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 noradrenaline, 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 12 and 13).
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 11-1). Mood abnormalities for the major diagnostic entities are summarized in Figure 11-2 and shown in more detail in Figures 11-3 through 11-29.
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 11-2 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.

Major Depression
Single Episode or Recurrent

FIGURE 11-3 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.
The most common and readily recognized mood disorder is major depression (Figure 11-3) as a single episode or recurrent episodes. Dysthymia is a less severe but often longer-lasting form of depression (Figure 11-4). 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 11-5).

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 11-6). When mania recurs at least four times a year, it is called rapid cycling (Figure 11-17A). Bipolar I patients can also have rapid switches from mania to depression and back (Figure 11-17B). By definition, this occurs at least four times a year, but it can happen much more frequently than that.

Bipolar II disorder is characterized by at least one hypomanic episode and one full depressive episode (Figure 11-8). 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 11-9). 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 11-10) and hyperthymic temperament (above normal mood but also not a mood disorder) (Figure 11-11). 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.
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.

Bipolar I

Manic or Mixed Episode ± Major Depressive 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.
Rapid Cycling Mania

FIGURE 11-7A 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 11-7B 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.
**Bipolar II**

Depressive and Hypomanic Episodes

- HYPOMANIA

- DYSTHYMIA

**FIGURE 11-8 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.

**Cyclothymic Disorder**

- HYPOMANIA

- DYSTHYMIA

**FIGURE 11-9 Cyclothymic disorder.** Cyclothymic disorder is characterized by mood swings between hypomania and dysthymia but without any full manic or major depressive episodes.
FIGURE 11-10 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 11-11 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.
The Bipolar Spectrum

The only formal unique bipolar diagnoses identified in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), are bipolar I, bipolar II, 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 11-12) and, in particular, to one of several additional descriptive categories proposed by experts such as Akiskal (Figures 11-12 through 11-21).

Two forms of mood disorder often considered to be “not quite bipolar” may include bipolar ¼ and bipolar ½ (Figures 11-13 and 11-14). Bipolar ¼ (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 11-13). 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 ½ (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 11-14). 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 II disorder, they are definitely part of the bipolar spectrum and may benefit from the mood stabilizers studied mostly in bipolar I disorder (Figure 11-15). Eventually such patients often develop a major depressive episode, and their diagnosis then changes to bipolar II disorder. In the meantime, they can be treated for hypomania while being vigilantly watched for the onset of a major depressive episode.
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).

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

FIGURE 11-13 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 11-14 Bipolar 1/2. Bipolar 1/2 has been described as schizobipolar disorder, which combines positive symptoms of psychosis with manic, hypomanic, and depressive episodes.
Bipolar I½
Protracted Hypomania Without Depression

Bipolar II ⅓ is the designation for patients with cyclothymic temperament who develop major depressive episodes (Figure 11-16). Many patients with cyclothymic temperament are just considered “moody” and do not consult professionals until they experience a full depressive episode. It is important to recognize patients in this part of the bipolar spectrum because treatment of their major depressive episodes with antidepressant monotherapy may actually cause increased mood cycling or even induce a full manic episode, just as can happen in patients with bipolar I or II depressive episodes.

In fact, patients who develop a manic or hypomanic episode on an antidepressant are sometimes called bipolar III (Figure 11-17). According to formal diagnostic criteria, however, when an antidepressant causes mania or hypomania, the diagnosis is not bipolar disorder but rather “substance-induced mood disorder.” Many experts disagree with this designation and feel that patients who have a hypomanic or manic response to an antidepressant do so because they have a bipolar spectrum disorder and can be more appropriately diagnosed as bipolar III disorder (Figure 11-17) until they experience a spontaneous manic or hypomanic episode while taking no drugs, at which point their diagnosis would be bipolar I or II, respectively. The bipolar III designation is helpful in the meantime, reminding clinicians that such patients are not good candidates for antidepressant monotherapy.

