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Disorders of Mood: Depression, Mania, and Anxiety Disorders

Making the distinction between a disturbance of cognitive faculties (a thought disorder) and a disturbance of emotion (a mood disorder) was an important step in the early development of the modern classification of mental illness. In clinical descriptions of emotional states the term mood refers to a sustained emotional state lasting weeks or more, while the term affect (or affective response) refers to immediate or momentary emotional state of a person. Affect is more directly responsive to external stimuli, although with significant mood disorders the range of affective responses is limited. Thus, affect is to mood as the weather (rainy or sunny) is to climate (tropical, moderate, or cold).

Normal affective responses serve important biological functions and range from euphoria to elation, pleasure, surprise, anger, anxiety, disappointment, sadness, grief, despair, and even depression. Three of these responses—euphoria, depression, and anxiety—can become so disordered, sustained, and dominant as to constitute a disease. We shall consider all three and discuss biological insights into these three disorders of mood. Although depression and euphoria (mania) have traditionally been referred to as disorders of affect, we use the more precise term mood. We shall then examine the anxiety states. Throughout we shall emphasize important interrelationships between the three mood disorders.

The Major Mood Disorders Can Be Either Unipolar or Bipolar

The most common mood disorder, unipolar depression, was described in the fifth century BC by Hippocrates. In the Hippocratic view moods were thought to depend on

The Major Mood Disorders Can Be Either Unipolar or Bipolar

Unipolar Depression Is Most Likely Several Mood Disorders
Bipolar Depressive (Manic-Depressive) Disorders Give Rise to Alternating Euphoria and Depression
Mood Disorders Have a Strong Genetic Predisposition
Familial Unipolar and Bipolar Depressions May Reflect an Abnormality in the Functioning of the Subgenual Region of the Frontal Cortex
Unipolar Depressive and Manic-Depressive Disorders Can Be Treated Effectively
Drugs Effective in Depression Act on Serotonergic and Noradrenergic Pathways
An Abnormality in Biogenic Amine Transmission May Contribute to the Disorders of Mood
Unipolar Depression May Involve Disturbances of Neuroendocrine Function
There Are at Least Four Major Types of Anxiety Disorders
Panic Attacks Are Brief Episodes of Terror
Post-Traumatic Stress Disorder Reflects Persistent Traces of Anxiety That Follow Traumatic Episodes
Generalized Anxiety Disorder Is Characterized by Long-Lasting Worries
In Obsessive-Compulsive Disorder Obtrusive Thoughts Are a Source of Anxiety and Compulsion
An Overall View
the balance of four humors—blood, phlegm, yellow bile, and black bile. An excess of black bile was believed to cause depression. In fact, the ancient Greek term for depression, *melancholia*, means black bile. Though this explanation of depression seems fanciful today, the underlying view that psychological disorders reflect physical processes is correct.

Modern efforts to update the Hippocratic formulation were, until very recently, hindered by a lack of precision in the classification of affective disorders. In his 1917 paper *Mourning and Melancholia*, Sigmund Freud wrote: "Even in descriptive psychiatry the definition of melancholia is uncertain; it takes on various clinical forms (some of them suggesting somatic rather than psychogenic affections) that do not seem definitely to warrant reduction to a unity." Only in the past two decades have relatively precise criteria for mood disorders been developed in parallel with those for cognitive disorders (see Chapter 60).

**Unipolar Depression Is Most Likely Several Mood Disorders**

The clinical features of unipolar depression are easily summarized. In Hamlet's words, "How weary, stale, flat, and unprofitable seem to me all the uses of this world!" Untreated, an episode of depression typically lasts 4–12 months. It is characterized by an unpleasant (*dysphoric*) mood that is present most of the day, day in and day out, as well as intense mental anguish, the inability to experience pleasure (*anhedonia*), and a generalized loss of interest in the world. The diagnosis also requires at least three of the following symptoms to be present: disturbed sleep (usually insomnia with early morning awakening, but sometimes oversleeping or hypersomnia), diminished appetite and loss of weight (but sometimes overeating), loss of energy, decreased sex drive, restlessness (psychomotor agitation), slowing down of thoughts and actions (psychomotor retardation), difficulty in concentrating, indecisiveness, feelings of worthlessness, guilt, pessimistic thoughts, and thoughts about dying and suicide. Other common symptoms, not required for diagnosis, are constipation, decreased salivation, and diurnal variation in the severity of symptoms, which are usually worse in the morning.

In addition to the inclusion criteria there are exclusion criteria; schizophrenia or other neurological diseases, for example, need to be excluded. There also should be no evidence of a recent death in the family or other traumatic events, since some of the symptoms of unipolar depression are also normal expressions of grief following trauma, personal loss, and mourning.

When the syndrome is defined in this manner, about 5% of the world's population have major unipolar depression. In the United States 8 million people at any given time are affected. Severe depression can be profoundly debilitating. In extreme cases patients stop eating or maintaining basic personal cleanliness. Although some people have only a single episode, usually the illness is recurrent. About 70% of patients who have one major depressive episode will have at least one more episode. The average age of onset is about 28 years, but the first episode can occur at almost any age. Indeed, depression also affects young children but is often unrecognized in them. Depression also occurs in the elderly; in fact, older people who become depressed often have not had an earlier episode. Women are affected about two to three times more often than men.

Unipolar depression is most likely not a single illness but a group of disorders. However, the attempt to distinguish three subtypes has been only partially successful so far. The subtypes that are commonly distinguished are melancholic depression, atypical depression, and dysthymia.

**Melancholic depression** represents the clearest subtype among the major depressions and accounts for 40–60% of people treated for unipolar depression. Because it often has no obvious external precipitating cause—no personal loss or rejection or obvious change in life events—it was formerly referred to as *endogenous depression*. The disorder is characterized by six symptoms: (1) depression with diurnal variations in mood (worse in the morning), (2) insomnia with early morning awakening, (3) anorexia with significant weight loss, (4) psychomotor agitation and mental pain, (5) loss of interest in almost all activity and lack of response to pleasurable stimuli, and (6) when severe, a complete loss of the capacity for joy (*anhedonia*).

