In 1952, reserpine was first isolated from the *Rauwolfia serpentina*, a plant known for its tranquilizing properties. In healthy volunteers, researchers not only verified reserpine’s tranquilizing effects but also noticed that it produced a depressed mood. Attempts to understand this drug’s actions divided opinion into two camps. On the one hand, Bernard...
The preceding chapters of this text concerned changes in brain function and behavior caused by psychoactive substances. Thus, normal behavior became abnormal after a drug was administered. For mental illness, we have the opposite. Behavior may appear abnormal before treatment, but the goal of drug treatment is for behavior to become normal. The subsequent chapters of this text shift from drugs of abuse to those used for treating mental disorders, which we refer to as therapeutic drugs or pharmacotherapeutic drugs.

Mental Disorders

Just as we have referred to the Diagnostic and Statistical Manual (DSM) for defining substance dependencies, we can also refer to the DSM for defining different types of mental disorders. We consider a mental disorder as an impairment in normal behavioral, cognitive, or emotional functioning. Mental disorders are highly prevalent throughout the world and occur across all demographics. According to the World Health Organization (WHO), an estimated 450 million people qualify for a mental disorder diagnosis, whereas many others have various symptoms associated with mental disorders. Based on 2002 estimates, WHO reported that 154 million individuals have depression, and 877,000 commit suicide annually. WHO also found that despite the

Brodie and others argued that serotonin depletion accounted for reserpine’s effects; on the other hand, Arvid Carlsson and others argued that dopamine and norepinephrine accounted for its effects. This debate sparked important discoveries about the production, release, and reuptake of monoamine neurotransmitters. When a drug was serendipitously found reducing depression in humans, researchers saw that these first antidepressant drugs reversed reserpine-induced depression in animals. Moreover, the wealth of research centered on reserpine convinced researchers that monoamine neurotransmitters were central to the actions of antidepressant drugs.

Despite the important discoveries resulting from studies on reserpine, it appears to be a part of forgotten history. As psychopharmacologist Silvio Garattini (2006) noted, “The new pharmacology texts no longer even mention this drug that was so instrumental in the generation of new knowledge about the chemical mediators in the brain that gave rise to the field of psychopharmacology.”
tremendous impact that poor mental health has on a society, only 1 percent of health costs are devoted to mental health in low- to middle-income countries (World Health Organization, 2016).

To diagnose a mental disorder, the DSM generally requires that an individual experience significant dysfunction and stress from the disorder and that the disorder does not arise from a medical condition with a clear physiological cause. For example, the DSM does not qualify Alzheimer’s disease as a mental disorder, despite clear changes in mental functioning, because Alzheimer’s disease derives from clear organic cause. This distinction makes sense less today than years past, when neuroscience technology had not advanced sufficiently to glean physiological causes for mental disorders. We will learn much about the neurobiology of DSM mental disorders in these remaining chapters and focus on how therapeutic drugs alter biological processes to improve mental functioning. The subsequent chapters cover the following major mental disorders: depression, bipolar disorder, anxiety, and schizophrenia.

### Depression

According to the DSM-5, **major depressive disorder** is characterized by at least five symptoms occurring within the same 2-week period. These symptoms can include a depressed mood, lack of interest or pleasure in activities once enjoyable, change in body weight, change in sleep patterns, fatigue, feelings of worthlessness, difficulties in thinking or in concentrating, and thoughts of suicide (Table 13.1). Moreover, these symptoms significantly interfere with normal everyday activities such as going to work, doing daily chores, and socializing with family and friends (American Psychiatric Association, 2013).

Depression also may occur in a milder form called **persistent depressive disorder** (or dysthymia). The primary symptoms for persistent depressive disorder include a depressed mood that occurs nearly every day for at least 2 years. In addition, individuals diagnosed with dysthymic disorder must have at least two symptoms listed for major depressive disorder.

Nonspecific descriptions may be used for some symptoms of depressive disorders. For example, “changes in body weight” doesn’t specify whether this consists of weight loss or weight gain. In depression, we might find either of these changes occurring. A severely depressed individual may eat excessively, possibly because eating provides temporary improvements in mood, or may eat too little, possibly because the individual lacks an appetite. The same may be true for sleeping; an individual may sleep most of the day or suffer long bouts of insomnia.

Clinicians also recognize that many other dimensions of depression exist, something that the DSM classifies as specifiers. A clinician, for example, might find significant features of anxiety accompanying a clear diagnosis of major depressive disorder. In this instance, the clinician would diagnose the patient with major depressive disorder, along with the specifier “with anxious distress.” Adding this specifier may inform treatment directions. For example, the patient may receive medications for both depression and anxiety.
In addition to a specifier for anxiety, we also find that some depressed individuals exhibit delusions or hallucinations. In this context, a clinician would add the specifier “with psychotic features.” When we find psychosis present in depression, hallucinations and delusions tend to relate to depressed mood and negative thoughts. For example, an individual may have delusions that she has cancer all throughout her body or that no one wants her to live. An individual may hear voices stating the same types of things. Those with psychosis and depression may benefit from medications to treat both types of symptoms (Spiker et al., 1985). There are many other types and specifiers for depression, but these go beyond the scope of this text.

We also find a degree of cognitive dysfunction in depression. The degree and types of cognitive impairment tend to vary across studies, owing in large part to the age of participants, severity of depression, and other population differences. In general, individuals with depression tend to exhibit impairments in episodic memory, an ability to explicitly describe one’s memory of certain past experiences (Goodwin, 1997; Zakzanis, Leach, & Kaplan, 1998). Further, those with major depressive disorder also exhibit reduced ability to sustain attention (Zakzanis et al., 1998). Cognitive function normalizes when depressive symptoms subside (Paelecke-Habermann, Pohl, & Leplow, 2005).

<table>
<thead>
<tr>
<th>TABLE 13.1</th>
<th>Symptoms of Depressive Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disorder</strong></td>
<td><strong>Symptoms May Include . . .</strong></td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>Depressed mood occurring daily and for most of the day</td>
</tr>
<tr>
<td></td>
<td>Anhedonia (lack of pleasure) and disinterest</td>
</tr>
<tr>
<td></td>
<td>Changes in body weight (gain or loss)</td>
</tr>
<tr>
<td></td>
<td>Changes in sleep patterns (insomnia or hypersomnia)</td>
</tr>
<tr>
<td></td>
<td>Fatigue and loss of energy</td>
</tr>
<tr>
<td></td>
<td>Feelings of worthlessness and guilt</td>
</tr>
<tr>
<td></td>
<td>Difficulty thinking and making decisions</td>
</tr>
<tr>
<td></td>
<td>Recurrent thoughts of suicide</td>
</tr>
<tr>
<td>Persistent depressive disorder</td>
<td>Same as those for major depressive disorder</td>
</tr>
<tr>
<td><strong>Specifiers</strong></td>
<td>Additional symptoms to those for depression, depending on the specifier. For example, the specifier “with anxious distress” includes anxiety symptoms and the specifier “with psychotic features” includes hallucinations and delusions.</td>
</tr>
</tbody>
</table>
The Prevalence of Depressive Disorders

Depression is the fourth leading cause of disability worldwide because of its prevalence and dramatic effects on quality of life (Murray & Lopez, 1997). According to a U.S. national survey conducted by Kessler, Petukhova, Sampson, Zaslavsky, and Wittchen (2012), the prevalence of major depressive disorder during a lifetime is 16.6 percent (Figure 13.1). Yet among university students we find a much higher rate. In a review of published reports on depression among university students, Ibrahim and

FIGURE 13.1 • The lifetime likelihood of experiencing depression is approximately 16 percent.

<table>
<thead>
<tr>
<th>Age</th>
<th>Total</th>
<th>13-17</th>
<th>18-64</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

SOURCE: Data from Kessler et al., 2012.
colleagues (2013) found that an average of approximately 30 percent of students met the DSM criteria for a depressive disorder.

Women are twice as likely to be diagnosed with major depressive disorder as men. Yet these differences in the prevalence of depression between men and women may derive from different depressive symptoms occurring in men than those in women. Depressed men tend to exhibit greater irritability, over-reactivity, impulsivity, anger, aggression, and substance abuse as symptoms more often than women. Women are more likely to exhibit feelings of heavy, leaden feelings in arms or legs (known as lead paralysis) and greater fatigue (Winkler, Pjrek, & Kasper, 2005). These differences may result in women meeting the standard definitions of major depressive disorder more often than men. To determine whether this might be a factor, Martin, Neighbors, and Griffith (2013) examined rates of depression by comparing more conventional diagnostic criteria to criteria that included certain depressive symptoms more common in men. When factoring in aggression, substance abuse, and risk-taking behavior, the researchers found no differences in rates of depression between men and women.

Approximately, one out of six individuals with major depressive disorder commit suicide, and the Centers for Disease Control and Prevention (CDC) estimates that as many as 12 to 25 suicide attempts are made for every suicide death. Men are nearly twice as likely to commit suicide as women. Suicide is the third-highest cause of death in teenagers, but it is far more likely to occur in male adolescents and young adults than in female adolescents and young adults. One-third of those who commit suicide test positive for alcohol (Centers for Disease Control and Prevention, 2015). As we learned in Chapter 8, alcohol produces disinhibition, which, in this case can result in a shift from someone considering suicide to actually going through with it. This obviously makes alcohol consumption among those struggling with depression especially concerning.

**Review!** Disinhibition consists of a weakening of behavioral control that manifests as poor risk assessment, engagement in dangerous behavior, and impulsivity. Impulsivity consists of decision making without reflecting adequately on the consequences of those decisions. (Chapter 8.)

Across age groups, the prevalence of depression appears to be relatively balanced, as shown in Figure 13.1 (Kessler et al., 2005). Yet we do find high rates of depression among the elderly, and twice as many suicides occur among the elderly compared to other adult groups. We also find high rates of depression, 17 percent, among those with Alzheimer’s disease. Most elderly receive a diagnosis of depression from their primary doctors. Studies find, however, that most primary care doctors fail to make a diagnosis of depression for their elderly patients, and when a diagnosis is made, their doctors prescribe incorrect treatments (Alexopoulos, 2005).