A variant of bipolar III disorder has been called bipolar III ⅓ to designate a type of bipolar disorder associated with substance abuse (Figure 11-18). Although some of these patients can utilize substances of abuse to treat depressive episodes, others have previously experienced natural or drug-induced mania and take substances of abuse to induce mania. This combination of a bipolar disorder with substance abuse is a formula for chaos and can often be the story of a patient prior to seeking treatment from a mental health professional.
Bipolar II½
Depressive Episodes With Cyclothymic Temperament

FIGURE 11-16 Bipolar II½. Patients may present with a major depressive episode in the context of cyclothymic temperament, which is characterized by oscillations between hyperthymic or hypomanic states (above normal) and depressive or dysthymic states (below normal) upon which a major depressive episode intrudes (bipolar II½). Individuals with cyclothymic temperament who are treated for the major depressive episodes may be at increased risk for antidepressant-induced mood cycling.

Bipolar III
Depressive Episodes with Antidepressant-Induced Hypomania

FIGURE 11-17 Bipolar III. Although the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), defines antidepressant-induced (hypo)mania as a substance-induced mood disorder, some experts believe that individuals who experience substance-induced (hypo)mania are actually predisposed to these mood states and thus belong to the bipolar spectrum (bipolar III).
Bipolar IV disorder is the association of depressive episodes with a preexisting hyperthymic temperament (Figure 11-19). Patients with hyperthymia are often sunny, optimistic, high-output, successful individuals whose temperaments have been stable for years but who then suddenly collapse into a severe depression. In such cases, it may be useful to be vigilant to the need for more than antidepressant monotherapy if the patient is unresponsive to such treatment or develops rapid cycling, hypomanic, or mixed states in response to antidepressants. Despite not having a formal bipolar disorder, such patients may respond best to mood stabilizers.

Bipolar V disorder is depression with mixed hypomania (Figure 11-20). Formal diagnostic criteria for mixed states require full expression of both depression and mania simultaneously. In the real world, however, many depressed patients can have additional symptoms that qualify as only hypomania or even just a few or mild manic symptoms. Depression coexisting with full hypomania is represented in Figure 11-20 and requires mood stabilizer treatment, not antidepressant monotherapy.

Related states include mood states where full diagnostic criteria are not reached; these can range from full mixed states [both full mania diagnostic criteria (M) and full depression diagnostic criteria (D)] to depression with hypomania or only a few hypomanic symptoms (mD), as already discussed. In addition, other combinations of mania and depression range from full mania with only a few depressive symptoms (Md, sometimes also called “dysphoric” mania), to subsyndromal but unstable states characterized by some symptoms of both mania and depression but not diagnostic of either (md) (Table 11-1). All of these states differ from unipolar depression and belong in the bipolar spectrum; they may require treatment with the same agents used to treat bipolar I or II disorder, with appropriate caution for antidepressant monotherapy. The fact that a patient is depressed does not mean that he or she should start.
Bipolar IV
Depressive Episodes With Hyperthymic Temperament

FIGURE 11-19 Bipolar IV. Bipolar IV is seen in individuals with long-standing and stable hyperthymic temperament into which a major depressive episode intrudes. Individuals with hyperthymic temperament who are treated for depressive episodes may be at increased risk for antidepressant-induced mood cycling and may instead respond better to mood stabilizers.

Bipolar V
Depression With Mixed Hypomania

FIGURE 11-20 Bipolar V. Bipolar V is defined as major depressive episodes with hypomanic symptoms occurring during the major depressive episode but without the presence of discrete hypomanic episodes. Because the symptoms do not meet the full criteria for mania, these patients would not be considered to have a full mixed episode, but they nonetheless exhibit a mixed presentation and may require mood stabilizer treatment as opposed to antidepressant monotherapy.
TABLE 11-1 Mixed States of Mania and Depression

