CHAPTER

12

Antipsychotic Drugs

Canst thou not minister to a mind diseased; pluck from the memory a rooted sorrow; raze out the written troubles of the brain; and with some sweet oblivious antidote cleanse the stuff'd bosom of that perilous stuff which weighs upon the heart?

—MACBETH

Macbeth asked this question of the doctor treating Lady Macbeth. The doctor's answer was no. Modern physicians are a bit better off when it comes to ministering to a "mind diseased". In fact, modern psychiatry has been revolutionized by many "antidotes" in the form of anxiolytics, antipsychotics, antidepressants, and antimanics. They are not as wonderful as Macbeth envisioned them; they have troublesome side effects, and they do not always work well, but they are probably a good deal better than the treatment that Lady Macbeth was offered. In this chapter, you will learn about the antipsychotics—drugs used to treat the psychoses, of which schizophrenia is the most well-known.

THE NATURE OF SCHIZOPHRENIA

Psychotic disorders are characterized by a loss of touch with reality; people with psychosis reach a state where they grossly misunderstand and misinterpret events going on around them, and they respond inappropriately in both an intellectual and emotional sense. They may experience bizarre hallucinations, and their behavior may be guided by *delusions*—beliefs that have no basis in reality. Psychosis may be brief, brought on by drugs or some toxin, or it may be a life-long battle. Psychotic behavior may arise early in adulthood or later in life from diseases such as Alzheimer's.

Schizophrenia and Other Psychotic Disorders, as the category exists in the *DSM-IV-TR* (2000), encompasses a variety of psychoses. The most well-known of these, *schizophrenia*, is often misunderstood. The word is derived from the Greek *schizein*, "to split," and *phren*, "mind." The splitting, however, does not refer to two different personalities in the same individual. It is, instead, a separation between thought, emotion, and behavior—different aspects of a single personality.

The *DSM-IV-TR* diagnostic criteria for schizophrenia are presented in Box 12-1.

At the time of evaluation, the clinician would also specify the subtype of schizophrenia, based on the combination of symptoms exhibited. Box 12-2 presents a case study of a patient suffering from the catatonic subtype of schizophrenia. One major revision suggested for the *DSM-5* is that these subtypes no longer be included.

The symptoms of schizophrenia are often classified into two types: positive and negative. *Positive symptoms* are traits that are abnormally present in psychosis. These include hallucinations, most often auditory or visual, and delusions or irrational beliefs that can be very

BOX 12-1 DSM-IV-TR Diagnostic Criteria for Schizophrenia

A. *Characteristic Symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. delusions
2. hallucinations
3. disorganized speech (e.g., frequent derailment or incoherence)
4. grossly disorganized or catatonic behavior
5. negative symptoms, i.e., affective flattening, alogia (poverty of speech), or avolition (inability to initiate and persist in goal-directed activities)

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

Source: Reprinted with permission from American Psychiatric Association. © 2000, DSM-IV-TR Diagnostic Criteria for Schizophrenia.

BOX 12-2 Schizophrenia: A Case Study

This account of a schizophrenic episode was published in the *Journal of Abnormal and Social Psychology* in 1955 ("An Autobiography,"). The author is not identified by name, but we are told that she is a college-educated social caseworker and was a 36-year-old mother of three children when she experienced her first schizophrenic episode. Her experience with schizophrenia was at a time before antipsychotic drugs were available, and common treatments were barbiturates (amobarbital) and shock treatment. Compare the symptoms this woman describes with the description of schizophrenia provided in Box 12-1. Do you feel that she fits the criteria for schizophrenia?

Most of what follows is based on an unpublished autobiography written in the spring of 1951 shortly after I returned home from the second of the three episodes of my schizophrenic experiences. . . .

Shortly after I was taken to hospital for the first time in a rigid catatonic condition,* I was plunged into the horror of a world catastrophe. I was being caught up in a cataclysm and totally dislocated. I myself had been responsible for setting the destructive force into motion, although I had acted with no intent to harm, and defended myself with healthy indignation against the accusations of others. If I had done anything wrong, I was suffering the consequences along with everyone else. Part of the time I was exploring a new planet (a marvelous and breathtaking adventure) but it was too lonely. I could persuade no one to settle there and I had to get back to earth somehow. The earth, however, had been devastated by atomic bombs and most of its inhabitants killed. Only a few people—myself and the dimly perceived nursing staff—had escaped. At other times I felt totally alone on the new planet.

After the first few weeks of extreme disorganisation, I began to acquire some relatively stable paranoid delusions. . . .

During the paranoid period I thought I was being persecuted for my beliefs, that my enemies were actively trying to interfere with my activities, were trying to harm me, and at times even trying to kill me. I was primarily a citizen of the larger community. I was trying to persuade people who did not agree with me, but whom I felt could be won over, of the correctness of my belief. . . .

In order to carry through the task which had been imposed upon me, and to defend myself against the terrifying and bewildering dangers of my external situation, I was endowed in my imagination with truly cosmic powers. The sense of power was not always truly defensive but was also connected with a strong sense of valid inspiration. I felt that I had power to determine the weather, which responded to my inner moods, and even to control the movement of the sun in relation to other astronomical bodies. . . . I was also afraid that other people had power to read my mind, and thought I must develop ways of blocking my thoughts from other people. . . .

(*continued*)

BOX 12-2 (Continued)

A mixture of sexual and ethical motivation became apparent during phases when I felt myself to be carrying through a predominantly maternal role and to be symbolically identified with Mary, the Mother of Christ. This identification was poetic; that is, I knew that I was myself and was Mary only in the figurative sense. The "Christ-Child" was apparently the human baby in general, the infant as the symbol of humanity, but I doubt that I would have made this identification if all my children had been girls.

**Catatonic schizophrenia* is characterized by a state of immobility in which the individual assumes a position without moving for extended periods of time.

complex and highly organized. Feelings of grandeur ("I am being spoken to by God") or paranoia ("The CIA is plotting to kill me because I know too much") may be involved. There may also be incoherent thought and speech, involving a loosening of associations between ideas where thoughts skip from one subject to a completely unrelated subject and the speaker is unaware that the topics are unconnected. This type of speech has been described as "word salad." There may be excessive motor activity that serves no apparent purpose or, in contrast, a lack of movement in which individuals maintain odd mannequin-like postures for hours.

Negative symptoms are traits that are abnormally absent in psychosis. These include *affective flattening* where the person's face is immobile and unresponsive, and he or she shows a diminished range of emotional expressiveness. *Anhedonia*, in which a person feels no pleasure, may also occur. Another negative symptom is *alogia*, or impoverished speech, where replies are brief and uncommunicative and seem to reflect diminished thinking. *Avolition* is an inability to initiate or engage in goal-directed activities. The person remains unmotivated for long periods of time and shows no interest in participating in work, social activities, or even personal hygiene. The person may also withdraw, socially. These negative symptoms do not appear exclusively in schizophrenia—they may be exhibited in a variety of other disorders, such as major depressive disorder or with brain injury.

In addition to the positive and negative symptoms, there are cognitive deficits that include an inability to sustain attention, problems with learning and memory, difficulties with problem solving and abstract thinking, and slowing of neuromuscular actions.

The symptoms of schizophrenia appear gradually, usually over a period of 3 to 5 years. The first symptoms are typically negative, followed by an onset of positive symptoms that may take some years to emerge. Men and women are equally likely to be affected by schizophrenia, although men typically experience signs and symptoms beginning at a slightly earlier age (late teens or early twenties) than do women (twenties or thirties).

Worldwide, the incidence of schizophrenia is approximately 1%, and rates are remarkably similar regardless of race, culture, society, or the region in which a person lives. However, having a close relative with schizophrenia, such as a sibling or parent, increases one's risk of developing the disorder by up to 10 times; having an identical twin with schizophrenia increases one's risk nearly 50 times. This is irrefutable evidence that genetic makeup plays a pivotal role in rendering individuals susceptible to developing schizophrenia. No one particular gene has been flagged as the "schizophrenia gene" and probably never will. Instead, genetic analysis has pinpointed a number of gene mutations on many chromosomes that, together, create vulnerability to develop schizophrenia. These genes are involved in such processes as neuronal migration during prenatal brain development, neuronal differentiation and growth, axonal projection, and the formation of receptors and synapses (Doherty, O'Donovan, & Owen, 2011; Walsh et al., 2008).

