CHAPTER

13

Antidepressants

THE NATURE OF DEPRESSION

From time to time, we all feel sad or "depressed" as a result of things that happen to us or to those we love, but this condition is not usually accompanied by physical symptoms, and it does not last. For some people, depression is much more serious; there may be no apparent cause in their environment, but their depression is deep, and either it does not go away or it keeps returning for no obvious reason. These people may also experience a loss of appetite, loss of interest in normally pleasurable activities (this is called *anhedonia*), lack of energy, problems sleeping, exaggerated feelings of worthlessness and guilt, and haunting thoughts of death and suicide. The symptoms just described are typical of a *major depressive episode*, which is the defining feature of *major depressive disorder*. Major depressive disorder, or more colloquially *depression*, is currently categorized in the *DSM-IV-TR* as a *mood disorder*, and Box 13-1 presents a summary of the *DSM-IV-TR* symptoms for major depressive episode.

As you learned in Chapter 5, the American Psychiatric Association plans to publish a new edition of the *DSM* (the *DSM-5*) in 2013. The *DSM-5* will include revisions to the diagnostic criteria for major depressive episode (see the *DSM-5* Web site at: www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=427#). One proposed revision is the removal of criterion E, related to symptoms of bereavement. This decision is based on findings that depression brought on by bereavement is similar to depression triggered by any other stressful experience. Failure to acknowledge, diagnose, or treat depression because it stems from the loss of a loved one is therefore inappropriate (Kendler, Myers, & Zisook, 2008).

Individuals who chronically experience a mildly depressed state but do not meet the full criteria for major depressive episode may be diagnosed with *dysthymic disorder*. An additional proposed change for the *DSM-5* is to split and rename the mood disorders category, shifting major depressive disorder and dysthymic disorder into a new category called *depressive disorders*.

Another interesting characteristic of depression is that it can occur in persons who do not actually feel depressed. Often older people show many of the physical symptoms of depression—insomnia, weight loss, and so on—but do not seem to feel sad. They may, however, show anhedonia. This type of depression can also be treated with antidepressant medications.

Traditionally, mild depression was labeled *neurotic depression*, and serious depression accompanied by physical symptoms was considered a *psychosis*. *DSM-IV-TR* no longer makes this distinction or considers depression to be psychotic, but it does recognize that depression may be associated with schizophrenia. In such cases, the depressed person will also exhibit hallucinations, delusions, or other symptoms of psychosis.

Recorded accounts of depression span millennia, from the ancient Greeks to contemporary cultures and societies. Because large segments of the population experience

BOX 13-1 *DSM-IV-TR* Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest in pleasure.
   1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
   2. markedly diminished interest in pleasure in all, or almost all, activities most of the day, nearly every day
   3. significant weight loss when not dieting or weight gain (e.g., a change of more than 5% body weight in a month) or decrease or increase in appetite nearly every day
   4. insomnia or hypersomnia nearly every day
   5. psychomotor agitation or retardation nearly every day
   6. fatigue or loss of energy nearly every day
   7. feelings of worthlessness or excessive or inappropriate guilt nearly every day
   8. diminished ability to think or concentrate, or indecisiveness, nearly every day
   9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet the criteria for a Mixed Episode.*

C. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. Symptoms are not due to direct physiological effects of a substance (e.g., a drug of abuse or medication) or a general medical condition.

E. Symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

*A mixed episode is where both manic and depressive symptoms occur at the same time.

Source: Reprinted with permission from American Psychiatric Association. © 2000, *DSM-IV-TR* Criteria for a Major Depressive Episode.

it at some time in their lives, depression has been called the "common cold of mental illness". In Western cultures, depression is ever more prevalent in each generation since World War II. The World Health Organization is projecting that, by the year 2030, depression will be the leading cause of premature mortality and disability leading to loss of productive life; currently, it is the second leading cause. In the United States, Canada, and Europe, approximately 13 to 17% of the population will experience depression at some point in their lifetime (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). The prevalence is much lower in Eastern cultures, such as Korea or Taiwan, where depression estimates are approximately 4% (Chang et al., 2008).

Women are twice as likely as men to suffer depression (depression affects approximately 24% of women and 12% of men), and the symptoms of depression also typically differ between the genders. Women with depression are more likely to have feelings of sadness, worthlessness, and excessive guilt whereas, men are more likely to be very tired and irritable, lose interest in once-pleasurable activities, and have difficulty sleeping (Cochran & Rabinowitz, 2000). Men may be more likely than women to turn to alcohol or drugs when they are depressed. They also may become frustrated, discouraged, irritable, angry, and sometimes abusive. Compared to the general population, there is an increased overall mortality rate for depressed people, and the probability of suicide is estimated to be five times greater (Bostwick & Pankratz, 2000). More than 90% of individuals who attempt suicide and 60% of those who commit suicide suffer from some form of mood disorder (Beautrais et al., 1996). Although women report more thoughts and attempts at suicide, men more often die of suicidal injuries.

THEORIES OF DEPRESSION

Monoamine Theory of Depression

It has been known for some time that mood is related to the functioning of the monoamines, in particular, serotonin (5-HT) and norepinephrine (NE), although dopamine (DA) may also play a role. Recall that all of the monoamine neurotransmitters have centers in the midbrain or upper brainstem and send projections forward to various parts of the limbic system and the forebrain through the *medial forebrain bundle*: (a) NE fibers that arise in the *locus coeruleus* in the midbrain, (b) serotonergic fibers that originate in areas of the *raphe system*, and (c) dopaminergic fibers of the mesocorticolimbic system that originate in the *ventral tegmental area*.

The *monoamine theory* of depression, in its original form, suggested that depression was a result of reduced levels of activity in these monoamine systems. The theory was supported by observations that changing monoamine activity levels affected mood. Drugs like cocaine or amphetamine that enhance monoamine neurotransmission make people feel good. Alternatively, decreased transmission at monoamine synapses is associated with depression. Depression is the most common psychiatric condition in individuals with Parkinson's disease, which is marked by severe depletion of dopamine (Ravina et al., 2009). The drug reserpine, which was once used to treat high blood pressure, depletes monoamines by blocking the activity of vesicular transporter proteins that reside in the axon terminals where they fill synaptic vesicles with monoamines. Coincidently, individuals administered reserpine showed improvement in their hypertensive symptoms but developed severe depression (reserpine is no longer prescribed). Similarly, depleting 5-HT by ridding its amino acid precursor, tryptophan, from the body also produces depression. All of these findings support the monoamine theory of depression.

There are, however, some observations that cannot be explained by the monoamine theory, as it originally existed. For example, we know that antidepressant medications produce an immediate physiological effect. That is, as soon as the drug reaches monoamine synapses, it increases transmitter levels. But, as with antipsychotic medications, there is a substantial problem. The effect on monoamine activity is immediate, but antidepressants need to be taken continuously before any relief from depression is felt. This lag time between the start of antidepressant treatment and any alleviation of depressive symptoms can be 4 to 6 weeks and perhaps up to 12 weeks by the time antidepressants reach their full effectiveness. In the context of the original monoamine theory, which simply stated that depression is a result of diminished monoamine activity, this does not make sense. Another finding that cannot be explained by the original monoamine theory is that the above-mentioned correlation between tryptophan depletion and depression does not hold true for everyone. In individuals with no personal or family history of depression, tryptophan depletion has no effect on mood (Riedel, Klaassen, & Schmitt, 2002). This suggests that other physiological differences must exist between those individuals who are susceptible to depression and those who are not. Therefore, the monoamine theory, in its simple form, is no longer tenable—the neurophysiological changes associated with depression are much more complicated than first thought. A wealth of research has advanced our understanding of the role monoamines play in mood disorders, and the monoamine theory in its updated form, as described later, continues to receive much support and attention.