<table>
<thead>
<tr>
<th>Description</th>
<th>Designation</th>
<th>Comment/Other Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV mixed</td>
<td>MD</td>
<td>Full diagnostic criteria for both mania and depression</td>
</tr>
<tr>
<td>Depression with hypomania</td>
<td>mD</td>
<td>Bipolar V</td>
</tr>
<tr>
<td>Depression with some manic symptoms</td>
<td>mD</td>
<td>Bipolar NOS</td>
</tr>
<tr>
<td>Mania with some depressive symptoms</td>
<td>Md</td>
<td>Dysphoric mania</td>
</tr>
<tr>
<td>Subsyndromal mania with subsyndromal depression</td>
<td>md</td>
<td>Prodrome or presymptomatic or state of incomplete remission</td>
</tr>
</tbody>
</table>

FIGURE 11-21 Bipolar VI. Another subcategory within the bipolar spectrum may be “bipolarity in the setting of dementia,” termed bipolar VI. Mood instability here begins late in life, followed by impaired attention, irritability, reduced drive, and disrupted sleep. The presentation may initially appear to be attributable to dementia or be considered unipolar depression, but it is likely to be exacerbated by antidepressants and may respond to mood stabilizers.

FIGURE 11-21 Bipolar VI. Another subcategory within the bipolar spectrum may be “bipolarity in the setting of dementia," termed bipolar VI. Mood instability here begins late in life, followed by impaired attention, irritability, reduced drive, and disrupted sleep. The presentation may initially appear to be attributable to dementia or be considered unipolar depression, but it is likely to be exacerbated by antidepressants and may respond to mood stabilizers.

treatment with an antidepressant. Patients with mixed states of depression and mania may be particularly vulnerable to the induction of activation, agitation, rapid cycling, dysphoria, hypomania, mania, or suicidality when treated with antidepressants, particularly without the concomitant use of a mood stabilizer or an atypical antipsychotic.

Finally, bipolar VI disorder (Figure 11-21) represents bipolarity in the setting of dementia, where it can be incorrectly attributed to the behavioral symptoms of dementia rather than recognized as a comorbid mood state and treated with mood stabilizers and even with atypical antipsychotics. Many more subtypes of mood disorders can be described within the bipolar spectrum. The important thing to take away from this discussion is that not all patients with depression have major depressive disorder requiring treatment with antidepressant monotherapy and that there are many states of mood disorder within the bipolar spectrum beyond just bipolar I and II disorders.
What Proportion of Mood Disorders Are Bipolar?

FIGURE 11-22 Prevalence of mood disorders. In recent years there has been a paradigm shift in terms of the recognition and diagnosis of patients with mood disorders. That is, many patients once considered to have major depressive disorder (old paradigm, left) are now recognized as having bipolar II disorder or another form of bipolar illness within the bipolar spectrum (shifting paradigm, right).

Can unipolar depression be distinguished from bipolar depression?

One of the important developments in the field of mood disorder in recent years, in fact, is the recognition that many patients once considered to have major depressive disorder actually have a form of bipolar disorder, especially bipolar II disorder or one of the conditions within the bipolar spectrum (Figure 11-22). Since symptomatic patients with bipolar disorder spend much more of their time in the depressed state than in the manic, hypomanic, or mixed state, this means that many depressed patients in the past were incorrectly diagnosed with unipolar major depression and treated with antidepressant monotherapy instead of being diagnosed as having a bipolar spectrum disorder and treated first with lithium, anticonvulsant mood stabilizers, and/or atypical antipsychotics prior to being given an antidepressant.

Up to half of patients once considered to have a unipolar depression are now considered to have a bipolar spectrum disorder (Figure 11-22), and although they would not necessarily be good candidates for antidepressant monotherapy, this is often the treatment that they receive when the bipolar nature of their condition is not recognized. Antidepressant treatment of unrecognized bipolar disorder may not only increase mood cycling, mixed states, and conversion to hypomania and mania, as mentioned above, but also contribute to the increase in suicidality of patients treated with antidepressants, with adults below twenty-five years of age being at greater risk for antidepressant-induced suicidality than older adults, adolescents more at risk than younger adults, and children more at risk than adolescents.