If schizophrenia were caused purely by genetics, we would expect identical twins (who are genetic clones of one another) to either both exhibit schizophrenia or for neither to be affected. In fact, the likelihood of both identical twins exhibiting schizophrenia, when one is affected, is only about 45%. We can conclude, then, that environmental influences must also play an important role in activating or promoting the expression of genes implicated in schizophrenia. Many environmental

factors have been discovered. If a mother contrasts a virus while pregnant, especially during the second trimester, brain development of the fetus can be affected, either by the virus itself or by the mother's immune system response to the virus. In large cities, where viruses are spread more readily, schizophrenia rates are approximately three times higher than those in rural areas. Schizophrenia rates are also higher in individuals whose gestation occurred during the winter flu season. During the dark winter months, levels of vitamin D (the "sunshine" vitamin) also tend to be lower. In pregnant women, vitamin D deficiency may predispose the developing offspring to schizophrenia as vitamin D is important for normal brain development. Other influential environmental factors include birth complications and a lack of oxygen to the child during labor and delivery, early childhood infection, head trauma, stress, and use of drugs such as cannabis or methamphetamine.

THEORIES OF SCHIZOPHRENIA

Our understanding of the etiology of schizophrenia has progressed in leaps and bounds over the past few decades. Various conceptions of the illness can be summed up as follows: Schizophrenia is the result of a genetic predisposition triggered by environmental factors. The positive symptoms of schizophrenia result from hyperactivity at mesolimbic dopaminergic synapses; the negative and cognitive symptoms result from degenerative processes in the brain that lead to hypoactivity at mesocortical dopaminergic synapses. Dysfunctional glutamate neurotransmission also occurs in schizophrenia. Other neurotransmitter systems, including serotonin, GABA, acetylcholine, and histamine, have all been implicated as well.

Next, you will find details supporting these claims and how, when they are pieced together, our understanding of the etiology of schizophrenia becomes much clearer.

Brain Structural and Functional Abnormalities in Schizophrenia

When the brains of individuals with schizophrenia are examined, either postmortem or using brain imaging technology, we see significant structural abnormalities; inherently, these lead to functional disturbances as well. One of the most noticeable abnormalities is the size of the lateral and third *ventricles*, cavities in which cerebrospinal fluid is produced and flows to cushion, cool, and nourish the brain. In individuals with schizophrenia, these ventricles are nearly twice as large as those of individuals unaffected by the illness. Most likely, a loss of brain tissue leads to this enlargement—the cerebrospinal-fluid-filled ventricles take over space opened due to the deterioration of neurons.

Compared to nonschizophrenic controls, individuals with schizophrenia have less brain tissue volume in up to 50 different brain regions (Kubicki et al., 2007). This deterioration is most pronounced in the corpus callosum, cerebellum, and areas of the frontal and temporal lobes, including structures of the limbic system, such as the hippocampus, amygdala, and cingulate gyrus (Borgwardt, McGuire, & Fusar-Poli, 2011). The deficits in brain volume are small in the beginning stages of the illness but become progressively greater as symptoms worsen. For example, MRI research shows that, as the cingulate gyrus deteriorates, there is a corresponding decrease in the ability to function socially (i.e., to perform social cognition, to attribute emotion to facial expressions; Fujiwara et al., 2007). Loss of volume in the dorsolateral prefrontal cortex is associated with impaired cognitive functioning and deficits in working memory (Volk & Lewis, 2010).

When does brain tissue loss begin, and what pathological processes are at play? Researchers suggest that the abnormal neurophysiological processes that underlie schizophrenia may begin even before birth and continue throughout childhood and adolescence. Children who have a parent with schizophrenia, and who are, thereby, at increased risk for developing the illness, often exhibit cognitive and behavioral warning signs of neurophysiological abnormalities. For example, high-risk individuals who, as adults, developed schizophrenia, showed speech and neuromotor deficits and delays, a lack of motor coordination, problems with social adjustment and competence, cognitive deficits, poor academic performance, attentional problems, short-term and verbal memory deficits, and problems with smooth-pursuit eye movements in childhood (Erlenmeyer-Kimling et al., 2000; Nicolson et al., 2000; Niemi, Suvisaari, Tuulio-Henriksson, & Lönnqvist, 2003; Schiffman et al., 2004, 2009).

During childhood and adolescence, the brain undergoes a period of *synaptic pruning* where weak, unused synapses are pruned out and strong, frequently used synapses remain and grow even stronger. Some researchers

believe that, in schizophrenia, this process is pathologically exaggerated so that too many connections are pruned and certain populations of neurons dwindle in number. These populations include, but are not necessarily limited to, dopaminergic and glutamatergic neurons, which you will learn more about shortly.

The Dopamine Hypothesis of Schizophrenia

Before discussing the dopamine hypothesis of schizophrenia, it might be helpful to do a quick review. Recall from Chapter 4 that there are multiple dopamine pathways in the brain. The nigrostriatal pathway contains dopamine neurons whose cell bodies reside in the substantia nigra and project to the dorsal striatum of the basal ganglia, which contains the caudate nucleus and the putamen. This dopaminergic system is important for the integration of smooth movements (it is the extrapyramidal motor system). When there is a deficiency of dopamine at these synapses, people show symptoms that resemble those of Parkinson's disease—tremors, slowed motor functions, stiff limbs, and trouble maintaining balance. These are called *extrapyramidal signs and symptoms* (*EPS*). Antipsychotic medications (especially the typicals) block the activity of dopamine in the nigrostriatal pathway, often producing serious EPS that make taking the medication intolerable.

In addition, two other dopamine systems are highly implicated in the development of schizophrenia. They have cell bodies that reside in the ventral tegmental area and send projections to release dopamine in the cortex (this is the mesocortical pathway) and in the nucleus accumbens and limbic structures, including the hippocampus and amygdala (this is the mesolimbic pathway).

The *dopamine hypothesis* has been the dominant theory of the neurological basis of schizophrenia from the 1960s to this day. The basic tenet of this theory, in its original form, was that schizophrenia and other psychoses result from excessive dopamine activity in the brain. Support for this assumption was based mainly on two important observations: (a) drugs that increase dopamine function (e.g., cocaine or amphetamine) can, in high doses or with chronic administration, produce a state almost indistinguishable from the positive symptoms of schizophrenia, and (b) the antipsychotics available at the time (i.e., the typicals) were all dopamine antagonists (more on this later).

As research into the role of dopamine in schizophrenia progressed, other lines of supporting evidence emerged. Available antipsychotic medications, such as chlorpromazine and reserpine, that were effective in reducing symptoms of schizophrenia, also produced severe EPS; in the 1960s, researchers already knew that Parkinson's disease was related to a depletion of dopamine in the brain, and so they extrapolated that antipsychotics must be exerting a similar effect. Also, the most effective antipsychotic drugs were found to be those with the greatest ability to block dopamine receptors. In fact, the correlation between the therapeutic dose of a typical antipsychotic and the drug's affinity for the dopamine receptor was found to be almost perfect (Seeman, Lee, Chau-Wong, & Wong, 1976). The weaker the drug's affinity for the dopamine receptor, the larger the dose required to produce a therapeutic effect.