Patients with melancholic depression often have a history of one or more previous episodes of major depression with recovery. Many patients show characteristic abnormalities in sleep pattern, as measured by electroencephalography. These abnormalities occur primarily during the first half of the night, when the latency for the rapid eye movement (REM) phase of sleep is shortened. More than half of patients with melancholic depression have frequent awakenings. Melancholic depression sometimes leads to psychomotor retardation, to emotional or intellectual underactivity (*retardation*). At other times there is a rather painful state of agitation and an active and persistent preoccupation with perceived deficiencies and inadequacies of one's character. Patients with melancholic depression tend to respond preferentially to electroconvulsive therapy (ECT), tricyclic antidepressants, and selective serotonin reuptake inhibitors.

**Atypical depression** is slightly less common than melancholic depression; accounting for about 15% of
patients hospitalized for major mood disorders. The disease is called atypical because symptoms are the opposite of melancholic depression: it first appears earlier in life and tends to be chronic rather than phasic. In addition, unlike patients with melancholic depression, patients with atypical depression cheer up temporarily when good things happen. Finally, patients with atypical depression do not have loss of appetite and weight loss but instead overeat and gain weight; they do not report insomnia but rather tend to sleep more; and their depression is worse, not better, in the evening. The patients also have prominent symptoms of anxiety. Patients with atypical depression tend to respond preferentially to monoamine oxidase inhibitors.

Finally, dysthymia is a persistent but milder depression lasting for at least two years with symptoms that fall short of the criteria of a major depression.

It is important to appreciate that we normally experience grief or despondency after loss of a family member, and this normal mourning can involve any of the individual symptoms of atypical or melancholic depression. Perhaps the most important distinction between bereavement and depression is that bereavement is rarely associated with persistent functional impairment. In addition, despondent or grief-stricken people have fewer suicidal thoughts and, more important, they have lower rates of suicide than patients with atypical or melancholic depression.

Most helpful in making a diagnosis of depression, however, is the finding of reactive affect. Unlike major depression, the depression normally experienced after a personal loss is not unrelenting and pervasive—it does not persist every day, all day. Two or three months after a personal loss, most people are able to experience and react to moments of pleasure and contentment that relieve the sadness, something a person with a major depression cannot do. Finally, normal mourning tends to remit after several months. It does not persist. When mourning does persist it usually reflects a transition to an episode of major depression, a transition that occurs in individuals with a genetic predisposition.

Bipolar Depressive (Manic-Depressive) Disorders Give Rise to Alternating Euphoria and Depression

About 25% of patients with major depression (or two million people in the United States) will also experience a manic episode, if only a mild one. Patients who experience both depressive and manic episodes have a distinct disorder called bipolar mood disorder. The illness affects men and women equally, and the average age of onset of the first episode is a decade younger than that of unipolar depression (the onset usually occurs at age 20 rather than 30).

Episodes of depression in bipolar disorders are clinically similar to those of the unipolar type. The manic episodes are characterized by an elevated, expansive, or irritable mood lasting at least one week, together with several of the following symptoms: over-activity, over-talkativeness (pressure of speech), social intrusiveness, increased energy and libido, flight of ideas, grandiosity, distractibility, decreased need for sleep, and reckless spending. In severe cases patients are delusional and hallucinate. Most episodes have no detectable psychosocial precipitant.

Bipolar disorder is typically recurrent. After an initial episode of euphoria, subsequent episodes of either depression or euphoria are likely to occur about twice as often in bipolar disorder as in unipolar disease. One of the most striking features of bipolar illness is that a subset of patients (rapid cyclers) may switch from depression to euphoria or vice versa quite rapidly, sometimes in a matter of minutes. Depression tends to become more pronounced with age and recur with greater frequency.

Mood Disorders Have a Strong Genetic Predisposition

As in schizophrenia, genetic factors are important in both unipolar and bipolar mood disorders. The morbidity rate of depression is modestly higher in first-degree relatives (parents, siblings, and children) of patients
with depressive illness than in the general population (Figure 61-1). The overall concordance rate for monozygotic twin pairs with bipolar depression may reach 80%; the rate for dizygotic twins is approximately 10% (the same as for siblings).

Seymour Kety, Paul Wender, and David Rosenthal extended their studies of patterns of schizophrenia in the families of adoptees (Chapter 60) to include manic-depressive disorders. They found that the rate of mood disorders among the biological parents of adoptees with depressive or manic-depressive illness was higher than among the adoptive parents (and higher than the rate among biological and adoptive parents of mentally healthy adoptees). Particularly impressive was the finding that the incidence of suicide among biological relatives of adoptees with depressive illness was six times higher than among the biological relatives of normal adoptees. Furthermore, the concordance rate of affective illness in monozygotic twins reared apart is 40–60%, similar to the concordance in those reared together.

These concordance rates for unipolar and bipolar depression in monozygotic twin pairs indicate that, like schizophrenia, major depression is polygenic. Several genes are likely to be involved, each making a small contribution. Nongenetic factors are also likely to be important in determining whether an affective disorder is expressed. Their importance is reflected in two important secular trends in depression over the past 50 years. Since 1940 the age of onset has become younger (28 years rather than 35), and the incidence of depression in the families of patients has increased. Perhaps people vulnerable to depression are now more likely to become depressed than they were half a century ago because of the increased stress of everyday life. In addition there may also be a genetic anticipation.

Genetic linkage analysis (see Chapter 3) has led to the identification of several loci that might contribute to affective illness. Although no specific gene has yet been identified, one locus on chromosome 18 (18q22-23) has the strongest supporting evidence.

**Familial Unipolar and Bipolar Depressions May Reflect an Abnormality in the Functioning of the Subgenual Region of the Frontal Cortex**

Positron emission tomography (PET) scanning and functional magnetic resonance imaging (fMRI) studies have recently defined a potential anatomical abnormality in...
Figure 61-3 The three types of antidepressants.

A Clinically useful monoamine oxidase inhibitors are chemically diverse. These drugs are
tught to act by decreasing the breakdown of biogenic amines in the brain, thereby making
more neurotransmitter available for release at
nergic synapses and prolonging the action of
nergic transmitters. The anti-depressant
ects of the drugs take several weeks to fully
dvelop.

B Tricyclic antidepressant drugs (see Figure
61-6) have immediate and long-term effects.
Blockade of the reuptake of biogenic amine
transmitters from the synapse is evident
soon after administration. The therapeutic ac-
tion of antidepressants usually begins 4 days to
weeks after starting the medication.