Thus it becomes important to recognize whether a depressed patient has a bipolar spectrum disorder or a unipolar major depressive disorder. How can this be done? In reality, these patients can have identical current symptoms (Figure 11-23), so obtaining the profile of current symptomatology is obviously not sufficient to distinguish unipolar from bipolar...
Is it unipolar or bipolar depression? Questions to ask

**Who's your daddy?**
- What is your family history of:
  - Mood disorder
  - Psychiatric hospitalizations
  - Suicide
  - Anyone who took lithium, mood stabilizers, antipsychotics, antidepressants
  - Anyone who received ECT

These can be indications of a unipolar or bipolar spectrum disorder in relatives.

**Where's your mama?**
- Additional history is needed about you from someone close to you, such as your mother or spouse.

Patients may especially lack insight about their manic symptoms and underreport them.

---

**Is It Unipolar or Bipolar Depression?**

**Identical Current Symptoms**

**Patient A:**
- Current Episode
  - HYPOMANIA
  - DYSTHYMIA

7 Days Ago 3 Days Ago Today 7 Days Ago

**Patient B:**
- Current Episode
  - HYPOMANIA
  - DYSTHYMIA

7 Days Ago 3 Days Ago Today

**FIGURE 11-23 Unipolar versus bipolar depression presentation.** The presenting symptoms of a major depressive episode in bipolar illness (Patient B) may be indistinguishable from those of a major depressive episode in unipolar depression (Patient A). Thus, the current presentation is not sufficient for making the differential diagnosis. The additional information needed includes family history, symptom and treatment-response history, and feedback from a friend or relative.

Depression. The answer may be to ask the two questions shown in Table 11-2, namely, “Who's your daddy?” and “Where's your mama?”

What this means is “What is your family history?” since the existence of a first-degree relative with a bipolar spectrum disorder can strongly suggest that the patient also has a bipolar spectrum disorder rather than unipolar depression. This also means, “I need to get additional history from someone close to you,” since patients tend to underreport their manic symptoms, and the insight and observations of an outside informant such as a mother or spouse can give a past history quite different from the one the patient is reporting and thus help establish a bipolar spectrum diagnosis that patients themselves do not perceive or may deny.
Is It Unipolar or Bipolar Depression?
Different Past Symptoms Make the Diagnosis

Patient A:
Current Episode and History

- - - - - HYPOMANIA - - -
- - ••• - - DYSTHYMIA •••

Patient B:
Current Episode and History

- - - - - HYPOMANIA - - -
- - - - - DYSTHYMIA - - -

FIGURE 11-24 Unipolar versus bipolar depression history. Patterns of past symptoms as well as treatment-response history may aid in distinguishing between unipolar and bipolar illness. As shown here, although Patients A and B both present with major depressive episodes, they have divergent histories that suggest a unipolar illness for Patient A and a bipolar illness for Patient B.

Pattern of past symptoms can also give a hint as to whether a patient has a bipolar spectrum depression rather than a unipolar depression, as discussed above and as shown in Figure 11-24. Thus, prior response to antidepressants, prior hyperthymia or hypomania, can be hints from past symptoms to help distinguish unipolar from bipolar spectrum depression. Some hints, but not sufficient for diagnostic certainty, can even come from current symptoms to suggest a bipolar spectrum depression, such as more time sleeping, overeating, comorbid anxiety, motor retardation, mood lability, or psychotic or suicidal thoughts (Figure 11-25). Hints that the depression may be in the bipolar spectrum can come from the course of the untreated illness prior to the current symptoms, such as early age of onset, high frequency of depressive symptoms, high proportion of time spent ill, and acute abatement or onset of symptoms (Figure 11-26). Prior responses to antidepressants that suggest bipolar depression can be multiple antidepressant failures, rapid recovery, and the activation of side effects such as insomnia, agitation, and anxiety (Figure 11-27).