A potential reason for depression in some elderly individuals may be poor blood flow to the brain. In advanced age, the vasculature throughout the body, including the brain, tends to harden and become less permeable to blood flow, which is critical for maintaining brain activity. In such a state, reduced brain activity may contribute
to a depressed mood. The term for depressed symptoms associated with poor blood flow in the brain is called **vascular depression** (Alexopoulos et al., 1997).

Just as we find a high prevalence of depression, we also find a high number of antidepressant prescriptions. In fact, the CDC states that antidepressants are the third most prescribed drugs among those 12 and older in the United States and the most prescribed drug among those between 18 and 44 years of age. Women are more than twice as likely to take antidepressant drugs than men, and more than one in five women ages 40 to 59 take antidepressant medications. In addition to the high frequency of being prescribed antidepressant drugs, most patients take these medications for at least 2 years (Pratt, Brody, & Gu, 2011).

### Neuroimaging Techniques and Functional Differences in Depression

The development of advanced neuroimaging equipment has significantly aided our understanding of depression. The structural abnormalities in depression involve many structures, including the amygdala, hippocampus, prefrontal cortex, and nucleus accumbens (**Table 13.2**). The **amygdala**, a brain structure that mediates feelings of fear and aggression, appears overactive in depression. Using positron emission tomography (PET), Drevets and colleagues showed that individuals with depression exhibit increased cerebral blood flow in the left amygdala (Drevets et al., 1992). This same research group later found increased glucose uptake, a further indication that neuronal activity also occurs in the amygdala during depression (Drevets, Bogers, & Raichle, 2002).

Magnetic resonance imaging (MRI) studies also reveal volume reductions in the hippocampus in depression. In an extensive review of imaging studies among depressed patients, Campbell, Marriott, Nahmias, and MacQueen (2004) found that
the majority of studies reported these reductions in depressed individuals compared to nondepressed individuals. As presented later in this chapter, researchers have an interest in the hippocampus because of the ability of antidepressant drugs to promote neuron growth in this structure.

Although the amygdala appears overactive in depression, studies indicate underactivity in the left dorsal prefrontal cortex during depression (Savitz & Drevets, 2009). For example, in a study conducted by Drevets and colleagues (2002), PET assessments using F-18-fluorodeoxyglucose in unmedicated patients with unipolar depression consistently revealed decreased metabolism in the dorsal prefrontal cortex. The volume of gray and white matter also appears reduced in the left and right dorsal prefrontal cortex in depression and seems to be related to the severity of depression (Chen et al., 2007).

Volume reductions also suggest irregularities in the basal ganglia. The basal ganglia includes the nucleus accumbens, found in the ventral portion of the basal ganglia, and the other basal ganglia structures that facilitate movement. Although movement disorders are not a feature of depression, approximately half of all Parkinson’s disease patients report a major depressive episode before the first occurrence of Parkinson’s symptoms (Santamaria, Tolosa, & Valles, 1986).

Experimental deep brain stimulation treatments for depression also suggest that the nucleus accumbens is underactive in depression. In one such procedure, Schlaepfer and colleagues (2008) implanted brain electrodes into the nucleus accumbens of three patients. After surgery, activating the electrode led to improvements in depression. In addition to these improvements, the patients spontaneously remarked about interests in doing something novel or something they had not done in many years. One patient, for example, said that she wanted to take up bowling again, and another patient wished to visit the Cologne Cathedral because it was nearby and he had never done so before.

**Antidepressant Drugs**

The first antidepressant drugs emerged during the 1950s when pharmacological treatments for mental illness were virtually unknown. The first antidepressant drug,
iproniazid (Marsilid), was developed for the treatment of tuberculosis in 1953 (Fox & Gibas, 1953). Loomer, Saunders, and Kline (1957) were the first to report a reduction in depressive symptoms among patients treated with iproniazid. Experimental animal findings showed that iproniazid reversed sedation and miosis produced by a drug called reserpine. (See Box 13.1 for information on the use of animal behavior models to identify antidepressant drugs.)

As was learned later, reserpine served to deplete the brain of monoamine neurotransmitters by irreversibly blocking transporters for synaptic vesicles (Carlsson, Lindqvist, Magnusson, 1957; Holzbauer & Vogt, 1956; Viveros, Arqueros, Connett, & Kirshner, 1969). This action subsequently leads to catabolism (i.e., enzymatic breakdown of a molecule) of these neurotransmitters. The irreversible blockage of transporters on synaptic vesicles prevents the storage of any newly synthesized neurotransmitters. As a result, newly synthesized neurotransmitters largely become catabolized before escaping the axon terminal (Plotscher, Shore, & Brodie, 1955). Early case reports in fact described a mental depression occurring from long-term treatment with reserpine (Freis, 1954). Thus, as noted earlier, reserpine served as an early model that helped to discover some of the first antidepressant drugs.

Another critical development stemming from studies on reserpine involved understanding the role that monoamine depletion played in Parkinson’s disease (a disorder we now link directly to dopamine depletion). During studies in the 1950s, researchers found that reserpine depleted norepinephrine in the brain (Carlsson, 2001; Holzbauer & Vogt, 1956). To determine if norepinephrine depletion might account for the sedation and loss of muscle movement caused by reserpine, Carlsson and colleagues administered a precursor for norepinephrine synthesis: levodopa. They reported their findings in 1957, stating that sedated rabbits woke up after treatment with levodopa and linked these effects to norepinephrine (recall that dopamine had yet to be identified as a neurotransmitter in the brain at this time) (Carlsson et al., 1957) (Figure 13.2). Oliver Sacks famously wrote of levodopa treatment in patients exhibiting catatonic-like behavior from encephalitis lethargica in his book Awakenings (1973), and you can see these accounts dramatized in the 1990 movie of the same title. Thus, studies on reserpine led to a greater understanding

**STOP & CHECK**

1. The _______________, a structure important for anxiety, is overactive in depression.
2. In depression, the left _______________ appears to be underactive and to have reduced gray and white matter volume.
3. The volume reduction in the _______________ is of particular interest because antidepressant drugs increase proliferation in this structure.

1. amygdala
2. dorsal prefrontal cortex
3. hippocampus
An important challenge during drug development is an ability to behaviorally identify effective medications. Researchers have developed animal behavioral procedures that, although not resembling depression in a human, predict antidepressant efficacy. The primary models used include the forced swim test, tail suspension test, and differential reinforcement of a low-rate, 72-second task.

The forced swim test is an animal behavioral model of depression that measures the length of time a small animal, usually a rat or mouse, will swim in a cylinder of water (Figure 1). When the animal determines escape is impossible, it assumes a floating posture and only commits movements necessary to keep its head above water. Antidepressant researchers coin this floating posture as behavioral despair. The test arose from studies by Porsolt, Le Pichon, and Jalfre (1977) showing the successful identification of clinically proven antidepressant drugs. The tail suspension test is an animal behavioral model of depression...
that measures the length of time a mouse will struggle to escape while being suspended by its tail (Figure 1). In this model, antidepressant treatments reduce the amount of time an animal gives up struggling, or despair (Cryan, Mombereau, & Vassout, 2005).

A differential reinforcement of low-rate reinforcement schedule (DRL-72 sec) requires a rat to withhold lever presses for food in an operant chamber until after 72 seconds have elapsed. If a rat presses the lever too soon, the 72-second counter resets. Only responses occurring after the full 72 seconds have passed result in food pellets. Thus, withholding responses for a period of time results in earning reinforcers. Antidepressant drugs, in this procedure, cause an increase in the reinforcement rate, defined as the number of food pellets earned over time, meaning that animals tend to wait

---

**FIGURE 2** Antidepressant drugs improve the efficiency of responding in rats trained on a differential reinforcement of low-rate 72-second operant schedule. Specifically, antidepressant drugs increase the reinforcement rate (shown by the solid symbols) and reduce the response rates (open symbols) compared to a control test (i.e., saline test). The data are graphed as percentages of control in order to easily show how each value can be compared to the control tests.

![Graph showing the effect of antidepressants on reinforcement and response rates](image)

**TABLE 13.1** ANIMAL BEHAVIORAL MODELS FOR IDENTIFYING ANTIDEPRESSANT DRUGS

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Reinforcement rate</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


(Continued)
longer before responding. In addition, response rates, defined as the number of responses that occur over a period of time, either increase or remain unchanged after acute administration of an antidepressant drug. We certainly many other drug classes capable of reducing responses in this procedure, but not without reducing overall response rates. Instead, antidepressant drugs enhance the likelihood of a rat waiting to respond until the right time, but they do not reduce responding overall. For example, benzodiazepine anxiolytic drugs (often referred to as tranquilizers) generally decrease both reinforcement and response rates. Figure 2 shows the effects of several tricyclic antidepressant effects on reinforcement and response rates in this task (O’Donnell, Marek, & Seiden, 2005).

of neurotransmission in the brain and helped to form theories about the causes of mental and neurological disorders.

Since these early days of the psychopharmacology era, the pharmaceutical industry has developed dozens of different antidepressant medications that vary in their pharmacological actions, clinical efficacy, and adverse effects. We classify antidepressant drugs according to their pharmacological actions and chemical structures, which has led to the following categories: monoamine oxidase (MAO) inhibitors, tricyclic antidepressant drugs, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and atypical antidepressant drugs (Table 13.3). Largely because of the actions of reserpine and early MAO inhibitors, researchers developed the monoamine hypothesis of depression. The monoamine hypothesis of depression states that a monoamine deficiency causes depressive mood. Although more than half a century of research has passed since these first drugs came out, we still develop antidepressant drugs largely based on this hypothesis (Skolnick & Basile, 2006).

Review! Monoamine neurotransmitters consist of dopamine, norepinephrine, and serotonin. (Chapter 3.)

Monoamine Oxidase Inhibitors Researchers have discovered and named two types of MAO: MAOₐ and MAOₐ. We find MAOₐ in the brain, peripheral nervous system, and the intestinal tract, whereas MAOₐ is found mainly in the brain and, to a lesser extent, in the peripheral nervous system. In the brain, MAOₐ resides in dopamine and norepinephrine neurons, and MAOₐ resides in serotonin and norepinephrine neurons (Mills, 1997).

