# 14

# Antidepressants and Mood Stabilizers

There are several types of antidepressants. The first drugs that were successfully used to treat depression were the *monoamine oxidase inhibitors* (MAOIs) and the *tricyclic antidepressants* (TCAs). Consequently, they are sometimes referred to as *first-generation antidepressants*. Newer drugs have been developed that do not belong to either of these categories, and they are often called *second-generation antidepressants*. This diverse group of chemicals includes the *selective serotonin reuptake inhibitors* (SSRIs), inhibitors of norepinephrine reuptake (NARIs or sometimes SNRIs) and dopamine reuptake, and drugs that selectively block or stimulate specific serotonin and norepinephrine receptors.

The first MAOI to be used was *iproniazid*, but it is no longer in use. Others include *phenelzine* (Nardil), *tranylcypromine* (Parnate), and *moclobemide* (Ludiomil, available in the United Kingdom and Canada but not in the United States).

The tricyclic antidepressants are so called because their molecular structure contains three rings. Common TCAs are *imipramine* (Tofranil), *amitriptyline* (Elavil), *desipramine* (Norpramin), *nortriptyline* (Aventyl), *doxepin* (Adapin), and *mirtazapine* (Remeron).

Some second-generation antidepressants are *maprotiline* (Manerex), *amoxapine* (Asendin), *trazodone* (Desyrel), *mianserin* (Tolvon, not used in the United States), *nomifensine* (Merital, now withdrawn), *buproprion* (Wellbutrin or Zyban, a DA reuptake inhibitor), and *reboxetine* (Edronax or Vestra, a NARI not available in the United States). Although many second-generation antidepressants have been used in Europe, strict drug development laws have delayed or prevented their use in the United States.

The SSRIs include *fluoxetine* (Prozac), *fluvoxamine* (Luvox), *sertraline* (Zoloft), *paroxetine* (Paxil), and *citalopram* (Celexa).

The element *lithium* is used to treat and prevent the bipolar disorder. It is usually sold as the salt *lithium carbonate* under many different trade names, including Carbolith, Eskalith, Lithonate, and Lithotabs. Lithium has many troublesome side effects and poor compliance, so when it was found that drugs originally developed as anticonvulsants to treat epilepsy and seizure disorders were effective in treating bipolar disorder, its use

declined substantially. These drugs include *carbamazepine* (Tegretol), *valproic acid* (Depakine), and *lamotrigine* (Lamictal). Anticonvulsant drugs are now more widely used to treat bipolar disorder than lithium.

## THE NATURE OF DEPRESSION AND MANIA

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 cause in their environment, but their depression is deep, and either it does not go away or it keeps returning for no apparent reason. These people also show a loss of appetite, loss of interest in normally pleasurable activities, loss of energy, problems sleeping, exaggerated feelings of worthlessness and guilt, and haunting thoughts of death and suicide. Box 14-1 presents a summary of the *DSM-IV* criteria for a major depressive episode.

An 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,

**BOX 14-1** *DSM-IV* Criteria for a 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.

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weight loss, and so on—but do not seem to feel sad. They may, however, show *anhedonia*, a loss of interest in activities that are normally pleasurable. This "clinical depression" or "depressive illness" can be treated with antidepressants.

Depression is classified as an *affective disorder* or *mood disorder*. Traditionally, mild depression was labeled "neurotic depression," but serious depression accompanied by physical symptoms was considered a psychosis. *DSM-IV* no longer makes this distinction or considers depression as psychotic, but it does recognize that depression (see Chapter 13) may be associated with schizophrenia. In such cases, the depressed person will also exhibit hallucinations, delusions, or other symptoms of psychosis.

Depression has been called the common cold of mental illness because large segments of the population experience it at some time in their lives. Modest estimates suggest that within any 6-month period, 3 percent of the population of the United States is experiencing a mood disorder, and about 6 percent have one at some point during their lives. (Some estimates range as high as 26 percent.) In Western cultures depression is more frequent in every generation since World War II.

Compared to men, women are twice as likely to suffer from depression, but there are no gender differences in bipolar disorder. Only about 20 percent of those with depressive illness receive help from a mental health professional (Lickey & Gordon, 1991, p. 149). The resulting disability in the form of health care utilization, absenteeism (172 million working days annually), injuries at work, and the like costs an estimated $26 billion annually in the United States (Janicak, Davis, Preskorn, & Ayd, 1993, p. 207). There are other costs, too. The overall mortality rate for depressed people is higher than for normal people, and the probability of suicide is 20 times greater in depressed people.