Although none of these features can discriminate bipolar depression from unipolar depression with certainty, the point is to be vigilant to the possibility that what looks like a unipolar depression might actually be a bipolar spectrum depression when investigated more carefully, and when response to treatment is monitored.

Are mood disorders progressive?

One of the major unanswered questions about the natural history of depressive illnesses is whether they are progressive (Figures 11-28 and 11-29). Specifically, it appears that many more patients in mental health practices have bipolar spectrum illnesses than unipolar illnesses, especially compared to a few decades ago. Is this merely the product of
Identifying Bipolar Depression:
Hints From Current Symptoms

**FIGURE 11-25 Bipolar depression symptoms.** Although all symptoms of a major depressive episode can occur in either unipolar or bipolar depression, some symptoms may present more often in bipolar versus unipolar depression, providing hints if not diagnostic certainty that the patient has a bipolar spectrum disorder. These symptoms include increased time sleeping, overeating, comorbid anxiety, psychomotor retardation, mood lability during episodes, psychotic symptoms, and suicidal thoughts.

Identifying Bipolar Depression:
History

**FIGURE 11-26 Identifying bipolar depression: history.** Even in the absence of any previous (hypo)manic episodes, there are often specific hints in the untreated course of illness that suggest depression as part of the bipolar spectrum. These include early age of onset, high frequency of depressive episodes, high proportion of time spent ill, acute onset or abatement of symptoms, and behavioral symptoms such as frequent job or relationship changes.
Identifying Bipolar Depression:
Response to Antidepressants

Prior responses that suggest bipolar depression may include multiple antidepressant failures, rapid response to an antidepressant, and activating side effects such as insomnia, agitation, and anxiety.

Is Major Depressive Disorder Progressive?

A currently unanswered question is whether mood disorders are progressive. Does undertreatment of unipolar depression, in which residual symptoms persist and relapses occur, lead to progressive worsening of illness, such as more frequent recurrences and poor inter-episode recovery? And can this ultimately progress to a bipolar spectrum condition and finally treatment resistance?
Is Bipolar Disorder Progressive?

![Diagram showing the progression from discrete manic and depressive episodes to mixed and dysphoric episodes, then to rapid cycling and treatment resistance.]

**FIGURE 11-29** Is bipolar disorder progressive? There is some concern that undertreatment of discrete manic and depressive episodes may progress to mixed and dysphoric episodes and finally to rapid cycling and treatment resistance.

Changing diagnostic criteria, or does unipolar depression progress to bipolar depression (Figure 11-28)?

A corollary of this question is whether chronic and widespread undertreatment of unipolar depression, allowing residual symptoms to persist and relapses and recurrences to occur, results first in more rapidly recurring episodes of major depression, then in poor inter-episode recovery, then progression to a bipolar spectrum condition, and finally to treatment resistance (Figure 11-28). Many treatment-resistant mood disorders in psychiatric practices have elements of bipolar spectrum disorder that can be identified, and many of these patients require treatment with more than antidepressants or with mood stabilizers and atypical antipsychotics instead of antidepressants. This is discussed in detail in Chapter 12, which covers antidepressants, and in Chapter 13, which covers mood stabilizers.

For patients already diagnosed with bipolar disorder, there is similar concern that the disorder may be progressive, especially without adequate treatment. Thus, discrete manic and depressive episodes may progress to mixed and dysphoric episodes and finally to rapid-cycling instability and treatment resistance (Figure 11-29). The hope is that recognition and treatment of both unipolar and bipolar depressions, causing all symptoms to remit for long periods of time, might prevent progression to more difficult states. This is not proved but is a major hypothesis in the field at present.

