a less severe but often longer-lasting form of depression (Figure 1-4). Patients with a major depressive episode who have poor inter-episode recovery, only to the level of dysthymia, which is then followed by another episode of major depression, are sometimes said to have “double depression,” alternating between major depression and dysthymia but not remitting (Figure 1-5).

Bipolar I patients have full-blown manic episodes and/or mixed episodes of full mania plus simultaneous full depression, often followed by a full depressive episode (Figure 1-6). When mania recurs at least four times a year, it is called rapid cycling (Figure 1-17A). Bipolar I patients can also have rapid switches from mania to depression and back (Figure 1-17B). By definition, this occurs at least four times a year, but it can happen much more frequently than that.

Bipolar disorder is characterized by at least one hypomanic episode and one full depressive episode (Figure 1-8). Cyclothymic disorder is characterized by mood swings less severe than full mania and full depression but still waxing and waning above and below the boundaries of normal mood (Figure 1-9). 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) (Figure 1-10) and hyperthymic temperament (above normal mood but also not a mood disorder) (Figure 1-11). Temperaments are lifelong personality styles of responding to environmental stimuli; they can be heritable patterns present early in life and persisting thereafter and include such independent personality dimensions as novelty seeking, harm avoidance, and conscientiousness. Some patients may have mood-related temperaments that may render them vulnerable to mood disorders, especially bipolar spectrum disorders, later in life.

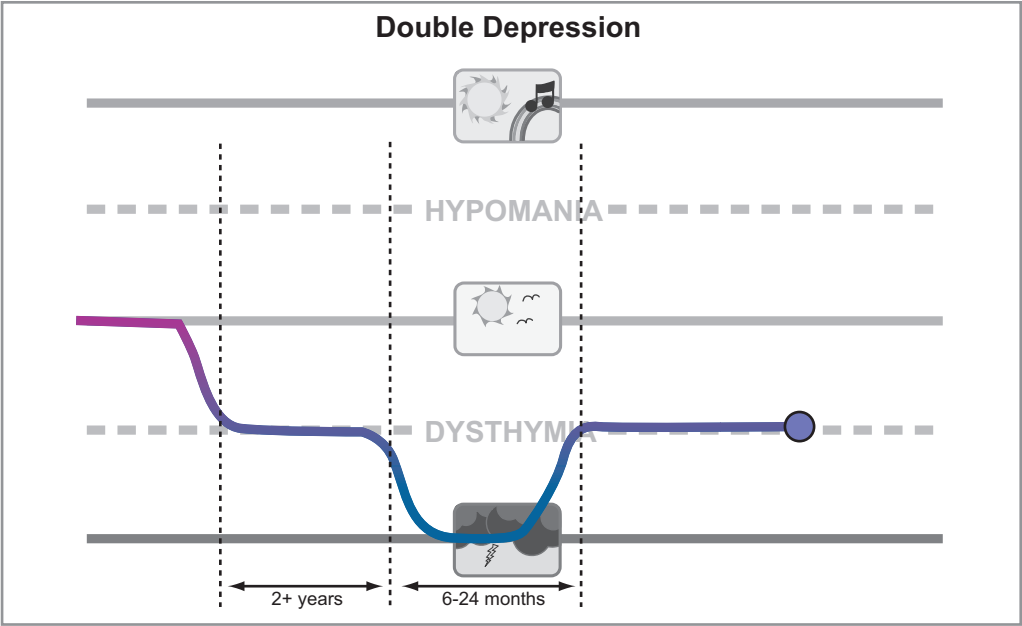


FIGURE 1-5 Double depression. Patients with unremitting dysthymia who also experience the superimposition of one or more major depressive episodes are described as having double depression. This is also a form of recurrent major depressive episodes with poor inter-episode recovery.