With the discovery and marketing of haloperidol in the late 1960s, however, came a problem. Haloperidol was more effective than the other typicals in alleviating the positive symptoms of schizophrenia, yet its affinity for dopamine receptors seemed to be lower. How could this be? The answer came in the late 1970s with the discovery that dopamine (and antipsychotic medications) could bind to more than one subtype of dopamine receptor. Some of the typicals, like chlorpromazine, which belongs to a group of chemicals known as the *phenothiazines*, have a high affinity for both D_1 and D_2 receptor subtypes. Others, like haloperidol, which belongs to the pharmacologically similar group of chemicals known as the *butyrophenones*, have a high affinity for the D_2 (but not the D_1) receptor subtype. There does not appear to be any relationship between the therapeutic effect of an antipsychotic and its affinity for the D_1 receptor (Seeman, 2002). In fact, many of the typical antipsychotics have a higher binding affinity for D_2 receptors than dopamine itself. They bind more tightly and have lower *dissociation constants*, compared to molecules of dopamine. A dissociation constant is a measure of the ease with which a ligand, such as a drug molecule, will dissociate or separate from the receptor to which it is bound. A lower dissociation constant entails stronger binding, and a higher dissociation constant entails weaker binding. With this discovery, the dopamine hypothesis was revised: Schizophrenia and other psychoses result from excessive dopamine activity, specifically at D_2 receptors. The most effective antipsychotics, then, were those with a high affinity for D_2 receptors.

The dopamine hypothesis, even in its revised form, still could not fully explain the etiology of schizophrenia. For one, there are inconsistencies in the research comparing D_2 receptor densities in individuals with and without schizophrenia, and no strong evidence that dopaminergic circuits progressively deteriorate along with other neurotransmitter circuits. Also, if schizophrenia were due simply to an overabundance of dopamine, antipsychotic drugs (which block dopamine activity as soon as they reach their site of action) should work immediately. Instead, the therapeutic effect may be delayed for several weeks, suggesting that alleviation of psychotic symptoms involves a more complex mechanism than simply blocking excessive dopamine activity (Carlsson, 1994). It may also involve the slow and long-lasting changes in the electrical properties or connectivity of cells, as discussed in Chapter 4. Finally, the negative and cognitive symptoms of schizophrenia do not improve with D_2 receptor blockade, suggesting that hyperactivity of D_2 receptors does not fully account for schizophrenia symptoms. Some researchers have suggested that perhaps D_3 or D_4 receptor dysfunction is also involved, as these receptor subtypes act similarly to D_2 receptors—their activation inhibits, rather than excites, second messenger activity.

An additional revision to the dopamine hypothesis, which has garnered a lot of support, states that excessive dopamine activity, specifically in the mesolimbic pathway, does indeed explain the positive symptoms of schizophrenia. However, the negative and cognitive symptoms of schizophrenia result from a lack of dopamine activity, specifically in the mesocortical pathway, as well as the structural abnormalities (and, thereby, functional deficits) resulting from the degeneration of various brain regions, as described earlier. As you will soon learn, when we put all of the pieces together, hypoactivity of the frontal lobes may actually be the driving force behind hyperactivity of the mesolimbic dopamine system.

The Glutamate Hypothesis of Schizophrenia

The original dopamine hypothesis of schizophrenia was supported by the discovery that stimulant drugs, like cocaine and amphetamine, produced effects that mimic the positive symptoms of schizophrenia. The *glutamate hypothesis* of schizophrenia was borne of a similar coincidental discovery (see Moghaddam & Javitt, 2012, for a review). In the late 1950s, researchers synthesized two dissociative drugs, phencyclidine (PCP) and ketamine (known by the street name Special K; see Chapter 15). These drugs produced symptoms similar to not only the positive but also the negative and cognitive symptoms of schizophrenia.

Some years later, researchers discovered that the PCP binding site (to which ketamine also binds) sits within the ion channel of the glutamate NMDA receptor (see Chapter 4 for a review). The ability of various compounds to produce schizophrenia-like symptoms is directly related to the affinity with which these drugs bind to the NMDA receptor's PCP binding site and, thereby, their ability to antagonize glutamate function. Antagonizing the NMDA receptor's binding sites for glutamate or for glycine produces similar effects.

In contrast to dopaminergic neurons, which exist in distinct pathways and brain regions, glutamatergic neurons are nearly ubiquitous in the brain. This is not all that surprising, given that glutamate is the major excitatory neurotransmitter in the central nervous system. All neural information leaving the cortex, travelling between cortical areas, and most information entering the cortex does so through glutamate neurons. So the repercussions of glutamate dysfunction are widespread.

According to early conceptions of the glutamate hypothesis, genetic factors predispose individuals to glutamate hypoactivity, specifically at the NMDA receptor. Many of the genes believed to contribute to the development of schizophrenia influence glutamate neuron connectivity, synaptogenesis, and neurotransmission at the NMDA receptor. The dysfunction may be the result of neurodevelopmental abnormalities in which NMDA receptor synapses do not form properly, or it may result from synaptic overpruning of glutamate neuronal connections during childhood and adolescence.

Despite its appealing simplicity, the original glutamate hypothesis could not explain some puzzling findings. If schizophrenia results from a lack of glutamate neurotransmission, why are measures of cerebrospinal fluid glutamate levels similar between individuals with schizophrenia and those without? An additional problem for the original glutamate hypothesis came from animal research showing that injections of NMDA receptor antagonists at doses that produce schizophrenia-like symptoms actually increased, rather than decreased,

glutamate release in the prefrontal cortex. Recall that glutamate also binds to another receptor subtype, the AMPA receptor. Researchers also discovered that blockade of AMPA receptors reversed the effects of the NMDA receptor antagonists. So glutamate dysfunction in schizophrenia might be the result of two combined processes: NMDA receptor hypoactivity and AMPA receptor hyperactivity.

How can it be that NMDA receptor blockade increases glutamate activity in the prefrontal cortex? This makes sense if we consider that neurons in the cortex are inhibited by GABA interneurons—if they were not, excitation of some glutamate neurons would set off a domino effect of ever-increasing cortical activation. Blockade of NMDA receptors present on these GABA interneurons decreases their firing; in other words, there is an *inhibition of inhibition*, or excitation, and increased glutamate release and activation of AMPA receptors. This would not be so at NMDA receptors, since they are antagonized through blockade of the PCP binding site. This disorganized pattern of glutamate neurotransmission may produce a state of noise and disruption in which the cortex is unable to properly assess information (Moghaddam & Javitt, 2012). One goal of antipsychotic drug development is to stabilize NMDA and AMPA receptor glutamate neurotransmission in the cortex. NMDA itself, or direct NMDA agonists, cannot be used as antipsychotic medications because they increase the risk of seizure and brain damage resulting from *excitotoxicity*, when neurons die from excessive stimulation. However, indirect NMDA agonists, such as glycine and d-serine (an agonist at the NMDA receptor glycine binding site), facilitate NMDA receptor activity and hold great promise.

Putting the Pieces Together

As you have learned, schizophrenia develops gradually, usually with the emergence of negative and cognitive symptoms followed, perhaps years later, by the onset of positive symptoms. This course of symptom development provides us with insight into the neuropathology of schizophrenia.

Deterioration of brain regions, including limbic structures and prefrontal regions, likely begins *in utero* and continues throughout childhood, getting fast-tracked during the synaptic pruning that takes place prior to and during adolescence. This process likely leads to a progressive and substantial loss of glutamate synapses, resulting in NMDA receptor hypoactivity and glutamate dysregulation. To understand the implications of glutamate dysfunction on dopamine systems, you must understand that NMDA receptor activity regulates dopamine function.

In the prefrontal cortex sit the cell bodies of glutamate neurons whose axons project to the ventral tegmental area. There, they synapse with dopaminergic neurons that form both the mesocortical and mesolimbic pathways. Recall that the most current conceptions of the dopamine hypothesis of schizophrenia state that the negative and cognitive symptoms of schizophrenia result from hypoactivity of the mesocortical pathway. Normally, cortical glutamate neurons projecting to the ventral tegmental area produce a tonic excitation of mesocortical dopamine neurons. These dopamine neurons, in turn, project their axons back to the prefrontal cortex (this is the mesocortical pathway) where they release dopamine in response to this excitation. This glutamate–dopamine interaction is illustrated in Figure 12-1, panel A.

