Antipsychotic Agents

- What makes an antipsychotic conventional?
  - D2 receptor antagonism makes an antipsychotic conventional
  - Neuroleptic
  - Extrapyramidal symptoms (EPS) and tardive dyskinesia
  - Prolactin elevation
  - The dilemma of blocking D2 dopamine receptors in all dopamine pathways
  - Muscarinic cholinergic blocking properties of conventional antipsychotics
  - Other pharmacological properties of conventional antipsychotic drugs
  - Risks and benefits of long-term treatment with conventional antipsychotics

- What makes an antipsychotic atypical?
  - Serotonergic neurotransmission and serotonin dopamine antagonism
  - Serotonin synthesis and termination of action
  - Serotonin receptors
  - 5HT1A and 5HT2A receptors have opposite actions in regulating dopamine release
  - 5HT2A antagonism makes an antipsychotic atypical
  - Rapid dissociation of D2 antagonism makes an antipsychotic atypical
  - D2 partial agonism (DPA) makes an antipsychotic atypical
  - 5HT1A partial agonism (SPA) actions make an antipsychotic atypical

- Receptor binding properties and pharmacokinetics of antipsychotics
  - Links between antipsychotic binding properties and clinical actions
  - Cardiometabolic risk and antipsychotics
  - Sedation and antipsychotics
  - Antipsychotic pharmacokinetics
  - Pharmacological properties of individual antipsychotics

- Antipsychotics in clinical practice
  - Schizophrenia symptom pharmacies
  - The art of switching antipsychotics
  - Combs and polypharmacy

- Future treatments for schizophrenia
  - Presymptomatic and prodromal treatments for schizophrenia: putting the cart before the horse or preventing disease progression?
  - Glutamate-linked mechanisms and new treatments for schizophrenia
  - Glutamate agonists or antagonists for schizophrenia?
  - Novel serotonin- and dopamine-linked mechanisms
  - Acetylcholine-linked mechanisms
  - Peptidic-linked mechanisms
  - Future combination chemotherapies for schizophrenia and other psychotic disorders

- Summary
This chapter explores antipsychotic drugs with an emphasis on treatments for schizophrenia. These treatments include not only conventional antipsychotic drugs but also the newer atypical antipsychotic drugs, which have largely replaced the older conventional agents in many countries. Atypical antipsychotics are also used as mood stabilizers for the manic, depressed, and maintenance phases of bipolar disorder in both adults and in children, but this is discussed in Chapter 13 on mood stabilizers. Atypical antipsychotics have many other "off-label" uses, from augmentation of antidepressants in treatment-resistant depression and of anxiolytics in treatment-resistant anxiety disorders to treatment of psychosis and behavioral disturbances in Alzheimer's disease and other dementias. The use of atypical antipsychotics for indications other than the treatment of psychosis and schizophrenia is discussed in chapters dealing with those other disorders. Here we will discuss the use of conventional and atypical antipsychotics for the treatment of schizophrenia and also take a look into the future by discussing numerous new drugs under development for schizophrenia.

Antipsychotic drugs exhibit possibly the most complex pharmacological mechanisms of any drug class in the field of clinical psychopharmacology. To assist the reader in mastering this critical area of therapeutics in psychopharmacology, we have organized this chapter into five sections: first, the classic conventional antipsychotics; second, the contrasting pharmacological properties that make an antipsychotic atypical; third, a discussion of the multiple receptor actions of antipsychotics as well as their pharmacokinetics, comparing and contrasting the properties of the various individual atypical antipsychotics; fourth, a practical analysis of how these agents are put to use in clinical practice; and fifth, a discussion of new therapeutics for schizophrenia currently in development.

The reader is referred to standard reference manuals and textbooks for practical prescribing information, such as drug doses, because this chapter emphasizes basic pharmacological concepts regarding mechanisms of action and not practical issues such as how to prescribe these drugs (for that information, see, for example, S. M. Stahl, Essential Psychopharmacology: The Prescriber's Guide, which is a companion to this book). The pharmacological concepts developed here should, however, help the reader understand the rationale for how to use antipsychotic agents based on their interactions with different neurotransmitter systems. Such interactions can often explain both the therapeutic actions and the side effects of antipsychotic medications and thus can provide very helpful background information for prescribers of these therapeutic agents.