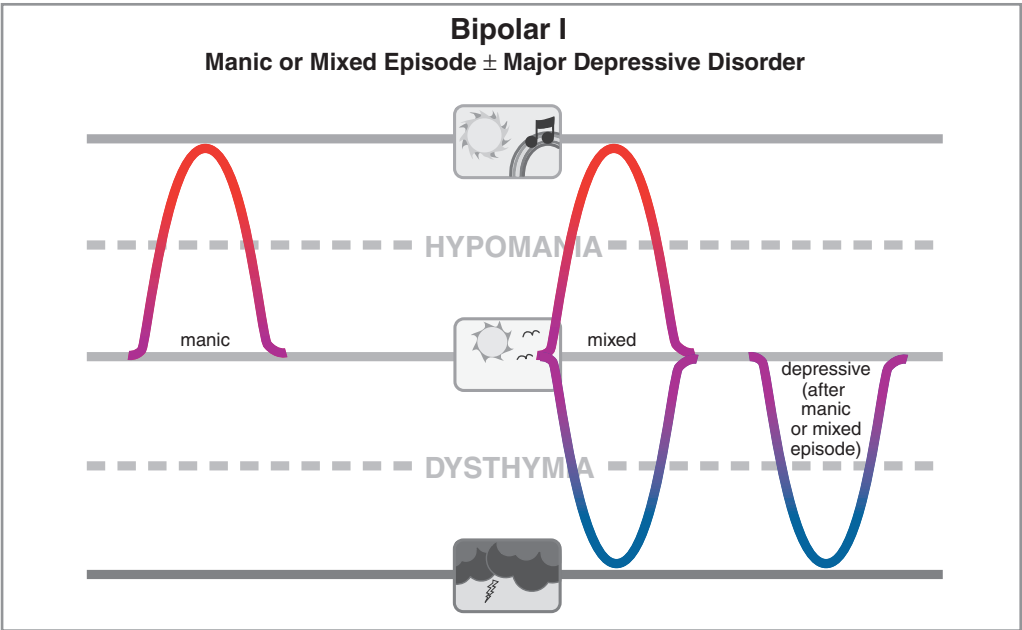


FIGURE 1-6 Bipolar I disorder. Bipolar I disorder is defined as the occurrence of at least one manic or mixed (full mania and full depression simultaneously) episode. Patients with bipolar I disorder typically experience major depressive episodes as well, although this is not necessary for the bipolar I diagnosis.

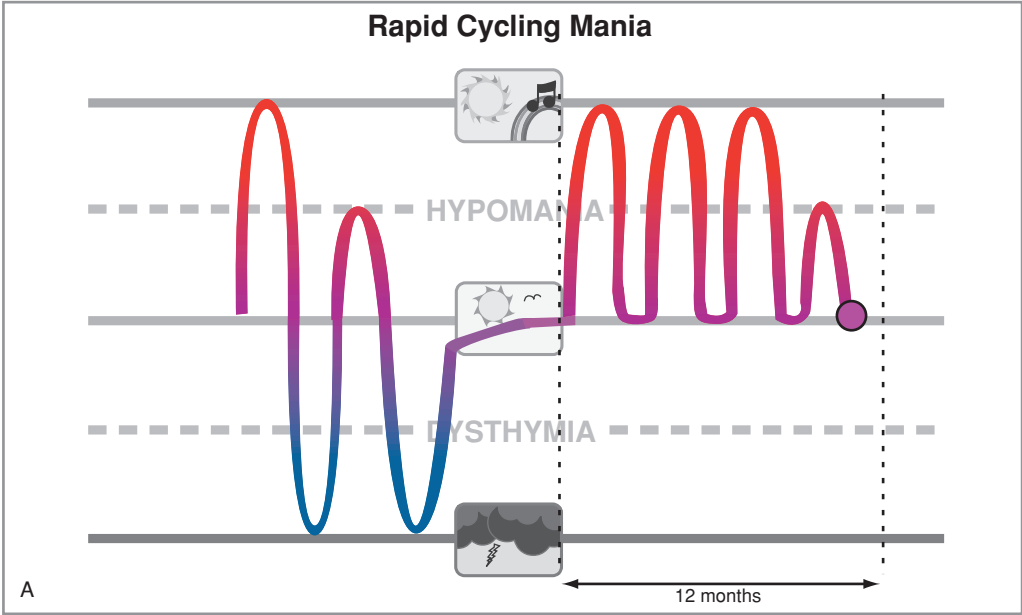


FIGURE 1-7A Rapid cycling mania. The course of bipolar disorder can be rapid cycling, which means that at least four episodes occur within a one-year period. This can manifest itself as four distinct manic episodes, as shown here. Many patients with this form of mood disorder experience switches much more frequently than four times a year.