Additionally, prefrontal cortical glutamatergic neurons form synapses with GABAergic interneurons within the ventral tegmental area. The axons of these GABAergic interneurons project to and inhibit the activity of the dopaminergic neurons that, in turn, project their axons to the nucleus accumbens (this is the mesolimbic pathway). Stimulation of glutamate neurons in the prefrontal cortex results in the inhibition of dopamine neurons that form the mesolimbic pathway, due to the presence of the GABAergic neurons that act as a chronic braking system. This glutamate–dopamine interaction is illustrated in Figure 12-1, panel B. Recall that the positive symptoms of schizophrenia are believed to be the result of hyperactivity of the mesolimbic dopamine pathway.

When cortical glutamate activity is diminished, due to PCP or ketamine blockade of NMDA receptors or due to neurodevelopmental pathology, resulting in a loss of NMDA receptors or glutamate connectivity, ventral tegmental area dopamine neurons are understimulated. As a result, the mesocortical dopamine pathway becomes hypoactive, and, at the same time, the mesolimbic dopamine pathway becomes hyperactive. These glutamate–dopamine interactions may explain why,

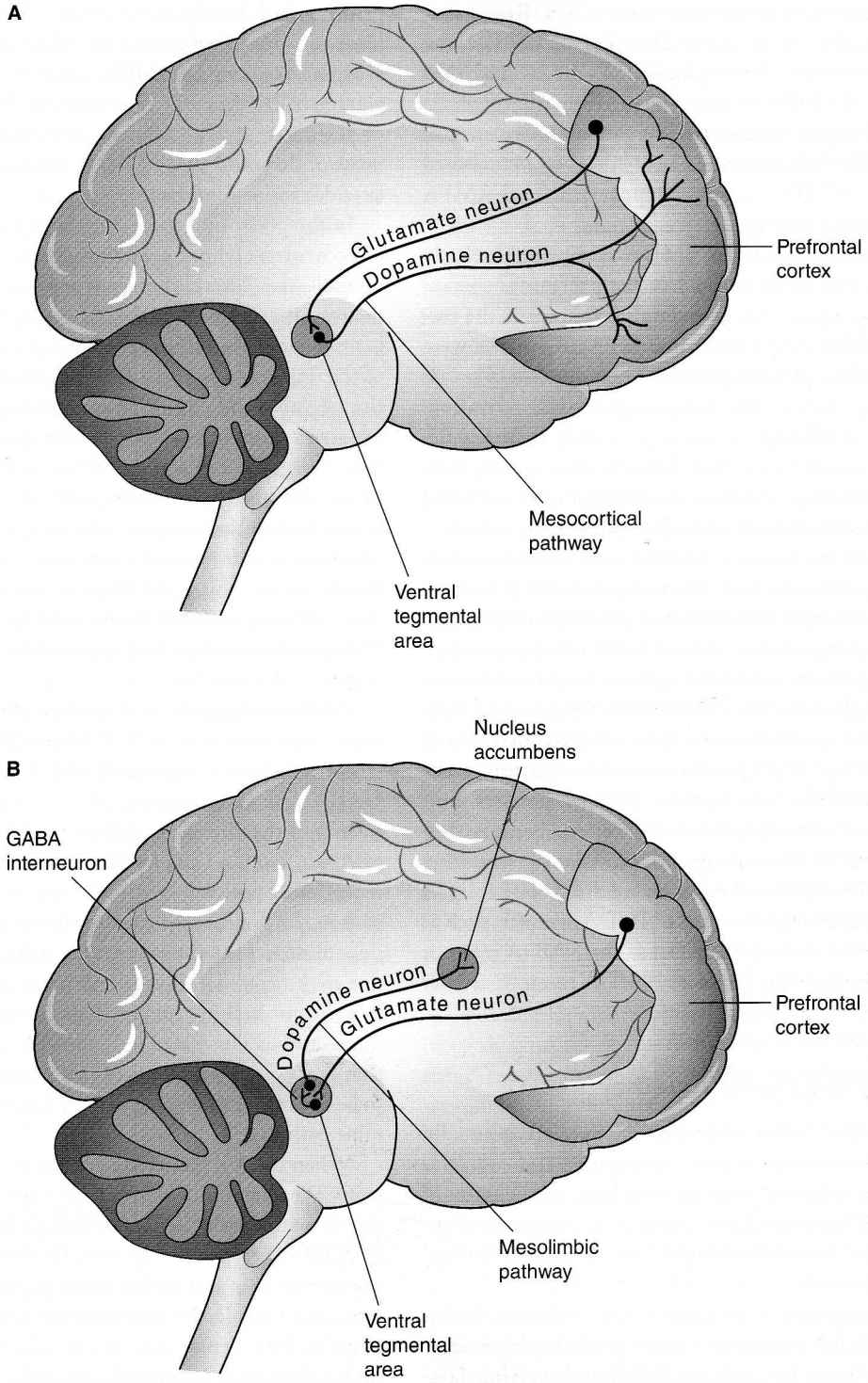


FIGURE 12-1 Glutamate–dopamine interactions.

with progressive deterioration of neurons and glutamate functionality, we see the emergence of negative and cognitive, followed by positive, symptoms of schizophrenia.

Other Neurotransmitter Systems Implicated in Schizophrenia

In addition to dopamine and glutamate, there may be other neurotransmitter systems that are rendered dysfunctional in schizophrenia. These include, but are not limited to, serotonin (Rasmussen et al., 2010), GABA (Lewis, Hashimoto, & Volk, 2005), acetylcholine (Lester, Rogers, & Blaha, 2010), and histamine (Ito, 2009). Research into neurotransmitter systems and their interactions continues to advance our understanding of the mechanisms of schizophrenia.

DISCOVERY OF ANTIPSYCHOTIC MEDICATIONS

Like most of the therapeutically useful drugs described in this book, drugs that treat the symptoms of schizophrenia were discovered by accident. In the 1950s, a French military surgeon, Henri Laborit, was looking for a preoperative medicine that would relieve patients' anxiety and reduce the high death rate that was associated with *surgical shock*, an acute and sometimes fatal state of weakness and reduction in vital functions that occur during surgery. Laborit theorized that shock was caused by excessive release of transmitters such as epinephrine, acetylcholine, and histamine; therefore, he tried out drugs known to block these substances to see if they would reduce the incidence of surgical shock. The drugs he tried included atropine, curare, and antihistamines. The first antihistamine Laborit tested was *promethazine*, which was supplied by the Rhône-Poulenc company. Like most antihistamines, it has sedating properties. Laborit was encouraged by the results he got with promethazine. In 1951, Rhône-Poulenc asked Laborit to try another antihistamine that it had synthesized several years earlier but had rejected because its sedating properties had been too strong. This was chlorpromazine.

The results were impressive. Laborit's patients did not lose consciousness but became sleepy and lost interest in everything going on around them (the sedating or tranquilizing effect) and could be anesthetized with a reduced dose of anesthetic. Laborit described the state induced by chlorpromazine as *artificial hibernation*. He recognized the significance of this effect and immediately suggested to some psychiatrist friends that the drug might be useful in treating agitated mental patients. Two Parisian psychiatrists named Delay and Deniker learned about these trials and requested samples from Rhône-Poulenc. They administered the drug in higher doses and did not mix it with other drugs as other psychiatrists had been doing. In 1952, they reported some amazing successes; in 1953, the drug was marketed in Europe as Largactil (Sneader, 1985; Snyder, 1986; Spiegel & Aebi, 1981).

Chlorpromazine was marketed in the United States in 1955 as Thorazine and was very successful. At that time, the number of patients in mental hospitals had been climbing steadily, but with the introduction of chlorpromazine, it started to decline dramatically. In the next 3 decades, the resident population of mental institutions in the United States dropped by 80% (Hollister, 1983), largely as a result of the use of antipsychotics.

The drugs that are useful in treating the symptoms of schizophrenia are called by several names, derived from three major effects of this class of drugs on behavior. In North America, they are often referred to as *antipsychotics* because their most useful effect is to diminish the symptoms of psychosis that appear in schizophrenia.

