13

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.

The drugs that are useful in treating the symptoms of schizophrenic psychoses are called by several names. In North America, they are often referred to as *antipsychotics*; in Europe, the term *neuroleptic* is preferred. They are also referred to as *major tranquilizers*. These three names are derived from three major effects of this class of drugs on behavior.

The drugs are called antipsychotic because their most useful effect is to diminish the symptoms of *psychosis*. There are two basic types of psychosis: (a) *schizophrenia* and (b) *bipolar disorder* (also called manic-depressive psychosis). The drugs referred to as antipsychotic are useful in the treatment of schizophrenic psychosis (described in this chapter) and in the treatment of symptoms of the manic phase of bipolar disorder (described in Chapter 14).

The term *neuroleptic* means "clasping the neuron." It refers to a capacity of these drugs to cause rigidity in the limbs and difficulty of movement similar to that seen in people suffering from Parkinson's disease. As a result, these effects are sometimes called *parkinsonian symptoms*. 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 (parkinsonian) effects.

The term *neuroleptic* is probably more common than *antipsychotic*, but we will 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.

The term *major tranquilizer* is sometimes used to refer to the antipsychotics because they have a sedating effect not only on agitated psychotic patients but also on 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 *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.

TYPES OF ANTIPSYCHOTICS

In recent years, a distinction has often been drawn between typical and atypical antipsychotic drugs. The drugs in the older group, the *typical antipsychotics*, were all developed before 1975. They are either *phenothiazines* (e.g., chlorpromazine, fluphenzine) or *phenothiazine-like* (e.g., haloperidol). These drugs tend to cause neuroleptic or parkinsonian symptoms in addition to their antipsychotic effects, and they seem to be most effective in treating the positive symptoms of psychosis (i.e., the hallucinations and delusional thinking) rather than the negative symptoms, such as flattened affect and alogia. (More on this later.) A number of drugs developed and introduced since 1990 have minimal parkinsonian effects and seem more effective in treating the negative symptoms; these are termed *atypical antipsychotics*. All of the antipsychotics presently under development fit into the atypical class.

TABLE 13-1 Typical and Atypical Antipsychotic Drugs

Generic Name	*Trade Name*
Typical antipsychotics:	
chlorpromazine	Thorazine, Largactil
promazine	Sparine
triflupromazine	Vesprin
thioridazine	Mellaril
mesoridizine	Serentil
trifluoperazine	Stelazine
fluphenazine	Prolixin
perphenazine	Trilafon
acetophenazine	Tindal
prochlorperazine	Stemetil, Compazine
carphenazine	Proketazine
thiothixene	Navane
chlorprothixene	Taractan, Tarasan
loxapine	Loxitane, Loxapac
haloperidol	Haldol
molindone	Lindone, Moban
Atypical antipsychotics:	
clozapine	Clozaril
respiridone	Resperdal
raclopride*	
remoxipride**	
quetiapine	Seroquel
olanzepine	Zyprexa
pimizide	Orap
sertindole	Serlect
ziprasidone	Zelox
amisulpride	Solian

* Not licensed in the United States or Canada.

** Found to have dangerous side effects and is not used therapeutically but is still used in nonhuman experimentation.

Sources: Churness (1988, pp. 529–530); J. Davis, Janicak, Linder, Maloney, and Avkovic (1983, p. 25); Jarvik (1970, p. 157); Julien (2001).

Typical Antipsychotics

Table 13-1 lists some commonly used antipsychotics alongside some of their more common trade names. Perhaps the best known antipsychotic is *chlorpromazine* (Thorazine or Largactil). Others include *promazine* (Sparine), *trifluoperazine* (Stelazine), *fluphenazine* (Prolixin), and *haloperidol* (Haldol).

Atypical Antipsychotics

Thioridazine (Mellaril) has been used for many years and was recognized as causing few parkinsonian symptoms. It is now often classified as an atypical antipsychotic. The next such drug to be developed was *clozapine* (Clozaril). Since the introduction of this drug, several more have been introduced, and many more are being developed. These include *respiridone* (Risperdal), *sulpride* (Sulmatil and Dolmatil), *amperozide* (Solian), *quetiapine* (Seroquel), and *olanzapine* (Zyprexa). Often these drugs are used in the United Kingdom or other European countries first and are slow to be approved for use in the United States and Canada.