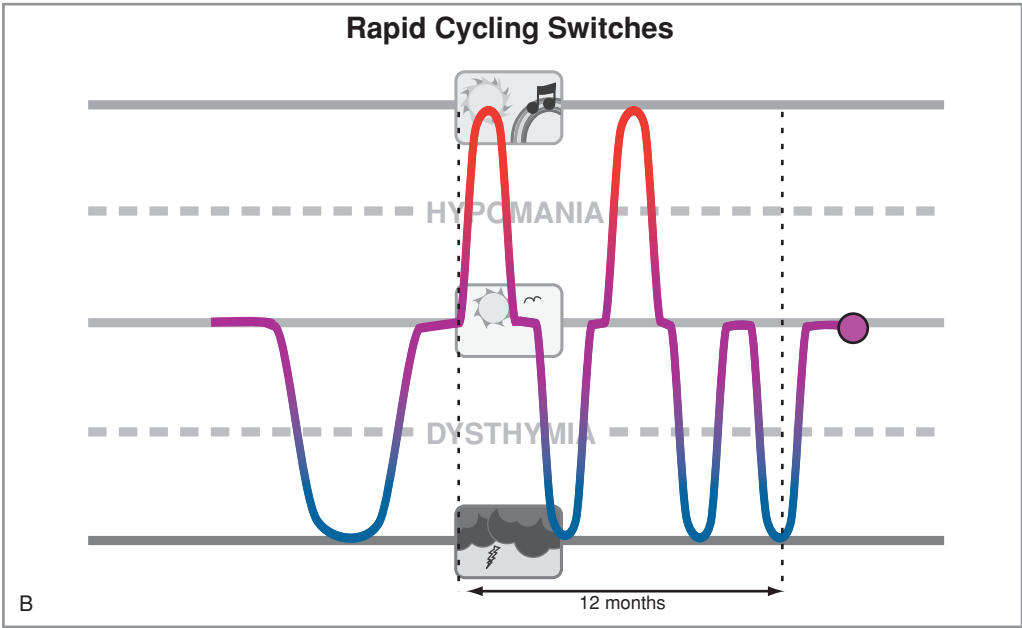


FIGURE 1-7B Rapid cycling switches. A rapid cycling course (at least four distinct mood episodes within one year) can also manifest as rapid switches between manic and depressive episodes.