Accounts of depressive illness were recorded by the ancient Greeks, and depression is common in contemporary cultures and societies. Similar symptoms are reported except that in non-Western societies, depressed people are more likely to report physical symptoms and less likely to express feelings of guilt and self-reproach (Lickey & Gordon, 1991, p. 175).

Depression is a chronic illness. Eighty-eight percent of those who suffer from depression and receive drug therapy improve within 6 months, but less than one-third of these remain well.

For most individuals, depression comes in cycles that may alternate with normal periods, but it may also alternate with *mania*. Mania is the exact opposite of depression. The person becomes excessively elated and hyperactive and takes on many ambitious and grandiose projects. The need for sleep is decreased, the sense of self-esteem is inflated, and behavior is often reckless. Manic individuals become very talkative, and ideas race through their heads. They are easily distracted, and conversation will switch from topic to topic. Manic people often become reckless and foolhardy, engaging in foolish investments or sexual indiscretions. Box 14-2 gives the *DSM-IV* criteria for a manic episode. The condition in which depression alternates with mania was called *manic-depressive psychosis*, but the *DSM-IV* now prefers the term *bipolar disorder*.

It has been known for some time that mood is related to the functioning of the monoamines (MAs), in particular, serotonin (5-HT) and norepinephrine (NE), although dopamine (DA) may also play a role. Drugs like cocaine and amphetamine make people feel good because they enhance transmission at these synapses, and drugs like reserpine, which depletes the brain of MAs, often cause severe depression. The *monoamine theory* of depression in its original form suggested that depression was a result of reduced levels of activity in these monoamine systems. As we shall see, this theory is no longer tenable in its simple form (Jimerson, 1987; Ordway, Klimek, & Mann, 2002; van Praag, de Kloet, & van Os, 2004, pp. 91–143). All of the three MAs are probably involved in some aspect of mood, and they interact with each other in complex ways, but it is now fairly clear that decreased activity in the serotonin system, although it may not be the direct cause of

**BOX 14-2** *DSM-IV* Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity

(2) decreased need for sleep

(3) more talkative than usual or pressure to keep talking

(4) flight of ideas or subjective experience that thoughts are racing

(5) distractibility (attention easily drawn to unimportant or irrelevant external stimuli)

(6) increase in goal-directed activity or psychomotor agitation

(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet the criteria for Mixed Episode.

D. The mood disturbance is sufficiently severe to cause a marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or medication, or other treatment) or a general medical condition.

*Source:* Reprinted with permission from American Psychiatric Association. © 1994, DSM-IV Criteria for a Manic Episode.

depression, certainly renders an individual vulnerable to depression. All treatments that have been shown to be effective in relieving depression have one thing in common: They ultimately change (almost always increase) transmission at serotonin synapses (Blier & de Montigny, 1994). It is clear, however, that these increases in serotonin transmission may be caused by, and may in turn cause changes in, activity of other transmitter systems—even some that do not use MAs (Charney, Southwick, Delgado, & Krystal, 1990; Janicak et al., 1993). An increase in serotonin transmission appears to be a necessary but not sufficient condition for effectiveness against depression (Leonard, 1993). Activity at specific serotonin synapses may in fact be only one link in a long and complex chain of neurological deficiencies that cause depression and mania.

Three brain systems that use MA transmitters have been implicated in some aspect of mood. All have centers in the midbrain or upper brain stem and send projections forward to the 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 *Raphé system*, and (c) dopaminergic fibers of the mesolimbic system that originate in the *ventral tegmental area*.

## HISTORY

The antidepressant properties of the MAOI iproniazid were discovered accidentally. The drug was developed as a treatment for tuberculosis, but its significant effect on the mood of patients was soon discovered; it relieved depression and made patients feel better. Later research determined that this effect was separate from relief of the symptoms of tuberculosis. When MAOIs were first

introduced in the 1950s, 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 used were too low. MAOIs were also known to interact with many other drugs and some foods. It is now known that MAOIs are just as effective as any other treatment for depression (more effective in some types of patients) and that they do not cause liver damage at therapeutic doses. New MAOIs have also been developed. They are more specific in their actions, reversible, and much less likely to interact with diet. This class of drugs is regaining a role as an effective and relatively safe treatment for depression (Kurtz, 1990).