What makes an antipsychotic conventional?

In this section we will discuss the pharmacological properties of the first drugs that were proven to treat schizophrenia effectively. These drugs are usually called conventional antipsychotics, but they are sometimes also called classic or "typical" antipsychotics. The earliest effective treatments for schizophrenia and other psychotic illnesses arose from serendipitous clinical observations more than 50 years ago, rather than from scientific knowledge of the neurobiologic basis of psychosis or of the mechanism of action of effective antipsychotic agents. Thus, the first antipsychotic drugs were discovered by accident in the 1950s, when a drug with antihistamine properties (chlorpromazine) was observed to have antipsychotic effects when tested in schizophrenic patients. Chlorpromazine indeed has antihistaminic activity, but its therapeutic actions in schizophrenia are not mediated by this property. Once chlorpromazine was observed to be an effective antipsychotic agent, it was tested experimentally to uncover its mechanism of antipsychotic action.
What Makes an Antipsychotic Conventional?

D2 Antagonist Actions

Early in the testing process, chlorpromazine and other antipsychotic agents were all found to cause “neurolepsia,” an extreme form of slowness or absence of motor movements as well as behavioral indifference in experimental animals. The original antipsychotics were first discovered largely by their ability to produce this effect in experimental animals and are thus sometimes called “neuroleptics.” A human counterpart of neurolepsis is also caused by these original (i.e., conventional) antipsychotic drugs and is characterized by psychomotor slowing, emotional quieting, and affective indifference.

D2-receptor antagonism makes an antipsychotic conventional

By the 1970s, it was widely recognized that the key pharmacological property of all neuroleptics with antipsychotic properties was their ability to block dopamine-2 (D2) receptors (Figure 10-1). This action has proven to be responsible not only for the antipsychotic efficacy of conventional antipsychotic drugs but also for most of their undesirable side effects, including neurolepsis.

The therapeutic actions of conventional antipsychotic drugs are due to blockade of D2 receptors, specifically in the mesolimbic dopamine pathway (Figure 10-2). This has the effect of reducing the hyperactivity in this pathway, which is postulated to cause the positive symptoms of psychosis, as discussed in Chapter 9 (see Figures 9-25 and 9-26). All conventional antipsychotics reduce positive psychotic symptoms about equally in schizophrenic patients studied in large multicenter trials. That is not to say that one individual patient might not occasionally respond better to one conventional antipsychotic agent than another, but there is no consistent difference in antipsychotic efficacy among the conventional antipsychotic agents. A list of many conventional antipsychotic drugs is given in Table 10-1.

Unfortunately it is not possible to block just these D2 receptors in the mesolimbic DA pathway with conventional antipsychotics because antipsychotic drugs are delivered throughout the entire brain after oral ingestion. Thus, conventional antipsychotics will seek out every D2 receptor throughout the brain and block them all (see Figures 10-3 through 10-7). This leads to a high “cost of doing business” in order to get the mesolimbic D2 receptors blocked for the treatment of positive symptoms.

Neurolepsia

D2 receptors in the mesolimbic dopamine system are postulated to mediate not only the positive symptoms of psychosis but also the normal reward system of the brain, and the nucleus accumbens is widely considered to be the “pleasure center” of the brain. It may be the final common pathway of all reward and reinforcement, including not only normal.