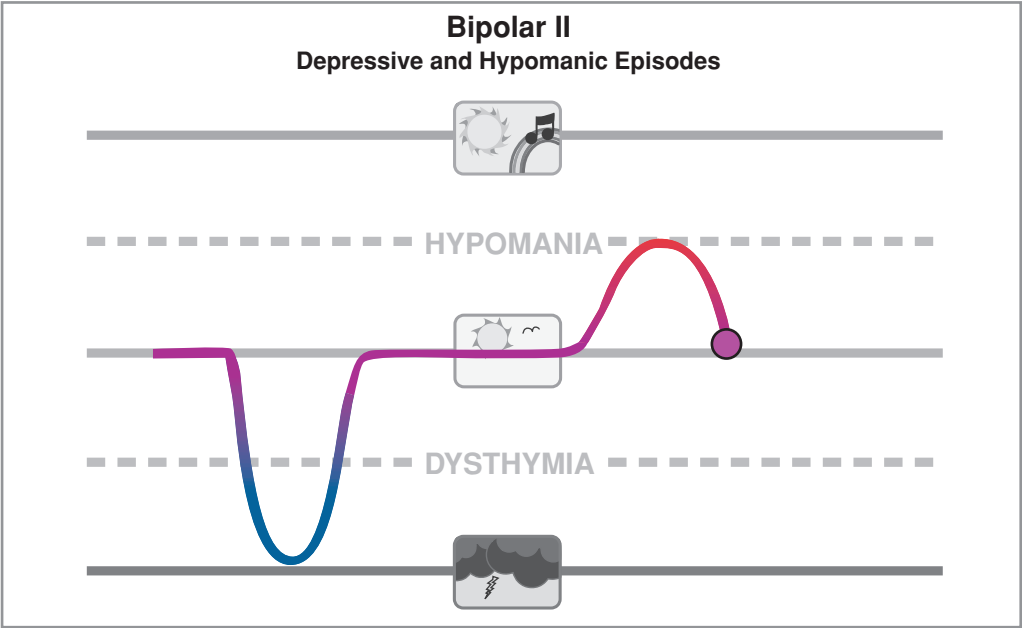


FIGURE 1-8 Bipolar disorder. Bipolar disorder is defined as an illness course consisting of one or more major depressive episodes and at least one hypomanic episode.

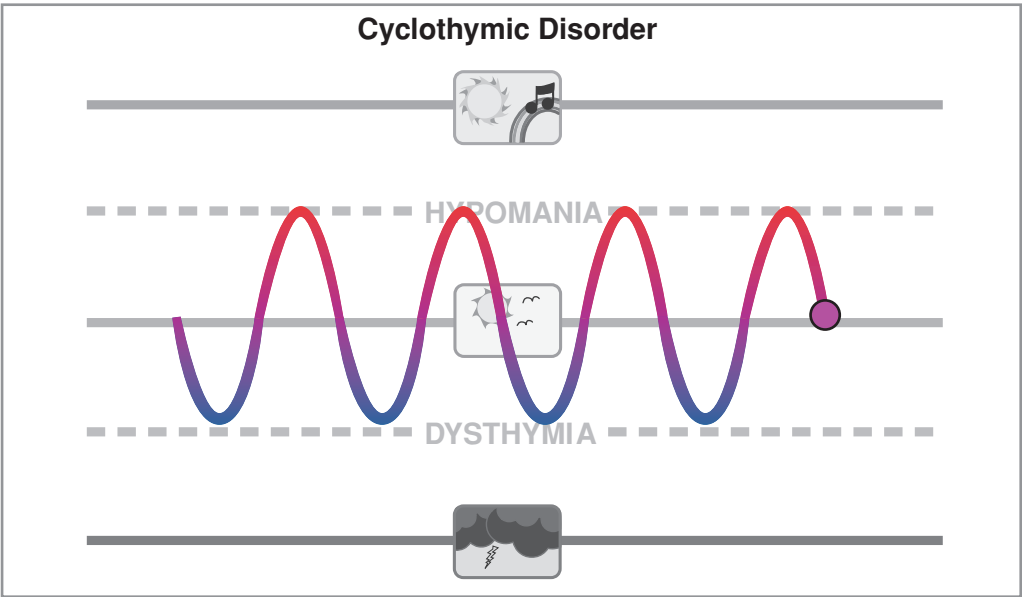


FIGURE 1-9 Cyclothymic disorder. Cyclothymic disorder is characterized by mood swings between hypomania and dysthymia but without any full manic or major depressive episodes.