In the meantime, practitioners must decide whether to commit “sins of omission” and be conservative with the diagnosis of bipolar spectrum disorder, thus erring on the side of undertreatment, or “sins of commission,” thus overdiagnosing and overtreating symptoms in the hope that this will prevent disease progression and “diabolical learning” in brain circuits, as discussed in Chapter 8 and illustrated in Figures 8-4 through 8-7.
Neurotransmitters and circuits in mood disorders

Three principal neurotransmitters have long been implicated in both the pathophysiology and treatment of mood disorders. They are norepinephrine, dopamine, and serotonin and comprise what is sometimes called the “trimonoaminergic” neurotransmitter system. These three monoamines often work in concert. Many of the symptoms of mood disorders are hypothesized to involve dysfunction of various combinations of these three systems. Essentially all known treatments for mood disorders act on one or more of these three systems.

We have extensively discussed the dopamine system in Chapter 9 and illustrated it in Figures 9-18 to 9-24. We have extensively discussed the serotonin system in Chapter 10 and illustrated it in Figures 10-15 to 10-20. Here we introduce both the norepinephrine system and also some interactions among these three monoaminergic neurotransmitter systems, showing how they interregulate one another. Although other neurotransmitter systems are undoubtedly involved in mood disorders, most is known about the links between trimonoaminergic neurotransmitters and mood disorders, so these neurotransmitters are emphasized here. New therapeutics based on glutamate and neurokinins are discussed briefly in Chapters 12 and 13. Neurotransmitters and hormones of the hypothalamic-pituitary-adrenal (HPA) axis are discussed briefly in Chapter 14, on anxiety and stress.

Noradrenergic neurons

The noradrenergic neuron utilizes norepinephrine (noradrenaline) as its neurotransmitter. Norepinephrine is synthesized, or produced, from the precursor amino acid tyrosine, which is transported into the nervous system from the blood by means of an active transport pump (Figure 11-30). Once inside the neuron, the tyrosine is acted on by three enzymes in sequence: first, tyrosine hydroxylase (TOH), the rate-limiting and most important enzyme in the regulation of NE synthesis. Tyrosine hydroxylase converts the amino acid tyrosine into dopa. The second enzyme then acts, namely, dopa decarboxylase (DDC), which converts dopa into dopamine (DA). DA itself is a neurotransmitter in dopamine neurons, as discussed in Chapter 9 and illustrated in Figure 9-18. However, for NE neurons, DA is just a precursor of NE. In fact the third and final NE synthetic enzyme, dopamine beta hydroxylase (DBH), converts DA into NE. NE is then stored in synaptic packages called vesicles until it is released by a nerve impulse (Figure 11-30).

NE action is terminated by two principal destructive or catabolic enzymes that turn NE into inactive metabolites. The first is monoamine oxidase (MAO) A or B, which is located in mitochondria in the presynaptic neuron and elsewhere (Figure 11-31). The second is catechol-O-methyl-transferase (COMT), which is thought to be located largely outside of the presynaptic nerve terminal (Figure 11-31).

The action of NE can be terminated not only by enzymes that destroy NE but also by a transport pump for NE that prevents NE from acting in the synapse without destroying it (Figure 11-31). In fact, such inactivated NE can be restored for reuse in a later neurotransmitting nerve impulse. The transport pump that terminates synaptic action of NE is sometimes called the “NE transporter” or “NET” and sometimes the “NE reuptake pump.” This NE reuptake pump is located on the presynaptic noradrenergic nerve terminal as part of the presynaptic machinery of the neuron, where it acts like a vacuum cleaner, whisking NE out of the synapse, off the synaptic receptors, and stopping its synaptic actions. Once inside the presynaptic nerve terminal, NE can either be stored again for subsequent reuse when another nerve impulse arrives or it can be destroyed by NE-destroying enzymes (Figure 11-31).
Norepinephrine is produced. Tyrosine, a precursor to norepinephrine (NE), is taken up into NE nerve terminals via a tyrosine transporter and converted into dopa by the enzyme tyrosine hydroxylase (TOH). Dopa is then converted into dopamine (DA) by the enzyme dopa decarboxylase (DDC). Finally, DA is converted into NE by dopamine beta hydroxylase (DBH). After synthesis, NE is packaged into synaptic vesicles via the vesicular monoamine transporter (VMAT2) and stored there until its release into the synapse during neurotransmission.