C Selective serotonin reuptake inhibitors are
the most easily tolerated antidepressants.

the prefrontal cortex ventral to the genu in the corpus cal-
sum that is affected in familial cases of unipolar and
bipolar depression. During the depressive phase of the
illness, activity in this region is decreased in patients
who have either unipolar or bipolar depression. This
decrease seems to be accounted for in large part by a reduc-
tion in the volume (by about 45%) of the gray matter of
this part of the prefrontal cortex. In contrast, in patients
with bipolar disease this region shows an increase in ac-
tivity during the manic phase of the illness.

This finding is of interest because other clinical
studies as well as studies in experimental animals have
shown that the subgenual region of the prefrontal cortex
is important for mood states (Figure 61-2). This region
of the prefrontal cortex has extensive connections with
other regions involved in emotional behavior, such as
the amygdala, the lateral hypothalamus, the nucleus ac-
cumbens, and the noradrenergic, serotonergic, and
dopaminergic systems of the brain stem (Chapter 50). People who have lesions in this area have difficulty ex-
periencing emotion and have abnormal autonomic re-
sponses to emotionally arousing stimuli. Moreover, le-
isons in this area severely compromise the ability to
reason and make intelligent, rational decisions. Con-
versely, Antonio Damasio and his colleagues have ob-
served that small irritative lesions in this region cause
episodes of anger and aggressive behavior.

Unipolar Depressive and Manic-Depressive
Disorders Can Be Treated Effectively

There are four effective treatments for unipolar and
bipolar illnesses: electroconvulsive therapy (ECT), an-
tidepressant drugs, lithium, and anticonvulsants. Of the
four, ECT has been used for the longest period of time,
over 50 years. Although antidepressants are generally
the first choice in the treatment of major depression,
ECT is very effective. It produces full remission or
marked improvement in about 85% of patients with
well-defined major depression.

The critical therapeutic factor in ECT is the induc-
tion of a generalized brain seizure. Since the motor com-
ponent of the seizure is not necessary for therapeutic re-
results, modern ECT is always given under anesthesia
with complete muscle relaxation. On average, six to
eight treatments given at two-day intervals over a pe-
riod of 2–4 weeks usually suffice to produce a complete
remission of symptoms. As might be predicted from our
knowledge of seizure activity (Chapter 46), ECT creates
Figure 61-4 The major serotonergic pathways arise in the raphe nuclei. (Adapted from Heimer 1995.)

A. Lateral view of the brain illustrates that the raphe nuclei form a fairly continuous collection of cell groups close to the midline throughout the brain stem. For clarity, they are illustrated here in distinct rostral and caudal groups. The rostral raphe nuclei project to a large number of forebrain structures (fibers that project laterally through the internal and external capsules to the neocortex are not shown here).

B. This coronal view of the brain illustrates some of the major targets of the serotonergic raphe nuclei neurons.

many temporary changes in brain functions. Although the therapeutic mechanism of ECT is not understood, it may be related to changes in aminergic receptor sensitivity, as we shall see later.

The most widely used antidepressant drugs fall into three major classes:

1. Monoamine oxidase inhibitors, such as phenelzine (Figure 61-3A). These were the first effective antidepressants to be used clinically but are now used only infrequently.

2. Tricyclic compounds, or general reuptake inhibitors of biogenic amines, such as imipramine, are so named for their three-ring molecular structure (Figure 61-3B). These compounds inhibit the uptake of both serotonin and norepinephrine and are probably the most effective drugs for patients who are severely depressed.

3. Selective serotonin reuptake inhibitors, such as fluoxetine (Prozac) (Figure 61-3C), paroxetine (Paxil), and sertraline (Zoloft). These are the most commonly used antidepressants, and they work by selectively inhibiting the uptake of serotonin. They are most commonly used for patients who are only moderately depressed. These are, after the tricyclic compounds, the most commonly used drugs in severely ill patients.

The monoamine oxidase inhibitors and the tricyclic antidepressants produce remission or marked improvement in about 70% of patients with major depressions. When optimal doses are given, the success rate with tricyclic drugs and the specific serotonin reuptake inhibitors may reach 85%, almost as effective as ECT. Patients with bipolar depression occasionally become manic during treatment with either class of antidepressant drugs. Although a few patients with bipolar disease begin to improve immediately, there usually is a lag of 1-3 weeks before the symptoms of depression begin to improve, and 4-6 weeks are generally required for a full response.
### Table 61-1 Serotonin Receptors

<table>
<thead>
<tr>
<th>Receptors linked to second-message systems</th>
<th>Gene family</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₁A linked to inhibition of adenylyl cyclase</td>
<td>Superfamily of receptors with seven transmembrane regions coupled to G proteins</td>
</tr>
<tr>
<td>5-HT₁B linked to inhibition of adenylyl cyclase</td>
<td></td>
</tr>
<tr>
<td>5-HT₁D linked to inhibition of adenylyl cyclase</td>
<td></td>
</tr>
<tr>
<td>5-HT₁E linked to inhibition of adenylyl cyclase</td>
<td></td>
</tr>
<tr>
<td>5-HT₁F linked to inhibition of adenylyl cyclase</td>
<td></td>
</tr>
<tr>
<td>5-HT₂A linked to phospholipase and PI turnover</td>
<td></td>
</tr>
<tr>
<td>5-HT₂B linked to phospholipase and PI turnover</td>
<td></td>
</tr>
<tr>
<td>5-HT₃ linked to phospholipase and PI turnover</td>
<td></td>
</tr>
<tr>
<td>5-HT₄ linked to stimulation of adenylyl cyclase</td>
<td></td>
</tr>
<tr>
<td>5-HT₅ unknown linkage</td>
<td></td>
</tr>
<tr>
<td>5-HT₆ linked to stimulation of adenylyl cyclase</td>
<td></td>
</tr>
<tr>
<td>5-HT₇ linked to stimulation of adenylyl cyclase</td>
<td></td>
</tr>
</tbody>
</table>

### Receptors linked to an ion channel

5-HT₄

5-HT = 5-hydroxytryptamine (serotonin); PI = Phosphatidylinositolide.

---

**Figure 61-5** The noradrenergic pathways arise in the locus ceruleus. (Adapted from Heimer 1995.)

**A** A lateral midsagittal view demonstrates the course of the major noradrenergic pathways from the locus ceruleus and lateral brain stem tegmentum. The pigmented locus ceruleus, located immediately beneath the floor of the fourth ventricle in the rostral pons, is the best understood noradrenergic nucleus in the brain. Its projections reach many areas in the forebrain, cerebellum, and spinal cord. Noradrenergic neurons in the lateral brain stem tegmentum innervate several structures in the basal forebrain, including the hypothalamus and the amygdaloid body.