All of the three monoamines are probably involved in some aspect of mood, and they interact with each other in complex ways, but the monoamine that has received the most focus in the past couple of decades is serotonin. Decreased activity in the serotonin system, although it may not be the direct cause of depression, certainly appears to play a role in vulnerability to depression. Many lines of research support this idea. For example, individuals diagnosed with major depressive disorder have low cerebrospinal-fluid levels of 5-HT, its amino acid precursor tryptophan, and its major metabolite 5-H1AA. Below-normal levels of 5-H1AA also correspond with a nearly fivefold increase in suicide risk (Pompili et al., 2010). Treatments that have been shown to be effective in relieving depression ultimately increase transmission at serotonin synapses.

SPECT imaging data indicate that depressed individuals also exhibit decreased numbers of 5-HT reuptake transporter proteins in the brainstem (Malison et al., 1998). At first glance, this appears counterintuitive. Because reuptake transporter proteins rid 5-HT from the synapse, a reduction in their quantity would seem like a protective mechanism, decreasing vulnerability to depression. Moreover, antidepressants such as the SSRIs

are effective because they inhibit the action of serotonin reuptake transporter proteins; with chronic treatment, SSRIs significantly reduce (i.e., by 30–40%) the amount of 5-HT transporter protein mRNA in the raphe nuclei (Lesch et al., 1993).

To understand this finding, we must consider the bigger picture—what this deficiency in 5-HT transporter proteins actually illustrates. Quite possibly, it indicates a pathological reduction in the sheer number of serotonin neurons (upon which the transporter proteins reside). Even a slight reduction in the number of raphe serotonergic neurons would translate into an exponentially greater loss of 5-HT release in projection areas, such as the cortex. It may also be an indication of a more widespread dysregulation of serotonin system function. In support of this explanation, genetic research has isolated a portion of a gene, found on chromosome 17, responsible for 5-HT transporter protein production. This portion of the gene, called a *promoter region*, regulates the number of 5-HT transporter proteins that get made. It comes in two forms—long and short. Possessing the short form of this portion of gene is associated with having significantly fewer 5-HT transporter proteins and a heightened risk of developing depression, whereas possessing the long form appears to create a protective effect. Finally, a reduction in 5-HT reuptake transporter protein quantity could indicate a compensatory mechanism, an attempt by neurons to overcome a preexisting state of synaptic 5-HT hypoactivity by reducing 5-HT reuptake activity (Malison et al., 1998).

Depressed individuals also exhibit abnormalities in the functioning and quantity of 5-HT receptors, particularly for the 5-HT_{1A} receptor subtype. Much of this evidence comes from PET imaging studies that measure the *binding potential* of 5-HT_{1A} receptors. Differences in receptor binding potential could indicate an upregulation or downregulation in the density of receptors present on neurons, a change in the sensitivity of the receptors to neurotransmitter molecules, or it could indicate an increase or decrease in the presence of neurons containing those receptors. This area of research is hotly debated because some evidence suggests increases and some suggests decreases in 5-HT_{1A} receptor binding potential in depression. The debate may be, at least in part, due to the different brain regions analyzed by researchers and to the varying roles 5-HT plays in those brain regions.

Remember that 5-HT_{1A} receptors act, not only as postsynaptic receptors, but also as autoreceptors. In the raphe nuclei, 5-HT_{1A} receptors are mostly autoreceptors, located on the presynaptic neuron. Stimulation of those receptors inhibits cell firing and reduces 5-HT activity. In other brain regions, such as the hippocampus, hypothalamus, amygdala, and cortex, 5-HT_{1A} receptors are located postsynaptically. Stimulation of those receptors increases serotonin neurotransmission. Changes in the sensitivity or number of 5-HT_{1A} receptors could result from genetic makeup, rendering the individual more vulnerable to depression. Or, these changes might represent an adaptive response to depression—a way for the brain to compensate for abnormal levels of serotonin activity, perhaps triggered by some physiological or environmental event. As you can see, when it comes to serotonin and depression, it is very difficult to tease apart cause and effect among the myriad of influencing variables.

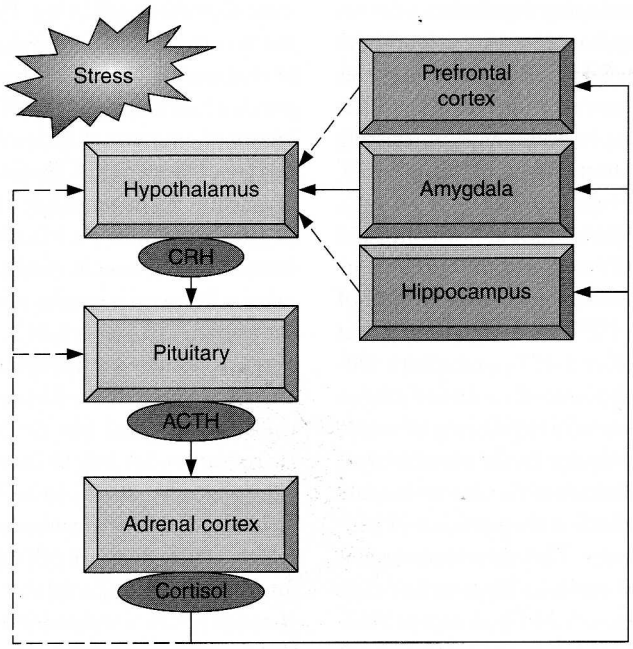
The increase in serotonin transmission produced by antidepressant medications appears to be a necessary, but not sufficient, condition for alleviating depression. It is believed that, in serotonergic synapses at least, increased levels of transmitter do not result in an immediate increase in cell firing. The presynaptic cell, through the action of autoreceptors, detects excessive amounts of transmitter in the cleft brought about by the antidepressant medication. When the autoreceptor detects increased amounts of transmitter, it actually inhibits the release of more 5-HT (typically by reducing the influx of calcium at the terminal). Thus, acute administration of reuptake inhibitors like the SSRIs does not cause an immediate increase in conduction at 5-HT synapses. It takes a few weeks for the autoreceptors to habituate to the presence of excess 5-HT, and only then does serotonergic conduction at the synapse actually increase. With chronic treatment, antidepressants are able to enhance the sensitivity and functioning of 5-HT_{1A} postsynaptic receptors, leading to increased monoamine activity (Drevets et al., 2007). In addition, there is a downregulation and desensitization of 5-HT_{1A} autoreceptors, which acts to decrease cell inhibition resulting from the antidepressant-induced rise in monoamine levels and thereby enhance monoamine neurotransmission. The delay experienced with other classes of antidepressants may result from similar adjustment mechanisms.

The bulk of evidence supports the theory that depression is a result of diminished activity in the 5-HT

system in the brain, which runs from the raphe nuclei through the medial forebrain bundle to the forebrain. The situation is very complicated, however, and many other explanations of depression exist. In the mid-1990s, antidepressant medications that target both serotonin and norepinephrine were introduced. Like 5-HT, NE activity is also dysregulated in depression, and more recently developed antidepressants target the NE system. In addition, altered transmission of serotonin, and perhaps even norepinephrine and dopamine, may be caused by, and may in turn cause changes in, activity of other transmitter systems—even some that do not use monoamines. Alternate theories of depression cite the importance of different neurotransmitters, such as GABA, acetylcholine, opioid peptides, and cannabinoids, and the balance achieved among levels of these neurotransmitters (Uppal, Singh, Gahtori, Ghosh, & Ahmad, 2010). Activity at monoamine synapses may in fact be only one link in a long and complex chain of neurological deficiencies that cause mood disorders. Still other theories suggest the involvement of second messengers, biological rhythms, hormone levels, and the immune system. Among these, one theory that has garnered substantial support and warrants attention is a theory based on stress—the glucocorticoid theory of depression.