The tricyclic antidepressants were also discovered by accident, during research on antipsychotic drugs (see Chapter 13). In the hope of finding better antipsychotics, many new drugs based on the antipsychotic drug molecule were synthesized; one of these was imipramine. In the late 1950s, imipramine was tested on psychiatric patients, and although it did not improve schizophrenic patients, it did elevate the mood of depressed patients. Because the tricyclics are safer than the early MAOIs, many more have been developed, and their use has become common in the treatment of depression.

The popularity of the tricyclics has been overshadowed by the second-generation antidepressants, which are safer and have fewer of the bothersome side effects of the tricyclic and MAOI drugs (Enna & Eilson, 1987; Feighner & Boyer, 1991; Leonard, 1993; Shopsin, Cassano, & Conti, 1981), although second-generation antidepressants do not seem to be more effective or to work faster in the treatment of depression. Like the TCAs and MAOIs, many second-generation antidepressants were developed for other purposes, and their antidepressant properties were discovered later.

The first SSRI, fluoxetine (more widely known by its trade name 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 aggressive acts and suicide. If such adverse effects occur, however, they are extremely rare. The use of fluoxetine and other SSRIs continues to increase both in the treatment of depression and as a personality "cosmetic."

Lithium, when given in the form of one of its salts, also works well in preventing both the mania and the depression that come in cycles in bipolar disorder. This effect was also discovered accidentally. In the 1940s, John Cade, an Australian psychiatrist, was testing a theory he had—that is, a toxin in the blood of manic patients caused their disease. He proposed that uric acid might protect experimental rats from the effects of this toxin, so he tried to inject rats with uric acid to see if it protected them from the lethal effects of being injected with the urine from manic patients. Unfortunately (or fortunately), he found that the uric acid did not readily dissolve, so he mixed it with lithium to make a soluble salt. He noticed that this mixture calmed the rats and did seem to offer them some protection. Later, he found that any salt of lithium would do the same thing, and he concluded that it was the lithium, not the uric acid, that was effective (Sneader, 1985, p. 185; Snyder, 1986). When he tested the lithium with his manic patients, he achieved amazing success. The lithium not only decreased symptoms but also prevented the recurrence of both mania and depression if taken regularly.

In spite of clear demonstrations of its effectiveness, lithium was slow to be used and was not available commercially in the United States until 1970.

Lithium is particularly effective in the treatment of bipolar disorder because it relieves mania and blocks the recurrence of depression. It is, however,

not effective in treating depression once it occurs. For this reason, lithium is not classed as an antidepressant. It may be referred to as an *antimanic* drug or a *mood stabilizer*. Antidepressants alone are not often used to treat bipolar disorder. They may relieve depression, but they sometimes can induce a manic episode. Lithium is often used in conjunction with an antidepressant in patients with bipolar disorder and may also be used with an antidepressant when the antidepressants are not effective by themselves.

## ABSORPTION

The MAOIs, the tricyclic antidepressants, and many second-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 is slower; 4 to 8 hours are needed to reach maximum concentrations. Antidepressants generally have high levels of protein binding (over 95 percent 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 are an exception; they appear to have little interaction with alcohol. In fact, SSRIs have been suggested as a treatment for alcoholism (Lejoyeux, 1996).

Orally administered lithium is rapidly absorbed. Peak levels in the blood occur between a half hour and 2 hours after consumption. However, lithium is much slower in getting inside cells, and this fact probably accounts for the drug's delayed therapeutic effect (Hollister, 1983, p. 181).

Lithium has a low therapeutic index of about 3 (Baldessarini, 1985, p. 35), so it is important to keep blood levels from becoming too high at any one time. Because lithium is absorbed rapidly, it peaks in the blood at high levels, and these peaks often exceed the therapeutic window (see Chapter 1). It is also excreted rapidly; several daily doses are needed to maintain the therapeutic level. This problem is often handled by using slow-release capsules in which the lithium is embedded in a material that dissolves slowly. This alternative prevents rapid-rise and high-peak blood levels and allows dosage to be cut back to two administrations per day (Cooper, 1987, p. 1366).

## DISTRIBUTION

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

Lithium enters and leaves the brain relatively slowly, reaching a peak after more than 24 hours. It seems to be concentrated in some parts of the brain. There is no protein binding. Lithium readily crosses the placental barrier, and because it easily finds its way into breast milk, it should not be used by breast-feeding mothers.