THE NATURE OF PSYCHOSIS AND SCHIZOPHRENIA

At this point, we take a brief look at psychosis, the disorder that these drugs are used to treat. *Psychotic disorders* are characterized by a loss of touch with reality; people with psychosis reach a state where they completely misunderstand and misinterpret the events going on around them, and they respond inappropriately in both an intellectual and an emotional sense. They often experience bizarre hallucinations, and their behavior is guided by delusions, beliefs that have no basis in reality.

Psychoses may be brief and temporary, brought on by drugs or some toxin, and psychotic behavior may arise from diseases such as Alzheimer's, but the major types of psychosis are bipolar disorder (which used to be known as manic-depressive psychosis, discussed in Chapter 14) and schizophrenia.

The term *schizophrenia* itself is often misunderstood. The word is derived from the Greek *schizein*, "to split," and *phren*, "mind." The splitting referred to, however, is not into two different personalities in the same individual. It is a separation between thought and emotion, the different aspects of one personality.

The diagnostic criteria for schizophrenia have been established by the American Psychiatric Association and are published in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (1994), which is more commonly referred to as the *DSM-IV*. Box 13-1 presents the characteristic symptoms for schizophrenia as listed in the *DSM-IV*.

The symptoms of schizophrenia are often classified into two types: positive and negative. *Positive symptoms* include hallucinations and delusions or irrational beliefs that can be very 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") are often involved. The disorder in thinking and speech involves a loosening of associations between ideas; thoughts skip from one subject to another, completely unrelated subject, and the speaker is unaware that the topics are unconnected. The speech of such people has been described as "word salad."

Negative symptoms include affective flattening; the person's face is immobile and unresponsive, and he or she shows a diminished range of emotional expressiveness. Another negative symptom is *alogia*, or impoverished speech; 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 sits for long periods of time and shows no interest in participating in work or social activities.

Box 13-2 presents a case study of a patient suffering from catatonic schizophrenia, one form of the disease.

BOX 13-1 *DSM-IV* Diagnostic Criteria for Schizophrenia

A. Characteristic Symptoms: Two (or more) of the following, each present for a significant proportion 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 thought), 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. © 1994, DSM-IV Diagnostic Criteria for Schizophrenia.

BOX 13-2 Schizophrenia: A Case Study

This account of a schizophrenic episode was published in the *Journal of Abnormal and Social Psychology* in 1955 ("An Autobiography," 1955). 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 13-1. 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. . . .

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.

HISTORY

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 Rhöne-Poulenc company. Like most antihistamines, it has both antihistamine and sedating properties. Laborit was encouraged by the results he got with promethazine. In 1951, Rhöne-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, p. 177; Snyder, 1986, p. 71; Spiegel & Aebi, 1981, p. 33).

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 three decades, the resident population of mental institutions in the United States dropped by 80 percent (Hollister, 1983, p. 3), largely as a result of the use of antipsychotics.

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 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. Depot injections release the drug into the system slowly, and a single injection may be effective for as long as 4 weeks (Lemberger, Schildcrout, & Cuff, 1987, p. 1288).

ABSORPTION AND DISTRIBUTION

Most antipsychotics are readily absorbed from the digestive system. Once absorbed, they are distributed throughout the body and easily cross the placental and blood–brain barriers. Blood protein binding is considerable, and the drugs tend to be absorbed into body fat and released very slowly.

EXCRETION

The drugs are destroyed entirely by metabolism, and almost no drug is excreted in the urine. Because of their strong protein binding and their tendency to stay in body fat, antipsychotics have very long half-lives of 11 to 58 hours, and metabolites can be found in the urine months after treatment. 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 pharmacokinetics, it is usually appropriate to take them once a day, usually at bedtime, so that their sedating effects will be maximal during sleep.

NEUROPHYSIOLOGY

The *dopamine hypothesis* has been the dominant theory of the neurological basis of schizophrenia since the 1970s. This theory holds that schizophrenia is the result of an excess of dopamine activity in the brain. The theory was developed in response to two major observations: (a) Drugs that increase dopamine function (e.g., cocaine) can cause a state almost indistinguishable from schizophrenia, and (b) the antipsychotics available at the time (the typicals) were all dopamine blockers (more on this later).