Glucocorticoid Theory of Depression

A system that has become a major focus of depression research is the *hypothalamic–pituitary–adrenal* (HPA) axis, illustrated in Figure 13-1. It is an important part of the neuroendocrine system that controls the body's response to stress. Stress is the most influential environmental factor that predisposes an individual to depression, so it is not surprising that research would veer in this direction. The HPA-axis response to stress is organized hierarchically so that the physiological changes that take place are like a domino effect. The stress response starts in the hypothalamus where neurons



Solid lines indicate stimulation; Dashed lines indicate inhibition
CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone

FIGURE 13-1 The hypothalamic–pituitary–adrenal axis and connections.

secrete corticotropin-releasing hormone (CRH). The release of CRH, in turn, initiates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which ultimately stimulates the secretion of glucocorticoids (cortisol in humans) from the cortex of the adrenal glands, which sit above the kidneys.

The stress response is important for our survival since it mobilizes us for fight or flight and helps us escape danger. Once a stressful experience ends, the HPA-axis response must be terminated. This is achieved through a series of negative-feedback loops—cortisol binds to glucocorticoid receptors in the pituitary, hypothalamus, and especially in the hippocampus, which then sends a signal to the hypothalamus to stop releasing CRH. In individuals who experience frequent or chronic stress, the HPA axis may become overactive. Animal research suggests that chronic-stress-induced hyperactivity of the HPA axis is due, at least in part, to a downregulation of glucocorticoid receptors in the hippocampus (Meyer, van Kampen, Isovich, Flügge, & Fuchs, 2001). Overactivity of the HPA axis, indicated by high levels of CRH and cortisol, is a frequent finding in patients with major depressive disorder and in suicide victims (Paez-Pereda, Hausch, & Holsboer, 2011).

Neurons that contain CRH are present, not only in the hypothalamus, but also in areas of the limbic system. Recall that the limbic system plays an important role in emotion and mood. One such limbic area is the prefrontal cortex, which, like the hippocampus, contains receptor sites for CRH and cortisol and sends inhibitory projections to the hypothalamus. Another limbic area is the amygdala, which, you will recall, plays an important role in fear and anxiety. The amygdala also contains receptors for HPA-axis stress hormones but sends excitatory projections to the hypothalamus. A very common finding in patients with depression is structural change in areas of the limbic system. These changes are believed to result from high levels of cortisol circulating through the bloodstream and entering the brain. In depression, both the prefrontal cortex and the hippocampus lose volume (i.e., they *atrophy*), whereas the amygdala increases in volume. Increases in metabolism and blood flow to the amygdala are related to the severity of depressive symptoms (Peluso et al., 2009).

Because the prefrontal cortex, hippocampus, and amygdala are interconnected with the hypothalamus, structural changes lead to a loss of balance between inhibition and excitation of the stress system, resulting in heightened stress hormone release. Heightened HPA-axis activity and resulting elevation of stress hormone levels substantially increases one's risk of depression and suicide. Investigation of the therapeutic potential of CRH receptor antagonists has produced mixed results. In some clinical trials, patients with major depressive disorder experienced significant reduction of depressive symptoms with CRH antagonists. In other trials, CRH receptor antagonists fared no better than a placebo. It may be that CRH antagonists benefit only those individuals whose depression is brought on by stress and resulting hyperactivity of the HPA axis (Paez-Pereda et al., 2011).

Two Sides of the Same Coin

You may be wondering whether the monoamine or glucocorticoid theory offers the best explanation of the physiological changes that take place in depression. It may be more appropriate, instead, to think about these theories as representing two sides of the same coin. This is because stress hormones interact in complex ways with monoamine systems, including DA, NE, and 5-HT. For example, dopamine and glucocorticoid receptors coexist in neurons of the ventral tegmental area that project to the nucleus accumbens (Ahima & Harlan, 1990). Under chronic stress, heightened cortisol levels encourage DA release and structural change within the mesolimbic DA system. One such change is an upregulation of DA receptors in the ventral tegmental area (Czyrak, Mackowiak, Chocyk, Fijal, & Wedzony, 2003).

CRH neurons originating in the amygdala are directly and indirectly connected to areas of the hindbrain and midbrain, including the serotonin-containing raphe nuclei and the norepinephrine-containing locus coeruleus. During stressful events, amygdala activity overrides that of the prefrontal cortex and activates stress pathways in the hypothalamus and brainstem, leading to increased levels of monoamines and perhaps even upregulation of their receptors. Therefore, any change in the structure or activity of the amygdala has the potential to produce changes in the functioning of monoamine systems.

Changes in glucocorticoid levels are also strongly associated with changes in 5-HT function. You have read that depressed individuals often demonstrate abnormalities in the number and function of 5-HT_{1A} receptors, but the exact nature of this relationship is hotly debated. One finding that is well established is the link between

stress, high levels of HPA-axis stress hormones, and a reduction in both number and function of postsynaptic 5-HT_{1A} receptors in the hippocampus (Drevets et al., 2007). Adrenalectomy (surgery to remove the adrenal glands and thereby rid the body of cortisol) increases 5-HT_{1A} receptor densities and binding (Grino et al., 1987), whereas 2 weeks of chronic stress (and elevated levels of cortisol) decreases 5-HT_{1A} receptor densities and binding in the rat hippocampus (López, Chalmers, Little, & Watson, 1998). This suggests that changes in 5-HT neurotransmission may actually be the result of hypersecretion of stress hormones, especially cortisol.

Research in patients with major depressive disorder suggests that abnormal HPA-axis function precedes the onset of clinical symptoms of depression. It may be that certain individuals are genetically predisposed to develop HPA-axis hyperactivity. In a study that spanned 2 decades, researchers discovered that the number of childhood and adolescent stressful experiences correlated with the development of depression and suicidal ideation. Moreover, this correlation was strongest in individuals with the short form of the 5-HT transporter protein gene (Caspi et al., 2003). Possessing the short form of the 5-HT transporter protein gene also makes people more susceptible to depression resulting from childhood maltreatment (Uher et al., 2011). The experience of stress, perhaps early in life, triggers and sensitizes the stress system so that when stressors occur later in life, the HPA axis overreacts.

Those patients who get relief from depressive symptoms are also those who show normalization of HPA-axis functioning. Antidepressant medications reduce HPA-axis activity by increasing the number of cortisol receptors to create more efficient negative-feedback loops. As a result, the stress-induced rise in glucocorticoid levels is blunted and shortened, and decreases in 5-HT_{1A} receptor densities and binding that occur with elevated stress hormone levels are prevented. This normalization of HPA-axis activity precedes the alleviation of depressive symptoms. Patients who show improvement with antidepressant medication but whose HPA-axis function fails to normalize are more likely to relapse into depression. This suggests that normalizing the stress response may be a necessary condition in order for antidepressants to work (Paez-Pereda et al., 2011). It is clear, then, that the interaction between HPA-axis stress hormones and monoamine neurotransmitters, perhaps especially 5-HT, is important in linking stressful events with the development of depression.

HISTORY OF ANTIDEPRESSANT MEDICATIONS

There are several types of antidepressants. The classes of antidepressant drugs discussed next, along with examples from each class, can be found in Table 13-1 (some of these may not be approved for use in parts of Europe or North America). The first drugs that were successfully used to treat depression were the *monoamine oxidase inhibitors* (MAOIs) and the *tricyclic antidepressants* (TCAs). Consequently, these two classes are referred to as *first-generation antidepressants*.

The first antidepressant ever marketed was an MAOI called *iproniazid*, developed in the late 1950s. Before its antidepressant properties were realized, iproniazid was used in the treatment of tuberculosis (TB). Physicians noticed a great improvement in the mood of TB patients that was separate from the relief of their TB symptoms, and the drug was redeveloped for its antidepressant properties. When MAOIs were first introduced, they became widely used. But in a few years, the initial enthusiasm waned because of several factors.