**B** A coronal section shows the major targets of neurons from the locus ceruleus. (Adapted from Heimer 1995.)
### Table 61-2 Noradrenergic Receptors Linked to Second-Messenger Systems

<table>
<thead>
<tr>
<th>Type</th>
<th>Second-messenger system</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_1 )</td>
<td>Linked to stimulation of adenylyl cyclase</td>
<td>Cerebral cortex, cerebellum</td>
</tr>
<tr>
<td>( \beta_2 )</td>
<td>Linked to stimulation of adenylyl cyclase</td>
<td>Cerebral cortex, cerebellum</td>
</tr>
<tr>
<td>( \alpha_1 )</td>
<td>Linked to phospholipase C, PI, PKC, DAG, ( \text{Ca}^{2+} ) in peripheral tissues</td>
<td>Brain, blood vessels, spleen</td>
</tr>
<tr>
<td>( \alpha_2 )</td>
<td>Linked to inhibition of adenylyl cyclase</td>
<td>Presynaptic nerve terminals throughout the brain</td>
</tr>
</tbody>
</table>

\( \text{PI} = \text{Phosphatidylinositol; PKC} = \text{Protein kinase C; DAG} = \text{Diacylglycerol.} \)

**Lithium salts**, first reported in the psychiatric treatment of manic-depressive illness in 1949 by John Cade, are effective in terminating manic episodes and are used as mood stabilizers. Moreover, maintenance therapy with lithium is of significant prophylactic value in preventing or attenuating recurrent manic and, to a lesser extent, depressive episodes. Lithium is rarely used by itself for treatment of unipolar depression. However, it is frequently used in conjunction with monoamine oxidase inhibitors, tricyclic compounds, or selective serotonin reuptake inhibitors to augment the response of these conventional antidepressants (see Figure 61-9).

Drugs effective as anticonvulsants (such as sodium valproate and carbamazepine) are also used as mood stabilizers and are quite effective in reducing psychotic symptoms in acute mania or severe depression. Antipsychotic drugs (Chapter 60) are also used frequently in combination with tricyclic drugs, and even with ECT when depression is accompanied by delusions and hallucinations.

**Drugs Effective in Depression Act on Serotonergic and Noradrenergic Pathways**

Drugs effective in treating depression act primarily on the serotonergic and noradrenergic systems of the brain (Chapter 45). The evidence is particularly impressive for serotonin—all selective serotonin reuptake inhibitors tested have been found to be effective against depression. The action of these drugs, therefore, provides the first clues to a neurochemical basis of depressive disorders. The major serotonergic pathways have their origin in the raphe nuclei in the brain stem (Figure 61-4). Cells from the rostral parts of these nuclei project to the forebrain; single serotonergic neurons project to hundreds of target cells in a large, diffuse distribution. (The cells of the caudal part of the raphe nuclei project to the spinal cord.)

The serotonergic receptors are traditionally classified into at least seven major types. Some types decrease adenylyl cyclase, some increase adenylyl cyclase, others are coupled to phosphatidylinositol turnover, and still others are ligand-gated ion channels (Table 61-1).

The noradrenergic pathways originate in the locus ceruleus (Figure 61-5). The axons of some locus ceruleus neurons ascend to innervate the hypothalamus and all regions of the cerebral cortex, including the hippocampus. Other neurons have descending axons that reach the dorsal and ventral horns of the spinal cord. Like serotonergic cells, noradrenergic neurons innervate broad areas and act on a number of receptor types (Table 61-2). Certain components of the noradrenergic system appear to be involved with arousal and fear (Chapter 50), while others are thought to be involved, together with the mesolimbic components of the dopaminergic system, in positive motivation and pleasure (Chapter 51). The pervasive anxiety and loss of pleasure characteristic of melancholia and atypical depression might therefore be related to dysregulation of these two components of the noradrenergic system.

**An Abnormality in Biogenic Amine Transmission May Contribute to the Disorders of Mood**

Norepinephrine is synthesized from tyrosine, and serotonin from tryptophan (Chapter 15). The transmitters are packaged in synaptic vesicles and released into the synaptic cleft by means of exocytosis when the neuron fires an action potential. Both norepinephrine and serotonin interact with postsynaptic receptors, and this activity is limited by active reuptake of the released transmitter into the presynaptic terminals as well as into glial cells. Inside the presynaptic terminals the transmitters are packaged again into vesicles or catabolized primarily by the mitochondrial enzyme monoamine oxidase.

Until recently the consensus view—expressed first in the *catecholamine hypothesis* and then in the more general *biogenic amine hypothesis*—was that depression rep-
### Table 61-3 Effects of Long-Term Administration of Antidepressant Drugs on the Serotonergic System

<table>
<thead>
<tr>
<th>Antidepressant treatment</th>
<th>Responsiveness of somatodendritic 5-HT$_{1A}$ autoreceptors</th>
<th>Function of terminal 5-HT autoreceptors</th>
<th>Function of terminal $\alpha_2$ adrenergic receptors</th>
<th>Responsiveness of postsynaptic receptors</th>
<th>Net serotonin transmission 5-HT receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Decreased</td>
<td>Decreased</td>
<td>NC</td>
<td>NC</td>
<td>Increased</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Decreased</td>
<td>NC</td>
<td>?</td>
<td>NC or decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>5-HT$_{1A}$ receptor agonists</td>
<td>Decreased</td>
<td>NC</td>
<td>ND</td>
<td>NC</td>
<td>Increased</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>NC</td>
<td>NC</td>
<td>ND</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Electroconvulsive shock</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

From Blier and deMontigny 1994; NC = no change; ND = no data; 5-HT = 5-hydroxytryptamine (serotonin).

...presented a decreased availability of either norepinephrine or serotonin or both. Mania was believed to result from the over-activity of noradrenergic systems. This hypothesis was derived from studies of the effects of various drugs on the serotonergic and noradrenergic systems of the brain. The idea originally came from the observation in 1950 that reserpine, a Rauwolfia alkaloid then used extensively in the treatment of hypertension, precipitated depressive syndromes in about 15% of treated patients. Reserpine also produced a depression-like syndrome, with motor retardation and sedation, in animals. Bernard Brodie and his colleagues found that reserpine depletes the brain of serotonin and norepinephrine (as well as dopamine) by inhibiting the uptake of the transmitter into synaptic vesicles in the presynaptic cell, thereby keeping the transmitter in the cytoplasm, where it undergoes degradation by monoamine oxidase (Figure 61-6).