Iproniazid became known as the first clinically used antidepressant drug among the MAO inhibitors. MAO inhibitors produce antidepressant effects by binding to MAO and preventing it from breaking down monoamine neurotransmitters, including...
serotonin, dopamine, and norepinephrine, as well as other monoamine compounds such as tyramine (Table 13.4). Depending on the particular drug, an MAO inhibitor may bind irreversibly or reversibly to MAO. For irreversible MAO inhibitors, the drug never releases from MAO. To make up for the loss of functional MAO enzymes, neurons synthesize more MAO. For reversible MAO inhibitors, the drug either temporarily binds to MAO or allows other compounds such as tyramine to displace the drug from MAO.

An adverse effect termed the cheese reaction limited the use of the first MAO inhibitors for treating depression. Clinicians characterize the cheese reaction as overactivation of the sympathetic nervous system because of MAO inhibition causing increased heart rate, hypertension, sweating, and inhibited digestion.
heart rate, hypertension (high blood pressure), sweating, and inhibited digestion. In fact, when severe enough, we refer to the high degree of hypertension occurring here as a hypertensive crisis. This reaction occurs when MAO inhibition increases the levels of norepinephrine and tyramine. Norepinephrine activates $\beta_1$ adrenoceptors on cardiac tissue, causing increased heart rate and strength of muscle contractions. Tyramine, which does not cross the blood-brain barrier, likely enhances these effects by displacing stored norepinephrine in sympathetic nervous system neurons, causing some norepinephrine to leak from axon terminals and contribute to the activation of $\beta_1$ adrenoceptors (Axelrod, Gordon, Hertting, Kopin, & Potter, 1962; Graefe, Bossle, Wolfel, & Burger, 1999).

Modern MAO inhibitors reduce, but do not eliminate, the risk of a cheese reaction. The first type of modern MAO inhibitors were selective inhibitors of MAO$_B$. $\textbf{Selective MAO}_B$ inhibitors, such as selegiline (Emsam), have a greater affinity for MAO$_B$ than MAO$_A$, thereby engendering most of their effects through acting in the brain. Selegiline also can be administered through a skin patch, allowing the drug to bypass the intestinal tract, where it would otherwise cause some build-up of tyramine.

The second type of modern MAO inhibitors are reversible inhibitors of MAO$_A$ (abbreviated as RIMA). $\textbf{RIMA drugs}$ selectively inhibit MAO$_A$ but allow for displacement…

<table>
<thead>
<tr>
<th>Monoamine Oxidase Inhibitors</th>
<th>Tricyclic Antidepressant Drugs</th>
<th>Selective Serotonin Reuptake Inhibitors</th>
<th>Serotonin-Norepinephrine Reuptake Inhibitors</th>
<th>Atypical Antidepressant Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iproniazid (Marsilid)</td>
<td>Amitriptyline (Elavil)</td>
<td>Citalopram (Celexa)</td>
<td>Duloxetine (Cymbalta)</td>
<td>Agomelatine (Valdoxan or Thymanax)</td>
</tr>
<tr>
<td>Moclobemide (Aurorix)</td>
<td>Clomipramine (Anafranil)</td>
<td>Dapoxetine (Priligy)</td>
<td>Milnacipran (Ixel, Savella)</td>
<td>Bupropion (Wellbutrin)</td>
</tr>
<tr>
<td>Phelozine (Nardil)</td>
<td>Desipramine (Pertofrane)</td>
<td>Escitalopram (Lexapro)</td>
<td>Venlafaxine (Effexor)</td>
<td>Mirtazapine (Remeron)</td>
</tr>
<tr>
<td>Selegiline (Emsam)</td>
<td>Imipramine (Tofranil)</td>
<td>Fluoxetine (Prozac)</td>
<td>Vortioxetine (Brintellix or Trintellix)</td>
<td></td>
</tr>
<tr>
<td>Tranylcypromine (Parnate)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Fluvoxamine (Luvox)</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Indalpine (Upstene)</td>
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<td></td>
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<tr>
<td></td>
<td>Paroxetine (Paxil)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sertraline (Zoloft)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Moclobemide (Aurorix, Manerix) is a RIMA clinically available for depression in Canada and Europe, but the weak efficacy of the drug failed to gain it FDA approval in the United States (Youdim, 2006).

TABLE 13.4 Pharmacological Actions of Antidepressant Drugs

<table>
<thead>
<tr>
<th>Antidepressant Drug Class</th>
<th>Pharmacological Actions</th>
<th>Neurotransmitter Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAO inhibitors</td>
<td>Inhibit MAO, preventing catabolism of monoamine neurotransmitters</td>
<td>Increase dopamine, norepinephrine, and serotonin</td>
</tr>
<tr>
<td>Tricyclic antidepressant drugs</td>
<td>Inhibit reuptake of serotonin and norepinephrine; binds to various receptors</td>
<td>Increase serotonin and norepinephrine levels</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>Inhibit reuptake of serotonin</td>
<td>Increase serotonin levels</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</td>
<td>Inhibit reuptake of serotonin and norepinephrine</td>
<td>Increase serotonin and norepinephrine levels</td>
</tr>
<tr>
<td>Atypical antidepressant drugs</td>
<td>Vary depending on the particular drug</td>
<td>Generally increase one or more monoamine neurotransmitters</td>
</tr>
</tbody>
</table>

STOP & CHECK

1. What was the first antidepressant drug, iproniazid, actually developed for?

2. A deficiency of dopamine, norepinephrine, or serotonin is the basis for the __________ hypothesis of depression.

3. MAO is found in the intestinal tract, peripheral nervous system, and the brain, whereas MAO is primarily found in the _________.

4. Why might a reversible MAO inhibitor be preferable to an irreversible MAO inhibitor to treat depression?

Tricyclic Antidepressant Drugs  Tricyclic antidepressant drugs inhibit reuptake of norepinephrine and serotonin and function as antagonists for various receptors, often including muscarinic acetylcholine receptors (Table 13.4) (Lenox & Frazer, 2002).
Tricyclic antidepressant drugs

Antidepressant drugs that inhibit the reuptake of norepinephrine and serotonin and function as antagonists for various receptors.

Tricyclic refers to three connected benzene rings shared by drugs in this category. Chemists developed the first drug tricyclic antidepressant drug, imipramine, in an attempt to produce drugs similar to the first antipsychotic drug chlorpromazine (Thorazine) for the purpose of treating schizophrenia (Davis, 2006). Although failing to effectively treat schizophrenia, clinicians noticed improvements in mood, prompting clinical testing for depression instead (Kuhn, 1958).

Tricyclic antidepressant drugs provide certain pharmacological actions similar to MAO, but do so through a different mechanism. Tricyclic antidepressants achieve elevations in serotonin and norepinephrine levels by inhibiting reuptake at membrane transporters, rather than through inhibiting catabolism of neurotransmitters as MAO inhibitors do. This also avoids a cheese reaction from occurring with tricyclic antidepressant drugs, although these drugs have unique adverse effects of their own.

A number of adverse effects occur from tricyclic antidepressant drugs binding to various receptors in the nervous system. Most tricyclic antidepressant drugs serve as antagonists for cholinergic muscarinic receptors. In the parasympathetic nervous system, blocking muscarinic receptors causes dry mouth, dry eyes, constipation, urinary retention (from a lack of bladder relaxation), and various other effects related to blocking neurotransmission in this system. As a result of dry eyes, blurred vision also may occur. In the brain, blocking muscarinic receptors can also lead to impairments in memory and cognitive functioning (Lenox & Frazer, 2002).

Many tricyclic antidepressants also block α₁ adrenoceptors, causing vasodilation and effects similar to orthostatic hypotension, low blood pressure typically noted by an individual feeling lightheaded or dizzy when suddenly standing up. Greater blood flow to the head resulting from vasodilation may also cause headaches and the feeling of a “head rush.” Many of these drugs act as histamine H₁ receptor antagonists, which cause sedative effects just as antihistamine cold medicines do. In addition, tricyclic antidepressants are known to cause weight gain, which can lead to a variety of health concerns, including type II diabetes (Brown, Majumdar, & Johnson, 2008; Lenox & Frazer, 2002). Taking all of these adverse effects in mind, it’s not surprising that patients prescribed tricyclic antidepressants report feeling “drug laden,” which can reduce patient compliance (i.e., the likelihood of a patient continuing to take the prescribed medication) (Lenox & Frazer, 2002).

STOP & CHECK

1. Tricyclic antidepressants reduce depressive symptoms by preventing the reuptake of ___________ and ___________.

2. What effect might the adverse effects of tricyclic antidepressant drugs have on patient compliance?
Review! Adrenoceptors are the receptors for the neurotransmitter norepinephrine. (Chapter 3.)

**Selective Serotonin Reuptake Inhibitors (SSRIs)** The pharmacological actions of tricyclic antidepressant drugs established a directed effort to develop drugs that selectively inhibited the reuptake of serotonin or norepinephrine. Based on these pharmacological actions and other experimental support for the specific influence of serotonin on mood, Arvid Carlsson worked with Astra Pharmaceuticals to develop zimelidine (Zelmid) for the treatment of depression (Shorter, 1997). Thus, zimelidine was the first selective serotonin reuptake inhibitor. A **selective serotonin reuptake inhibitor (SSRI)** elevates serotonin levels by blocking reuptake through serotonin membrane transporters (Table 13.4). Beginning in 1981, zimelidine was marketed in Europe for a limited time, but was abruptly withdrawn from the market because it damaged myelin sheathing around central and peripheral nervous system axons.

Researchers at Eli Lilly discovered a safer SSRI—fluoxetine—which is best known by its trade name Prozac. Fluoxetine met FDA approval for the treatment of depression in 1987. It was found to be generally safer than MAO inhibitors and tricyclic antidepressant drugs, and fluoxetine became one of the most prescribed drugs in history (Shorter, 1997).

Because of their perceived safety, SSRIs have been prescribed for depression in teens and children. However, in 2005 the FDA issued a **black box warning** (or **boxed warning**), a warning on the package insert given a black border around to draw special attention to it, that SSRIs increased suicide risk in teens and children (Food and Drug Administration, 2005). This warning was based on a review of published clinical studies in teens that together indicated a higher suicide rate (4 percent) compared to placebo-treated patients (2 percent). This warning does not ban the use of these medications in children and teens, but rather, indicates that physicians must carefully monitor suicidal tendencies after prescribing these medications.