## 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-generation antidepressants have shorter half-lives than the tricyclics and often require more frequent dosing (Rudorfer & Potter, 1987). Newer SSRIs generally have a short to medium half-life (15 to 20 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 6 days, and its active metabolite, norfluoxetine, has a half-life of 16 days. 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 (R. 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 (G. M. 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).

Lithium is excreted unchanged in the urine and has a half-life of between 12 and 21 hours (Hollister, 1983, p. 181). The excretion rate varies considerably among individuals and increases with age to as long as 36 hours (Baldessarini, 1985, p. 96). For this reason, the blood levels must be carefully monitored when a patient is started on lithium therapy.

## NEUROPHYSIOLOGY

### Antidepressants

Antidepressants generally work by increasing the activity of one or more of the MA systems of the brain. There are several ways that they can do this, and antidepressants are usually classified by the way in which they work.

The MAOIs do exactly what their name implies—they block the activity of monoamine oxidase, the enzyme that destroys the MAs: dopamine DA, NE, and 5-HT. With this enzyme blocked, MA transmitters released into the synaptic cleft will not be metabolized, and the level of transmitter can rise as the transmitter accumulates. Activity at the synapse will increase unless the synapse has some other means of adjusting its activity. The effect of the older MAOIs is not selective, and the level of all MAs is affected. Some newer MAOIs, however, selectively affect NE and 5-HT and have little effect on DA.

As their name suggests, the selective 5-HT reuptake inhibitors (SSRIs) block the ability of presynaptic cells to reabsorb and recycle 5-HT and have the effect of causing a buildup of 5-HT at synapses. This action is specific to 5-HT; the SSRIs have minimal effect on other MAs.

At one point it was believed that all the tricyclics worked in the same way; that is, that they prevented the reabsorption or uptake of monoamines after they were released into the cleft, but there are now many drugs that have the three-ring structure of the tricyclics but have various effects on functioning of other MAs (Ordway et al., 2002). For this reason we can talk about some tricyclics along with newer or second-generation antidepressants.

Nortriptyline, amoxapine, and venlafaxine are MA reuptake blockers with varying degrees of selectivity for the different MAs. Reboxetine and malprotiline are selective blockers of NE reuptake (NARIs). Amitriptyline is an antagonist at 5-$HT_2$ and NE $alpha_2$ receptors. Buproprion is known to block some MA reuptake, particularly DA, but it is not known whether this is responsible for its antidepressant properties. Buproprion is also widely sold as Zyban, an aid to smoking cessation. Nefazodone and terazodone are potent antagonists of the 5-$HT_{2a}$ receptor but also have MA reuptake blocking action.

A side effect of the tricyclics is that they act as anticholinergics, blocking transmission at cholinergic synapses. The effect on 5-HT and

NE is believed to be responsible for their therapeutic action, and the anticholinergic effect is responsible for many of the side effects, such as dry mouth and blurry vision, of some antidepressants.

A few second-generation antidepressants, such as amisulpride and sulpride, appear to exert their primary effects not at serotonergic synapses but at dopaminergic synapses in the mesolimbic system through blockade of $D_2$, $D_3$, and $D_4$ receptors. These drugs are sometimes also used as antipsychotic drugs. Finally, a new type of antidepressants are direct agonists at 5-$HT_1$ receptors. This final class includes buspirone, ipsapirone, and gepirone (Bonhomme & Esposito, 1998). These drugs may also be used as anxiolytics.

We know that antidepressants have an immediate effect; they increase transmitter levels in MA synapses. In the context of the monoamine theory, which states that depression is a result of diminished MA activity, this makes sense. But, as with antipsychotic medications, there is a substantial problem. The effect on reuptake is immediate—it takes place as soon as the drug gets to the synapse—but the antidepressants need to be taken continuously for 2 to 3 weeks before there is any relief from depression.

This delay must mean one of two things: (a) increased activity at MA synapses does not relieve depression and the MA theory of depression is wrong, or (b) antidepressants do not immediately increase activity at the MA synapses because something delays the effect for about 2 weeks.

When a synapse is overstimulated for a period of time, the postsynaptic cell may reduce the number or the sensitivity of receptor sites. This change, called *down-regulation* of receptors, depends on long-term changes in protein synthesis, as described in Chapter 4. It has been pointed out that down-regulation of some receptors has a time lag of about 2 weeks—the same delay as the therapeutic effect of antidepressants. This similarity has led to speculation that depression might be caused by supersensitivity of MA systems rather than low levels of transmitter and that the antidepressants work by reducing this supersensitivity, that is, by causing the receptors to down-regulate (Lickey & Gordon, 1991, p. 226; Mobley & Sulser, 1981; Sulser, Vetulani, & Mobley, 1978).