As was discussed in Chapter 4, there are two major dopamine systems in the brain: the *mesolimbic system*, which is implicated in motivation and reinforcement, and the *nigrostriatal system* of the basal ganglia, which plays a role in the

control of movement. The effect of antipsychotic drugs on the mesolimbic system seems to be responsible for their therapeutic effect, and their effect on the nigrostriatal system seems to be responsible for their main side effect, parkinsonian or neuroleptic effects.

The Mesolimbic Dopamine System

This system has its cell bodies in the ventral tegmental area (VTA) of the lower brain and synapses in the nucleus accumbens in the limbic system (see Figure 13-1). The cell bodies in the VTA also synapse on cells in other parts of the brain, including the frontal cortex and other parts of the limbic system.

The original dopamine hypothesis maintains that psychoses, both schizophrenia and bipolar disorder, are a result of excessive dopamine activity in the mesolimbic dopamine system and that antipsychotic drugs work because they block dopamine receptors in the mesolimbic dopamine system and decrease this excessive activity.

More recently, we have come to understand that the situation is much more complicated. Other neurotransmitters are involved, including serotonin, and other brain systems also play important roles. This is supported by the observation that antipsychotic drugs block dopamine as soon as they are taken, but the therapeutic effect may be delayed for days or weeks. This delay suggests that there is more involved than simply blocking excessive dopamine activity (Carlsson, 1994). The therapeutic effectiveness of antipsychotics may also involve the slow and long-lasting changes in the electrical properties or connectivity of cells, as discussed in Chapter 4.

One clue to the involvement of dopamine in schizophrenia is the observation that psychomotor stimulants like cocaine that increase dopamine levels can cause psychotic symptoms if taken in excess. Other drugs are also known to