The noradrenergic neuron is regulated by a multiplicity of receptors for NE (Figure 11-32). The norepinephrine transporter or NET is one type of receptor, as is the vesicular monoamine transporter (VMAT2), which transports NE in the cytoplasm of the presynaptic neuron into storage vesicles (Figure 11-32). NE receptors are classified as alpha 1A, 1B, 1C or alpha 2A, 2B, or 2C, or as beta 1, beta 2, or beta 3. All can be postsynaptic, but only alpha 2 receptors can act as presynaptic autoreceptors (Figures 11-32 through 11-34). Postsynaptic receptors convert their occupancy by norepinephrine at alpha 1A, B, or C; alpha 2A, B, or C; or beta 1, 2, or 3 receptors into physiological functions and ultimately into changes in signal transduction and gene expression in the postsynaptic neuron (Figure 11-32).

Presynaptic alpha 2 receptors regulate norepinephrine release, so they are called "autoreceptors" (Figures 11-32 and 11-33). Presynaptic alpha 2 autoreceptors are located both on the axon terminal (i.e., terminal alpha 2 receptors; Figures 11-32 and 11-33) and at the cell body (soma) and nearby dendrites; thus, these latter alpha 2 presynaptic receptors are called somatodendritic alpha 2 receptors (Figure 11-34). Presynaptic alpha 2 receptors are important because both the terminal and somatodendritic alpha 2 receptors are autoreceptors. That is, when presynaptic alpha 2 receptors recognize NE, they turn off further release.
FIGURE 11-31 Norepinephrine's action is terminated. Norepinephrine's action can be terminated through multiple mechanisms. Dopamine can be transported out of the synaptic cleft and back into the presynaptic neuron via the norepinephrine transporter (NET), where it may be repackaged for future use. Alternatively, norepinephrine may be broken down extracellularly via the enzyme catechol-O-methyl-transferase (COMT). Other enzymes that break down norepinephrine are monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B), which are present in mitochondria both within the presynaptic neuron and in other cells, including neurons and glia.

Stimulating this receptor (i.e., stepping on the brake) stops the neuron from firing. This probably occurs physiologically to prevent overfiring of the NE neuron, since it can shut itself off once the firing rate gets too high and the autoreceptor becomes stimulated. It is worthy of note that drugs can not only mimic the natural functioning of the NE neuron by stimulating the presynaptic alpha 2 neuron but that those which antagonize this same receptor will have the effect of cutting the brake cable, thus enhancing release of NE.

**Monoamine interactions: NE regulation of 5HT release**

We have shown above that norepinephrine regulates norepinephrine neurons (Figures 11-33 and 11-34) and, in Chapter 10, that 5HT also regulates 5HT neurons (see Figures 10-18 and 10-19). In both cases, the regulation is that of negative feedback inhibition: both neurotransmitters inhibit their own release.

We now show that NE regulates 5HT neurons and reciprocally, that 5HT also regulates NE neurons. In the case of NE regulation of 5HT (Figures 11-35 through 11-38), there...
FIGURE 11-32 Norepinephrine receptors. Shown here are receptors for norepinephrine that regulate its neurotransmission. The norepinephrine transporter (NET) exists presynaptically and is responsible for clearing excess norepinephrine out of the synapse. The vesicular monoamine transporter (VMAT2) takes norepinephrine up into synaptic vesicles and stores it for future neurotransmission. There is also a presynaptic alpha 2 autoreceptor, which regulates release of norepinephrine from the presynaptic neuron. In addition, there are several postsynaptic receptors. These include alpha 1, alpha 2A, alpha 2B, alpha 2C, beta 1, beta 2, and beta 3 receptors.

is not only negative feedback inhibition of NE on 5HT release at alpha 2 receptors on axon terminals, thus acting as a brake on 5HT release (Figures 11-35 and 11-36), but also positive feedback at alpha 1 receptors at the somatodendritic area, thus acting as an accelerator of 5HT release (Figures 11-35 and 11-37). Thus, NE has bidirectional control of 5HT release, depending on whether input to the axon terminal alpha 2 heteroreceptor or to the somatodendritic alpha 1 receptor predominates (Figure 11-38).