Monoamine oxidase inhibitors, such as isoniazid, were later found to be effective antidepressants. Isoniazid was initially developed in the 1950s to treat tuberculosis. In the course of clinical trials it was noted that some patients who had depression as well as tuberculosis experienced elevations in mood when treated with the drug. Isoniazid was next tried in patients with depression who did not have tuberculosis and was found to be effective. Monoamine oxidase inhibitors increase the concentration of serotonin and norepinephrine in the brain by reducing the degradation of these transmitters by monoamine oxidase. In experimental animals monoamine oxidase inhibitors prevent reserpine's sedative effects on behavior as well as its degradation of cytoplasmic monoamines.

Further support for the view that monoamine oxidase inhibitors act therapeutically by increasing the availability of serotonin and biogenic amines came with the discovery of a second class of effective antidepressants: the tricyclics. These agents block the active reuptake of serotonin and norepinephrine by presynaptic neurons, thereby prolonging the action of these transmitters in the synaptic cleft (see Figure 61-6). Finally, the third group of compounds that proved to be effective in depression, the selective serotonin reuptake inhibitors, affect only serotonin and not norepinephrine. Thus, all three major classes of antidepressants maximize synaptic transmission of serotonin by inhibiting the reuptake of the transmitter or its degradation (Table 61-3). Even electroconvulsive shock increases serotonergic transmission (Table 61-3). It does so by increasing the sensitivity of the 5-HT$_{1A}$ receptors in the hippocampus and increasing the number of 5-HT$_{2A}$ receptors.

The remarkable effectiveness of selective serotonin reuptake inhibitors on depression provides the most compelling evidence that enhancement of serotonergic transmission underlies the therapeutic response to some antidepressant treatments. However, the biogenic amine hypothesis fails to account for a number of important clinical phenomena. In particular, it fails to explain why the clinical response to all antidepressant drugs is so slow after administration of the drugs, whereas the tricyclic agents and the selective serotonin reuptake inhibitors rapidly block the high-affinity reuptake
Figure 61-6 (Opposite) Action of antidepressant and other drugs at serotonergic and noradrenergic synapses.

4. Antidepressant and other drugs have five possible sites of action at serotonergic synapses.

1. Enzymatic synthesis. Both p-chlorophenylalanine and propoxyphene can effectively inhibit the enzyme tryptophan pyrrolase, which converts tryptophan to 5-OH-tryptophan, the precursor of 5-hydroxytryptophan (5-HT, serotonin).

2. Storage. Reserpin and tetrabenazine interfere with the storage mechanism of the amine granules, causing a marked depletion of serotonin.

3. Receptor interactions. These fall into two categories.

a. Autoreceptor 5-hydroxy-diprolamino-tetraline (5-OH-DPAT) is an agonist of the 5-HT receptor. b. Lysergic acid diethylamide (LSD) acts as a partial agonist at postsynaptic serotonergic receptors in the central nervous system. A number of specific compounds are now candidates to act as receptor-blocking agents at various serotonergic synapses.

4. Reuptake. Tricyclic drugs with a tertiary nitrogen, such as imipramine and amitriptyline, inhibit the reuptake of serotonin into the presynaptic terminal and thus increase the efficacy of transmission. Fluoxetine and sertraline are even more selective inhibitors of serotonin uptake.

5. Degradation by monoamine oxidase (MAO). Iproniazid and dorgline are effective inhibitors of MAO, which is located in the outer membrane of mitochondria and can degrade serotonin present in a free state within the presynaptic terminal. 5-HIAA = 5-hydroxyindoleacetic acid.

8. Antidepressants and other drugs have seven possible sites of action at noradrenergic synapses.

1. Enzymatic synthesis. a. The competitive inhibitor a-methyltyrosine blocks the reaction catalyzed by tyrosine hydroxylase. b. A dithiocarbamate derivative, FLA 63, blocks the reaction catalyzed by dopamine 3-hydroxylase, which converts DOPA to dopamine.

2. Storage. Reserpin and tetrabenazine interfere with the reuptake-storage mechanism of the amine granules. The depletion of norepinephrine (NE) by reserpin is long-lasting and the storage granules are reversibly damaged, causing permanent depletion of NE available for release transmission. Tetrabenazine also interferes with the reuptake of free cytoplasmic NE into the granules.

3. Release. Amphetamine appears to cause an increase in the net release of NE, most likely because of its ability to block the reuptake.

4. Receptor interaction. a. Clonidine is a very potent alpha-adrenergic agonist. b. Phenoxymethylamine and phenotolamine are effective alpha-adrenergic blocking agents. Recent experiments have indicated that these drugs also have a presynaptic site of action.

5. Degradation by COMT. Tropoline inhibits COMT, which deactivates NE. COMT is believed to be localized outside the postsynaptic neuron.

6. Reuptake. The tricyclic drug desipramine is a potent inhibitor of the reuptake of NE into the presynaptic terminal. As a result, NE remains in the synapse longer and has a greater postsynaptic effect.

7. Degradation by monoamine oxidase (MAO). Pargyline is an effective inhibitor of MAO, which appears to be localized in the outer membrane of mitochondria and can degrade the NE present in a free state within the presynaptic terminal. Noradrenaline (NM) is formed by the action of the enzyme catechol O-methyltransferase (COMT) on NE.

Systems. This blockade is much more rapid than the clinical response. If the clinical response is a result of an increase in serotonergic synaptic transmission, what accounts for the delay in the response? In addition, the tricyclic drugs vary widely in their relative ability to block serotonin or norepinephrine reuptake, yet their clinical efficacy in patients with depression is about the same. Finally, in some patients with depression the onset of the illness is associated not with a decrease but with an increase in the level of norepinephrine in spinal fluid and plasma, and treatment leads to a reduction to a normal level.