We find other significant concerns for SSRIs as well. They may cause a **serotonin syndrome**, a life-threatening condition characterized by agitation, restlessness, disturbances in cognitive functioning, and possibly hallucinations. This syndrome is usually avoided by taking low or moderate doses of an SSRI, although a drug reaction with another serotonin compound, such as a different antidepressant drug or lithium can increase the risk of serotonin syndrome (Sternbach, 1991).

Just as taking SSRIs might lead to a serotonin syndrome, abrupt withdrawal from SSRI treatment may cause a serotonin **discontinuation syndrome**. The **serotonin discontinuation syndrome** is characterized by sensory disturbances, sleeping disturbances, disequilibrium, flu-like symptoms, and gastrointestinal effects. Those seeking to discontinue SSRI use must slowly wean themselves from the medication by reducing the amount taken over time (Sternbach, 1991).

Elevations in serotonin levels are likely to cause **sexual side effects**, including erectile dysfunction, inability to achieve orgasm, and loss of sexual drive. In a survey asking patients taking SSRIs to determine how they felt compared to their usual state, the majority of those surveyed reported far less interest in having sex and less pleasure during sex (Opbroek et al., 2002; see Figure 13.2). These side effects negatively affect one’s quality of life and contribute to poor patient compliance with these medications.
An often overlooked adverse effect of SSRIs is a condition referred to as *emotional blunting*. **Emotional blunting** (or **affective blunting**) consists of feelings of emotional detachment along with experiencing reduced positive and negative emotions. Patients describing these reduced emotional feelings insist that they result from the medication, rather than depression, and use labels such as “dulled,” “flattened,” or “numbed” to express how they feel (Price, Cole, & Goodwin, 2009). Thus, a person with emotional blunting may not seem particularly sad or happy, just neutral.

We gain some insight into emotional blunting among patients treated with SSRIs from a survey conducted by Opbroek and colleagues (2002). The patients studied consisted of those reporting sexual dysfunction and in the course of evaluation were surveyed on other items to determine how they felt compared to their “usual” feelings of emotional detachment along with experiencing reduced positive and negative emotions.

![Average scores on a questionnaire asking SSRI-treated patients how they currently felt compared to their “usual” state.](image)

**FIGURE 13.3**

<table>
<thead>
<tr>
<th>LEIS items</th>
<th>A lot more</th>
<th>Somewhat more</th>
<th>Same as usual</th>
<th>Somewhat less</th>
<th>A lot less</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to cry</td>
<td>Feel motivaed</td>
<td>Feel interested in sex</td>
<td>Feel satisfied</td>
<td>Feel irritated or upset</td>
<td>Feel sad</td>
</tr>
<tr>
<td>Care about others’ feelings</td>
<td>Enjoy eating</td>
<td>Have erotic dreams</td>
<td>Have creativity</td>
<td>Become interested and involved in work</td>
<td>Experience worry</td>
</tr>
<tr>
<td>Experience sexual interest</td>
<td>Have energetic</td>
<td>Feel surprised</td>
<td>Expression of feelings</td>
<td>Pleasure during sex</td>
<td>Involved and interested in work</td>
</tr>
</tbody>
</table>
state. Figure 13.3 provides their average responses. In particular, we find a substantial reduction in sexual interest and enjoyment, as reported above, and many of the participants reporting a lower ability to cry, become angry, care about the feelings of others, and feel creative.

STOP & CHECK

1. SSRIs enhance serotonin levels by blocking ______________.  
2. High doses of an SSRI may cause a ______________, which is characterized by agitation, restlessness, cognitive disruption, and hallucinations.  
3. Abrupt withdrawal from SSRI treatment causes a _________________.

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) Serotonin–norepinephrine reuptake inhibitors (SNRIs), which are also called dual serotonin and norepinephrine reuptake inhibitors, enhance levels of serotonin and norepinephrine by blocking serotonin and norepinephrine membrane transporters. The push for a new antidepressant drugs led to the development of venlafaxine (Effexor), the first of the class of SNRIs. Venlafaxine (Effexor) received FDA approval for the treatment of depression in 1993. Venlafaxine and other SNRIs, such as duloxetine (Cymbalta), are at least as effective as SSRIs for the treatment of depression, and some studies conclude that SNRIs are more effective. As inhibitors of serotonin reuptake, they share the same adverse effects as SSRIs.

Papakostas, Thase, Fava, Nelson, and Shelton (2007) conducted a meta-analysis on clinical depression studies that used either an SSRI or an SNRI to determine which class was the most effective. The literature review was extensive, including more than 90 trials and more than 17,000 patients. In each comparison, an SNRI produced a slightly greater improvement than an SSRI. The effects were modest, but consistent (Figure 13.4).

Another disorder linked, at least in part, to stress is fibromyalgia. Fibromyalgia syndrome is a musculoskeletal disorder characterized by widespread pain occurring as muscle tenderness in addition to other symptoms including fatigue, disrupted sleep, and depressed mood (Abeles, Pillinger, Solitar, & Abeles, 2007). The disorder occurs in among 3.4 percent of women and 0.5 percent of men in the United States (Wolfe, Ross, Anderson, Russell, & Herbert, 1995). The cause of fibromyalgia remains unknown but likely involves multiple interaction mechanisms including sensitization of pain pathways, reduced neurotransmission of monoamine neurotransmitters, and a current or previous mental disorder, such as depression or anxiety (Abeles et al., 2007). Pain levels, which fluctuate throughout the day, are particularly worsened by stress (Fischer et al., 2016).
According to a review of antidepressant clinical trials, SNRIs (shown in light blue) consistently reveal greater improvements in depressive symptoms than SSRIs (shown in dark blue). However, these differences were seldom robust. The particular SNRI studied is noted on the x-axis, and the “combined” label refers to all studies combined.

Both norepinephrine and serotonin, among many other neurotransmitters, have been shown to modulate pain signaling (Millan, 2002). The notion that diminished norepinephrine and serotonin levels in fibromyalgia may contribute to increased pain sensitivity led to testing different types of antidepressant drugs. Arnold and colleagues (2004) reported one of the major findings in this area—that the SNRI duloxetine reduced pain and other features of fibromyalgia in both depressed and non-depressed patients. Antidepressant drugs, especially those of the SNRI class, have become the first-line pharmacological treatments for fibromyalgia. Aside from antidepressant drugs, the drug pregabalin (Lyrica) also is used (Crofford et al., 2005). Unlike the antidepressant drugs, pregabalin facilitates GABA neurotransmission, thereby attenuating pain signals to the brain as well as potentially reducing stress. Non-pharmacological treatment strategies include physical therapy, relaxation techniques, cognitive–behavioral therapy, and exercise (Rossy et al., 1999).

**Atypical Antidepressant Drugs**

Atypical antidepressant drugs (or multimodal antidepressant drugs) reduce depression through mechanisms that differ from those of other antidepressant classifications. They are neither MAO inhibitors nor tricyclic antidepressants. Nor do atypical antidepressant drugs selectively block either serotonin reuptake, norepinephrine reuptake, or both. Thus, this category is a bit of a catch-all for antidepressant drugs that do not fit into other antidepressant drug categories. All
atypical antidepressants drugs currently available alter neurotransmission for one or more
monoamine neurotransmitters.

One of the most prescribed atypical antidepressant drugs is *bupropion* (*Wellbutrin*). Bupropion is a reuptake inhibitor for norepinephrine and dopamine and therefore is unique among the antidepressants for its lack of serotonin elevation. Given the lack of serotonin effects, bupropion does not carry a risk for serotonin syndrome, and it does not have a risk of sexual side effects (Ascher et al., 1995).

Controversy surrounds the atypical antidepressant drug *reboxetine*, which functions as a selective norepinephrine reuptake inhibitor. Clinical study data released in the 1990s indicated superior, long-term antidepressant effects and a low rate of adverse effects compared to placebo (Burrows, Maguire, & Norman, 1998). Such findings allowed approval of reboxetine for use in Europe, but the FDA denied approval based on unpublished clinical data that reboxetine’s drug maker, Pfizer, was required to release under U.S. law (but not required to release in Europe) (Szalavitz, 2010). A study examining these unpublished data together with published data concluded that reboxetine not only lacked clinical efficacy for depression, but that the unpublished data revealed greater adverse effects from the drug than published data had indicated (Eyding et al., 2010).

A recently developed atypical antidepressant drug is *vortioxetine* (*Brintellix, Trintellix*), which met FDA approval in 2013. Like SNRIs, vortioxetine inhibits serotonin reuptake, and to a more modest extent, also inhibits norepinephrine reuptake (Bang-Andersen et al., 2011). Researchers classified vortioxetine as an atypical antidepressant because of its additional effects at a host of serotonin receptors, serving as an antagonist for some serotonin receptors (e.g., 5-HT3) and an agonist for other receptors (e.g., 5-HT1A) (Sanchez, Asin, & Artigas, 2015).

Another atypical antidepressant drug is *agomelatine* (*Valdoxan or Thymanax*), a drug approved for use in Europe but not currently approved by the FDA for use in the United States. Agomelatine acts as an agonist for melatonin receptors and an antagonist for serotonin 5-HT2c receptors. Studies find that agomelatine restores sleep patterns among study participants with major depressive disorder, likely by acting on melatonin receptors. Researchers also report reduced depression among agomelatine-treated patients compared to those treated with placebo. While not serving as a reuptake inhibitor for monoamine neurotransmitters, antagonism of 5-HT2c receptors may produce increased levels of dopamine, as discussed later in this chapter. Consistent with these pharmacological actions, clinical trials with agomelatine did not find increased rates of sexual dysfunction (Sansone & Sansone, 2011).

**STOP & CHECK**

1. How does the efficacy and safety of SNRIs compare to SSRIs?
2. What is atypical about atypical antidepressant drugs?
Review! Melatonin is a sleep inducing hormone that plays an important role in circadian rhythm, our natural sleep cycle. (Chapter 3.)

Limitations in Antidepressant Drug Effectiveness and Development

Although antidepressant drug classes differ pharmacologically and have unique adverse effects, they share many of the same limitations for treating depression. We consider three issues in this section: length of response time, treatment resistance, and strong placebo effects in clinical trials. The “From Actions to Effects” section later in this chapter also considers pharmacogenetic factors in antidepressant response.