FIGURE 10-1 D2 antagonist. Conventional antipsychotics, also called first-generation antipsychotics or typical antipsychotics, share the primary pharmacological property of D2 antagonism, which is responsible not only for their antipsychotic efficacy but also for many of their side effects. Shown here is an icon representing this single pharmacological action.
FIGURE 10-2 Mesolimbic dopamine pathway and D2 antagonists. In untreated schizophrenia, the mesolimbic dopamine pathway is hypothesized to be hyperactive, indicated here by the pathway appearing red as well as by the excess dopamine in the synapse. This leads to positive symptoms such as delusions and hallucinations. Administration of a D2 antagonist, such as a conventional antipsychotic, blocks dopamine from binding to the D2 receptor, which reduces hyperactivity in this pathway and thereby reduces positive symptoms as well.

reward (such as the pleasure of eating good food, orgasm, listening to music) but also the artificial reward of substance abuse. If D2 receptors are stimulated in some parts of the mesolimbic pathway, this can lead to the experience of pleasure. Thus if D2 receptors in the mesolimbic system are blocked, this may not only reduce positive symptoms but also block reward mechanisms, leaving patients apathetic, anhedonic, lacking motivation, and with reduced interest and joy from social interactions – a state very similar to that due to the negative symptoms of psychosis and sometimes called secondary negative symptoms.

Antipsychotics also block D2 receptors in the mesocortical DA pathway (Figure 10-3), where DA may already be deficient in schizophrenia (see Figures 9-27 through 9-29). This can cause or worsen negative and cognitive symptoms. However, since the density of D2 receptors in the cortex is much lower than in other brain areas, the lack of pleasure and negative symptoms produced by antipsychotic drugs may be more closely linked to profound blockade of D2 receptors in the mesolimbic dopamine system than to blockade of D2 receptors in the mesocortical dopamine system. An adverse behavioral state can be produced by conventional antipsychotics and is sometimes called the “neuroleptic-induced deficit
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**FIGURE 10-3 Mesocortical dopamine pathway and D2 antagonists.** In untreated schizophrenia, the mesocortical dopamine pathways to dorsolateral prefrontal cortex (DLPFC) and to ventromedial prefrontal cortex (VMPFC) are hypothesized to be hypoactive, indicated here by the pathways appearing blue. This hypoactivity is related to cognitive symptoms (in the DLPFC), negative symptoms (in the DLPFC and VMPFC), and affective symptoms of schizophrenia (in the VMPFC). Administration of a D2 antagonist could further reduce activity in this pathway and thus not only not improve such symptoms but actually potentially worsen them.
**FIGURE 10-4 Nigrostriatal dopamine pathway and D2 antagonists.** The nigrostriatal dopamine pathway is theoretically unaffected in untreated schizophrenia, illustrated here by the purple hue of the pathway. However, blockade of D2 receptors, as with a conventional antipsychotic, prevents dopamine from binding there and can cause motor side effects that are often collectively termed extrapyramidal symptoms (EPS).

syndrome” because it looks so much like the negative symptoms produced by schizophrenia itself and is reminiscent of neurolepsis in animals.

**Extrapyramidal symptoms (EPS) and tardive dyskinesia**

When D2 receptors are blocked in the nigrostriatal DA pathway, it produces disorders of movement that can appear very much like those of Parkinson’s disease; that is why this is sometimes called drug-induced parkinsonism (Figure 10–4). Since the nigrostriatal pathway is part of the extrapyramidal nervous system, these motor side effects associated with blocking D2 receptors in this part of the brain are sometimes also called extrapyramidal symptoms, or EPS.

Worse yet, if these D2 receptors in the nigrostriatal DA pathway are blocked chronically (Figure 10–5), they can produce a hyperkinetic movement disorder known as tardive dyskinesia. This causes facial and tongue movements, like constant chewing, tongue protrusions, and facial grimacing as well as limb movements that can be quick, jerky, or choreiform ("dancing"). Tardive dyskinesia is thus caused by long-term administration of conventional
antipsychotics and is thought to be mediated by changes, sometimes irreversible, in the D2 receptors of the nigrostriatal DA pathway. Specifically, these receptors are hypothesized to become supersensitive or to “upregulate” (i.e., increase in number), perhaps in a futile attempt to overcome drug-induced blockade of these receptors (Figure 10-5).