The term *major tranquilizer* is sometimes used to refer to the antipsychotics because they have a sedating effect, not only in agitated psychotic patients but also in healthy people. This name is inappropriate because it suggests that these drugs are useful only because they *tranquilize* agitated patients. Even though there is a tranquilizing effect, these drugs seem to produce their antipsychotic effect by directly blocking the symptoms of psychosis. Rather than simply making psychotic people more tranquil or sedated, they cause psychotic people to be less psychotic and, in many cases, less agitated. Another problem is that the term major tranquilizer implies that they are just a stronger version of *minor tranquilizers*, a term sometimes applied to drugs such as the benzodiazepines or barbiturates (see Chapter 7). This terminology is misleading because it implies that both drugs have a similar effect and that one class is more powerful than the other. In fact, there is very little similarity, in chemistry or effect, between the barbiturates and benzodiazepines on the one hand and the antipsychotics on the other.

In Europe, the term *neuroleptic* is preferred. Neuroleptic means *clasping the neuron*. It refers to a capacity of these drugs to cause EPS, such as rigidity in the limbs and difficulty of movement, similar to those symptoms seen in people suffering from Parkinson's disease. This property of these drugs is a persistent and bothersome side effect, and it is indeed strange that a family of drugs should be named after a side effect rather than its most useful therapeutic effect. This name may have been chosen because at one time it was believed that both effects were related; that is, people believed that these drugs would not relieve psychosis unless they were causing neuroleptic effects as well. It is now known that the two types of effects are independent (Creese, 1983). In fact, we now have drugs that seem to be effective antipsychotics but have few, if any, neuroleptic (EPS) effects. Although the term *neuroleptic* is probably more common than *antipsychotic*, we use the latter term here because it seems more appropriate to think of drugs in terms of their useful effects rather than their side effects.

COMPARING TYPICAL AND ATYPICAL ANTIPSYCHOTICS

A distinction is drawn between *typical* (or *first-generation*) and *atypical* (or *second-generation*) antipsychotic medications. Examples of both types can be found in Table 12-1 (some of these may not have gained approval or may no longer be approved, for use in parts of Europe or North America).

The older drugs, the *typical antipsychotics*, were all developed before 1975 and are either phenothiazines or butyrophenones. They are primarily D_2 receptor blockers and are most effective in treating the positive symptoms of psychosis, rather than the negative or cognitive symptoms (which, in fact, may even be worsened). Approximately one-third of individuals with schizophrenia experience no improvement of symptoms when taking typical antipsychotics (Wiersma, Nienhuis, Slooff, & Giel, 1998). Adverse EPS are *typical* of these drugs, hence the name. The neuroleptic side effects range from being inconvenient, for some individuals, to producing major, life-long physical disability for others. For this reason, it is often difficult for individuals to comply with taking their prescribed dose.

More recently developed schizophrenia medications, and those currently in development, are pharmacologically unlike the typicals. These are the *atypical antipsychotics*. Although their individual profiles vary considerably, they share an important property: a very weak affinity for the

TABLE 12-1 Examples of Typical and Atypical Antipsychotic Drugs

Generic Name	Trade Name
Typical antipsychotics	
acetophenazine	Tindal
carphenazine	Proketazine
chlorpromazine	Thorazine, Largactil
chlorprothixene	Taractan, Tarasan
fluphenazine	Prolixin
haloperidol	Haldol
loxapine	Loxitane, Loxapac
mesoridazine	Serentil
molindone	Lindone, Moban
perphenazine	Trilafon, Etrafon**
pimizide	Orap
prochlorperazine	Stemetil, Compazine
promazine	Sparine
reserpine	Serpasil
thioridazine	Mellaril
thiothixene	Navane
trifluoperazine	Stelazine
triflupromazine	Vesprin
Atypical antipsychotics	
amisulpride	Solian
aripiprazole	Abilify
clozapine	Clozaril
olanzapine	Zyprexa
paliperidone	Invega
quetiapine	Seroquel
raclopride	Dogmatil
remoxipride*	Roxiam
risperidone	Risperdal
sertindole	Serlect
ziprasidone	Zeldox; Geodon
zotepine	Nipolept

*Found to have dangerous side effects and is not used therapeutically but is still used in nonhuman experimentation.
**Etrafon is a combination of perphenazine and the tricyclic antidepressant amitriptyline.

D_2 receptor—they bind to D_2 receptors very loosely and have dissociation constants that are significantly higher than that of dopamine or the typicals (Seeman, 2002). Because of this, adverse EPS are *atypical* effects of these drugs.

Panel A of Figure 12-2 compares the D_2 receptor dissociation constants of a number of typical and atypical antipsychotic medications.

Positron emission tomography research reveals that about 60 to 80% of D_2 receptors must be occupied in the striatum of the basal ganglia to produce EPS (Seeman, 2002). Because of their weak affinity for the D_2 receptor, atypical antipsychotics avoid the problem of blocking dopamine in the nigrostriatal system and, therefore, produce far fewer EPS compared to the typicals. They are also more effective than the typicals in treating a wider range of schizophrenic symptoms.

Instead, the atypicals have high affinities for D_3 and D_4 receptors. Neither of these receptor subtypes is found in high quantities in the basal ganglia. The D_3 receptor is localized largely in the nucleus accumbens, the terminal point of the mesolimbic projection, with many fewer receptors in the basal ganglia (Landwehrmeyer, Mengod, & Palacios, 1993). The D_4 receptor is localized largely in the cortex, amygdala, and hippocampus—the regions that are important in cognition, emotion, and learning. There are very few, if any, D_4 receptors in human motor systems (Primus et al., 1997). Thus, it is possible for the atypical antipsychotics to depress dopamine activity in the mesolimbic system and treat psychoses without having a great effect on the nigrostriatal system and causing Parkinsonian side effects.