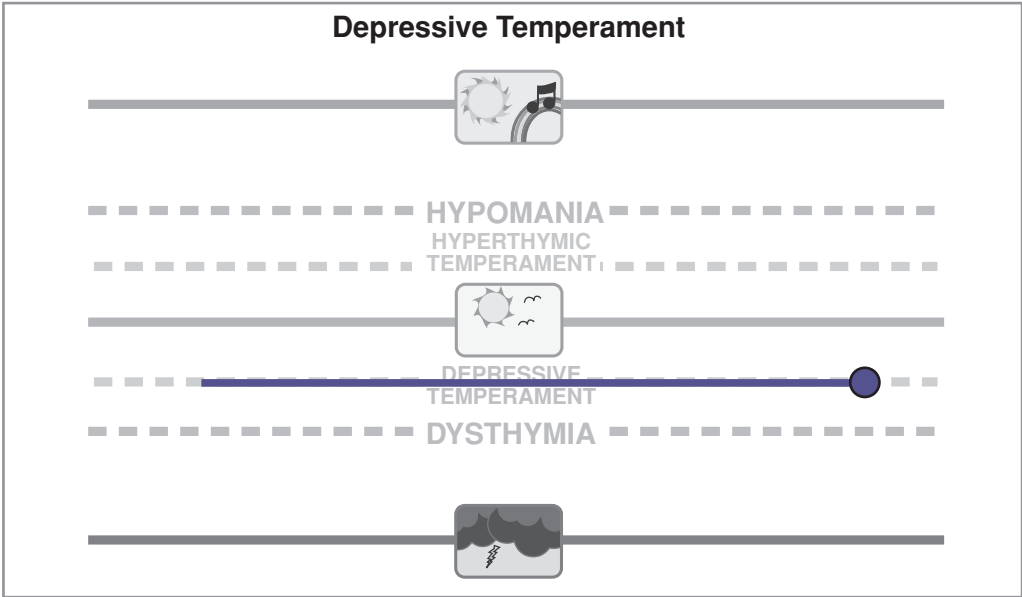


FIGURE 1-10 Depressive temperament. Not all mood variations are pathological. Individuals with depressive temperament may be consistently sad or apathetic but do not meet the criteria for dysthymia and do not necessarily experience any functional impairment. However, individuals with depressive temperament may be at greater risk for the development of a mood disorder later in life.

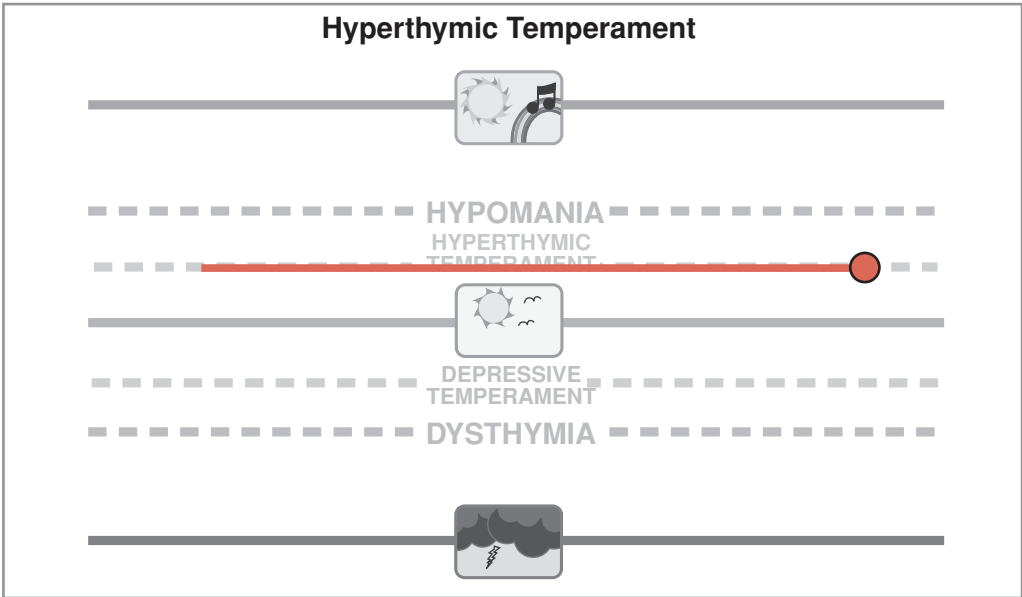


FIGURE 1-11 Hyperthymic temperament. Hyperthymic temperament, in which mood is above normal but not pathological, includes stable characteristics such as extroversion, optimism, exuberance, impulsiveness, overconfidence, grandiosity, and lack of inhibition. Individuals with hyperthymic temperament may be at greater risk for the development of a mood disorder later in life.