Another possibility—and one that is now widely accepted—is that in serotoninergic synapses at least, increased levels of transmitter do not result in an immediate increase in firing. The presynaptic cell is equipped with an autoreceptor, a receptor that detects excessive amounts of transmitter in the cleft. When the autoreceptor detects excessive transmitter caused by the drug, it inhibits the release of more 5-HT (typically by reducing the influx of calcium at the terminal). Thus, reuptake inhibitors like the SSRIs do not cause an immediate increase in conduction at 5-HT synapses. It takes about 2 weeks for the autoreceptors to habituate to the presence of excess 5-HT, and only then does serotoninergic conduction at the synapse actually increase (Blier & de Montigny, 1994). Studies of the electrical activity at serotoninergic synapses have shown that acute administration of SSRIs does not increase activity; only after 2 weeks of chronic treatment will the electrical activity increase greatly. The delay experienced with other types of antidepressants may be a result of similar adjustment mechanisms.

The bulk of evidence supports the theory that (a) depression is a result of diminished activity in the 5-HT system in the brain, which runs from the Raphé nuclei through the medial forebrain bundle to the forebrain, and (b) mania is a result of excessive activity in this system. The situation is very complicated, however, and many other explanations of depression and mania exist. Alternate theories involve different neurotransmitters, such as GABA, ACh, and DA, and the balance achieved among levels of these neurotransmitters. Other theories suggest the involvement of second messengers, biological rhythms, hormone levels, stress, and the immune system (Janicak et al., 1993, pp. 211–219; Leonard, 1993; Maes & Meltzer, 2000; Ordway et al., 2002).

### Mood Stabilizers and Antimanics

No one knows how lithium works, but it appears to stabilize the neurochemical mechanisms that control mood and to keep them from swinging radically between extremes. Lithium is known to do several things in the brain, including (a) altering the balance of ions such as $Cl^-$ and $K^+$, which are important in the formation of resting and action potentials and post synapyic potentials, (b) altering the functioning of many transmitters, such as 5-HT, NE, DA, ACh, and GABA, and (c) inhibiting the second-messenger cyclic AMP. Lithium also has been shown to cause a down-regulation of some NE receptors (Bunney & Garland-Bunney, 1987). It is still not known which of these effects, if any, is responsible for the therapeutic effect of lithium, but the augmentation of serotonin and its effect on second-messenger activity are the promising candidates. Lithium is also known to stabilize membranes; that is, it makes membranes less excitable. This is a property it shares with the anticonvulsant drugs, and likely arises from (a) listed previously.

The anticonvulsant mood stabilizers valproic acid and carbamazepine and lamotrigine have different neurological effects. Valproic acid increases GABA levels in the brain by blocking *GABA-transaminase*, the enzyme that destroys GABA, but carbamazepine and lamotrigine prevent seizures by blocking sodium channels and inhibiting the release of glutamate and aspartate. Clearly membrane stabilization or inhibition is important in the effectiveness of drugs in treating bipolar disorder, but it is still not clear why.

## EFFECTS OF ANTIDEPRESSANTS AND MOOD STABILIZERS

### Effects on the Body

Unlike the psychomotor stimulants, the tricyclics do not stimulate the sympathetic nervous system. Instead, their anticholinergic effects block the parasympathetic nervous system, which uses ACh as a transmitter. These effects are characterized by symptoms such as dry mouth, constipation, dizziness, irregular heartbeat, blurred vision, ringing in the ears, and retention of urine. Excessive sweating is also common. Tremors are seen in about 10 percent of patients receiving the 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 percent in patients over 70 (Baldessarini, 1985, p. 191). Extrapyramidal symptoms or parkinsonian symptoms, similar to the side effects of antipsychotics (see Chapter 13), are unusual with tricyclics but have been reported (Gill, DeVane, & Risch, 1997).