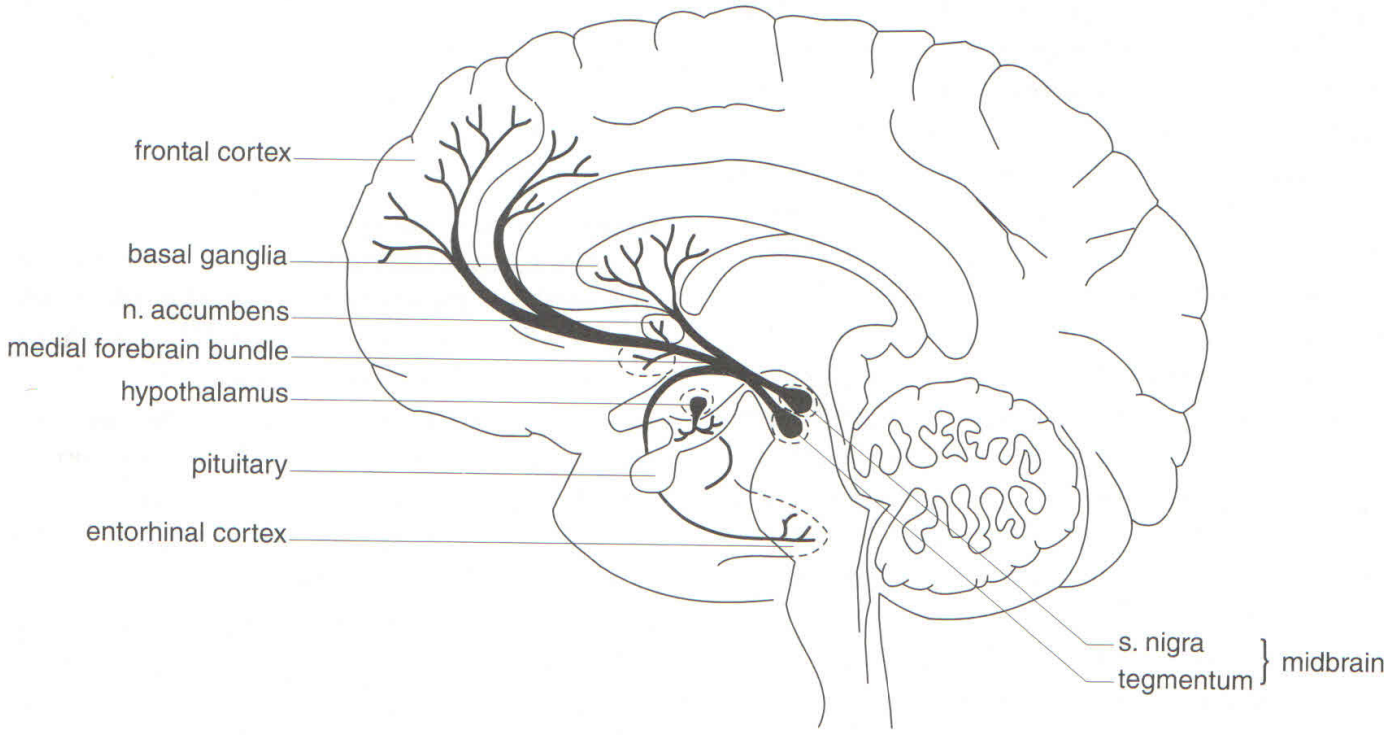

Figure 13-1 Dopamine systems in the human brain. The mesolimbic system originates in the midbrain in the ventral tegmentum and runs to the nucleus accumbens and forward to the forebrain. The nigrostriatal system originates in the midbrain in the substantia nigra and runs forward to the basal ganglia in the striatum.

cause psychotic-like symptoms. These are the hallucinogens, such as LSD, that alter serotonin and PCP, which blocks NMDA receptors for glutamate. So both serotonin and glutamate may have a role to play in psychosis (see Chapter 16). It is also known that there is an interaction between serotonin and glutamate activity. As we shall see, the atypical antipsychotic drugs also alter serotonin functioning. Exactly how dopamine, serotonin, and glutamate interact to cause psychosis is not clear at this time.

The Nigrostriatal System

The integration of smooth movements is thought to be the function of a part of the brain known as the basal ganglia. The basal ganglia consist of the caudate nucleus, the putamen, the globus pallidus, and the substantia nigra. Together, they form part of what is known as the *extrapyramidal motor system* or *motor loop* (see Chapter 4). Cell bodies located in the substantia nigra in the midbrain (close to the VTA) send axons to synapses in the basal ganglia (close to the nucleus accumbens), as shown in Figure 13-1. These synapses use dopamine as the transmitter, and it is known that proper functioning of the extrapyramidal motor system depends on normal levels of dopamine being released at these synapses. When there is a deficiency of dopamine at these synapses, people show symptoms of the movement disorder known as Parkinson's disease. When antipsychotic drugs are given, they block the activity of dopamine in the basal ganglia as well as the mesolimbic dopamine system and can cause parkinsonian movement disorders (sometimes called *extrapyramidal symptoms* or neuroleptic symptoms, as described earlier).

Differences Between Typical and Atypical Antipsychotics

The typical antipsychotics (which were the only antipsychotics available when the dopamine hypothesis was developed) are primarily blockers of D_2 receptors. In fact, if one examines the relationship between the therapeutic dose of a typical antipsychotic and the drug's affinity for the D_2 receptor, there is almost a perfect correlation (Seeman, Lee, Chau-Wing, & Wong, 1976). The weaker the drug's affinity for the D_2 receptor, the larger the dose that is required to have a therapeutic effect. This relationship is powerful evidence that these drugs exert their primary therapeutic effect at the D_2 receptor. But there are other dopamine receptors in the nucleus accumbens.

Atypical antipsychotics avoid the problem of blocking dopamine in the nigrostriatal system because they do not have a high affinity for the D_2 receptor but have high affinities for the D_3 and D_4 subtypes. Neither of these receptor subtypes is found in the basal ganglia in high numbers. The D_3 receptor is localized largely to 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 atypicals is the extent to which they block one of the serotonin receptors, the 5-HT_{2A} receptor. Both classes of antipsychotics have some 5-HT_{2A} blocking activity, but this activity is much higher for the atypicals than for the typicals. Figure 13-2 shows the different profiles of a number of drugs. The typical antipsychotics tend to have greater effects at D_2 receptors than at 5-HT_{2A} receptors (the notable difference is chlorpromazine), and just the opposite is true for atypical antipsychotic drugs. Lieberman et al. (1998) developed a model in which the D_2 blockade leads to parkinsonian symptoms, but an additional blockade of 5-HT_{2A} receptors counteracts the D_2 blockade. Atypical antipsychotics then may avoid parkinsonian side effects three ways: (a) They have a high affinity