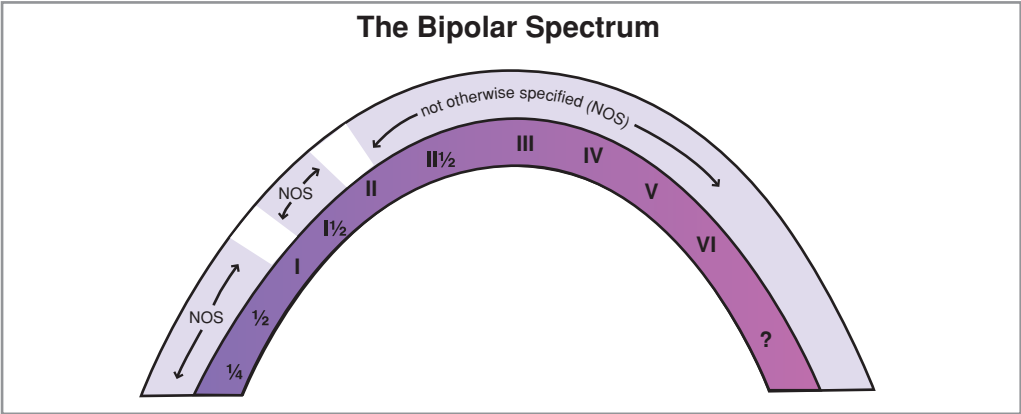


FIGURE 1-12 Bipolar spectrum. The only formal unique bipolar diagnoses identified in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-), are bipolar I, bipolar , and cyclothymic disorder, with all other presentations that include mood symptoms above the normal range lumped together in a single category called “not otherwise specified (NOS).” However, there is a huge variation in the presentation of patients within this bipolar NOS category. 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.

The bipolar spectrum

From a strict diagnostic point of view, our discussion of mood disorders might now be complete. However, there is growing recognition that many or even most patients seen in clinical practice may have a mood disorder that is not well described by the categories outlined above. 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 1-12) and, in particular, to one of several additional descriptive categories proposed by experts such as Akiskal (Figures 1-12 through 1-21).

Two forms of mood disorder often considered to be “not quite bipolar” may include bipolar $\frac{1}{4}$ and bipolar $\frac{1}{2}$ (Figures 1-13 and 1-14). Bipolar $\frac{1}{4}$ (or 0.25) could designate an unstable form of unipolar depression that responds sometimes rapidly but in an unsustained manner to antidepressants. Such an uneven response is sometimes called antidepressant “poop out” (Figure 1-13). These patients have unstable mood but not a formal bipolar disorder, yet they can sometimes benefit from mood-stabilizing treatments added to robust antidepressant treatments. Bipolar $\frac{1}{2}$ (or 0.5) may indicate a type of “schizobipolar” disorder, also sometimes called schizoaffective disorder, combining positive symptoms of psychosis with manic, hypomanic, and depressive episodes (Figure 1-14). The placement of these patients within the bipolar spectrum can provide a rationale for treating them with mood stabilizers and atypical antipsychotics as well as antidepressants.

Although patients with protracted or recurrent hypomania without depression are not formally diagnosed as having bipolar disorder, they are definitely part of the bipolar spectrum and may benefit from the mood stabilizers studied mostly in bipolar I disorder (Figure 1-15). Eventually such patients often develop a major depressive episode, and their diagnosis then changes to bipolar disorder. In the meantime, they can be treated for hypomania while being vigilantly watched for the onset of a major depressive episode.