About 5 percent of patients maintained on conventional antipsychotics will develop tardive dyskinesia every year (i.e., about 25 percent of patients by 5 years) — not a very encouraging prospect for a lifelong illness starting in the early twenties. The risk of developing tardive dyskinesia in elderly subjects may be as high as 25 percent within the first year of exposure to conventional antipsychotics. Thus, the number of patients that a psychopharmacologist needs to treat in order to harm 1 patient with tardive dyskinesia may be only 4 young patients over 5 years of conventional antipsychotic treatment or only 4 elderly patients over 1 year of conventional antipsychotic treatment. Statisticians sometimes call this the “number needed to harm.”

If the D2 receptor blockade is removed early enough, tardive dyskinesia may reverse. This reversal is theoretically due to a “resetting” of these receptors by an appropriate decrease in the number or sensitivity of D2 receptors in the nigrostriatal pathway once the drug that had been blocking these receptors is removed. However, after long-term treatment, the D2 receptors apparently cannot or do not reset back to normal, even when conventional antipsychotic drugs are discontinued. This leads to irreversible tardive dyskinesia, which continues whether conventional antipsychotic drugs are administered or not.

Is there any way to predict those who will be harmed with the development of tardive dyskinesia after chronic treatment with conventional antipsychotics? Patients who develop...
FIGURE 10-6 Tuberoinfundibular dopamine pathway and D2 antagonists. The tuberoinfundibular dopamine pathway, which projects from the hypothalamus to the pituitary gland, is theoretically "normal" in untreated schizophrenia. D2 antagonists reduce activity in this pathway by preventing dopamine from binding to D2 receptors. This causes prolactin levels to rise, which is associated with side effects such as galactorrhea (breast secretions) and amenorrhea (irregular menstrual periods).

FIGURE 10-7 Integrated theory of schizophrenia and D2 antagonists. In untreated schizophrenia, dopamine output is high in the mesolimbic pathway, causing positive symptoms; it is low in the mesocortical pathway to the dorsolateral prefrontal cortex (DLPFC), causing cognitive and negative symptoms; it is low in the mesocortical pathway to ventromedial prefrontal cortex (VMPFC), causing affective and negative symptoms; and it is normal in the nigrostriatal and tuberoinfundibular pathways (upper panel). With administration of a D2 antagonist, dopamine output is reduced throughout the brain (lower panel). This can reduce the positive symptoms of psychosis, although it may also reduce the experience of pleasure or reward, since these emotions are also mediated by the mesolimbic pathway. Reduction of dopamine output in mesocortical pathways would not improve cognitive, negative, or affective symptoms and might even worsen them. In the nigrostriatal and tuberoinfundibular pathways, reduction of dopamine output could lead to extrapyramidal symptoms (EPS) and prolactin elevation, respectively.
EPS early in treatment may be twice as likely to develop tardive dyskinesia if treatment with a conventional antipsychotic is continued chronically. Also, specific genotypes of dopamine receptors may confer important genetic risk factors for developing tardive dyskinesia with chronic treatment with a conventional antipsychotic. However, risk of a new onset of tardive dyskinesia can diminish considerably after 15 years of treatment with a conventional antipsychotic, presumably because patients who have not developed tardive dyskinesia over this treatment period have lower genetic risk factors.

**Prolactin elevation**

D2 receptors in the tubero-infundibular DA pathway are also blocked by conventional antipsychotics, which causes plasma prolactin concentrations to rise, a condition called hyperprolactinemia (Figure 10-6). This is associated with a condition called galactorrhea (i.e., breast secretions) and amenorrhea (i.e., irregular menstrual periods). Hyperprolactinemia may thus interfere with fertility, especially in women. It might also lead to more rapid demineralization of bones, especially in postmenopausal women who are not receiving estrogen replacement therapy. Other possible problems associated with elevated prolactin levels may include sexual dysfunction and weight gain, although the role of prolactin in causing such problems is not clear.