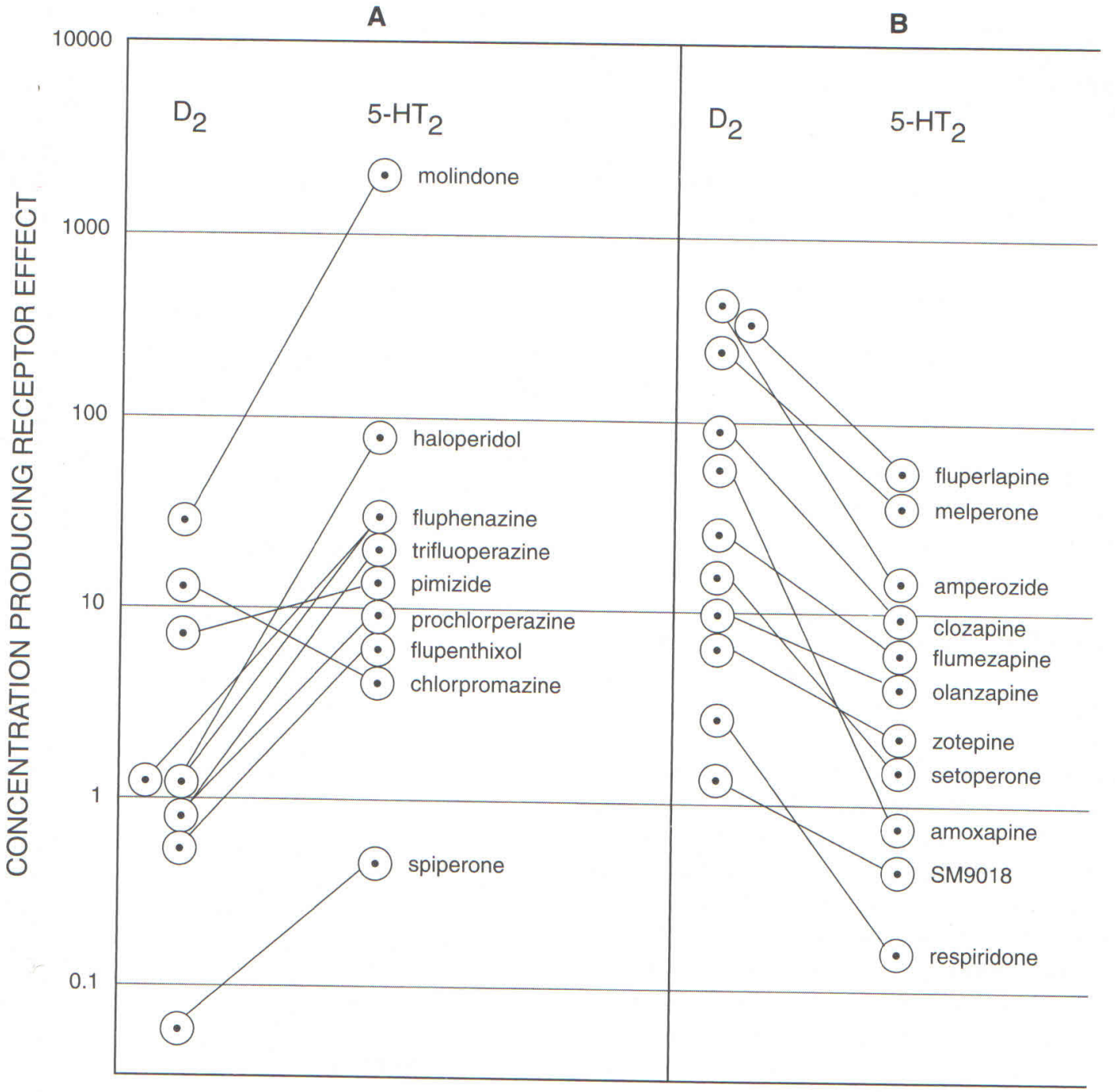

Figure 13-2 Panel A shows the relative effectiveness of various typical antipsychotic drugs on dopamine (D_2) and serotonin (5-HT_2) receptors (the lower the number, the greater the effect). Most of these drugs, with the exception of chlorpromazine, have a greater effect on dopamine receptors than serotonin receptors. Panel B shows the same analysis for many atypical antipsychotic drugs, which show a greater effect on serotonin than dopamine receptors. (Adapted from Seeman & Van Tol, 1994)

for D_3 and D_4 receptors; (b) they have a low affinity for D_2 receptors; and (c) their 5-HT_{2A} activity cancels out their D_2 activity.

There is another reason why the effects of atypical antipsychotic drugs on $5HT_{2A}$ receptors may be important. Drugs like LSD are agonists at $5HT_{2A}$ receptors, and this effect causes an increased response of large glutaminergic neurons in the cortex to input. This effect on glutaminergic neurons on the frontal cortex is thought to be

important in the hallucinations caused by many LSD-type drugs. By blocking these receptors, the atypical antipsychotic drugs may be reducing psychotic symptoms (see Chapter 16).

All of the antipsychotics have actions at all of these dopamine and serotonin receptors and the receptors of other transmitter systems as well, including acetylcholine and histamine. In addition, they may alter the effects of gamma-aminobutryic acid (GABA) and peptide transmitters, and they block norepinephrine (NE) receptors and increase NE synthesis and release (Roth, 1983, p. 127). In some cases, these effects on other receptor sites appear to be responsible for differences in the effect of various antipsychotic drugs on positive and negative symptoms and in the side effects they cause.

EFFECTS OF ANTIPSYCHOTICS

Effects on the Body

The effects of the different antipsychotics show considerable variation but not as much variability as can be seen among different individuals taking the same drug. Each drug's effectiveness as an antipsychotic and the sort and intensity of side effects will 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 and has the fewest side effects.

As we have already seen, the most pronounced side effect is alterations in movement that resemble the symptoms of Parkinson's disease. This effect is reported in about 40 percent of patients on typical antipsychotics. It includes a dulled expression on the face, rigidity and tremor in the limbs, weakness in the extremities, and very slow movements. In addition, about 20 percent of patients show *akathesia*, a condition characterized by uncontrolled restlessness, constant compulsive movement, and sometimes a protruding tongue and facial grimacing.