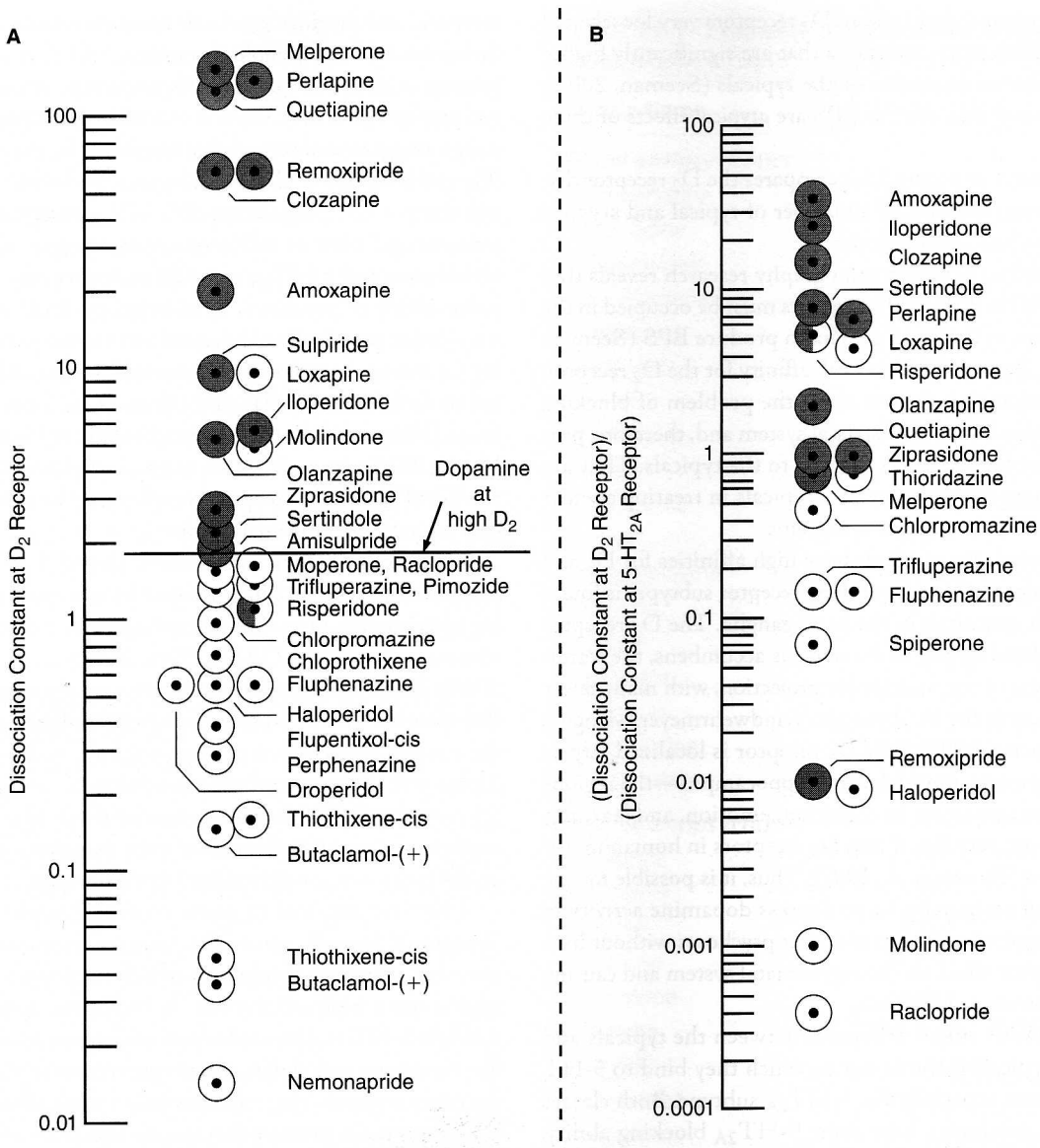
Another major difference between the typicals and the atypicals is the extent to which they bind to 5-HT receptors, especially the 5-HT_{2A} subtype. Both classes of antipsychotics have some 5-HT_{2A} blocking ability, but this activity is much higher for the atypicals. Panel B of Figure 12-2 illustrates the dissociation constants of typical and atypical antipsychotics for D_2 receptors as compared to 5-HT_{2A} receptors. Overall, the typicals tend to have greater effects at D_2 receptors than at 5-HT_{2A} receptors, and the opposite is true for atypical antipsychotic drugs, although there are some notable exceptions to this rule, such as remoxipride.

There is another reason why the effects of atypical antipsychotics on 5-HT_{2A} receptors may be important. Drugs like LSD and psilocybin are agonists at 5-HT_{2A} receptors and produce psychotic symptoms such as hallucinations. Metabotropic glutamate (mGlu) receptors interact with 5-HT_{2A} receptors to create a functional receptor complex that, when activated by hallucinogenic drugs, triggers unique cellular responses in the cortex (González-Maeso et al., 2008). In untreated schizophrenia, there is an upregulation of 5-HT_{2A} receptors and a downregulation of mGlu receptors, suggesting that an imbalance of 5-HT_{2A} to mGlu receptors may create vulnerability to psychosis. In addition, mGlu knockout mice (mice genetically engineered so that the gene coding for the mGlu receptor is inactivated, i.e., *knocked out*) fail to demonstrate behavioral effects of hallucinogenic drugs (Moreno, Holloway, Albizu, Sealfon, & González-Maeso, 2011). As such, mGlu receptors and, specifically, the 5-HT_{2A}–mGlu receptor complex may be ideal targets for antipsychotic medications.

In addition to their actions on DA and 5-HT, the atypicals affect other neurotransmitter systems, including acetylcholine, histamine, norepinephrine, and peptide transmitters such as GABA (Pira, Mongeau, & Pani, 2004). These additional actions may contribute to their therapeutic efficacy and side effect profiles. For example, the anticholinergic effects of some atypicals, such as olanzapine and clozapine, provide an additional mechanism for reducing EPS. However, some of these additional actions may cause unpleasant or even dangerous effects on the body, as you will read later in this chapter.

The first atypical to come onto the market was *clozapine* (Clozaril), which alleviates the positive, negative, and cognitive symptoms of schizophrenia. Clozapine has a high affinity for D_4 receptors, as well as multiple 5-HT receptor subtypes, muscarinic acetylcholine receptors, and $alpha_1$ adrenergic receptors. As with the other atypicals, clozapine has only a weak affinity for D_2 receptors. Its primary therapeutic effects are thought to result from antagonism of D_4 and 5-HT_{2A} receptors (Meltzer, 1994). Clozapine, and the many other atypicals that have since been developed, are often first used in the United Kingdom or other European countries and are slow to be approved for use in the United States and Canada.

In 2002, the FDA approved a new drug, aripiprazole (Abilify) for the treatment of schizophrenia. This drug is unlike its predecessors and, for that reason, is sometimes referred to as a third-generation antipsychotic. Aripiprazole has a mechanism of action unlike the other



Typical antipsychotics are represented by unshaded rings; atypical antipsychotics are represented by shaded rings. Risperidone, a weak atypical, is half shaded, half unshaded.

FIGURE 12-2 Typical and atypical antipsychotic dissociation constants. Typical antipsychotics are represented by unshaded rings; atypical antipsychotics are represented by shaded rings. Risperidone, a weak atypical, is half shaded, half unshaded. *Panel A*: Typical antipsychotics bind more tightly than dopamine to the D_2 receptor (in its functional high-affinity state), with dissociation constants lower than that of dopamine. The atypical antipsychotics bind more loosely than dopamine to the D_2 receptor, with dissociation constants higher than that of dopamine. Out of the 31 antipsychotics illustrated, there are two or three apparent exceptions to this rule. *Panel B*: Typical and atypical antipsychotics' dissociation constants at D_2 vs. 5-HT_{2A} receptor subtypes. In general, typical antipsychotics have lower dissociation constants at D_2 receptors than at 5-HT_{2A} receptors, and the reverse is true of atypical antipsychotics. However, of the 20 antipsychotics illustrated, there are three or four apparent exceptions. Remoxipride is one of these. (Adapted from Seeman, 2002, Figure 4A and 4B, p. 54; reprinted with permission.)

atypicals. It is a DA receptor partial agonist—it modulates, rather than blocks, dopamine activity at D_2, D_3, and D_4 receptor subtypes. Recall from Chapter 4 that a partial agonist has a high affinity for the receptor to which it binds, but it activates that receptor to a lesser degree than would the natural ligand (i.e., dopamine). Because of this, in regions of the brain where dopamine activity is too low (i.e., in the prefrontal cortex where the mesocortical pathway terminates), aripiprazole acts as an agonist by binding to and increasing the activation of DA receptors. In regions of the brain where dopamine activity is too high (i.e., in the nucleus accumbens where the mesolimbic pathway terminates), aripiprazole acts as an antagonist by preventing DA from binding to its receptors and activating those receptors to a lesser degree. Aripiprazole also acts as a partial agonist or antagonist at various 5-HT receptor subtypes and affects histamine and alpha-adrenergic receptor function. Because aripiprazole stabilizes dopamine activity, it is able to treat positive, negative, and cognitive symptoms of schizophrenia.

In terms of their efficacy in relieving positive, negative, and cognitive symptoms of schizophrenia and their ability to increase quality of life and improve one's overall mental state, the atypicals are not overwhelmingly superior to the typicals. In some cases and for certain symptoms, they may be less efficacious (Leucht, Kissling, & Davis, 2009; Melnik, Soares, Puga, & Atallah, 2010). Overall, their greatest benefit is the lack of EPS they produce.

ROUTES OF ADMINISTRATION

The antipsychotics are usually taken orally, but preparations are available to be given in intramuscular or intravenous injections. They are seldom injected when given as antipsychotics, but they are injected when used as a presurgical or preanesthetic medication because the sedating effects appear more quickly when given parenterally. Intravenous injection also avoids any irregularities or delays in effect arising from erratic absorption from the digestive system. It is doubtful, however, that antipsychotic effects can be significantly speeded by giving the drug parenterally; the antipsychotic effects take several days or weeks to develop. The antipsychotics may be injected in circumstances where it may be difficult to induce agitated schizophrenic patients to take the drugs orally.