Length of Response Time All antidepressant drugs have a lengthy response time. For those who eventually respond to antidepressant drugs, clinically significant effects occur after 2 weeks of treatment and generally show full effects after 4 weeks. If patients fail to respond sufficiently after 4 weeks, then the likelihood of successful treatment with the drug diminishes. The long response time is particularly concerning when treating patients with a high risk of suicide (Nierenberg et al., 2000).

Treatment Resistance Many patients may fail to respond adequately to antidepressant treatment. Fava and Davidson (1996) estimated that between 29 and 46 percent of patients fail to fully recover with antidepressant drug treatment. In these cases, clinicians may increase the dose of the SSRI, add another medication (see following), or switch altogether to a different antidepressant drug. We identify an individual as having treatment-resistant depression after successive failed attempts to significantly reduce depressive symptoms by antidepressant medication, including a treatment course with an SSRI (Trivedi et al., 2006).

Placebo Effects in Clinical Studies Placebo effects present an important issue for drug developers during clinical trials for antidepressant drugs. To gain governmental approval, novel antidepressant drugs must be tested in clinical trials that compare the novel drug to placebo. When conducting clinical trials with antidepressant drugs, a clinically significant improvement often occurs in placebo-treated patients. This requires a novel antidepressant drug to produce clinical effects that significantly exceed those found with placebo. Given these strong placebo effects combined with the cautious nature of clinical drug testing, researchers may fail to find clinically significant antidepressant drug effects.

The placebo effect is a criticism of antidepressant efficacy. As raised by Kirsch (2014) and many others, the placebo effect indicates a lack of clinical efficacy by many antidepressant drugs brought to clinical trials. According to analysis conducted of FDA clinical trials, only 43 percent reported clinical improvements beyond those observed from placebo. Moreover, the observation that non-antidepressant drugs occasionally produced supposedly antidepressant effects over placebo in some trials has led to the criticism that perhaps any perceived drug effect by a study participant interpreted an antidepressant effect, thus resulting in reduced rates of depression. Said another way, an antidepressant drug might actually be a placebo (Kirsch, 2014).

In an unexpected way, the lack of efficacy by reboxetine (mentioned earlier) might serve as a counterargument to claims that antidepressant drugs are simply placebos. As
noted earlier, unpublished clinical data revealed a lack of efficacy for depression, but also higher rates of adverse effects. Thus, study participants found a lack of antidepressant efficacy despite experiencing clear drug effects (Szalavitz, 2010).

STOP & CHECK

1. How many weeks does it take for antidepressant drugs to become effective?
2. Treatment-resistant depression is often identified after failed treatment with a(n) ____________.
3. A particular challenge in antidepressant clinical trials is that patients often improve when taking a(n) ________________.

1. At least two to four weeks
2. SSRI
3. placebo

Combination Strategies for Treating Depression With Antidepressant Drugs

Recent years have seen an emergence of combination strategies for antidepressant treatments. The purpose of a combination drug strategy is to administer a medication to adjust the effects of another medication. We find a number of different terms used to describe these approaches. For drugs intended to boost the therapeutic effects of a medication, we use the term augmentation strategy (or adjunctive treatment or adjunctive therapy). Add-on treatments simply imply an adjustment of a medication’s effects by another drug, in this case identical to the term combination drug strategy referred to earlier. Yet, most times we find “add-on treatment” regarded as synonymous with “augmentation strategy.” Unfortunately, the imprecise usage of these common terms for describing combined treatment strategies leaves one guessing as to the purposes of a combined drug strategy.

We find the use of antipsychotic drugs—drugs developed for treating schizophrenia—as adjunctive treatments (i.e., to strengthen antidepressant effects in this context) for patients who do not respond adequately to antidepressant drugs. Normally, these patients meet the criteria for treatment resistance, as described earlier. Chapter 15 covers antipsychotic drugs in detail, but in general we find that antipsychotic drugs act at dopamine and serotonin receptors, usually as antagonists.

The antipsychotic drugs most commonly used as adjunctive medications, as well as meeting FDA approval for this purpose, are aripiprazole (Abilify), quetiapine (Seroquel), and olanzapine (Zyprexa). We also find risperidone (Risperdal) used off-label (that is, a nongovernment approved use of a clinically available drug) for this purpose. Olanzapine is approved for use only in combination with fluoxetine; in fact, we find a combined olanzapine and fluoxetine pill marketed under the trade name Symbyax. These antipsychotic drugs fall under the atypical class of antipsychotic drugs, which differ in

Combination drug strategy The administration of a medication to adjust the effects of another medication
Augmentation strategy (or adjunctive treatment/therapy) Administration of a drug intended to boost the therapeutic effects of a medication
Add-on treatment The administration of a medication to adjust the effects of another medication; often used to describe a drug boosting the therapeutic effects of a medication
Off-label A nongovernment approved use of a clinically available drug
their therapeutic and adverse effects in some ways compared to many older antipsychotic drugs, termed typical antipsychotic drugs (again, more on this in Chapter 15).

<table>
<thead>
<tr>
<th>Drug Profile: sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade name</strong></td>
</tr>
<tr>
<td><strong>Properties</strong></td>
</tr>
<tr>
<td><strong>Uses</strong></td>
</tr>
<tr>
<td><strong>Similar drugs</strong></td>
</tr>
</tbody>
</table>

In a review of clinical studies that examined the efficacy of atypical antipsychotic drugs as adjunctive treatments for depression, Speilmans and colleagues (2013) found that atypical antipsychotic drugs do provide improvements, albeit modest, in depression symptoms, quality of life, and functional outcomes (e.g., improvements in social and occupational functioning). The study authors also noted that a lack of long-term studies on antipsychotic drugs used adjunctively with antidepressant drugs left them uncertain as to whether potential adverse effects might offset the minimal therapeutic benefits derived from these adjunctive treatment approaches.

We also find drugs used as combination treatments to remedy certain adverse effects brought on by antidepressant medications. A typical example of this is bupropion (Wellbutrin) as an add-on medication for treating sexual dysfunction produced by antidepressant drugs, particularly for drugs that inhibit serotonin reuptake (e.g., SSRIs and SNRIs). While used off-label for this purpose, practitioners have for years prescribed bupropion as an add-on therapy to address this particular adverse effect. In reviews of published studies evaluating bupropion for reducing sexual dysfunction from SSRIs or SNRIs, bupropion appears to reduce sexual dysfunction from a moderate to substantial degree. These improvements mostly occur in women. Among men, medications that treat erectile dysfunction (i.e., impotence), such as sildenafil (Viagra) and tadalafil (Cialis), instead appear more effective than bupropion as add-on treatments for treating sexual dysfunction from antidepressants drugs (Taylor et al., 2013). These drugs treat erectile dysfunction by inhibiting phosphodiesterase isozymes that diminish the duration and rigidity of an erection (Boolell et al., 1996; Brock et al., 2002).

**Combining Psychotherapy and Pharmacotherapy for Treating Depression**

The general consensus reached from clinical studies is that a combination of psychotherapy and antidepressant drugs is superior to using antidepressant drugs alone. One of the more common psychotherapies evaluated in combination studies consists of cognitive therapy. Cognitive therapy attempts to adjust one’s depressive thoughts (e.g., “I’ll never be happy” or “I fail at everything”) as a means for improving mood. Combining a cognitive therapy with an SSRI, SNRI, or atypical antidepressant drug has
been shown to produce greater efficacy for major depressive disorder than using an antidepressant alone or cognitive therapy alone (Hollon et al., 2014; Keller et al., 2000; Thase et al., 1997). Yet a combination of a tricyclic antidepressant drug with psychotherapy does not appear more effective than psychotherapy alone (Blackburn, Bishop, Glen, Whalley, & Christie, 1981; Hollon et al., 1992).

The benefits derived from a combined approach versus using an antidepressant drug or psychotherapy alone may also depend on the severity of depression. In one study, those with milder depressive symptoms benefited just as well with psychotherapy alone as they did with a combination of psychotherapy with an antidepressant drug. Yet in severe cases of depression, the combination appeared most effective (Thase et al., 1997).

STOP & CHECK

1. What terms describe a drug used to boost the therapeutic effects of a medication?
2. What type of drug is used to boost the antidepressant effects of an antidepressant drug?
3. Which particular adverse effect might bupropion or a drug like Viagra be prescribed as an add-on for an antidepressant drug?
4. Aside from another medication, what might be combined with an antidepressant drug to improve a patient’s response to treatment?

Antidepressant Drugs and Monoamine Neurotransmitter Systems

Although imaging procedures conducted in depressed patients help us to identify brain regions involved in depression, these techniques tell us nothing about the neurochemical abnormalities found in depression. Thus, we are largely left to study the actions of antidepressant drugs as a means to infer potential neurochemical abnormalities in depression. Although this approach is not ideal, it has led to the development of many therapeutic psychoactive drugs on the market today.

Antidepressant Drugs and Serotonin Neurotransmission One of the mechanisms important for producing antidepressant effects concerns altering serotonin neurotransmission. We find that most antidepressant drugs increase serotonin levels after administration, either through reducing catabolism of serotonin (as with the MAO inhibitors) or by preventing reuptake of serotonin (as with SSRIs, SNRIs, and many
tricyclic antidepressant drugs). As a result, greater activation of serotonin receptors occurs. Some antidepressant drugs also directly bind to serotonin receptors, which helps researchers to understand which serotonin receptors may be most important for treating depression.

The serotonin receptor most studied for a role in depression and as a target for treating depression is the 5-HT$_{2c}$ receptor. We find 5-HT$_{2c}$ receptors activated when antidepressants drugs increase serotonin levels. Yet we also find that many antidepressant drugs directly bind to and serve as antagonists for these receptors. Antidepressant drugs serving as antagonists for 5-HT$_{2c}$ receptors include the tricyclic antidepressant drugs imipramine and clomipramine and the SSRI fluoxetine (Millan, 2005; Ni & Miledi, 1997). Further, drugs acting as selective antagonists for 5-HT$_{2c}$ receptors produce antidepressant effects in animal models. Antagonism of 5-HT$_{2c}$ receptors appears to increase dopamine levels in the brain (see following), which may contribute to antidepressant effects. To account for antidepressant drugs that produce an activation of 5-HT$_{2c}$ receptors (i.e., through increasing serotonin levels), researchers generally agree that chronic treatment with an antidepressant drug will eventually desensitize 5-HT$_{2c}$ receptors. The desensitization of 5-HT$_{2c}$ receptors results in a state similar to one achieved by an antagonist acting at these receptors (Martin, Hamon, Lanfumey, & Mongeau, 2014).