After taking the typical antipsychotics for a period of time, about 30 percent of patients show a condition called *tardive dyskinesia*, characterized by involuntary, repetitive movements of the face, such as smacking of the lips and twitching. 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, p. 10).

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.

In certain susceptible individuals, epileptic seizures may increase. Other side effects include reduced food intake, altered pigmentation of the skin, changes in heart rate and blood pressure (due to the effect of these drugs on NE receptors), dry mouth, impaired vision, constipation (due to anticholinergic effects), and jaundice.

The major problem with clozapine is that it is known to cause a disorder called *agranulocytosis*, a potentially fatal suppression of bone marrow activity. It occurs in 1 to 2 percent of all patients receiving clozapine and can happen at any time. For this reason, clozapine is administered only to patients who have not responded to any other antipsychotic drug, and patients on this drug must be carefully and continuously monitored. This serious side effect kept clozapine off the market for many years.

Effects on Sleep

Antipsychotics at therapeutic doses have very little effect on sleep, but some antipsychotics that have sedating effects (e.g., chlorpromazine) 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, p. 116).

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, pp. 35, 38, 81). 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 in 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, p. 62).

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, Squire, Butters, Salmon, & Paller, 1987, p. 1469).

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 have 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 (Courvousier, 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, p. 27).

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 (J. Stewart, 1962).

TOLERANCE

There is no evidence that tolerance develops to the antipsychotic effects of these drugs. Once a patient has been established on a therapeutically effective dose, it is often maintained for years without any decrease in effectiveness. Tolerance seems to develop to the sedating effects of the drugs seen when it is first given, and tolerance also seems to develop to the parkinsonian effects.