Some clues are emerging that may help to resolve these issues. For example, it is now clear that antidepressant agents affect processes other than the reuptake and accumulation of serotonin. In addition to their rapid biochemical effects on reuptake, both monoamine oxidase inhibitors and tricyclic antidepressants produce a delayed but long-term increase in the sensitivity of serotonin receptors. Conversely, the selective serotonin reuptake inhibitors produce a delayed decrease in the sensitivity of 5HT1A and 5HT1B inhibitory autoreceptors on many serotonergic cells, leading to increased release of serotonin. Both of these actions lead to a slow increase in the effectiveness of serotonergic synaptic transmission.

Given these findings, where does the biogenic amine hypothesis stand? The initial, simple form of the biogenic amine hypothesis, which states that reduction of biogenic amines leads to depression and elevation to mania, is no longer valid. There probably is no simple relationship between biogenic amines and depression. If a relationship exists at all, which seems likely, it is complicated by three factors.

First, the subtypes of major depression are most likely not single disorders, but a group of disorders with several underlying pathologies. Second, disturbances in one of several transmitter systems can lead to depression. Finally, the various modulatory systems of the brain—the serotonergic, dopaminergic, and adrenergic systems—do not function independently of each other but rather interact at several levels. Specifically, the distribution of the serotonergic system overlaps with and interacts with the noradrenergic system. Moreover, receptors for the two amines exist on the same neurons, and there is cross-talk between second messengers activated by these transmitters. Long-term administration of antidepressants fails to downregulate the beta-adrenergic receptors when serotonergic systems have been eliminated experimentally.

In addition, antidepressants act on the cholinergic and GABA-ergic systems. Cholinergic neurons excite the noradrenergic cells of the locus ceruleus through
Figure 61-7  The exact therapeutic action of lithium, used to treat bipolar depression, is unknown. However, lithium has been shown to affect the phosphoinositide second-messenger system. Many synaptic receptors act through a G protein to mediate the conversion of phosphoinositide diphosphate (PIP2), a membrane lipid, into diacylglycerol (DAG) and inositol triphosphate (IP3). IP3 is further broken down to inositol phosphate (IP), which is then converted to free inositol by the enzyme inositol-1-phosphatase. Lithium blocks this enzyme and therefore reduces the responsiveness of these neurons by causing IP3 to accumulate in the cytoplasm. The roles of IP3 and protein kinase C are discussed in Chapter 13.

Muscarnic receptors, and cholinergic agonists can induce depression. Indeed, patients with a history of depression tend to be hyperresponsive to cholinergic agonists, even when their mood is normal.

Since most serotonergic and adrenergic receptors act on second-messenger pathways—activating or inhibiting adenyl cyclase or stimulating phosphoinositide turnover—it is perhaps not surprising that drugs acting directly on these pathways are now being developed. For example, lithium salts, which are highly effective in bipolar disorder, block the enzyme inositol-1-phosphatase, which recycles inositol triphosphate back to inositol. This results in a buildup of inositol 1,4,5-triphosphate (IP3), which is known to be active in regulating intracellular Ca2+ levels. Inhibition of this enzyme is thought to reduce the responsiveness of those neurons with transmitter receptors coupled to the IP3 pathway (Figure 61-7). This could be the way lithium acts therapeutically, perhaps by dampening excessive neural activity in mania.

Unipolar Depression May Involve Disturbances of Neuroendocrine Function

As first pointed out by Edward Sachar, depression is associated with clinical signs of hypothalamic disturbance. The best-understood hypothalamic disturbance in severe depression is neuroendocrine and is reflected in excessive secretion of adrenocorticotropic hormone (ACTH) by the pituitary, leading to excessive secretion of cortisol from the adrenal cortex. The hypersecretion of ACTH is so great that enlargement of the adrenal gland can be detected on computerized axial tomography (CAT) scans of some patients with depression.

In normal people the secretion of cortisol follows a circadian rhythm; secretion peaks at 8:00 AM and is relatively lower in the evening and early morning hours. This circadian cycle is disturbed in about one-half of patients with depression, who secrete excessive amounts of cortisol throughout the day (Figure 61-8). The disturbance is not dependent on stress and is not found in other psychiatric disorders. Cortisol secretion returns to normal with recovery.

Philip Gold and his colleagues found that the increased secretion of cortisol results from hypersecretion of corticotropin-releasing hormone (CRTH) from the hypothalamus, and that the level of CRTH correlates positively with depression. Release of CRTH is stimulated by norepinephrine and acetylcholine, and release of CRTH induces anxiety in experimental animals. Thus, Gold and his colleagues have suggested that CRTH and the noradrenergic system may reinforce one another.

Hypersecretion of cortisol is sometimes resistant to feedback suppression by the potent synthetic corticosteroid dexamethasone, which depresses secretion of adrenocorticotropin. The dexamethasone suppression test has been used to diagnose depression because in at least 40% of rigorously diagnosed patients with depression the hypersecretion of cortisol is resistant to feedback suppression by dexamethasone. However, the test is not specific; dexamethasone suppression is also abnormal in patients who have dementia, anorexia nervosa, bulimia, alcohol withdrawal, or weight loss.

There Are at Least Four Major Types of Anxiety Disorders

Just as grief is a normal response to personal loss, anxiety is a normal response to threatening situations. Perceived threats that generate anxiety may be active and direct or indirect, such as the absence of people or ob-
jects that represent security. Anxiety is adaptive; it signals potential danger and can contribute to the mastery of a difficult situation and thus to personal growth. Excessive anxiety, on the other hand, is maladaptive, either because it is too intense or because it is inappropriately provoked by events that present no real danger. Thus, anxiety is pathological when excessive and persistent, or when it no longer serves to signal danger.

The key feature of anxiety disorders is increased fearfulness accompanied by subjective as well as objective manifestations. The subjective manifestations range from a heightened sense of awareness to a deep fear of impending disaster and death. The objective manifestations are a racing heart, avoidance behavior and signs of restlessness, heightened responsiveness, palpitations, tremor, sweating, increased blood pressure, dry mouth, and a desire to run or escape. Depression and anxiety often occur together.

Anxiety disorders are the most common psychiatric disorders, found in 10–30% of the general population. Anxiety disorders can be subdivided into several types based on clinical characteristics and response to psychopharmacologic agents. These major categories include panic disorder, post-traumatic stress disorder, (PTSD), generalized anxiety disorder, social phobia, and obsessive-compulsive disorder (OCD).