The 5-HT$_{1A}$ receptor is another receptor implicated in depression and the actions of antidepressant drugs. In people with major depressive disorder who were never treated with an antidepressant drug, PET imaging studies reveal greater 5-HT$_{1A}$ receptors levels compared to those without depression (Parsey et al., 2006; Parsey et al., 2010; Kaufman, DeLorenzo, Choudhury, & Parsey, 2016). In mice bred to exhibit helplessness as a model of depression, researchers found increased levels of 5-HT$_{1A}$ receptors in structures thought important for depression, including the prefrontal cortex, amygdala, and hippocampus (Naudon, El Yacoubi, Vaugeois, Leroux-Nicollet, & Costentin, 2002). This study further found that chronic administration with an SSRI reduced both depression-like behavior in these mice and 5-HT$_{1A}$ receptor levels. 5-HT$_{1A}$ receptors may also account for depression observed among some individuals treated with the medication isotretinoin (Accutane) for acne (Hull & D’Arcy, 2003). A study examining this medication and receptor expression found that isotretinoin increased 5-HT$_{1A}$ receptor levels on cell lines, providing a potential explanation for greater rates of depression among those treated with isotretinoin (O’Reilly, Trent, Bailey, and Lane, 2007; Kaufman et al., 2016).

The black box warning noted earlier for SSRIs concerned a potential increased risk of suicide in teens. This increased risk likely occurs from a potential reduction in serotonin during the first days of treatment. After these first days, serotonin should increase as desensitization of receptors that would otherwise inhibit the activity of serotonin neurons occurs. We address the model and precise receptors that may be responsible for diminished serotonin levels in the next chapter (Chapter 14, “From Actions to Effects”).

The hypothesis that diminished serotonin levels initially caused by antidepressants may increase risk of suicide coincides with studies examining serotonin metabolite levels in the cerebrospinal fluid of suicide attempters. Many studies have examined metabolite levels in cerebrospinal fluid among suicide attempters in order to infer the level of serotonin neurotransmission occurring in the central nervous system. Low
metabolite levels suggest diminished production of serotonin in the central nervous system. Researchers consistently find diminished serotonin metabolite levels among depressed patients who attempt suicide compared to depressed patients who do not attempt suicide, irrespective of treatment type (Åsberg, Träskman, & Thorén, 1976; Mann, & Malone, 1997; Nordström et al., 1994).

**Antidepressant Drugs and Dopamine Neurotransmission** Several lines of evidence also suggest that dopamine is critical for antidepressant effects. We begin by noting that acute administration of most antidepressant drugs fails to increase dopamine release or cause other changes in dopamine neurotransmission within the limbic system (Pozzi, Invernizzi, Garavaglia, & Samanin, 1999). Yet during the course of chronic administration with antidepressant drugs, including the tricyclic antidepressant drugs tianeptine, imipramine, and the SSRI fluoxetine, dopamine levels increase in the nucleus accumbens (D’Aquila, Collu, Gessa, & Serra, 2000). These actions in the nucleus accumbens may treat anhedonia (a lack of joy) in depression.

Chronic administration with fluoxetine also increases the availability of dopamine D_2 receptors in the limbic system. In a study by Maj, Dziedzicka-Wasylewska, Rogoz, Rogoz, and Skuza (1996), a greater density of limbic system D_2 receptors was found in rats chronically treated with fluoxetine compared to rats treated with vehicle (i.e., placebo). In another study, chronic administration with fluoxetine, the tricyclic antidepressant drug desipramine, or the MAO inhibitor tranylcypromine, produced increases in nucleus accumbens levels of mRNA that encode for the synthesis of D_2 receptors (Ainsworth, Smith, & Sharp, 1998). Given that increases in dopamine release and dopamine D_2 receptors occur in the limbic system after chronic administration, many researchers suspect that these changes, in part, account for the lengthy response time for antidepressant drugs (Skolnick & Basile, 2006).

Elevations in dopamine levels in the prefrontal cortex may occur after acute or chronic administration of an antidepressant drug, depending on the particular drug. For example, Bymaster and colleagues (2002) found that among the SSRI drugs they studied after acute administration, only fluoxetine produced increases in prefrontal cortex dopamine levels as assessed using microdialysis in rats. The researchers noted that fluoxetine was the only drug in their study that served as an antagonist for 5-HT_2c receptors. Selective antagonism of 5-HT_2c has been shown to increase dopamine concentrations in the frontal cortex, suggesting a potential mechanism for some antidepressant drugs to increase dopamine levels in the prefrontal cortex after acute administration (Gobert et al., 2000). Otherwise, antidepressant drugs increase dopamine levels in the prefrontal cortex after chronic administration (Carlson, Visker, Nielsen, Keller, & Glick, 1996; Tanda, Frau, & Di Chiara, 1996).

A potential link between prefrontal cortical dopamine levels and antidepressant effects may account for observations of antidepressant efficacy from the dissociative anesthetic drug ketamine. Ketamine’s antidepressant effects were first reported by Berman and colleagues (2000), who assessed intravenous infusion of a low ketamine dose to seven volunteers with major depressive disorder. Patients exhibited an immediate reduction in depressive symptoms that lasted as long as 3 days after treatment. A subsequent study found that ketamine’s antidepressant effects lasted as long as 1 week (Zarate et al., 2006).
Ketamine is an NMDA noncompetitive receptor antagonist and dissociative anesthetic that causes visual hallucinations, out-of-body experiences, cognitive impairment, and psychosis. (Chapter 12.)

These antidepressant effects appear to result from ketamine’s actions in the prefrontal cortex. In laboratory rats, ketamine administration increases both dopamine and glutamate concentrations in the prefrontal cortex (Lorrain, Baccei, Bristow, Anderson, & Varney, 2003). Moreover, Li and colleagues (2010) revealed rapid prefrontal cortical synaptic changes, including dendritic spine growth and increased proteins used for intracellular signaling, after acute administration. In particular, ketamine activated a protein kinase called mammalian target of rapamycin, which is normally abbreviated as mTOR. The effects of ketamine also may alter dopamine levels in the limbic system, based on the finding that a direct administration of the NMDA receptor antagonist called CPP (an abbreviation of its chemical name\(^1\)) into the prefrontal cortex causes increased dopamine levels in the nucleus accumbens (Del Arco, Segovia, & Mora, 2008) (Figure 13.5). It remains to be seen if ketamine will someday be used as an antidepressant drug itself or instead if ketamine will remain a compound for research purposes, perhaps paving the way for a new class of antidepressant drugs (Hillhouse & Porter, 2015; Krystal, Sanacora, & Duman, 2013).

Recent studies have also evaluated cholinergic muscarinic receptor antagonists as antidepressant drugs. In particular, the drug scopolamine, which is known as a psychedelic drug used for recreational purposes (see Chapter 12), has been tested in multiple clinical trials for treating depression. Furey and Drevets (2006) first demonstrated that scopolamine produces a rapid antidepressant effect lasting several days after a single intravenous infusion. A subsequent study found sustained antidepressants by administering scopolamine every 3 to 4 days to patients with major depressive disorder (Drevets & Furey, 2010).

These results with scopolamine suggest that cholinergic muscarinic receptor antagonism may contribute the antidepressant effects of many tricyclic antidepressant drugs. Yet tricyclic antidepressant drugs do not produce the rapid antidepressant effects observed after scopolamine infusion. These considerations led Voleti and colleagues (2013) to examine further the potential mechanisms responsible for scopolamine antidepressant effects. They found that scopolamine, like ketamine, stimulates intracellular signaling involving mTOR as well as increasing the number and activity of dendritic spines in the prefrontal cortex. Thus, at present, researchers believe that scopolamine engenders antidepressant effects through a mechanism similar to ketamine.

**Neuronal Growth Occurs During Antidepressant Treatment** Chronic administration of antidepressant drugs causes neuronal growth and production in the hippocampus (Dranovsky & Hen, 2006; Duman, Malberg, & Thome, 1999; Sahay & Hen, 2007). Because an increase in neuron density occurs over weeks during chronic administration,
Researchers suspect a link between these changes and the response delay for antidepressant effects (Santarelli et al., 2003). Thus, learning how antidepressant drugs increase proliferation in the hippocampus may aid in developing ways to shorten the response time to these drugs.

The SSRI fluoxetine (Prozac) has been shown to increase the activation of TrkB receptors, which are activated by BDNF. In turn, activation of TrkB receptors has been shown to increase the production of neurons in the hippocampus (Li et al., 2008). Together, these findings suggest that SSRIs may produce new cells in the hippocampus via the BDNF system.

**Review!** Brain-derived neurotrophic factor (BDNF) is a neurotrophin, which facilitates neurogrowth and neuroconnectivity. (Chapter 3.)
Bipolar Disorder

Bipolar disorder is a mental disorder characterized by abnormal changes between depressive and manic mood states, representing two “poles” of mood. Depression in bipolar disorder exhibits the same features of depression characterized earlier in this chapter. In many ways, mania exhibits opposite features of depression. Mania consists of an abnormal elevation or irritation in mood along with increased arousal or energy levels. Manic behavior may occur as fast speaking, rapidly changing ideas and impulsive decision making. During a manic episode, individuals may engage in excessive spending, reckless behaviors, drastic decision making, drug abuse and hypersexuality. We use the term euthymia to refer to a stable mood state; in bipolar disorders, we characterize euthymia as expressing neither manic nor depressed symptoms.

We also find cognitive dysfunction as a feature of bipolar disorder. Martínez-Arán and colleagues (2004) sought to examine cognitive functioning in bipolar disorder by examining participants during a euthymic state and comparing test results to healthy control participants. In these comparisons, those with bipolar disorder exhibited poorer performance on tests for problem solving and working memory. In other studies, those with bipolar disorder tested during a euthymic state have shown deficits in sustained attention (Clark, Iversen, & Goodwin, 2002; Bora, Vahip, & Akdeniz, 2006). The appearance of cognitive deficits during a euthymic state shows that they are likely inherent to the disorder rather than something shown only during depressive or manic state.