To begin with, iproniazid was taken off the market soon after it was released because of reports that it caused liver damage. It turned out that the liver damage occurred only because the doses used were too high. In addition, some clinical studies concluded that MAOIs were ineffective. Once again, these reports were unfounded. The studies used inadequate research design, and we now know that the doses studied were too low. It is now known that MAOIs are just as effective as any other treatment for depression. Up to 70% of patients who fail to respond to newer classes of antidepressants show improvements in mood with MAOIs. New MAOIs are more specific in their actions, they are reversible, they are much less likely to interact with diet (discussed later), and they do not cause liver damage at therapeutic doses. This class of drugs is regaining a role as an effective and relatively safe treatment for depression.

The tricyclic antidepressants are so named because their molecular structure contains three rings of atoms. The tricyclics were also discovered by accident, during research on antipsychotic drugs (see Chapter 12); the first of these was *imipramine*. In the late 1950s,

TABLE 13-1 First- and Second-Generation Antidepressants

Drug Class	Generic Name	Trade Name
Monoamine oxidase inhibitors (MAOIs)	iproniazid	Euphozid
	phenelzine	Nardil
	tranylcypromine	Parnate
	isocarboxazid	Marplan
	selegiline	Eldepryl
	moclobemide	Aurorix
Tricyclic antidepressants (TCAs)	imipramine	Tofranil
	amitriptyline	Elavil
	desipramine	Norpramin
	doxepin	Sinequan
	nortriptyline	Pamelor
	clomipramine	Anafranil
Selective serotonin reuptake inhibitors (SSRIs)	fluoxetine	Prozac
	citalopram	Celexa
	escitalopram	Lexapro
	paroxetine	Paxil
	sertraline	Zoloft

imipramine was tested on psychiatric patients, and although it did not improve symptoms of schizophrenia, it did elevate the mood of depressed patients. Because the tricyclics were considered safer than the early MAOIs, many more were developed, and their use became common in the treatment of depression.

The popularity of the tricyclics was overshadowed by the introduction of a newer class of drugs that worked differently from the MAOIs or TCAs. This diverse group of chemicals is often called *second-generation antidepressants* and includes the *selective serotonin reuptake inhibitors* (SSRIs). The first and probably most well-known SSRI to be marketed is *fluoxetine* (Prozac). Its structure is only slightly different from that of imipramine and the other TCAs. Yet the SSRIs appeared safer with fewer of the bothersome side effects of the first-generation antidepressants and could be used to treat a variety of psychiatric conditions, such as anxiety, that frequently co-occur with depression.

Prozac was introduced in the United States in 1987 and soon received considerable attention in the popular media because it was being used not to treat depression but as a means of altering personality (more on this later). The media also carried reports that the drug could precipitate violent acts and suicide. If such adverse effects occur, however, they are extremely rare. Fluoxetine and other SSRIs are often a first-line treatment for depression. Although many second-generation antidepressants have been used in Europe, strict drug development laws have delayed or prevented their use in North America.

Riding on the success of second-generation antidepressants, the *third-generation antidepressants*, sometimes called the *atypicals*, are the more recently approved medications used to fight depression. These drugs include the *serotonin and norepinephrine reuptake inhibitors* (SNRIs) that affect the functioning of both of those monoamines. Enhancing NE activity, through stimulation of the reticular activating system, is helpful for those individuals who exhibit symptoms of fatigue and loss of energy associated with depression. Third-generation antidepressants do not alter the functioning of muscarinic acetylcholine receptors and therefore do not produce some of the side effects associated with older antidepressants. Some of the atypicals do affect nicotinic acetylcholine and histamine receptor functioning and influence the dopamine system. Examples of these drugs and their

TABLE 13-2 Third-Generation Antidepressants/Atypicals

Generic Name	Trade Name	Mechanism of Action
venlafaxine	Effexor	5-HT and NE reuptake blockade, DA reuptake blockade only at high doses
desvenlafaxine*	Pristiq	5-HT and NE reuptake blockade
duloxetine	Cymbalta	5-HT, NE, and DA reuptake blockade
mirtazapine	Remeron	NE α_2 autoreceptor and 5-HT_{1A} autoreceptor blockade; 5-HT_{2-3} receptor antagonist; histamine H1 receptor antagonist
nefazodone	Serzone	5-HT and NE reuptake blockade; 5-HT_{2-3} receptor antagonist
amoxapine	Asendin	NE reuptake blockade
bupropion	Wellbutrin; Zyban	DA reuptake blockade; partial NE reuptake blockade; ACh nicotinic receptor antagonist
maprotiline	Ludiomil	NE reuptake blockade
reboxetine	Norebox, Edronax	NE reuptake blockade
trazodone	Desyrel	5-HT reuptake blockade, 5-HT_2 receptor antagonist

*Major metabolite of venlafaxine.

mechanisms of action can be found in Table 13-2 (some of these may not be approved for use in parts of Europe or North America).

NEUROPHYSIOLOGY

Antidepressants generally work by increasing activity in one or more of the monoamine systems of the brain. In addition, other transmitter systems may be affected. There are several ways that they can do this, and antidepressants are usually classified by their principal mechanism of action. Regardless of the class of antidepressant, alleviation of depressive symptoms comes weeks after treatment begins. It is believed that this lag time is the result of the neuroadaptations that must take place before symptoms (specifically, the downregulation of 5-HT_{1A} autoreceptors and increase in serotonin system function; Uppal et al., 2010).

First-Generation Antidepressants: MAOIs and TCAs

All monoamine neurons produce the enzyme *monoamine oxidase* (MAO). This enzyme degrades monoamine molecules that float freely (i.e., those that are outside of vesicles) in the cytoplasm of the axon terminal, thereby depleting available neurotransmitter. The MAOIs do exactly what their name implies—they inhibit (block) the activity of monoamine oxidase so that molecules of DA, NE, and 5-HT that float freely in the cytoplasm are not destroyed but, instead, are available for vesicle storage and later release. Thus, MAOIs increase the availability and activity of DA, NE, and 5-HT. There are actually two types of MAO: *MAO-A* degrades all three monoamines, whereas *MAO-B* is most active in metabolizing DA. The effect of the older MAOIs was nonselective and irreversible–they inhibited both MAO-A and MAO-B, and their effects persisted for several days or weeks, even when the drug was not taken, until enzyme stores became replenished. Because both forms of MAO enzymes are present throughout the body, the nonselective MAOIs produced numerous unpleasant side effects. Some newer MAOIs, such as selegiline, act selectively on MAO-B at low doses and, at higher doses, affects MAO-A. In addition, some newer MAOIs are reversible, meaning that they can detach from MAO rather than deactivate it permanently.

Although they are grouped with the MAOIs as first-generation antidepressants, the tricyclics are

actually more similar in function to the second- and third-generation SSRIs and SNRIs. Their principal mechanism of action is to block reuptake transporter proteins on the terminal buttons of 5-HT and NE neurons so that, after these monoamines are released into the cleft by an action potential, their reuptake is inhibited and their duration of action on the postsynaptic cell is prolonged. At one point it was believed that all tricyclics worked in the same way, but there are now many drugs that have the three-ring structure of the tricyclics but produce various effects on functioning of other monoamines (Ordway, Klimek, & Mann, 2002). In addition, the TCAs affect other transmitter systems—they act as anticholinergics, blocking muscarinic acetylcholine receptors, and they antagonize histamine and α_1 adrenergic receptors. Although the TCAs are a safer and sometimes more effective alternative to the MAOIs, these additional actions can produce unpleasant and even dangerous side effects in some people.

Second- and Third-Generation Antidepressants: SSRIs and SNRIs/ Atypicals

As their name suggests, the SSRIs, through blockade of reuptake transporter proteins, diminish the ability of presynaptic cells to reabsorb and recycle 5-HT. This causes a buildup of 5-HT at synapses and prolongs postsynaptic receptor stimulation. This action is specific to 5-HT; the SSRIs have minimal effect on other monoamines or other neurotransmitters, such as histamine and acetylcholine. SSRIs are not selective as to which serotonin receptor they bind. It is believed that the antidepressant effects of the SSRIs result from changes to 5-HT_{1A} receptor functioning whereas the unpleasant side effects of the SSRIs may be due to activation of 5-HT_2 receptors.