WITHDRAWAL

Physical dependence, if it occurs at all, is rare. There are reports of muscular discomfort, exaggeration of psychotic symptoms and movement disorders, and difficulty in 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, p. 38).

SELF-ADMINISTRATION IN HUMANS AND NONHUMANS

As we have seen in Chapter 5 (see Table 5-1), chlorpromazine is not self-administered by laboratory animals. In fact, these drugs appear to be aversive. 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 percent of the programmed infusions. It appears that the aversive properties of chlorpromazine develop slowly, with repeated doses (Hoffmeister & Wuttke, 1975, p. 424).

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 less of a problem with the atypical antipsychotics.

HARMFUL EFFECTS

Reproduction

Apart from the movement disorders already described, the antipsychotic drugs can have serious effects on reproductive functions.

In males, the 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 both anticholinergic properties of the antipsychotics and their effect on hormone levels (N. F. Woods, 1984, p. 440). Figure 13-1 shows that there is a short dopamine pathway running from the hypothalamus to the pituitary. When this system is activated, it suppresses the release of *prolactin*, a hormone that suppresses male sexual activity. Drugs like cocaine, which activate this system, can stimulate male sexual performance by suppressing prolactin release, but drugs like antipsychotics, which block dopamine, have the opposite effect. Atypical antipsychotics do not seem to alter prolactin release.

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 will sometimes ooze from the nipples (N. F. Woods, 1984, p. 441).

OTHER THERAPEUTIC EFFECTS OF ANTIPSYCHOTIC DRUGS

Antipsychotic drugs are useful in the treatment of other medical problems. 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 patients show involuntary muscle tics, twitches, and vocalizations (often swearing). Surprisingly, antipsychotics are also used to treat tardive dyskinesia.

Antipsychotics have also been used to treat hiccups, stuttering, and delirium tremens caused by alcohol withdrawal (Van Woert, 1983) and psychotic behaviors induced by psychomotor stimulants, LSD, and other hallucinogens.

CHAPTER SUMMARY

- Antipsychotic drugs are also referred to as neuroleptic drugs or major tranquilizers. They are used in the treatment of schizophrenia and bipolar disorder.
- Extrapyramidal motor effects (also known as parkinsonian effects or neuroleptic effects) are common side effects of antipsychotic drugs. These effects constitute a movement disorder similar to Parkinson's disease.
- People suffering from schizophrenia lose touch with reality. They misunderstand events going on around them and make inappropriate intellectual and emotional responses to those events. Positive symptoms include hallucinations and delusions. Negative symptoms include a loss of initiative, flattening of affect, and alogia (impoverished speech and thought).
- Typical antipsychotic drugs are effective only against positive symptoms, but the newer, atypical antipsychotic drugs are effective on both positive and negative symptoms and have fewer side effects on movement.
- Chlorpromazine was marketed in 1955. Along with other similar antipsychotics, it dramatically reduced the number of patients in mental hospitals throughout the world.
- Antipsychotics are administered orally and are distributed throughout the body. They easily cross the placental and blood–brain barriers. Because they are highly lipid soluble, they have very long half-lives.
- Antipsychotics work by blocking the dopamine D_2 receptors in the mesolimbic system. They cause

parkinsonian movement disorders and tardive dyskinesia by blocking D_2 receptors in the nigrostriatal system.

- Newer, atypical antipsychotic drugs have a low affinity for D_2 receptors but a high affinity for D_3 and D_4 receptors that are not located in the nigrostriatal system. They also block a serotonin receptor that has the effect of diminishing the activity of glutaminergic activity in the cortex. These differences may explain why the atypical drugs do not have serious extrapyramidal side effects and are effective in treating negative symptoms.
- When given to normal people, antipsychotics cause a feeling of tiredness, and the effects are never described as pleasant.
- Antipsychotics decrease general activity levels of nonhumans and have a rate-dependent effect on operant behavior. They decrease avoidance behavior in doses that have no effect on escape behavior.
- Tolerance to the antipsychotic effect of these drugs does not appear to develop, and withdrawal symptoms are rare. They are never self-administered by nonhumans and are not abused by humans.
- Antipsychotics can depress sexual interest and performance in males and interfere with menstruation in females.