Panic Attacks Are Brief Episodes of Terror

Panic attacks are brief, recurrent, unexpected episodes of terror without a clearly identifiable cause. The attacks are usually brief, most commonly lasting 15–30 minutes; occasionally, but only rarely, they last up to an hour. An essential feature of these attacks is that they are unexpected. They do not occur in situations that normally evoke fear or in which the patient is the focus of other people’s attention. The attacks are characterized by a sense of impending doom accompanied by an intense over-activity of the sympathetic nervous system (referred to as a sympathetic crisis): The heart races, there is shortness of breath; dizziness; trembling or shaking of the hands and legs; flushes or chills; chest pain; and fear of dying, or of going crazy, or of doing something uncontrolled. Shortness of breath is characteristic of panic attacks but not of the acute terror evident in battle, suggesting that panic attacks may represent a false alarm for suffocation.

When panic attacks recur the resulting syndrome is called panic disorder. Attacks recur over a period ranging from months to several years and are often experienced several times a week. Panic disorders usually begin in adolescence.

An interesting aspect of panic attacks is that they can be induced in some patients who have this disorder, but not in most normal subjects, by the infusion of sodium lactate into the blood or the inhalation of carbon dioxide. Thus, sodium lactate infusion provides an approach for studying the mechanism underlying this disorder because the onset of an attack can be timed precisely. Moreover, regular use of antidepressants that are effective against spontaneous panic attacks also prevent the panic induced by the infusion. Similarly, yohimbine, a drug that activates central noradrenergic neurons (by blocking the α2 adrenergic receptors that serve as inhibiting autoreceptors), precipitates panic attacks in patients but not in normal subjects, indicating that panic attacks involve an abnormality in the biogenic amine system of the brain.

A significant proportion of patients with panic disorders have a genetic predisposition. Half of patients
with panic attacks also have depression, a finding that has led to the suggestion that panic attacks may be a variant of depressive illness or a precursor to it. This is consistent with the initially surprising finding that panic disorder is successfully treated with both tricyclic antidepressants and monoamine oxidase inhibitors. Now that more is known about the function of the locus ceruleus, this finding is perhaps less surprising. The noradrenergic cells in this nucleus respond most effectively to stimuli that produce intense fear. In fact, cognitive therapy for panic attacks trains patients not to act on their autonomic signals.

Post-Traumatic Stress Disorder Reflects Persistent Traces of Anxiety That Follow Traumatic Episodes

An interesting variant of panic attacks is post-traumatic stress disorder. Although now appreciated as fairly common, this disorder was not clearly recognized in its present form until the 1980s. Post-traumatic stress disorder occurs in people after an extremely stressful event, such as life-threatening combat or physical abuse. It is manifested in recurrent episodes of fear, often triggered by reminders of the initial trauma. One of the most striking features of this disorder is that the memory for the traumatic experience remains powerful for decades and is readily reactivated by a variety of stimuli and stressors. This is thought to be due to the recruitment of the noradrenergic system by these reactivating stimuli. As we shall learn in Chapter 63, biogenic amines are important in modulating various memory processes.

Vietnam War veterans with post-traumatic stress disorder show heightened noradrenergic functioning. They excrete high levels of norepinephrine in their urine, presumably reflecting high circulating catecholamine levels. When exposed to gunfire or other stimuli associated with combat, these veterans respond with dramatic increases in blood pressure and heart rate. When patients with post-traumatic stress disorder are given yohimbine, they experience a type of panic attack: An intense memory is accompanied by autonomic symptoms (increase in blood pressure and heart rate) and an increase in the core symptoms, such as frightening thoughts, emotional numbing, and grief.

These manifestations are all consistent with the idea that uncontrollable stress produces substantial increases in noradrenergic functioning in the brain. Propranolol and clonidine, which act to decrease noradrenergic transmission, greatly ameliorate the symptoms of post-traumatic stress disorder. Interestingly, a large percentage (about 50%) of patients with post-traumatic stress disorder also show a concurrent panic disorder.

Generalized Anxiety Disorder Is Characterized by Long-Lasting Worries

The key feature of generalized anxiety disorder is unrealistic or excessive worry, lasting not minutes but continuously for six months or longer. The symptoms are motor tension (trembling, twitching, muscle aches, restlessness), autonomic hyperactivity (palpitations, increased heart rate, sweating, cold hands), and vigilance and scanning (feeling on edge, exaggerated startle response, difficulty in concentrating). The disorder sometimes follows an episode of depression.

One group of drugs that is particularly effective in treating generalized anxiety disorder is the benzodiazepines, such as chlordiazepoxide (Librium) and its derivative, diazepam (Valium). Benzodiazepines produce their therapeutic effect by enhancing the activity of the GABA_A receptor. GABA is the major inhibitory transmitter in the brain (Chapter 12). The GABA_A receptor opens Cl^- channels and the resulting influx of Cl^- hyperpolarizes and thus inhibits target cells. Benzodiazepine increases the affinity of the receptor for GABA, resulting in an increase in Cl^- influx through the Cl^- channels and thereby prolonging the synaptic inhibition produced by GABA (Figure 61-9).

The GABA_A receptor has separate binding sites for GABA, barbiturates, and benzodiazepines (Chapter 11). The protein is allosteric; binding of any one of the three ligands (GABA, benzodiazepine, or barbiturate) influences the binding of the other two and facilitates GABA's action. In particular, GABA will bind more tightly when a benzodiazepine also is bound to its site on the receptor. Nevertheless, all three sites are distinct. Analysis of the primary structure of the GABA receptor indicates that there are at least three subunits (α, β, γ); benzodiazepine binds to the γ subunit.

The calming effects of benzodiazepines are therefore best explained by an enhancement of certain of the inhibitory effects of GABA. Inverse agonists of benzodiazepine reduce rather than enhance GABA-ergic transmission and produce anxiety as well as predisposition to convulsions. Yet these inverse agonists bind to the benzodiazepine site on the GABA receptor and are blocked by benzodiazepine antagonists.

This has raised the possibility that endogenous inverse agonists might mediate naturally occurring anxiety states. High concentrations of GABA receptors have been found in the limbic system, specifically in the amygdala, an area thought to be of central importance for emotional behavior. However, as with other mental illnesses, it is unlikely that a single transmitter system is responsible for the illness. In fact, many patients with anxiety states respond extremely well to selective serotonin reuptake inhibitors and tricyclic antidepressants.
Figure 61-9 Benzodiazepines act on the GABA channel.