The DSM-5 defines two types of bipolar disorder that differ primarily by the severity of mania. Type I bipolar disorder consists of exhibiting depression and episodes of severe mania. When presented with a severe manic episode, a mental health
professional need not require evidence of depression to make a type I diagnosis. **Type II bipolar disorder** consists of exhibiting depression along with episodes of less-severe mania. We also use the term hypomania to refer to this form of mania.

Some researchers propose a type III bipolar disorder. This suggestion comes from evidence that antidepressant drugs cause some patients to shift into a manic state. Because this occurs in only a subpopulation of patients, this may represent a distinct type of bipolar disorder. Currently, the DSM does not recognize a third type of this disorder (Akiskal & Pinto, 1999).

Many patients with bipolar disorder receive an incorrect diagnosis when first presenting to a clinician. According to a study conducted by Hirschfeld, Lewis, and Vornik (2003), nearly 70 percent of individuals with bipolar disorder receive a misdiagnosis, and many of these misdiagnosed patients required seeing an average of four physicians and require more than 10 years or longer to receive a correct diagnosis. Reasons cited for misdiagnosis include gathering limited or incorrect clinical histories from patients and a lack of understanding about bipolar disorder among physicians making the misdiagnosis. The most common incorrect diagnosis is depression, which tends to occur most frequently in bipolar disorder. Further, individuals in manic states seldom see a reason to seek help, feeling that nothing is wrong with them. Thus, an individual may be more likely seek help while feeling depressed (Bowden, 2001).

Bipolar disorder is far less prevalent than major depressive disorder. According to a national survey conducted by the National Institute of Mental Health, the lifetime prevalence of any type of bipolar disorder in the United States is 4.4 percent. The average age for the first diagnosis of a bipolar disorder is 20.8 years old (Merikangas et al., 2007).

**Neurobiology of Bipolar Disorder**

Neuroimaging studies have revealed that areas of reduced activity in the frontal and temporal lobes of the right hemisphere have a tendency to produce manic episodes, whereas those occurring in the left hemisphere have a tendency to produce depressive episodes. Several studies have shown that the volume of the basal ganglia and thalamus tends to be larger in patients with bipolar disorder.

Functional MRI in bipolar disorder reveals areas of excessive activity in cortical white matter areas from unknown causes. Subsequently, these areas of activity are called unidentified bright objects (UBOs). The occurrence of UBOs in bipolar disorder reportedly ranges between 5 to 50 percent. The presence of UBOs in white matter areas might interfere with interconnectivity between the frontal and temporal cortex, which may relate to reduced activity in these regions as previously noted (Berns & Nemeroff, 2003).

Diffusion tensor MRI reveals diminished integrity and damage of axons in white matter in the cingulate cortex among those with bipolar disorder. This same imaging method has shown abnormalities in neurons connecting the amygdala to the cingulate cortex and connecting the lateral prefrontal cortex with the orbitofrontal cortex, a structure that closely communicates with the amygdala. Taken together, the altered connections between these structures in bipolar disorder may account for poor regulation of mood (Benedetti et al., 2011).
Mood Stabilizers, Anticonvulsants, Antipsychotics, and Antidepressants for Bipolar Disorder

Many of the treatments for bipolar disorder were first developed and approved for the treatment of other mental disorders. Thus, we have few drugs that are considered purely mood stabilizers—that is, drugs that reduce both depressive and manic symptoms. Beyond mood stabilizers, other treatments include anticonvulsant drugs and antipsychotic drugs. Although clinicians may also prescribe antidepressant drugs to bipolar disorder patients, they seldom administer antidepressant drugs alone, instead preferring to combine them with another bipolar treatment.

Lithium Is One of the Oldest and Most Effective Treatments for Bipolar Disorder

Lithium was the first mood stabilizer found effective for bipolar disorder. We find some uses of lithium by early neurologists and psychiatrists, including Silas Weir Mitchell, who referred to using lithium bromide for epilepsy and as a calming agent in 1870, and William Hammond, who administered lithium bromide for acute mania in 1871. Yet we see references to “bromide” as attributable to the effects of lithium bromide, perhaps more than “lithium” (Cade, 1949; Shorter, 2009). We do find, however, the Danish psychiatrist Frederik Lange using lithium carbonite for treating depression in 1894 (Shorter, 2009).

Its effectiveness for mania was later evaluated in 1949 by John Cade, who is most often credited with reintroducing lithium as a medicine for modern psychiatry. Cade served as a physician and superintendent of a hospital in Australia, a position he assumed after spending three years in a Japanese prisoner-of-war camp. After noticing that lithium chloride appeared to calm down guinea pigs, he administered the compound to several manic patients, finding striking reductions in mania. After other investigators validated these findings in Europe and the United States, lithium became a primary treatment for bipolar disorder (Cade, 1949; Shorter, 1997).
Since this discovery, hundreds of studies have reported on the mood-stabilizing effects of lithium in bipolar disorder. We can determine the general consensus of lithium’s efficacy by reviewing randomized double-blind, placebo-controlled trials conducted in patients with bipolar disorder. Geddes and colleagues (2004) conducted an assessment of five studies that used this design. They found that lithium overall proved consistently more effective than placebo for preventing manic symptoms. However, they failed to see substantial reductions in depressive symptoms. Thus, we find that lithium provides greater efficacy for mania than for depression.

Lithium treatment poses a risk of serious adverse effects. The risk for these adverse effects accompany a narrow therapeutic index and narrow therapeutic dose range. For these reasons, blood monitoring is used to carefully adjust lithium dosing (Figure 13.6). When first beginning lithium therapy, therapeutically effective concentrations fall within a range of 0.8 to 1.2 milliequivalents per liter (mEq/l) of blood. After lithium has accumulated in the body over the course of approximately 2 weeks, the concentration must be reduced to 0.6 to 0.8 mEq/l to avoid adverse effects. At this stage, these lower concentrations sufficiently maintain therapeutic effects (Ferrier, Tyrer, & Bell, 1995).

Drug Profile: lithium

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Camcolit, Eskalith, Lithobid, Lithionate, among others</th>
</tr>
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<tbody>
<tr>
<td>Properties</td>
<td>Intracellular actions, including second messengers and gene expression; may have neuroprotective effects; may inhibit GSK-3</td>
</tr>
<tr>
<td>Uses</td>
<td>Used for treating bipolar disorder; appears more effective for mania than depression</td>
</tr>
</tbody>
</table>

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**FIGURE 13.6** The dose window for the therapeutic effects of lithium stray near those that produce serious adverse effects. Largely because of this, lithium dosing is adjusted based on levels in blood as expressed as concentration in milliequivalents of blood per liter (mEq/l). The first two weeks of treatment require concentrations near, and possibly overlapping, concentrations noted for serious adverse effects. After the desired therapeutic effects are achieved, lower concentrations of lithium will maintain these effects (noted as “maintenance” in the figure).

**Lithium Concentrations and Their Effects**

- **Therapeutic effects**
  - Maintenance
    - 0.6–0.8 mEq/l
  - Therapeutic effects first two weeks
    - 0.8–1.6 mEq/l
- **Adverse effects**
  - 1.5–2.0 mEq/l
- **Lethality**
  - 2.0 mEq/l

Review! A therapeutic index represents the difference between lethal and therapeutic drug doses. (Chapter 1.)

At lithium blood concentrations of 1.5 to 2.0 mEq/l, gastrointestinal effects become prominent, including nausea, vomiting, and diarrhea. Adverse effects may occur at therapeutic blood concentrations as well, including thirst and increased urination, largely because of lithium-induced inhibition of kidney function. Lithium may also produce tremor at therapeutic doses. Higher lithium concentrations, beginning at approximately 2.0 to 2.5 mEq/l, may produce renal failure and muscle rigidity. Moreover, these concentrations pose a serious risk of coma and death. Taken together, even an accidental second ingestion of lithium might increase blood concentrations to near fatal levels.

Lithium’s Mechanisms of Action  Lithium (Li+) is element number 3 on the periodic table and is part of the same grouping as sodium (Na+, atomic number = 11) and potassium (K+, atomic number = 19). As you may recall from Chapter 3, Na+ and K+ play important roles in generating action potentials. Lithium enters neurons through Na+ channels. Once inside a neuron, lithium takes part in a large variety of intracellular actions, including second-messenger actions and gene expression. This presents a great challenge to researchers who are endeavoring to unravel the pharmacological actions important for lithium’s mood-stabilizing properties. Based on such studies, the current general consensus among researchers is that lithium’s efficacy for bipolar disorder derives from neuroprotective effects against neurodegeneration (Chiu & Chuang, 2010).

We find these neuroprotective effects in preclinical studies. In particular, lithium promotes the survival of neurons during excitotoxicity. Lithium also protects neurons during detrimental conditions, including the absence of growth factor, heat shock, and high doses of anticonvulsant drugs. A key action for lithium’s neuroprotective effects may involve inhibition of the enzyme glycogen synthase kinase 3 (Chiu & Chuang, 2010).

Review! Excitotoxicity consists of neuronal damage and death caused by overstimulation by glutamate. (Chapter 3.)

Although involved in many processes, glycogen synthase kinase 3 (GSK-3) is a protein kinase that promotes apoptosis and regulates inflammation. Apoptosis is referred to as a programmed cell death, a process important for normal brain development. Excitotoxicity also produces apoptosis. In mice, overexpression of the GSK-3 gene causes an increase in behavioral activity, whereas inhibition of GSK-3 enzyme activity decreases behavioral activity (O’Brien et al., 2004). These results suggest that GSK-3 inhibition may lead to decreases in hyperactivity, which is somewhat analogous to mania in humans. In another study, an inhibitor of GSK-3 enzymes led to decreased immobility time in a forced swim test, an indication of antidepressant effects (Figure 13.7) (Gould, Einat, Bhat, & Manji, 2004).