**The dilemma of blocking D2 dopamine receptors in all dopamine pathways**

It should now be obvious that the use of conventional antipsychotic drugs presents a powerful dilemma. That is, there is no doubt that conventional antipsychotic medications have dramatic therapeutic effects on positive symptoms of psychosis by blocking hyperactive dopamine neurons in the mesolimbic dopamine pathway. However, there are several dopamine pathways in the brain. It appears that blocking dopamine receptors in only one of them is useful, whereas blocking dopamine receptors in the remaining pathways may be harmful (Figure 10-7).

Specifically, delusions and hallucinations are reduced when mesolimbic D2 receptors are blocked, but this may come at the expense of loss of reward in this same pathway (Figure 10-7). The near shutdown of the mesolimbic dopamine pathway necessary to improve the positive symptoms of psychosis in some patients may contribute to anhedonia, apathy, and negative symptoms of schizophrenia; this may be a partial explanation for the high incidence of smoking and drug abuse among such patients.

In addition to blocking reward mechanisms in the mesolimbic dopamine system, conventional antipsychotic actions in other dopamine systems may cause the negative, cognitive, and affective symptoms of psychosis to be worsened when mesocortical D2 receptors are blocked; EPS and tardive dyskinesia may be produced when nigrostriatal D2 receptors are blocked; and hyperprolactinemia and its complications may be produced when tubero-infundibular D2 receptors are blocked. The pharmacological quandary here is what to do if one wishes simultaneously to decrease dopamine in the mesolimbic dopamine pathway in order to treat positive psychotic symptoms and yet increase dopamine in the mesocortical dopamine pathway to treat negative and cognitive symptoms while leaving dopaminergic tone unchanged in both the nigrostriatal and tubero-infundibular dopamine pathways in order to avoid side effects.

This dilemma may have been solved in part by the atypical antipsychotic drugs described in the following sections and is one of the reasons why the atypical antipsychotics have largely replaced conventional antipsychotic agents in the treatment of schizophrenia and other psychotic disorders throughout the world.
Muscarinic cholinergic blocking properties of conventional antipsychotics

In addition to blocking D2 receptors in all dopamine pathways (Figure 10-7), conventional antipsychotics have other important pharmacological properties (Figures 10-8 through 10-13). One particularly important pharmacological action of some conventional antipsychotics is their ability to block muscarinic cholinergic receptors (Figures 10-8, 10-10, and 10-11). This can cause undesirable side effects such as dry mouth, blurred vision, constipation, and cognitive blunting (Figure 10-10). Differing degrees of muscarinic cholinergic blockade may also explain why some conventional antipsychotics have a greater propensity to produce extrapyramidal side effects (EPS) than others. That is, those conventional antipsychotics that cause more EPS are the agents that have only weak anticholinergic properties, whereas those conventional antipsychotics that cause fewer EPS are the agents that have stronger anticholinergic properties.

How does muscarinic cholinergic receptor blockade reduce the EPS caused by dopamine D2 receptor blockade in the nigrostriatal pathway? This effect seems to be
FIGURE 10-10 Side effects of muscarinic cholinergic receptor blockade. In this diagram, the icon of a conventional antipsychotic drug is shown with its M1-anticholinergic/antimuscarinic portion inserted into acetylcholine receptors, causing the side effects of constipation, blurred vision, dry mouth, and drowsiness.

FIGURE 10-11A Reciprocal relationship of dopamine and acetylcholine. Dopamine and acetylcholine have a reciprocal relationship in the nigrostriatal dopamine pathway. Dopamine neurons here make postsynaptic connections with the dendrite of a cholinergic neuron. Normally, dopamine suppresses acetylcholine activity (no acetylcholine being released from the cholinergic axon on the right).
FIGURE 10-11B Dopamine, acetylcholine, and D2 antagonism. This figure shows what happens to acetylcholine activity when dopamine receptors are blocked. As dopamine normally suppresses acetylcholine activity, removal of dopamine inhibition causes an increase in acetylcholine activity. Thus if dopamine receptors are blocked at the D2 receptors on the cholinergic dendrite on the left, then acetylcholine becomes overly active, with enhanced release of acetylcholine from the cholinergic axon on the right. This is associated with the production of extrapyramidal symptoms (EPS). The pharmacological mechanism of EPS therefore seems to be a relative dopamine deficiency and a relative acetylcholine excess.