The SNRIs and atypicals block the reuptake of 5-HT, NE, and in some cases DA. For example, bupropion, which blocks DA reuptake transporter proteins, is used to treat depression (Wellbutrin) and also as a smoking cessation aid (Zyban). In addition to its dopaminergic actions, bupropion affects the functioning of NE and ACh. Some newer antidepressants, like mirtazapine, act by antagonizing autoreceptors, specifically for NE and 5-HT, to prevent inhibitory feedback to the cell and thereby increase the amount of transmitter released. In addition, mirtazapine and some other atypicals block histamine receptors to induce sedation and drowsiness in those individuals who experience difficulty falling and staying asleep.

ABSORPTION

The MAOIs, tricyclics, and many second- and third-generation antidepressants have similar absorption pharmacokinetics. The TCAs reach maximal blood concentrations in 1 to 3 hours (although some TCAs may take as long as 8 hours). The absorption of SSRIs and SNRIs is slower; 4 to 8 hours are needed to reach maximum concentrations. Antidepressants generally have high levels of protein binding (over 95% for fluoxetine; DeVane, 1998).

A significant proportion of a dose of most antidepressants is destroyed by the digestive system and liver before it reaches the bloodstream. This first-pass metabolism is inhibited by alcohol; as a result, alcohol will greatly increase the amount of drug absorbed from a specific dose. Overdoses of TCAs are much more serious when taken in conjunction with alcohol. SSRIs and SNRIs are exceptions; they appear to have little interaction with alcohol. In fact, SSRIs have been suggested as a treatment for alcoholism (Lejoyeux, 1996).

DISTRIBUTION

Antidepressants readily cross the blood–brain and placental barriers. They tend to become concentrated in the lungs, kidneys, liver, and brain. Some antidepressants can be found in significant quantities in breast milk.

EXCRETION

The MAOIs have a short half-life of 2 to 4 hours (Preskorn, 1993). Some MAOIs may be taken once a day because they have an irreversible effect on MAO and their effects persist long after they are eliminated from the body. Newer MAOIs, like moclobemide, have a reversible effect, and two or three daily doses are required. The TCAs have a half-life of about 24 hours and, in most people, reach a steady-state level after about 5 days. Usually, only a single daily dose is needed.

Most second- and third-generation antidepressants have shorter half-lives than the tricyclics and often

require more frequent dosing (Richelson, 2001). Newer SSRIs generally have a short to medium half-life (15 to 25 hours) and do not have active metabolites. With these drugs, a steady-state blood level can be achieved in a few days with single daily dosing. One major exception, fluoxetine, has an extremely long half-life and an active metabolite that blocks the enzyme responsible for its destruction. Fluoxetine has a half-life of nearly 4 days, and its active metabolite, norfluoxetine, has a half-life of 7 to 15 days (Richelson, 2001). It may take as long as 75 days for the drug and its metabolite to reach a steady-state level in the body. It can also take this long for the drug and its metabolite to be completely eliminated from the body after the drug is discontinued (Lane & Baldwin, 1997).

There is considerable variability between individuals in the pharmacokinetics of the antidepressants. After a fixed daily dose of a tricyclic, individual steady-state blood levels may be as much as 36 times higher in some individuals than in others because some people have a genetic deficiency in one of the enzymes the body uses to destroy these drugs. In these people, antidepressants can have extremely long half-lives (Preskorn, 1993; Rudorfer & Potter, 1987). Thus, doses vary for individuals, and, in many cases, blood levels must be monitored (Simpson & Singh, 1990). Swanson, Jones, Krasselt, Denmark, and Ratti (1997) have reported two deaths caused by tricyclics taken at normal clinical doses. The individuals seem not to have cleared the metabolites as rapidly as most people, and the metabolites built up to a toxic level. Like many other genetic factors, the distribution of the enzyme can be associated with ethnicity (Sramek & Pi, 1996).

EFFECTS OF ANTIDEPRESSANTS

Effects on the Body

MAOIs alone do not produce serious or life-threatening side effects. Some of their side effects include tremors, weight gain, blurry vision, dry mouth, and a lowering of blood pressure and *postural hypotension* (fainting or dizziness when moving to a standing position after being seated or lying down). Unfortunately, MAOIs can have dangerous side effects that result from interaction with other drugs or foods. Drugs like amphetamines, decongestants, and nose drops that cause the release of NE are potentiated by MAOIs because they block the breakdown of NE, which then accumulates. In some cases, they block the metabolism of other drugs or may interact with them in unexplained ways. Drugs potentiated by MAOIs include alcohol and some opioids.

Another problem with MAOIs is that MAO not only destroys the monoamines but is also responsible for the breakdown of some substances in food. One of these substances is *tyramine*, which is found in aged cheese, pickled herring, beer, wine, and chocolate. MAO-A, which is present in the intestine, normally metabolizes tyramine just after it is consumed. Any tyramine missed by intestinal MAO-A is destroyed by MAO-B in the liver and the lungs before it gets into general circulation throughout the body. Normally, less than 1% of tyramine gets past this MAO and into the system (Fitton, Faulds, & Goa, 1992). If tyramine-rich foods are eaten while taking MAOIs, the body is unable to break down the tyramine, and it accumulates. Tyramine causes effects that mimic sympathetic nervous system activation, such as sweating, nausea, and increased blood pressure, which in turn can cause headaches, internal bleeding, and even stroke or death. This is known as the *cheese effect*. As a consequence, people on MAOIs have always had to watch their diet.

The older MAOIs blocked both forms of MAO, but newer MAOIs are more selective. As an example, moclobemide selectively blocks MAO-A and has minimal effect on MAO-B. As a result, tyramine that gets past the inhibited MAO-A in the intestine can still be metabolized by the MAO-B in the liver and lungs. Selective MAO-A inhibitors are, therefore, much safer, and patients do not have to be as careful with their diet (Fitton et al., 1992). It also helps if the pill is taken well after eating, allowing any dietary tyramine to be metabolized before the MAOI has its maximum effect.

An additional danger associated with MAOIs, as well as the other types of antidepressants, is the development of *serotonin syndrome*, which is caused by an acute increase in serotonergic transmission. Oftentimes, it is the result of interaction between a drug and a food (such as those containing *tryptophan*, the 5-HT precursor amino acid) or the coadministration of multiple drugs, including herbal remedies, that increase serotonin levels. In some cases, an insufficient *washout time* (the time allowed for a drug to be eliminated from the body) when medications are changed can cause serotonin syndrome

(Lane & Baldwin, 1997). This may happen when patients are switched to another antidepressant from fluoxetine, which has a particularly long half-life. Serotonin syndrome may also result when patients taking antidepressants use psychostimulants such as amphetamine or cocaine. Serotonin syndrome is characterized by such cognitive symptoms as disorientation, agitation, and confusion. It is also life-threatening, mainly because of dysregulation of autonomic nervous system functions, leading to increased blood pressure, flushing, fever, shivering, irregular heartbeat, diarrhea, and shock. It may lead to coma and can cause death.

The tricyclics also affect autonomic nervous system function through their anticholinergic effects. Specifically, TCAs inhibit the parasympathetic division of the autonomic nervous system, which uses ACh as a transmitter. These effects are characterized by symptoms such as dry mouth, constipation, blurred vision, ringing in the ears, and retention of urine. Excessive sweating is also common. Tremors are seen in about 10% of patients taking tricyclics. Side effects are usually worse during the first 2 weeks of treatment or when the dose is increased suddenly. Older patients are also more likely to show confusion and delirium; incidence can be as high as 50% in patients over 70 (Baldessarini, 1985).