The SSRIs may cause nausea, headache, nervousness, and insomnia, all of which, apart from the insomnia, tend to disappear with time. More serious is the danger of *serotonin syndrome*, which is caused by an acute increase in serotonergic transmission. Serotonin syndrome is characterized by such cognitive symptoms as disorientation, agitation, and confusion, in addition to autonomic symptoms such as fever, shivering, or diarrhea. Extrapyramidal symptoms (see Chapter 13) may also be part of the symptomology. Serotonin syndrome can be caused by SSRIs alone, but it is most often seen when antidepressants are coprescribed with other medications that alter serotonergic activity or when patients taking antidepressants combine them with psychostimulants such as amphetamine or cocaine. 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 (R. Lane & Baldwin, 1997). This may happen when patients are changed to another antidepressant from fluoxetine, which has a particularly long half-life.

Patients taking the tricyclics often report an increase in appetite and an increased preference for sweets, accompanied by an increase in body weight. One study reported an increase of 1.3 to 2.9 pounds per month. In fact, excessive weight gain has been reported to be the major reason why patients stop taking these drugs. The MAOIs and lithium also cause weight gain, but the opposite effect has been reported with the SSRIs, which

are sometimes used to treat obesity and help with weight loss (Boyer & Feighner, 1991, p. 142).

MAOIs alone do not have very marked effects apart from 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 interact with many other drugs. Drugs like amphetamines, decongestants, and nose drops that cause the release of NE (see Chapter 11) are potentiated by MAOIs because they block the metabolism of NE, which then accumulates. In some cases, they block the metabolism of the other drugs or may interact with them in unexplained ways. Drugs potentiated by MAOIs include alcohol and some opiates.

Another problem with MAOIs is that MAO not only destroys the MAs but also is responsible for the digestion of some substances in food. One of these substances is *tyramine*, which is found in aged cheese, pickled herring, beer, wine, and chocolate. After eating such foods when MAO is inhibited, tyramine accumulates in the body and causes high blood pressure, which in turn can cause headaches, internal bleeding, and even stroke or death. As a consequence, people on MAOIs have always had to watch their diet closely and were at some risk.

There are actually two types of MAO: *MAO-A* is responsible primarily for the breakdown of the 5-HT and NE, and *MAO-B* is most active in metabolizing DA. MAO-A is located in the intestine and normally metabolizes the tyramine just after it is consumed. Any tyramine missed by the 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 percent of tyramine gets past this MAO and into the system (Fitton, Faulds, & Goa, 1992). The older MAOIs blocked both forms of MAO, but new MAOIs like moclobemide selectively block MAO-A and have a 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 after eating, allowing any dietary tyramine to be metabolized before the MAOI has its maximum effect.

As many as 90 percent of patients on lithium have complaints about unwanted physical effects. The most common are hand tremors, increased thirst, nausea and vomiting, diarrhea, swelling, and weight gain. After extended treatment, patients may experience fatigue and muscle weakness. Another problem associated with long-term use is kidney damage.

The anticonvulsant drugs used as mood stabilizers—carbamazepine and valproic acid and lamotrigine—can cause frequent urination, nausea, and vomiting and in higher doses can cause tremors (Calabrese & Bowen, 2000). Other side effects include weight gain, hair loss, and dizziness, and lamotrigine causes a rash in about 10 percent of patients (Julien, 2001).

### Effects on Sleep

Strangely, the tricyclics cause sleepiness, although this may have more to do with their anticholinergic properties than their MA-stimulating effects. Unlike the antidepressant effect, which takes days to develop, a single dose of a tricyclic can cause drowsiness 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 venlaxafine, reduce REM time significantly, although some do not seem to have any effect on REM (Spiegel & Aebi, 1981, p. 116). Bupropion actually increases REM sleep (DeVane, 1998). Reduction in REM sleep may be associated with a drug's antidepressant effects because it has been shown that sleep deprivation, particularly REM deprivation, can actually decrease symptoms of depression temporarily, and sleep can make depression worse (Janicak et al., 1993, p. 322).

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

## 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 produce impaired comprehension and a confusion that is described as unpleasant. Amitriptyline causes feelings of calmness and relaxation (Spiegel & Aebi, 1981, p. 64).

Lithium has few, if any, subjective effects apart from those associated with side effects such as nausea. Subjects sometimes report a feeling of mental slowing and difficulty in concentration (Judd, Squire, Butters, Salmon, & Paller, 1987, p. 1467).

### Effects on Performance

Acute doses of the tricyclic antidepressants imipramine and amitriptyline can 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, p. 230).

There is evidence that moclobemide impairs psychomotor performance, but there is no evidence of any impairment by the SSRIs (Mattila, Mattila, & Nuotto, 1993, p. 181).