FIGURE 10-11C D2 antagonism and anticholinergic agents. One compensation for the overactivity that occurs when dopamine receptors are blocked is to block the acetylcholine receptors with an anticholinergic agent (M1 receptors being blocked by an anticholinergic on the far right). Thus, anticholinergics overcome excess acetylcholine activity caused by removal of dopamine inhibition when dopamine receptors are blocked by conventional antipsychotics. This also means that extrapyramidal symptoms (EPS) are reduced.
based on the fact that dopamine and acetylcholine have a reciprocal relationship with each other in the nigrostriatal pathway (see Figure 10-11). Dopamine neurons in the nigrostriatal dopamine pathway make postsynaptic connections with cholinergic neurons (Figure 10-11A). Dopamine normally inhibits acetylcholine release from postsynaptic nigrostriatal cholinergic neurons, thus suppressing acetylcholine activity there (Figure 10-11A).
If dopamine can no longer suppress acetylcholine release because dopamine receptors are being blocked by a conventional antipsychotic drug, then acetylcholine becomes overly active (Figure 10-11B).

One compensation for this overactivity of acetylcholine is to block it with an anticholinergic agent (Figure 10-11C). Thus drugs with anticholinergic actions will diminish the excess acetylcholine activity caused by removal of dopamine inhibition when dopamine receptors are blocked (Figure 10-8 and Figure 10-11C). If anticholinergic properties are present in the same drug with D2-blocking properties, they will tend to mitigate the effects of D2 blockade in the nigrostriatal dopamine pathway. Thus, conventional antipsychotics with potent anticholinergic properties (for example, Figure 10-8) have a lower tendency to cause EPS than conventional antipsychotics with weak anticholinergic properties (Figure 10-9). Furthermore, the effects of D2 blockade in the nigrostriatal system can be mitigated by coadministering an agent with anticholinergic properties. This has led to the common strategy of giving anticholinergic agents along with conventional antipsychotics in order to reduce EPS. Unfortunately, this coadministration of anticholinergic agents does not lessen the ability of the conventional antipsychotics to cause tardive dyskinesia. It also causes the well-known side effects associated with anticholinergic agents, such as dry mouth, blurred vision, constipation, urinary retention, and cognitive dysfunction (Figure 10-10).

Other pharmacological properties of conventional antipsychotic drugs
Still other pharmacologic actions are associated with the conventional antipsychotic drugs. These include generally undesired blockade of histamine-1 receptors (Figures 10-8 and 10-12), causing weight gain and drowsiness, as well as blockade of alpha-1 adrenergic receptors (Figures 10-8, 10-9, and 10-13), causing cardiovascular side effects such as orthostatic hypotension and drowsiness. Conventional antipsychotic agents differ in terms of their ability to block the various receptors represented in Figures 10-8 and 10-9. [For example, haloperidol, a popular conventional antipsychotic (Figure 10-9), has relatively little anticholinergic or antihistaminic binding activity.] Because of this, conventional antipsychotics differ somewhat in their side-effect profiles even if they do not differ overall in their therapeutic profiles. That is, some conventional antipsychotics are more sedating than others, some have more ability to cause cardiovascular side effects than others, and some have more ability to cause EPS than others.

Risks and benefits of long-term treatment with conventional antipsychotics
Although the conventional antipsychotics reduce positive psychotic symptoms in most patients after several weeks of treatment, discontinuing these drugs causes relapse of psychosis in patients with schizophrenia at the rate of approximately 10 percent per month, so that 50 percent or more have relapsed by 6 months after medication discontinuation. Despite this powerful incentive for patients to continue long-term treatment with conventional antipsychotics to prevent relapse, the unfortunate fact that all dopamine pathways are blocked by these drugs means that many patients do not consider the benefits of long-term treatment worth the resultant problems they cause. This leads many to discontinue treatment, become noncompliant, and relapse with a "revolving door" lifestyle in and out of the hospital. Patients too commonly select the risk of relapse over the subjectively unacceptable side effects of the conventional antipsychotics. Especially unacceptable to patients are motor restlessness and EPS such as akathisia, rigidity, and tremor as well as cognitive blunting and social withdrawal, anhedonia, and apathy. There is even the possibility of a
rare but potentially fatal complication called the “neuroleptic malignant syndrome,” which is associated with extreme muscular rigidity, high fevers, coma, and even death.