Extrapyramidal or Parkinsonian symptoms, similar to the side effects of antipsychotics (see Chapter 12), are unusual with tricyclics but have been reported (Gill, DeVane, & Risch, 1997). Dizziness, irregular heartbeat, and postural hypotension may develop because of the influence of TCAs on adrenergic receptor functioning. Patients taking the tricyclics often report increased appetite and preference for sweets, accompanied by weight gain. This may be due to the influence of TCAs on histamine activity. One study reported an increase of 1.3 to 2.9 pounds per month. In fact, excessive weight gain is a major reason why patients stop taking these drugs. An additional, dangerous side effect is reduction in seizure threshold, which can cause convulsions, especially in those with seizure disorders.

The SSRIs have fewer nonspecific actions on systems outside of serotonin and, therefore, have far fewer unpleasant side effects. SSRIs may cause nausea, gastrointestinal problems, headache, dizziness, sweating, nervousness, and agitation, but these symptoms tend to dissipate with time. These side effects likely result from SSRI effects on 5-HT_2 receptors. In contrast with the MAOIs, the SSRIs decrease appetite, cause weight loss, and are sometimes used to treat obesity (Boyer & Feighner, 1991).

Most of the side effects associated with third-generation antidepressants are due to this class's antagonism of acetylcholine and histamine receptors and enhancement of 5-HT_{2-3} receptor activity. These side effects include increased appetite and weight gain, changes in blood pressure, dizziness, dry mouth, and gastrointestinal problems. Side effects associated with bupropion include restlessness and agitation, tremor, constipation, nausea, headache, dry mouth, and loss of appetite. An additional, dangerous side effect of bupropion is that, like some TCAs, it increases the risk of seizure. The reason nefazodone (Serzone) is no longer sold in Canada or the United States is because of the risk of liver damage. It is, however, available in other countries and in generic form in North America.

Effects on Sleep

All classes of antidepressants have been found to affect sleep. The MAOIs can cause either insomnia or sedation. Strangely, the tricyclics cause drowsiness, although this may have more to do with their anticholinergic properties than their monoamine-stimulating effects. Unlike the antidepressant effect, which takes days to develop, a single dose of a tricyclic can cause sleepiness and is sometimes prescribed to treat insomnia. The drug does not, however, increase total sleeping time. High doses of tricyclics at bedtime can cause nightmares.

Many antidepressants, like fluoxetine and venlafaxine, reduce REM (rapid eye movement) sleep time significantly. Reduction in REM sleep may be associated with a drug's antidepressant effects because sleep deprivation, particularly REM deprivation, has been shown to decrease symptoms of depression, and sleep can make depression worse (Janicak, Davis, Preskorn, & Ayd, 1993). The beneficial effects of REM deprivation build with time and even persist after deprivation ceases. Not all antidepressants reduce REM sleep time (Spiegel & Aebi, 1981), and bupropion actually increases it (DeVane, 1998).

Fluoxetine is reported by some patients to increase the vividness of their dreams. While some enjoy this side effect, others find it disturbing. Others experience insomnia while taking SSRIs. While some of the

third-generation antidepressants, such as mirtazapine, have antihistaminergic actions and cause sedation and sleepiness, others, like bupropion, can produce insomnia.

EFFECTS ON THE BEHAVIOR AND PERFORMANCE OF HUMANS

Subjective Effects

The antidepressants do not produce euphoric or even pleasant effects. At low doses, imipramine's effects are similar to those of the antipsychotics. It causes feelings of tiredness, apathy, and weakness. Higher doses impair comprehension and produce confusion that is described as unpleasant. Amitriptyline causes feelings of calmness and relaxation (Spiegel & Aebi, 1981). Even the atypicals that increase dopaminergic activity do not produce euphoria. Recall, from Chapter 5, that both the magnitude and the rate of dopamine surge associated with a drug correspond with individuals' reports of euphoria and pleasure. Because increases in dopamine activity are achieved slowly, any pleasurable effect one might feel is greatly blunted.

Effects on Performance

Because impairments in memory, attention, and cognition are characteristics often experienced by individuals with major depression, it is difficult to determine whether declines in performance are due to the depression or the medication. Acute doses of the TCAs imipramine and amitriptyline appear to have detrimental effects on vigilance tasks and can cause cognitive, memory, and psychomotor impairment that seems to be related to sedation. These drugs should not be used by people who must drive, use heavy equipment, or do intellectual work. Some studies have shown improvement in cognitive functioning after chronic drug treatment, suggesting that these impairments show tolerance. Other studies, however, have not (Lickey & Gordon, 1991). An evaluation of SSRIs and SNRIs on episodic- and working-memory task performance, mental processing speed, and motor performance showed significant drug-induced improvements. SNRIs improved memory performance to a greater extent than did SSRIs (Herrera-Guzmán et al., 2009).

There is evidence that the MAOI moclobemide impairs psychomotor performance. An investigation of the influence of long-term SSRI or SNRI treatment on driving performance found poorer driving (more weaving) in medicated patients than controls, but attributed the impairment to depressive symptoms, not the medication (Wingen, Ramaekers, & Schmitt, 2006).

Effects on Personality

In 1990, fluoxetine (Prozac) attracted national attention by appearing on the cover of *Newsweek*. Quoted in that issue was a psychiatrist, Peter Kramer, who had written about giving fluoxetine to people not to treat depression but to modify their personalities. Prozac "seemed to give social confidence to the habitually timid, to make the sensitive brash, and to lend the introvert the social skills of a salesman" (Kramer, 1993, p. xv). Kramer quoted one of his patients as saying that the drug had made him feel "better than well." He also coined the term *cosmetic psychopharmacology*, suggesting that people could take drugs such as fluoxetine to cover, by neurochemical means, some aspect of their personality that they were not satisfied with in the same way that facial blemishes could be hidden by makeup or the shape of a nose could be made more attractive by cosmetic surgery.

It has been established that fluoxetine and other SSRIs are useful in treating people with diagnosed personality disorders, such as obsessive-compulsive personality, and with compulsive behaviors (Gitlin, 1993). However, the use of fluoxetine and SSRIs as a personality cosmetic for people who do not have a diagnosed disorder, but are just not happy with their personality, is a matter of some debate. It raises a number of interesting issues, not the least of which concerns the origins of personality. If a drug can cause such immediate and profound changes in personality, this effect has far-reaching implications for the way we view personality. Is our personality determined by our past, our childhood experiences, and the like, as many theorists have long believed, or is it determined by 5-HT levels in the raphe nuclei (Kramer, 1993)?

Effectiveness in Treating Depression

There is little doubt that antidepressant medications are an effective means of combating depression. Efficacy rates are roughly similar for all classes—MAOIs, TCAs, SSRIs, and SNRIs—although there are significant individual differences as to which class works best, as well as differences in the way that different types of depression

respond to different antidepressants. It is likely that the neurochemical and neurophysiological manifestations of depression differ between individuals so that certain classes of antidepressants work better for some than others. The severity of the depression also influences whether antidepressants are effective in relieving symptoms (Fournier et al., 2010). The presence of a comorbid disorder, such as anxiety, is an additional important consideration since some newer antidepressants, like the SSRIs and SNRIs, are also used to treat other psychiatric conditions.

There are also considerable differences in the severity of side effects in different individuals. This is one reason why there are so many antidepressant drugs available. It is often necessary to change a drug treatment several times to find a drug and a dose that works for a specific person (Rush & Ryan, 2002). Advances in the development of antidepressant medications usually involve finding drugs with fewer side effects, rather than drugs with new or novel mechanisms of action, greater therapeutic effectiveness, or faster onset (Ordway et al., 2002).