Extensive systematic studies of mental abilities after acute and chronic lithium administration indicate a small but significant slowing of mental processes. There appear to be few effects on performance of tasks and reaction time. The difficulty appears to be in a slowing of information processing and memory (Judd et al., 1987, p. 1468; Kocsis et al., 1993). The anticonvulsant drugs also cause a slowing of cognitive function and learning and can be sedating.

### 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" (P. D. 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 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 believed for years, or is it determined by 5-HT levels in the Raphé nuclei (P. D. Kramer, 1993)?

Some patients who have used fluoxetine as a personality cosmetic have become disenchanted with the changes in themselves over a period of time and have discontinued the drug because

they felt that it had taken some of the edge or tension out of their lives and made them too bland.

### Effectiveness in Treating Depression

There is little doubt that antidepressants are effective in treating depression. Numerous clinical trials have shown that many of these drugs are more effective than a placebo, although there is often a strong placebo effect seen in these studies. A recent meta-analysis of clinical trials with antidepressants has shown that the percentage of patients with major depressive disorder that responded to antidepressant treatment was 50.1 percent, while the percentage in the placebo control group was 29.7 percent. Interestingly, this study found that the percentage of responders in the placebo group has been increasing over the past 20 years (Walsh, Seidman, Sysko, & Gould, 2002).

There are considerable individual differences in the effectiveness of different drugs as well as differences in the way that different types of depression respond to different antidepressants. There are also considerable differences in the severity of different side effects in different individuals. This is one reason why there are so many different antidepressant drugs. 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 antidepressant drugs have usually involved the development of drugs which have fewer side effects rather than drugs with new or novel mechanisms of action, greater therapeutic effectiveness, or faster onset (Ordway et al., 2002).

There has been a considerable interest lately 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 with children. 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. It is been observed in these studies that there is a higher rate of adverse symptoms in the SSRI group than in the placebo group (1 to 6 percent vs. 0 to 4 percent). These include agitation, hyperactivity, and symptoms of mania.

## EFFECTS ON THE BEHAVIOR OF NONHUMANS

### Conditioned Behavior

Tricyclic antidepressants are more effective than methamphetamine in increasing operant response rates. They even appear to increase high rates where amphetamine tends to decrease them (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 also do not increase punishment-suppressed behavior. If anything, they tend to decrease it. The tricyclics are similar to amphetamine and the psychomotor stimulants in this regard.

## DISCRIMINATIVE STIMULUS PROPERTIES

Neither the MAOIs nor the tricyclics are discriminable at doses that produce most of their behavioral effects. However, at very high but sublethal doses, they can be discriminated. Lithium does not appear to have any discriminative stimulus properties (Overton, 1982, 1987). There does not appear to be any generalization between the antidepressants and the antipsychotics or any other drug class (J. Stewart, 1962).

The SSRIs and the NARIs, however, do have discriminate stimulus properties at therapeutic doses. Dekeyne and Millan (2003) trained rats to discriminate citalopram (an SSRI), buproprion (a dopamine reuptake inhibitor), and

reboxetine (an NARI). They also found that antidepressants that blocked both serotonin and norepinephrine would substitute for either citalopram or reboxetine, but SSRIs generalize only to citalopram. Buproprion, the DA uptake inhibitor, did not substitute for either citalopram or reboxetine. Taken together with the observation that the MAOIs and the tricyclics 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 $alpha_1$ 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, p. 143).

Tolerance to the many of the side effects of the antidepressants usually occurs within several weeks, although tolerance may not develop to the tiredness reported to the SSRIs.

## WITHDRAWAL

Sudden discontinuation of high doses of the tricyclics can cause withdrawal symptoms, which include restlessness, anxiety, chills, muscle aches, and akathesia, a feeling of a compulsion to move (Baldessarini, 1985, pp. 143, 192). For this reason, these drugs should not be discontinued abruptly.

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).

## SELF-ADMINISTRATION IN HUMANS AND NONHUMANS

Neither the tricyclic antidepressants 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 the tricyclic antidepressants nor the MAOIs 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, p. 425).

Interestingly, some of the second-generation antidepressants, particularly the SSRIs, have been successfully used to treat addiction to other drugs, including alcohol. Buproprion is marketed as Wellbutrin as an antidepressant but also as Zyban, a drug to aid people who want to quit smoking.