Given these problems with conventional antipsychotics, when are these agents worth-while to administer? Recently, long-term cardiometabolic risks for some of the atypical antipsychotics have been uncovered (discussed later in this chapter), and this, combined with their higher cost, is leading to a resurgence of interest among some psychopharmacologists in going back to conventional antipsychotic treatment, where the cardiometabolic risks (and costs) may be lower. This may be prudent for some patients who experience a robust therapeutic effect at low doses of a conventional antipsychotic and thus show improvement in positive symptoms without worsening of negative symptoms and without “neurolepsia.” Furthermore, if such patients have had 15 years of treatment with a conventional antipsychotic without developing tardive dyskinesia, there may be little additional risk that this will occur with continued treatment with a conventional antipsychotic. It is interesting to note that some so-called first generation conventional antipsychotics (such as loxapine, cyamemazine, and sulpiride) may have the pharmacological properties of an atypical antipsychotic, particularly at low doses (discussed later in this chapter). Administering one of these agents may be a way to treat with a less expensive agent that could potentially have atypical antipsychotic properties.

On the other hand, psychopharmacologists who no longer see tardive dyskinesia in their patients (owing to the conversion of most of their patients to an atypical antipsychotic) must not forget that most patients remain at much higher risk for developing tardive dyskinesia on a conventional antipsychotic than for developing cardiometabolic risks on an atypical antipsychotic, particularly on certain atypical antipsychotics that pose little cardiometabolic risk.

Selecting which antipsychotic to administer to an individual patient thus requires weighing tardive dyskinesia, neurolepsia, EPS, and cardiometabolic risks for that individual against the particular clinical benefits for that same patient in terms of improvement in negative, cognitive, and affective symptoms as well as positive symptoms. In order to make prudent antipsychotic choices for each individual patient, it is necessary to understand the differentiating properties not only of conventional antipsychotics compared to atypical antipsychotics but of each individual antipsychotic drug. These issues are developed in detail throughout this chapter.

What makes an antipsychotic atypical?

What is an “atypical” antipsychotic? From a clinical perspective, it is defined in part by the “atypical” clinical properties that distinguish such drugs from conventional antipsychotics, namely “low EPS” and “good for negative symptoms.” From a pharmacological perspective, the atypical antipsychotics as a class may be defined in at least four ways: as “serotonin dopamine antagonists” (Figure 10–14), as “D2 antagonists with rapid dissociation” (Figure 10–39), as “D2 partial agonists (DPA)” (Figure 10–45) or as “serotonin partial agonists (SPA)” at 5HT1A receptors (Figure 10–55). In the following section, we will discuss all four of these proposed pharmacological mechanisms of action of atypical antipsychotics.

Serotonergic neurotransmission and serotonin dopamine antagonism

Here, we will first discuss how some atypical antipsychotics obtain their atypical clinical properties by exploiting the different ways that serotonin and dopamine interact within the key dopamine pathways in the brain. In order to understand the powerful consequences of adding 5HT2A receptor antagonism to D2 antagonism, it is very important to grasp the
principles of serotonin receptor pharmacology and also the nature of serotonin-dopamine interactions in each of the dopamine pathways.

**Serotonin synthesis and termination of action**

Serotonin is also known as 5-hydroxytryptamine and abbreviated as 5HT. Synthesis of 5HT begins with the amino acid tryptophan, which is transported into the brain from the plasma to serve as the 5HT precursor (Figure 10-15). Two synthetic enzymes then convert tryptophan into serotonin: first tryptophan hydroxylase (TRY-OH) converts tryptophan into 5-hydroxy-tryptophan and then aromatic amino acid decarboxylase (AADC) converts 5HTP into 5HT (Figure 10-15). After synthesis, 5HT is taken up into synaptic vesicles by a vesicular monoamine transporter (VMAT2) and stored there until it is used during neurotransmission.