We are not yet at the point where we can say that antidepressants are a cure-all for depression. Approximately 60 to 70% of individuals with major depression get some relief from antidepressant medications, but only 28 to 50% show full remission of symptoms (Trivedi et al., 2006). Moreover, much of the improvement associated with antidepressant treatment is also evident in patients treated with placebos. Placebo response rates are as high as 30%, which, compared to a 50% response rate in drug-treated individuals, means that the mere expectation of improvement can account for up to 75% of the improvement that actually occurs (Mora, Nestoriuc, & Rief, 2011). Placebo response rates vary according to the assessment method; physicians and clinicians are more likely to note improvement in depressive symptoms compared to when individuals self-report. Placebo effect rates have also grown across the past few decades; with millions of individuals having taken antidepressants, there is a growing belief that they work. So the expectancy that there will be improvement (and, therefore, the placebo effect) is increasing. When the effectiveness of tricyclics is compared to that of an *active placebo* (in this case, the anticholinergic drug atropine, which produces side effects similar to those of the TCAs), the active placebo is as effective in reducing depression as the TCA—patients are convinced they are receiving the antidepressant medication, as opposed to the placebo, because they experience physiological symptoms. The expectation that they will feel better makes them feel better (Moncrieff, Wessely, & Hardy, 2004).

Our belief in the effectiveness of antidepressants over placebos is also influenced by the way in which research is published. Studies that fail to find benefits of a drug over a placebo frequently do not get published. Therefore, what we read in the literature are only the good-news stories. A recent analysis of published and unpublished data sets obtained from clinical trial research revealed that the placebo effect can account for up to 82% of the effectiveness of antidepressant medication treatment (Kirsh et al., 2008). Furthermore, in patients experiencing mild or moderate depression, placebos were no more effective than antidepressants. Only in the most extremely depressed patients was there a relatively small difference in treatment outcome between the placebo and drug groups, and this was due to a decreased effectiveness of the placebo rather than an increased effectiveness of the antidepressant (Kirsh et al., 2008).

There has been a considerable interest in the use of antidepressants in treating depression in children and adolescents. A number of studies have shown that the TCAs are generally not effective in this population, but the SSRIs do work. As with adults, children show a very high rate of placebo effect (between one-third and one-half of the patients in the placebo group improve). Fluoxetine is the only SSRI that has been shown to be effective at a higher rate than placebos, but there are problems. In these studies, there is a higher rate of adverse symptoms in the SSRI group than in the placebo group (1 to 6% vs. 0 to 4%). These include agitation, hyperactivity, and symptoms of mania. In 2004, the U.S. Food and Drug Administration issued a *black box* warning against prescribing antidepressants to children and adolescents. You will learn more about this in the upcoming section on violence and suicide.

EFFECTS ON THE BEHAVIOR OF NONHUMANS

Conditioned Behavior

Tricyclic antidepressants are more effective than methamphetamine at increasing operant response rates. They even appear to further increase high rates of responding,

whereas amphetamine tends to decrease those rates (Dews, 1962).

The tricyclic antidepressants tend to decrease avoidance behavior at doses that have no effect on escape behavior (McMillan & Leander, 1976), thus making them similar to the antianxiety drugs and the antipsychotics. The tricyclics do not increase punishment-suppressed behavior. If anything, they tend to decrease it, making them similar to amphetamine and the psychomotor stimulants, in this regard.

DISCRIMINATIVE STIMULUS PROPERTIES

Neither the MAOIs nor the TCAs are discriminable at doses that produce most of their behavioral effects. However, at very high but sublethal doses, they can be discriminated. There does not appear to be any generalization between the antidepressants and the antipsychotics or any other drug class (Stewart, 1962).

The SSRIs and the SNRIs/atypicals, however, do have discriminate stimulus properties at therapeutic doses. Dekeyne and Millan (2003) trained rats to discriminate citalopram, bupropion, and reboxetine. They also found that antidepressants that blocked both serotonin and norepinephrine would substitute for either citalopram or reboxetine, but SSRIs generalize only to citalopram. Bupropion did not substitute for either citalopram or reboxetine. Taken together with the observation that the MAOIs and the TCAs do not appear to have any discriminable properties, this suggests that the stimulus properties of antidepressant drugs do not arise from their antidepressant properties.

The stimulus properties of citalopram were blocked by drugs that block 5-HT_{2C} receptors, and the reboxetine cue was blocked by NE α_1 antagonists, showing that the stimulus properties of these drugs arise from interactions with very specific receptors (Dekeyne & Millan, 2003).

TOLERANCE

There are reports that the therapeutic effectiveness of some drugs may show tolerance in some individuals after a few months of use, but the extent to which this happens and its clinical significance is not clear (Baldessarini, 1985). Tolerance to many of the side effects of the antidepressants usually occurs within several weeks, although tolerance may not develop to the tiredness reported with the SSRIs.

WITHDRAWAL

Sudden discontinuation of high doses of the tricyclics can cause withdrawal symptoms, which include restlessness, anxiety, chills, akathisia (a feeling of a compulsion to move), and muscle aches (Baldessarini, 1985). For this reason, these drugs should not be abruptly discontinued.

Withdrawal from SSRIs has been reported. The symptoms include dizziness, light-headedness, insomnia, fatigue, anxiety, nausea, headache, and sensory disturbances. These symptoms may last for 3 weeks and can be relieved by resuming antidepressant medication (Zajecka, Tracy, & Mitchell, 1997).

Withdrawal from SNRIs, especially venlafaxine, can be serious and include both bodily symptoms, such as heart palpitations and nausea, and psychiatric symptoms including delusions. Some individuals experience symptoms that are similar to stroke.

SELF-ADMINISTRATION IN HUMANS AND NONHUMANS

Neither the TCAs nor the MAOIs are self-administered unless prescribed by a physician for the treatment of depression. They are seldom sold illicitly on the street and do not appear to be used nonmedically. Apart from their medical application, neither of these classes appear to be reinforcing to either humans or nonhumans (Griffiths, Bigelow, & Henningfield, 1980).

To determine whether imipramine has aversive effects, an experiment was conducted in which monkeys were able to avoid infusions of various doses of imipramine by pressing a lever. Imipramine was avoided only at very high doses. It appears to be one of the few drugs tested that has neither positive nor negative reinforcing properties (Hoffmeister & Wuttke, 1975).

Interestingly, some of the second- and third-generation antidepressants have been successfully used to treat addiction to other drugs, including alcohol. Bupropion, as an antidepressant, is marketed as Wellbutrin, but it is also marketed as Zyban, a smoking-cessation aid.

Compliance

Because depression is a chronic disorder, it is important to find effective ways of preventing relapses. Chronic administration of therapeutic doses of most antidepressants has been shown to do just that. Patients, however, must be willing to tolerate the side effects of the drug over an extended period of time. Comparative trials have shown that the SSRIs are far superior to any other antidepressants in terms of patients' remaining compliant to chronic drug regimens. This success was due to the comparatively low rate of unwanted side effects of the SSRIs (Tollefson, 1993).

HARMFUL EFFECTS

Reproduction

Early studies indicated that the tricyclic antidepressants can interfere with male sexual functioning, but they suggested that the problems are not extensive (Harrison et al., 1986). A later study, however, found evidence that the problem may be more serious than it was first thought. Monteiro, Noshirvani, Marks, and Lelliott (1987) compared a group of men and women receiving the tricyclic clomipramine for obsessive-compulsive disorder with a placebo control group. In response to general questions about sexual functioning, there did not appear to be any difference between the drug group and the controls, but when questioned more closely in a structured interview about changes in sexuality, nearly all (96%) of the drug group reported severe difficulties in achieving orgasm. No difficulties were reported in the control group. This effect did not seem to be a result of sedation or fatigue and did not show any tolerance. Delayed or impaired ejaculation has also been reported with the MAOIs (Woods, 1984). Also, patients taking newer antidepressants, including the SSRIs and SNRIs, frequently report delayed ejaculation and loss of interest in sex. Because the atypical bupropion does not affect 5-HT function, it is unlike the others in that it is not associated with sexual dysfunction; it may, in fact, enhance sexual activity through its dopaminergic effects.

There is little evidence that the antidepressants cause any adverse effects to the fetus during pregnancy in humans, but a teratogenic effect has been noted in laboratory animals. As a general rule, antidepressants should be discontinued during pregnancy. In one study, pregnancy outcomes of women on fluoxetine and tricyclic antidepressants were compared with a matched control group. There were no differences in fetal malformations between the groups, but the women in the fluoxetine and tricyclic antidepressant groups were nearly twice as likely as controls to miscarry (Pastuszak et al., 1993).