Because antipsychotic drugs are often taken chronically and patients do not always take them reliably, they are sometimes given in the form of a slowly dissolving *depot injection* , as described in Chapter 1. Typical antipsychotics (e.g., fluphenazine, haloperidol, and perphenazine) can be dissolved in an oily base, such as sesame, coconut, or synthetic vegetable oil, and injected intramuscularly. Newer atypical antipsychotics administered as depot injections are not suspended in oil. For example, risperidone can be encapsulated in a biodegradable polymeric microsphere preparation, which erodes slowly to release the drug. Olanzapine and paliperidone can be combined with the salt form of pamoic acid (pamoate salt) and suspended in water. Following intramuscular injection, the pamoate salt slowly dissolves to release the drug into the body (Haddad, Lambert, & Lauriello, 2011). A single depot injection of oil-, microsphere-, or crystalline-salt-based preparation may be effective for as long as 4 weeks (Haddad et al., 2011).

ABSORPTION AND DISTRIBUTION

Most antipsychotics are readily absorbed from the digestive system. Once absorbed, they are distributed throughout the body and easily cross placental and blood–brain barriers. Blood protein binding is considerable, and the drugs tend to be absorbed into body fat and released very slowly. Oil-based depots can take weeks or months to reach steady-state levels with regular injections and are slowly eliminated. Depot injections of the atypicals, because they are not dissolved in oil, do not accumulate in body fat over time. Long-acting risperidone reaches peak release at about 28 days. Long-acting olanzapine and paliperidone show peak blood levels after about 2 to 4 days (Haddad et al., 2011).

EXCRETION

The typicals and atypicals undergo extensive metabolism prior to excretion in urine and feces (Sheehan, Sliwa, Amatniek, Grinspan, & Canuso, 2010). There is considerable individual variability in the metabolism of antipsychotics and in the optimal blood concentration. Finding the best dose for any individual is largely a matter of trial and error. Because of their strong protein binding and tendency to stay in body fat, typical antipsychotics have very long half-lives of 11 to 58 hours, and

metabolites can be found in the urine months after treatment. This is not the case for the atypicals. Cytochrome P450 enzymes play a major role in the metabolism of antipsychotics. This can be problematic for individuals taking a variety of additional medications, such as antidepressants, mood stabilizers, or anxiolytics, as many of these drugs also rely on cytochrome P450 enzymes for their metabolism. Individuals taking antipsychotics are also at increased risk of renal failure.

EFFECTS OF ANTIPSYCHOTICS

Effects on the Body

The effects of antipsychotics are widely variable, both within an individual taking different drugs and between individuals taking the same drug. Each drug's effectiveness as an antipsychotic and the sorts and intensity of side effects vary considerably from person to person. This is one reason why so many of these drugs are on the market. Psychiatrists may try giving an individual a number of different drugs at different doses until one is found that produces the most favorable therapeutic effect with the fewest side effects.

There is no cure for psychosis, and treatment is lifelong. With prolonged use, antipsychotic medications can take a significant toll on one's body. As we have already seen, the most pronounced side effect of the typical antipsychotics is EPS—alterations in movement that resemble the symptoms of Parkinson's disease. This effect is reported in about 40% of patients on typical antipsychotics. It includes a dulled facial expression, rigidity and tremor in the limbs, loss of coordinated movement, weakness in the extremities, and a slowing of movements. Anti-Parkinson's medications are frequently given to combat these EPS. In addition, about 20% of patients show *akathisia*, a condition characterized by uncontrolled restlessness, constant compulsive movement, and sometimes a protruding tongue and facial grimacing.

Because the typicals accumulate in brain tissue, prolonged use can lead to a neurological condition called *tardive dyskinesia*. It is characterized by involuntary, tic-like, repetitive movements of the face, such as muscle twitching, smacking of the lips, or flicking of the tongue, sometimes dozens of times per minute. Unfortunately, for some individuals, the symptoms of tardive dyskinesia are permanent and do not go away even after the drug is stopped (Enna & Coyle, 1983). Rates of tardive dyskinesia tend to be higher in elderly individuals and in women. In contrast to the typicals, the atypicals are far less fat-soluble and bind only briefly to D_2 receptors. As a result, their likelihood of causing tardive dyskinesia is extremely low (Seeman, 2002).

With regard to clozapine specifically, a major problem is increased risk of a disorder called *agranulocytosis*, a potentially fatal loss of white blood cells and decline in immune system function due to the suppression of bone marrow activity. It occurs in 1 to 2% of all patients receiving clozapine and can happen at any time. For this reason, patients taking clozapine must be carefully and continuously monitored with frequent blood testing. This serious side effect kept clozapine off the market for many years.

Antipsychotics also seem to cause the body to have trouble regulating temperature, which becomes easily influenced by changes in the environment. In hot environments, patients are more susceptible to heat stroke; in cold climates, they are more vulnerable to hypothermia. The skin also develops an oversensitivity to the sun so that it burns quickly.

Other side effects of typical antipsychotics include weight gain, changes in cardiac function and blood pressure (due to the effect of these drugs on NE receptors), dry mouth, impaired vision, dizziness, constipation (due to anticholinergic effects), and jaundice. In certain susceptible individuals, there is an increased risk of seizures.

Although they produce far fewer EPS than do the typicals, the atypicals have their own set of problematic or even life-threatening side effects. Like the typicals, long-term use of atypicals is associated with disturbances in glucose metabolism and fat regulation, significant weight gain, and onset of diabetes (Üçok & Gaebel, 2008). Increases in triglycerides and cholesterol have also been found in individuals taking clozapine and olanzapine. Like the typicals, the atypicals can produce abnormal cardiac function that can be life threatening, especially in older adults (Mehta, Chen, Johnson, & Aparasu, 2011). The U.S. Food and Drug Administration warns against treating dementia-related psychotic symptoms in the elderly with olanzapine or risperidone due to a near doubling of risk of death related to cardiac dysfunction or respiratory infections. People taking atypical antipsychotics also experience thermodysregulation, dry mouth, dizziness, nausea, and are more prone to developing cataracts.

Aripiprazole has a relative absence of most of the side effects mentioned earlier and, for that reason, has a higher compliance rate compared to typicals and many of the atypicals. Its most significant side effects are nausea and dizziness (Melnik et al., 2010).

Effects on Sleep

Antipsychotics at therapeutic doses have very little effect on sleep, but some antipsychotics that have sedating effects (e.g., chlorpromazine, quetiapine) will increase sleep time when given at high doses or when first administered. The antipsychotics do not alter sleep cycles or REM sleep (Spiegel & Aebi, 1981). There is evidence that the atypicals may increase the risk of obstructive sleep apnea (Shirani, Paradiso, & Dyken, 2011).

Lethal Effects

The antipsychotics produce many side effects, but these drugs are not lethal. In fact, they are extremely safe and have a high therapeutic index (see Chapter 1), about 100. For some antipsychotics, the therapeutic index is as high as 1,000 (Baldessarini, 1985). It is practically impossible to use antipsychotics to commit suicide.

EFFECTS ON THE BEHAVIOR AND PERFORMANCE OF HUMANS

Subjective Effects

Chlorpromazine, when given to healthy subjects, causes a very pronounced feeling of tiredness. Subjects report slower and confused thinking, difficulty concentrating, and feelings of clumsiness. They also report a need for sleep, dejection, anxiety, and irritability. Simple tasks such as walking seem to take great effort.

Haloperidol is not as sedating as chlorpromazine, but, along with other atypical antipsychotic drugs, it makes subjects feel internally aroused and externally sedated at the same time; that is, they feel restless and want to do something but also feel restrained and have difficulty moving (Spiegel & Aebi, 1981).