**Monoamine interactions: 5HT regulation of NE and DA release**

In the other direction, 5HT also regulates NE release, but only as negative feedback at either 5HT2A or 5HT2C receptors, thus inhibiting NE release (Figures 11-39 and 11-40). This same serotonergic negative feedback regulation occurs for dopamine release and was discussed for 5HT2A receptors in Chapter 10 and illustrated in Figures 10-21, 10-24, and 10-25. Here we show the simultaneous negative feedback regulation of 5HT on both NE and DA release in the prefrontal cortex due to the actions of 5HT in the brainstem on 5HT2A receptors (Figure 11-39) or on 5HT2C receptors (Figure 11-40). In both cases, 5HT blocks release of both NE and DA in the prefrontal cortex. In truth, the regulation of DA release by 5HT at 5HT2A receptors is more complicated than this, but
FIGURE 11-33A and B Alpha 2 receptors on axon terminal. Shown here are presynaptic alpha 2 adrenergic autoreceptors located on the axon terminal of the norepinephrine neuron. These autoreceptors are “gatekeepers” for norepinephrine. That is, when they are not bound by norepinephrine, they are open, allowing norepinephrine release (A). However, when norepinephrine binds to the gatekeeping receptors, they close the molecular gate and prevent norepinephrine from being released (B).
BE occupying somatodendritic alpha 2 adrenergic autoreceptor causes a decrease in firing and a decrease of NE release.

FIGURE 11-34 Somatodendritic alpha 2 receptors. Presynaptic alpha 2 adrenergic autoreceptors are also located in the somatodendritic area of the norepinephrine neuron, as shown here. When norepinephrine binds to these alpha 2 receptors, it shuts off neuronal impulse flow in the norepinephrine neuron (see loss of lightning bolts in the neuron in the lower figure), and this stops further norepinephrine release.
our discussion here is aimed at providing a background for understanding the actions of atypical antipsychotics in mood disorders; this is not meant to be a comprehensive review of all aspects of 5HT2A receptor regulation of DA release. Other evidence suggests that some 5HT2A receptors in some brain areas under certain circumstances can actually facilitate DA release (as discussed in Chapter 10 and illustrated in Figure 10-31).

A separate circuit also regulates 5HT2C inhibition of DA release in the nucleus accumbens (Figure 11-41). In this case, 5HT acts upon GABA neurons in the brainstem, one of which inhibits the mesolimbic dopamine projection when 5HT2C receptors are occupied (Figure 11-41). 5HT actions on a second GABA neuron that projects to prefrontal cortex result in inhibition of a descending excitatory glutamate projection to the dopamine neuron, further inhibiting dopamine release in the nucleus accumbens (Figure 11-41).

In summary, there are numerous known interregulatory pathways and receptor interactions among the trimonoaminergic neurotransmitter systems so that they can influence each other and change the release not only of their own neurotransmitters but also of others within this system.

The monoamine hypothesis of depression

The classic theory about the biological etiology of depression hypothesizes that depression is due to a deficiency of monoamine neurotransmitters. At first, there was a great argument about whether norepinephrine (NE) or serotonin (5-hydroxytryptamine; 5HT) was the more important deficiency, and dopamine was relatively neglected. Now the monoamine theory suggests that the entire trimonoaminergic neurotransmitter system may be malfunctioning in various brain circuits, with different neurotransmitters involved depending on the patient’s symptom profile.
FIGURE 11-36A and B Norepinephrine as a brake on serotonin release. Alpha 2 adrenergic heteroreceptors are located on the axon terminals of serotonin neurons. When these receptors are unoccupied by norepinephrine, serotonin is released from the serotonin neuron (A). However, when norepinephrine binds to the alpha 2 receptor this closes the molecular gate and prevents serotonin from being released (B).