Some antidepressants have been detected in breast milk of nursing mothers, but usually there is no evidence of the drug in the blood of the baby. It appears that the first-pass metabolism of the baby is able to get rid of the drug before it gets into his or her system.

Violence and Suicide

Soon after fluoxetine was introduced to the U.S. market, there were reports that it induced intense, violent, suicidal preoccupations in some patients (Teicher, Glod, & Cole, 1990). In fact, Prozac-induced violence became a defense in some courtrooms and was the subject of extensive coverage by television talk shows. There have since been many high-profile court cases where fluoxetine in particular has been blamed by the defense for causing many terrible crimes. Despite their increased safety over first-generation antidepressants and growing popularity, public health officials began to worry that the SSRIs may be having unintentional effects, especially on young people.

In 2004, the U.S. Food and Drug Administration (FDA) thoroughly reviewed clinical trial data, both published and unpublished, involving more than 4,000 children and adolescents. The review revealed that those taking antidepressant medications were twice as likely as those taking placebos to have suicidal ideations and attempt suicide (4% of those in the drug group vs. 2% in the placebo group). European and North American public health agencies issued warnings. The FDA mandated a *black box* warning, the most serious type of warning, to be placed on all antidepressant medications prescribed to children and adolescents. Friends and family members should closely monitor the young person for worsening depression, indications of suicidal thoughts, and changes in behavior. In 2007, this warning was widened to include young adults up to age 24. In subsequent studies, researchers did not find significant evidence that suicidal ideation increases with antidepressant drug use but, instead, that the benefits of

antidepressant treatment for young people outweighed the risks (Bridge et al., 2007). Yet, European and North American warnings prompted discontinuation of antidepressant treatment in many children and adolescents, and far fewer new prescriptions were written. Between 2003 and 2005, suicide rates increased dramatically (by 14% in the United States; by 49% in the Netherlands) as young people were not treated for their depression (Gibbons et al., 2007).

One reason why there is such confusion around this issue is because it is inherently difficult to research. Antidepressant drugs are often prescribed for people who are very agitated, depressed, and suicidal anyway. Suicide and violence after taking an antidepressant drug may represent only a lack of effect—an inability to prevent a suicide, not a drug-induced effect (Walsh & Dinan, 2001). In addition, if a drug causes suicide and violence in only a small number of people but reduces these acts in most others, large-scale studies that average across everyone would not detect it.

After being taken for 3 to 4 weeks, fluoxetine may induce an activating effect with racing thoughts, nervousness, and tremor (Boyer & Feighner, 1991). Sometimes this develops to the point where it is called *akathisia*, a movement disorder characterized by restlessness, agitation, an inability to sit still, and a compulsion to be continuously active. Akathisia is also one of the movement disorders seen after the administration of antipsychotics (see Chapter 12). Reports of violence and suicide seem to be associated with akathisia in certain individuals (Rothschild & Locke, 1991). Even though many large-scale studies have not shown increased akathisia caused by fluoxetine in the general population, studies in teenagers and children have shown that it does occur more often after fluoxetine than a placebo (Vitiello & Swedo, 2005).

For most people, fluoxetine is relatively safe and effective, but, like any drug, it has the capacity to cause serious problems for some patients, and its use and dosage should be monitored closely, especially for the first few weeks.

Overdose

The SSRIs and SNRIs are considerably safer than first-generation antidepressants, and unintentional overdose is extremely rare. As described earlier, SSRIs in combination with other antidepressants or psychomotor stimulants can cause serotonin syndrome. If this syndrome is unrecognized and untreated, it can ultimately cause respiratory, circulatory, and kidney failure. Serotonin syndrome is relatively common in SSRI overdose, certainly compared to the incidence of seizures or coma. Both the SSRI citalopram and the SNRI venlafaxine appear to be more dangerous due to their influence on cardiac function (Christoph et al., 2010; Isbister, Bowe, Dawson, & Whyte, 2004).

The tricyclics are potentially dangerous medications. The toxicity of the tricyclics is due primarily to their effect on the contractility of the heart muscle. They have a therapeutic index of around 10 to 15. This is a serious concern, especially when these drugs are prescribed for people who are severely depressed and contemplating suicide. There is considerable variability in the death rates attributed to drugs within the same class. Among the tricyclics, clomipramine is relatively safe, but many deaths have been attributed to amitriptyline. Tranylcypromine, an MAOI, is responsible for a high rate of deaths, but the rate of isocarboxazid fatalities is low (Leonard, 1993).

OTHER TREATMENTS FOR DEPRESSION

Antidepressant medications are not the only treatments for depression. Some individuals choose herbal remedies, such as St. John's wort, which you read about in Chapter 1. Other herbal treatments, such as saffron stigma and petal, lavender, echium, and rhodiola, have been shown to be more effective at alleviating the symptoms of depression than a placebo and, in some instances, are as effective as the SSRI fluoxetine and the TCA imipramine (Dwyer, Whitten, & Hawrelak, 2011).

Electroconvulsive therapy (ECT), in which seizures are induced in anesthetized patients, is most often considered a therapeutic alternative for those who fail to respond to a variety of antidepressant medications. MRI studies show that ECT treatments and improvement in depressive symptoms are associated with neurogenesis (growth of new neurons) in the hippocampus. Recall from earlier in this chapter that atrophy (cell death) of hippocampal neurons is a hallmark of depression. It is thought to result, at least in part, from high circulating levels of cortisol and may, in turn, facilitate hyperactivity of the HPA-axis stress response in a sort of perpetually damaging feedback loop. In animal studies,

electroconvulsive shock increases hippocampal levels of a protein, called *brain derived neurotopic factor (BDNF)*, in a dose-dependent, long-term manner (Bolwig, 2011). BDNF acts within the cell nucleus and performs vital roles in the growth and survival of existing and new neurons and receptors. Some researchers suggest that hippocampal degeneration associated with depression is the result of monoamine neurons failing to produce enough BDNF. Stress hormones, especially cortisol, contribute significantly to the loss of BDNF in the hippocampus and regions of the limbic system. ECT increases BDNF levels and neurogenesis in these regions, as do antidepressant drugs (Bolwig, 2011; Rojas, Fritsch, Rojas, Jara, & Fiedler, 2011).

Other methods of stimulating the brain have also proven effective in treating depression. These include *deep brain stimulation*, in which electrodes are chronically implanted within the prefrontal cortex, and *transcranial magnetic stimulation*, in which neuron depolarization is induced by applying a strong magnetic field to the scalp. Indirectly stimulating the brain, through electrical activation of the ascending fibers of the vagus nerve, which, in turn, excites regions of the brainstem, has also proven effective in some people.

Physical inactivity is recognized as a risk factor for depression, and a cost-effective and natural way to combat mild to moderate depression is through exercise. Exercise can also be used as an adjunct to boost symptom alleviation that results from antidepressant medications. Some of the proposed mechanisms by which exercise can ease depression include promotion of hippocampal neurogenesis, increases in 5-HT and BDNF levels, and a decrease in HPA-axis activity and cortisol production (Carek, Laibstain, & Carek, 2011).

Different forms of therapy, including cognitive behavioral therapy (CBT), psychodynamic therapy, and interpersonal therapy, have all proven effective in the treatment of depression. With symptom alleviation comes measurable physiological changes. For example, after several sessions of CBT or psychoanalysis, improvements in depressive symptoms correspond with reductions in cortisol to normal levels (Sharpley, 2010). Moreover, imaging studies reveal increases in blood flow to the hippocampus, normalization of amygdala activity, and improved PFC–limbic connectivity following therapy. Serotonin transporter protein levels also show normalization after a year of psychodynamic therapy (Sharpley, 2010).

It appears, then, that the way in which neurochemical and neurophysiological changes associated with depression become normalized is not as important as the fact that they do normalize.