The subjective experience of antipsychotics is never described as pleasant. This fact is probably responsible for the poor compliance rates with these drugs; patients often do not take them. This does not appear to be true, however, of many of the atypical antipsychotics, such as clozapine (Meltzer, 1990).

Effects on Performance

Reports on the effects of typical antipsychotics on attention and cognitive performance have been variable. Most studies of the acute effects show impairment probably related to sedative effects. Tolerance to these effects has also been reported to occur within 14 days. Clozapine and remoxipride, both atypical antipsychotics, have been shown to interfere with performance. The findings with sulpride, however, have been mixed (King, 1993).

Surprisingly, few studies of the effects of antipsychotics on cognitive functioning have been conducted. Those that were done have been inconclusive, reporting no effect, deficits, or improvements (Judd et al., 1987).

EFFECTS ON THE BEHAVIOR OF NONHUMANS

Effects on Unconditioned Behavior

Unlike the antianxiety drugs, such as the benzodiazepines, the most remarkable effect of the antipsychotic drugs is that they suppress spontaneous movement in an open field, and higher doses render most laboratory animals immobile. In fact, these animals take on a sort of *plastic immobility*. Their limbs will remain in any position in which they are placed, as though the animals were made out of modeling clay. This immobility gave rise to the name *neuroleptic*.

At doses that do not seem to produce these neuroleptic effects, antipsychotic drugs diminish the frequency and intensity of attack behaviors in most species. This decrease in aggression coincides with an overall decrease in activity, so it is possible that it results from an overall debilitation in motor abilities (Miczek & Barry, 1976).

Effects on Conditioned Behavior

In general, the antipsychotic drugs cause a decrease in responding on schedules maintained by positive reinforcement, although at lower doses there are reports that low response rates may be increased. This rate-dependent effect is similar to the effect seen with many other drugs, including amphetamine.

As far back as 1953, when chlorpromazine was first being tested on humans by Laborit, Simone Courvousier and her associates at the Rhône-Poulenc company (Courvoisier, Fournel, Ducrot, Kolsky, & Koetschet, 1953) discovered that the drug would decrease

avoidance at doses that would have no effect on escape from a shock, an effect now known to be shared by antianxiety drugs such as barbiturates and benzodiazepines. In fact, this was the first time that this technique had been adopted for use in testing drugs, and it has since become one of the most widely used screening devices for new psychotherapeutics (Laties, 1986).

DRUG STATE DISCRIMINATION AND DISSOCIATION

It has been demonstrated that chlorpromazine will cause dissociation. In one study, rats trained on an avoidance task under the influence of chlorpromazine were unable to remember what they had learned when tested under saline but could recall the task when returned to the drug state again (Otis, 1964). This finding has caused some concern among psychotherapists because psychotherapy involves learning, and patients often receive psychotherapy while they are being treated with these drugs. Consequently, when they are taken off the drugs, they may not recall what they learned in psychotherapy.

In drug state discrimination studies, the antipsychotics are not well discriminated. For an antipsychotic to act as a discriminative stimulus, large doses are required, and many more training trials are needed, compared with most other behaviorally active drugs (Overton, 1987; Overton & Batta, 1977).

Once an animal has been trained to discriminate an antipsychotic, the response will generalize to most other antipsychotics at sufficiently high doses. There are some exceptions. For example, a rat trained to discriminate clozapine will not generalize to haloperidol or chlorpromazine (Goas & Boston, 1978). There is no generalization between the antipsychotics and the antidepressants or any other class of drugs (Stewart, 1962).

TOLERANCE

Once a therapeutic dose has been established for a patient, it is often maintained for years without any decrease in effectiveness. Haloperidol's ability to increase dopamine release in the cortex does decline with prolonged use; clozapine does not show tolerance of this sort (Advokat, 2005). Tolerance seems to develop to the sedating effects of antipsychotics when first given, and tolerance also seems to develop to the EPS.

WITHDRAWAL

Physical dependence, if it occurs at all, is rare or mild. There are reports of muscular discomfort, exaggeration of psychotic symptoms and movement disorders, and difficulty sleeping when some antipsychotics are suddenly withdrawn, but such effects are not normally seen even after years of use at normal doses. It is possible that the failure to notice withdrawal symptoms is due to the extremely slow excretion of the drug from the body (Baldessarini, 1985). In an examination of 28 patients who abruptly discontinued clozapine use, 11 showed no withdrawal symptoms at all, 12 showed mild symptoms that included headache and nausea, 4 experienced more significant symptoms including vomiting and diarrhea, and 1 experienced a rapid reemergence of psychotic symptoms (Shiovitz et al., 1996).

SELF-ADMINISTRATION IN HUMANS AND NONHUMANS

As we learned in Chapter 5, some drugs have aversive properties, and antipsychotic drugs appear to be included in this group. In one experiment, monkeys learned to bar press to avoid infusions. At first, the monkeys did not respond to avoid chlorpromazine; after a week, they were successfully avoiding 90% of the programmed infusions. It appears that the aversive properties of chlorpromazine develop slowly, with repeated doses (Hoffmeister & Wuttke, 1975).

Experience with humans is similar. The antipsychotics are never abused; in fact, they are a class of drugs that have considerable compliance problems. *Compliance* refers to the extent to which a patient adheres to a regimen of medical treatment. In the case of typical antipsychotics, most schizophrenic patients show poor compliance; they often stop taking their medication, with the usual result that their symptoms reappear. For this reason, various administration techniques have been developed that do not depend on the patient's compliance. Among them is administration of depot injections, which slowly release the drug and maintain the appropriate blood levels. Noncompliance is slightly less of a problem with the atypical antipsychotics.

HARMFUL EFFECTS

Reproduction

Antipsychotics can have serious effects on reproductive functions. In males, antipsychotics reduce sexual interest, an effect that may arise from their sedative properties. Sexual performance may also be impaired. The primary difficulty is a failure to ejaculate; erection and orgasm are unaffected. These problems arise from cholinergic, adrenergic, histaminergic, and dopaminergic properties of the antipsychotics and their effect on hormone levels (Üçok & Gaebel, 2008; Woods, 1984). Recall from Chapter 4 that, in the *tuberoinfundibular pathway*, dopamine acts as a neurohormone to inhibit the release of prolactin from lactotroph cells of the pituitary. Prolactin suppresses male sexual activity. Drugs like cocaine, which activate this system, can stimulate male sexual performance by suppressing prolactin release, but the antipsychotics, which block D_2 receptors on lactotroph cells, cause excess release of prolactin. This is less of a concern with the atypicals, although risperidone elicits elevations in prolactin levels to a similar extent as the typicals (Üçok & Gaebel, 2008).

In females, there may be abnormal menstrual cycles and infertility. In both males and females, there is sometimes an enlargement of the breasts and fluid discharge from the nipples (Woods, 1984).

OTHER THERAPEUTIC EFFECTS OF ANTIPSYCHOTIC DRUGS

Antipsychotic drugs are useful in the treatment of other medical problems and forms of mental illness. They are effective *antiemetics*; that is, they prevent nausea and vomiting and are useful in the treatment of motion sickness. In addition, they were originally developed by Laborit as presurgical and preanesthetic medications and are still used for that purpose.

A number of movement disorders thought to result from excessive dopamine activity in the brain can, not surprisingly, be treated effectively with antipsychotics. These disorders include *Huntington's chorea*, an inherited degenerative disease. Huntington's is fatal, but antipsychotics help control some of the symptoms. Antipsychotics are also useful in treating *Tourette's syndrome*; Tourette's patients show involuntary muscle tics, twitches, and vocalizations. Surprisingly, antipsychotics are also used to treat tardive dyskinesia.

Antipsychotics have also been used to treat hiccups, stuttering, delirium tremens caused by alcohol withdrawal, and psychotic behaviors induced by psychomotor stimulants, LSD, and other hallucinogens. Atypicals, including aripiprazole, have been used in the treatment of major depressive disorder, bipolar disorder, mania, and irritability in autistic children.