A. Structural model of the GABA<sub>δ</sub> chloride channel. The channel protein contains at least five different subunit types, of which only three are illustrated here (α, β, γ). Benzodiazepines bind to the γ subunits, GABA to the α subunit, and barbiturates to the β subunit. All the subunits contribute to forming the Cl⁻ channel. When GABA binds to GAB<sub>α</sub> receptors the Cl⁻ channels open and the influx of Cl⁻ hyperpolarizes the cell.

B. Diazepam, a benzodiazepine, is an effective drug in treating generalized anxiety disorders. The traces compare the responses of a mouse spinal cord neuron to GABA, the major inhibitory neurotransmitter in the brain, and to GABA in the presence of diazepam. Diazepam increases the affinity of the receptor for GABA and thus increases the Cl⁻ conductance and the hyperpolarizing current.

C. Benzodiazepine (Benzo) modulates Cl⁻ flux through the channel by enhancing the effect of GABA, which itself enhances the influx of Cl⁻ into the nerve cell. As a result, basal levels of GABA become more effective in gating the channel. Benzodiazepine antagonists prevent enhancement of GABA effects but do not reduce the basal conductance of Cl⁻. GABA antagonists prevent gating of Cl⁻ channels in spite of the presence of benzodiazepines.

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In Obsessive-Compulsive Disorder Obsessive Thoughts Are a Source of Anxiety and Compulsion

Obsessive-compulsive disorders are usually chronic disorders with recurrent obsessions and compulsions as the predominant features. Obsessions are persistent and intrusive ideas, thoughts, images, or impulses that commonly fall into one of two categories: doubts or fears. Obsessive doubting can penetrate daily life, leaving patients repeatedly unsure whether the apartment door was locked, whether the stove was turned off, or whether their hands are clean enough. This preoccupation can result in excessive hand washing, sometimes to the extent of soreness or removal of skin. Obsessive fears focus on unrealistic and improbable dangers, such as the prospect of killing someone driving a car or lighting the stove. Interestingly, the person experiencing these fears typically views them as alien—senseless and unwanted invasions of consciousness. When the fears first become prominent, the patient attempts to ignore or suppress them, usually unsuccessfully. Later in the course of the illness the patient may no longer actively resist these fears.

To alleviate the anxiety and diminish the discomfort of the obsessive thoughts or urges, the patient often begins to carry out compulsive acts. In contrast to obsessions, which are repetitive ideas, compulsions are repetitive acts. To be defined as a compulsion a behavior must be repeated excessively and the repetition must not be realistically related to any environmental condition. The most common compulsions are handwashing, counting, checking, touching, and pulling out of hair.

The severe symptoms of obsessive-compulsive disorder are thought to represent the extreme end of a behavioral continuum that includes a compulsive lifestyle that typically begins between 18 and 25 years of age. Although the symptoms may disappear or become less severe for periods of time, the disorder rarely disappears.
Indeed, people with obsessive-compulsive disorder may also have other mental illness, such as depression, other anxiety disorders (panic attacks, eating disorders), or social phobias.

Obsessive-compulsive disorder is thought to reflect a disturbance of the basal ganglia. In fact, some forms of obsessive-compulsive disorder seem to be related to Tourette syndrome, a hereditary chronic motor tic disorder that has its locus in the basal ganglia. Patients with Tourette syndrome erupt in repetitive grunts, noises, and even obsessions that are not under the patient’s control. Several other neurological syndromes that involve the basal ganglia, such as postencephalitic Parkinson disease, Sydenham chorea, bilateral necrosis of the globus pallidus, and Huntington disease, often are associated with a component of obsessive-compulsive disorder.

The head of the caudate nucleus and the pathway that connects the caudate with the prefrontal (orbitofrontal) cortex and cingulate gyrus seems to be hyperactive in obsessive-compulsive disorder. The caudate nucleus sends GABA-ergic inhibitory projections to the globus pallidus (one of the two major output elements of the striatum), which sends inhibitory projections to the thalamus, which then projects to the orbitofrontal cortex. The presence of serial inhibitory pathways—from the caudate nucleus to the globus pallidus, and from there to the thalamus—suggests the possibility that a disease state produces a disinhibition, which could lead to reverberating activity in this circuit. Perhaps an increase in the first inhibitory pathway causes the second pathway to become less of an inhibitor of its targets, leading to the reverberatory state.

Obsessive-compulsive disorder is responsive to two types of treatments: (1) specific behavioral therapies based on conditioning (Chapter 62) and (2) specific serotonin reuptake inhibitors. The effectiveness of the serotonin reuptake inhibitors raises two questions: Is central serotonergic transmission abnormal in obsessive-compulsive disorder and, if so, can psychotherapy reverse this effect? In fact, serotonergic innervation of the striatum is extensive. This innervation is localized to the medial-ventral aspects of the head of the caudate nucleus and to the nucleus accumbens, regions that receive input from the orbitofrontal and cingulate cortex regions thought to be involved in emotional behavior. Surgical lesions of these tracts from the frontal cortex to subcortical sites has improved the symptoms of some otherwise intractable cases. After effective treatment of the disease with either serotonin reuptake inhibitors or behavioral therapy, hyperactivity of the caudate nucleus and orbitofrontal cortex decreases significantly (Figure 61-10). This suggests that psychotherapy and pharmacologic therapy lead to a similar biological change.

An Overall View

Certain major depressive illnesses may be the result of genetically determined defects in chemical synaptic transmission involving at least two major transmitter pathways of the brain: the serotonergic and noradrenergic systems. Although the mechanisms that cause the defects in transmission remain obscure, progress in studying allelic variations in the human genome provide hope that aspects of the molecular basis of affective disorders might soon be elucidated.

Because there are good animal models of anxiety and we now know a great deal about the amygdala and the neural circuitry in learned fear, it is likely that anxiety may soon be better understood. Like major depression and schizophrenia, two types of anxiety—panic disorder and generalized anxiety disorder—seem to reflect alterations in synaptic functioning. Since panic disorder responds well to certain antidepressants, it too may reflect an abnormality in the biogenic amine pathways of the brain. In contrast, generalized anxiety disorder may involve the GABA_α receptor system, or more likely an abnormality in the interaction of the GABA_α receptor and the serotonergic system.
Perhaps the most powerful insight into obsessive-compulsive disorders is the finding that psychotherapy and selective serotonin reuptake inhibitors are equally effective in reversing the symptoms and in so doing they also reverse the anatomical abnormalities.

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Selected Readings

References