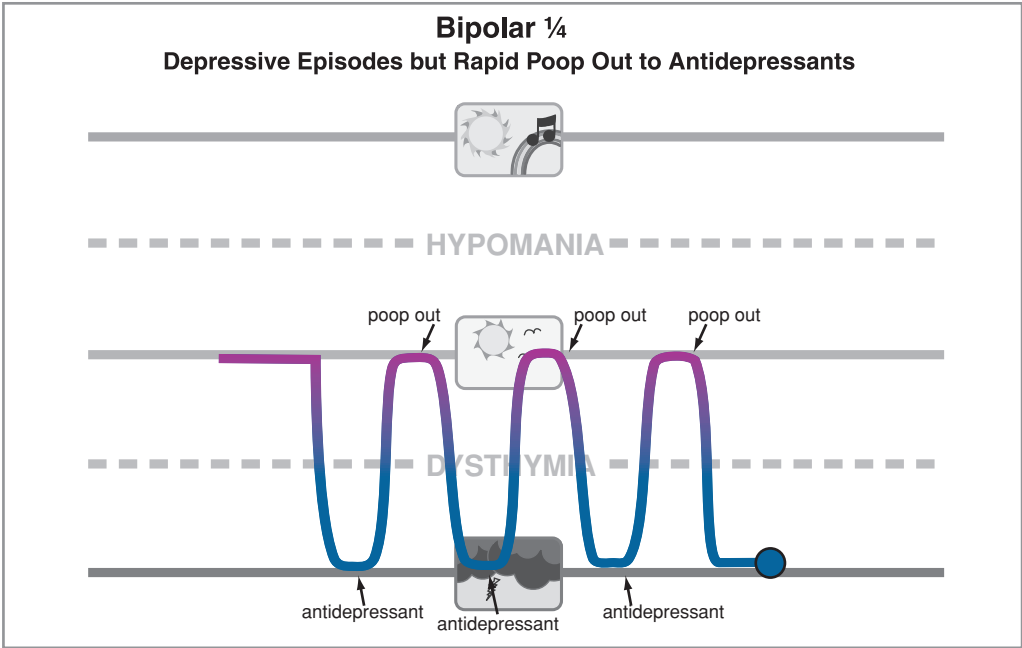


FIGURE 1-13 Bipolar 1/4. Some patients may present only with depressive symptoms yet exhibit rapid but unsustained response to antidepressant treatment (sometimes called rapid “poop out”). Although such patients may have no spontaneous mood symptoms above normal, they potentially could benefit from mood-stabilizing treatment. This presentation may be termed bipolar 0.25 (or bipolar 1/4).

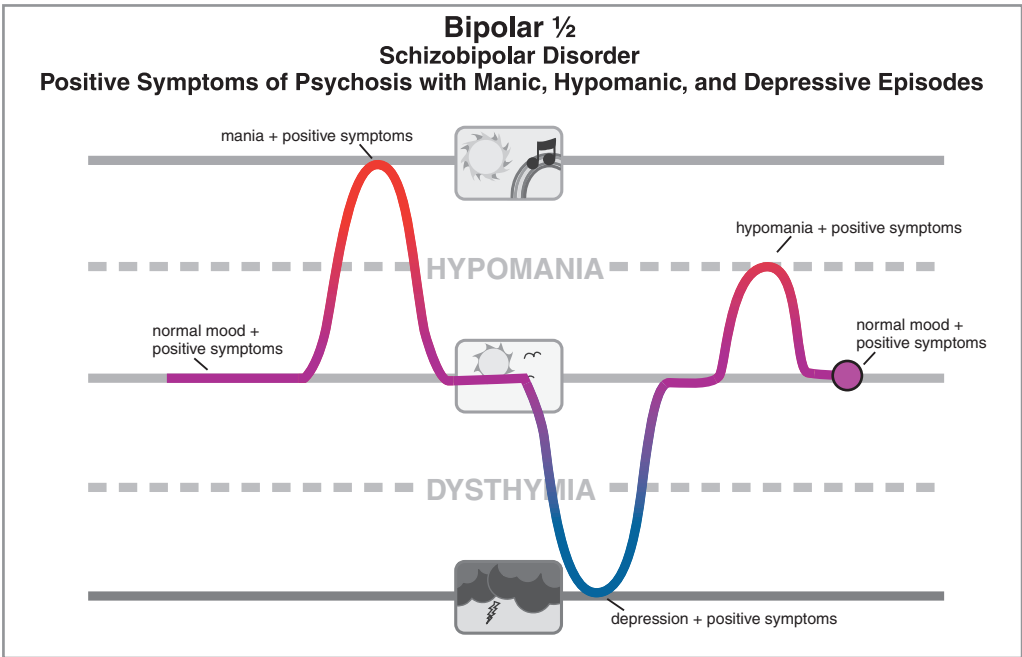


FIGURE 1-14 Bipolar 1/2. Bipolar 1/2 has been described as schizobipolar disorder, which combines positive symptoms of psychosis with manic, hypomanic, and depressive episodes.