Anticonvulsant Drugs  Clinicians also use anticonvulsant drugs to treat bipolar disorder, including carbamazepine (Tegretol), valproic acid (or valproate; trade name is Depakote), oxcarbazepine (Trileptal), and lamotrigine (Lamictal). Most anticonvulsant drugs serve as positive modulators for GABA, receptors, although we find that other GABA, positive modulators such as barbiturates appear ineffective for treatment of bipolar disorder.
FIGURE 13.7 Lithium may reduce depressive and manic symptoms, at least in part, through inhibition of GSK-3, an enzyme that promotes apoptosis and regulates inflammation. A selective inhibitor of GSK-3 activity called AR-A014418 has been shown to decrease immobility time in rats in a forced swim task, suggesting an antidepressant effect (left figure). In this figure, dimethyl sulfoxide (DMSO) was the vehicle for AR-A014418 and was tested alone to provide a control group. AR-A014418 also reduced hyperactivity induced by amphetamine (right figure).


STOP & CHECK

1. Although effective for bipolar disorder, lithium’s adverse effects are coupled with a narrow __________ index, requiring careful monitoring of blood concentrations.

2. How does lithium enter neurons?

3. Although lithium has many neurobiological effects, perhaps the most implicated action for treating bipolar disorder is inhibition of the _______ enzyme.

Instead, other actions produced by anticonvulsant drugs may account for reduced symptoms in bipolar disorder.

Beyond facilitating GABA neurotransmission, anticonvulsant drugs produce a variety of other effects on neurons. First, many of the anticonvulsant drugs for bipolar disorder inhibit Na+ channel functioning. At therapeutic doses, Na+ channel inhibition largely
affects high-frequency action potentials. This action not only likely plays a role in their antiseizure effects, but also may reduce manic symptoms in bipolar disorder. Second, many of these anticonvulsant drugs inhibit GSK-3 activity, a mechanism of action comparable to the effects of lithium (Chiu & Chuang, 2010; Keck, McElroy, & Nemeroff, 1992).

**Atypical Antipsychotic Drugs** Although clinicians use antipsychotic drugs for the treatment of schizophrenia, antipsychotic drugs are also used for the treatment of bipolar disorder. In particular, the *atypical* antipsychotic drugs have become safer first-line treatments compared to lithium. These drugs include quetiapine (Seroquel), aripiprazole (Abilify), olanzapine (Zyprexa), and risperidone (Risperdal), among others. The compounds serve to reduce and prevent mania from occurring in this disorder (Pae, Serretti, Patkar, & Masand, 2008; Tohen & Zarate, 1998).

One of the most common treatment approaches involves a combination of both an atypical antidepressant drugs and an antidepressant drug. One of the first treatment combinations reported for bipolar disorder consisted of the atypical antipsychotic drug olanzapine and the SSRI antidepressant drug fluoxetine (as noted earlier, this combination is now sold as Symbyax). During the course of 8 weeks, Tohen and colleagues (2003) administered placebo, olanzapine alone, or a treatment combination of olanzapine and fluoxetine in patients with type I bipolar disorder. They found significantly reduced depression scores after treatment with the drug combination compared to either placebo or olanzapine given alone. Manic symptoms occurred too infrequently in the placebo-treated patients to allow for studying treatment effects on mania in this study.

Treatment time course serves as the most clinically important finding in this study. After 3 weeks of treatment, 50 percent of participants were responsive to the olanzapine and fluoxetine combination compared to only 30 percent of olanzapine-treated patients. Thus, the addition of fluoxetine decreased the amount of time it took for a reduction in depressive symptoms to occur (Figure 13.8).

This study provided an important shift in treatment strategies for bipolar disorder. In an extensive review of clinical studies evaluating antipsychotic drugs and other traditional medications for depressive symptoms in bipolar disorder, the fluoxetine–olanzapine combination provided the greatest effects. The atypical antipsychotic drug quetiapine was shown to be the second most effective for depressive symptoms, whereas other antipsychotic drugs and the more traditional treatments for bipolar disorder were inconsistently effective for depressive symptoms (Vieta et al., 2010).

The ability of quetiapine alone to be effective for depressive symptoms is a bit of mystery because, after all, the receptor binding profile for quetiapine is very similar...
to other atypical antipsychotic drugs, including olanzapine. The unique efficacy quetiapine has for depression may not actually be a result of the quetiapine molecule but of N-desalkylquetiapine, one of the metabolites for quetiapine. N-desalkylquetiapine chemically resembles a tetracyclic antidepressant drug (like a tricyclic antidepressant, except with four rings), and pharmacological studies reveal that N-desalkylquetiapine inhibits reuptake of serotonin and norepinephrine (Jensen et al., 2008). In this way, quetiapine treatment may functionally serve like a combination of an atypical antipsychotic drug and an antidepressant drug.

STOP & CHECK

1. Like lithium, anticonvulsant drugs effective for bipolar disorder inhibit the ________ enzyme.

2. Another common bipolar treatment is a combination of an atypical antipsychotic drug and a(n) ________ drug.

3. How might the effects of quetiapine be similar to those produced by a combination of olanzapine and fluoxetine?
From Actions to Effects: Pharmacogenetic Factors and Treatment Response in Depression

Earlier in this chapter, we presented significant limitations for the efficacy of antidepressant medications. Another limitation involves pharmacogenetic differences, which may inhibit a patient’s response to antidepressant drugs. For example, genetic differences may alter the ability of an antidepressant drug to cross the blood–brain barrier. In a study conducted by Uhr and colleagues (2008), variations in the ABCB1 gene were examined because this gene encodes for P-glycoprotein, a transporter important for the ability of certain antidepressants drugs to cross the blood–brain barrier. In patients who had a polymorphism in the ABCB1 gene, full recovery from depression was less likely if they were treated with a drug transported by P-glycoprotein, such as the tricyclic antidepressant drug amitriptyline (Elavil), the SSRIs paroxetine (Paxil) and citalopram (Celexa), or the SNRI venlafaxine (Effexor) (Table 13.5). They did not find a correlation with the antidepressant drug mirtazapine (Remeron), which does not rely on P-glycoprotein to cross the blood–brain barrier.

Pharmacogenetic factors may also alter serotonin transporter function, an important site of action for many antidepressants drugs. The gene for the serotonin transporter is SLC6A4, and it includes a region important for serotonin transporter function called the serotonin transporter-gene–linked polymorphic region. Clinicians find a poorer treatment response and shorter time until depressive symptoms return in patients who have a short variation of this region (Horstmann & Binder, 2009; Serretti, Kato, De Ronchi, & Kinoshita, 2007). These effects may be due to a reduced levels of serotonin transporters among individuals with this polymorphism, leading to few sites for antidepressant drugs to act on (Lesch et al., 1996; Smeraldi et al., 1998).

Finally, genetic expression of neurotrophins may affect antidepressant treatment response. These investigations stem from findings that chronic antidepressant drug

<table>
<thead>
<tr>
<th>Pharmacogenetic Factor</th>
<th>Function</th>
<th>Impact on Antidepressant Response</th>
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</thead>
<tbody>
<tr>
<td>ABCB1 gene polymorphism</td>
<td>Affects P-glycoprotein transporter function in blood-brain barrier</td>
<td>Inhibits passage of certain antidepressant drugs from entering the brain through the blood-brain barrier, reducing antidepressant effects</td>
</tr>
<tr>
<td>Short variation of serotonin transporter-gene–linked polymorphic region</td>
<td>Affects function of the serotonin membrane transporter; may find fewer serotonin transporters in those with this polymorphism</td>
<td>Reduced antidepressant effects possibly by having fewer transporters to bind to</td>
</tr>
<tr>
<td>Val66Met polymorphism on the gene for BDNF</td>
<td>May reduce BDNF levels and levels of TrkB receptors</td>
<td>Reduced ability of antidepressant drugs to promote neurogenesis and proliferation</td>
</tr>
</tbody>
</table>

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administration promotes neural proliferation in the hippocampus. In particular, several studies have focused on the polymorphism called Val66Met existing on the gene for BDNF. This polymorphism reduces BDNF levels and may subsequently lead to reduced density of TrkB receptors (Bath et al., 2008; Egan et al., 2003). As noted previously, antidepressant drugs may promote proliferation by indirectly activating TrkB receptors. Patients with this polymorphism tend to have poorer treatment response to antidepressant drugs (Horstmann & Binder, 2009; Shimizu, Hashimoto, & Iyo, 2004).

**Review!** Neurotrophins are a family of molecules that promote the survival and plasticity of neurons during development and in adulthood. BDNF binds selectively to TrkB receptors. (Chapter 3.)

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### STOP & CHECK

1. How might a short variation of the serotonin-transporter-gene-linked polymorphic region impact the effectiveness of antidepressant drugs?

2. Two pharmacokinetic factors important for antidepressant drugs that are affected by pharmacogenetic factors are ____________ and ____________.

3. Gene polymorphisms for neurotrophins may diminish the effects on antidepressant drugs on ____________.

---

### Chapter Summary

A major depressive disorder is characterized by feelings of sadness, worthlessness, and other symptoms that persist for 2 weeks. Persistent depressive disorder consists of fewer symptoms, but these symptoms persist for at least 2 years. Depression is highly prevalent across age groups and carries a significant risk of suicide.

Neuropsychologically, depression appears to be associated with overactivity in the amygdala, reduced activity in the left dorsal prefrontal cortex, and reduced volume of the hippocampus. The classes of antidepressant drugs include MAO inhibitors, tricyclic antidepressant drugs, SSRIs, SNRIs, and atypical antidepressant drugs. Important challenges to using antidepressant drugs to treat depression include a lengthy response time, treatment resistance, large placebo effects in clinical trials, and pharmacogenetic differences.

*(Continued)*
Bipolar disorder is a mental disorder that is characterized by abnormal changes between depressive and manic mood states. Mania is most severe in type I bipolar disorder and less severe in type II disorder. Bipolar disorder is associated with a larger basal ganglia and thalamus and disruptions of normal cortical processing. A long-used and still common treatment for bipolar disorder is lithium, which is effective for reducing manic symptoms and, to a lesser extent, depressive symptoms. However, lithium’s severe adverse effects coupled with a small therapeutic index makes lithium less desirable if other effective treatments are available. Subsequently, bipolar disorder may be treated with anticonvulsant drugs or antipsychotic drugs. In particular, combined treatment with an antipsychotic drug and an antidepressant drug may be effective for improving depression in bipolar disorder.