### Compliance

Because depression is a chronic disorder, it is important to find effective ways of preventing relapses. If taken chronically, lithium is effective in preventing relapse. Chronic administration of therapeutic doses of most antidepressants has been shown to be an effective way of preventing relapse. 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 first thought. Monteiro, Noshirvani, Marks, and Elliott (1987) compared a group of patients of both sexes who were receiving the tricyclic clomiprimine 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 percent) 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 (N. F. Woods, 1984, p. 439). Also, patients on SSRIs frequently report delayed ejaculation and loss of interest in sex.

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 its system.

Lithium is known to cause cardiac malformations in the developing fetus if taken early in pregnancy (Hollister, 1983, p. 195), so its use should be avoided if pregnancy is possible. Since it readily passes into breast milk, it should not be taken by nursing mothers. The anticonvulsants are also known to have teratogenic properties.

### 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.

The scientific evidence suggesting a link between fluoxetine and violence and suicide has largely been in the form of case studies. On the other hand, large-scale drug trials have actually shown that fluoxetine reduces the incidence of suicide and violence. The issue has not been clearly settled because it is difficult to research. Such 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 this 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 *akathesia*, a movement

disorder characterized by restlessness, agitation, an inability to sit still, and a compulsion to be continuously active. Akathesia is also one of the movement disorders seen after the administration of antipsychotics (see Chapter 13). Reports of violence and suicide seem to be associated with akathesia in certain individuals (Rothschild & Locke, 1991). Even though many large-scale studies have not shown increased akathesia caused by fluoxetine in the general population, studies with fluoxetine and teenagers and children have shown that it does occur more often after fluoxetine than a placebo (Vitiello & Swedo, 2005); consequently, the U.S. Food and Drug Administration and drug regulatory agencies in other countries have insisted that a warning be placed on SSRIs and other antidepressants that they could cause increased suicidal thoughts in children.

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

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.

The tricyclics are the third most common cause of drug-related deaths, exceeded only by alcohol drug combinations and heroin. 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 seriously depressed and contemplating suicide. There is considerable variability in the death rates attributed to drugs within the same class. Among the tricyclics, clomiprimine 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 isocarboxazide fatalities is low (Leonard, 1993).

The SSRIs are considerably safer. No overdose deaths have been attributed to fluoxetine (Boyer & Feighner, 1991; Leonard, 1993).

## CHAPTER SUMMARY

- There are two types of first-generation antidepressants: (a) monoamineoxidase inhibitors (MAOIs) and (b) tricyclic antidepressants. Second-generation antidepressants make up a diverse group that includes the selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors, dopamine reuptake inhibitors, and a variety of others. In addition, the element lithium is used in the treatment of bipolar disorder (formerly called manic-depressive psychosis) as well as drugs that were originally developed as anticonvulsants.
- Depression has symptoms such as loss of appetite, loss of energy, sleeping problems, intense feelings of guilt or worthlessness, and thoughts of suicide. For some, depression comes in cycles and alternates with mania, a state of elated hyperactivity. This condition is called bipolar disorder.
- The antidepressants are absorbed orally and reach peak blood levels in about 4 hours.
- Most tricyclics have very long half-lives; the half-lives of the second-generation antidepressants are usually shorter.
- All agents that act as antidepressants have the effect of increasing transmission at serotonergic synapses. There is a delay of about 2 weeks in the start of the therapeutic effect of the antidepressants. This could be due to serotonin receptor down-regulation or habituation of a serotonin autoreceptor.
- The MAOIs also block the destruction of toxic substances found in some foods. People taking MAOIs should not eat foods like pickled herring and some types of cheese; they can cause a buildup of tyramine. This is less of a problem with newer, reversible MAO-A inhibitors. Lithium also causes unwanted side effects such as thirst, tremor, and nausea.
- Clinical trials show that there is a high rate of placebo effect for antidepressants, but antidepressants are more effective than a placebo. SSRIs are

the only antidepressants that have been shown to be effective in children, although there is a high rate of side effects.

- Increases in violence and suicide have been reported with SSRIs after they have been taken for several weeks. This is sometimes associated with restlessness and akathesia, especially in children and young people.
- Tolerance develops to many of the effects of antidepressants. Withdrawal symptoms are sometimes seen when the drug is discontinued abruptly.
- Antidepressants do not appear to be reinforcing in nonhumans and are never abused or taken for recreational purposes.
- The tricyclics and SSRIs have been shown to cause problems in sexual functioning; both sexes report difficulty in achieving orgasm. Lithium has been shown to cause cardiac malformations in the fetus when taken by the mother early in pregnancy.