The action of 5HT is terminated when it is enzymatically destroyed by MAO and converted into an inactive metabolite (Figure 10-16). Serotonergic neurons themselves contain MAO B, which has low affinity for 5HT; therefore much of 5HT is thought to be enzymatically degraded by MAO A outside of the neuron once 5HT is released. The 5HT neuron also has a presynaptic transport pump for serotonin called the serotonin transporter (SERT), which is unique for 5HT and terminates serotonin’s actions by pumping it out of the synapse and back into the presynaptic nerve terminal, where it can be re-stored in synaptic vesicles for subsequent use in another neurotransmission (Figure 10-15).

**Serotonin receptors**

Serotonin has many different receptor subtypes (Figures 10-17 through 10-20). For a general understanding of 5HT receptors, the reader can begin with the two key receptors that are presynaptic (5HT1A and 5HT1B/D) (Figures 10-17 through 10-19) and several that are postsynaptic (5HT1A, 5HT1B/D as well as 5HT2A, 5HT2C, 5HT3, 5HT4, 5HT5, 5HT6, and 5HT7) (Figure 10-17).
FIGURE 10-15 Serotonin is produced. Serotonin (5-hydroxytryptamine [5HT]) is produced from enzymes after the amino acid precursor tryptophan is transported into the serotonin neuron. The tryptophan transport pump is distinct from the serotonin transporter. Once transported into the serotonin neuron, tryptophan is converted by the enzyme tryptophan hydroxylase (TRY-OH) into 5-hydroxytryptophan (5HTP), which is then converted into 5HT by the enzyme aromatic amino acid decarboxylase (AAADC). Serotonin is then taken up into synaptic vesicles via the vesicular monoamine transporter (VMAT2), where it stays until released by a neuronal impulse.

Presynaptic 5HT receptors are autoreceptors and detect the presence of 5HT, causing a shutdown of further 5HT release and 5HT neuronal impulse flow. When 5HT is detected in the synapse by presynaptic 5HT receptors on axon terminals, it occurs via a 5HT1B/D receptor, which is also called a terminal autoreceptor (Figure 10-18A). In the case of the 5HT1B/D terminal autoreceptor, 5HT occupancy of this receptor causes a blockade of 5HT release (Figure 10-18B). On the other hand, drugs that block the 5HT1B/D autoreceptor can promote 5HT release. When 5HT is detected in the cell dendrites and cell body, it occurs via a 5HT1A receptor, which is also called a somatodendritic autoreceptor (Figure 10-19). This causes a slowing of neuronal impulse flow through the serotonin neuron (Figure 10-19B).

Postsynaptic 5HT receptors translate the chemical signal from serotonin into a signal within the postsynaptic neuron (Figures 10-17 and 10-20). All of these receptors in one way or another regulate various neuronal circuits. More specifically, postsynaptic 5HT1A receptors inhibit cortical pyramidal neurons and are thought to regulate hormones, cognition, anxiety, and depression (Figure 10-20). 5HT2A receptors, on the other hand, excite cortical pyramidal neurons, enhance glutamate release, and inhibit dopamine release while
Serotonin Action Is Terminated

**FIGURE 10-16** Serotonin’s action is terminated. Serotonin’s (5HT) action is terminated by the enzymes monoamine oxidase A (MAO-A) and MAO-B outside the neuron, and by MAO-B within the neuron when it is present in high concentrations. These enzymes convert serotonin into an inactive metabolite. There is also a presynaptic transport pump selective for serotonin, called the serotonin transporter or SERT, that clears serotonin out of the synapse and back into the presynaptic neuron.

playing a role in both sleep and hallucinations (Figure 10-20). 5HT2C receptors regulate both dopamine and norepinephrine release and may play a role in obesity, mood, and cognition (Figure 10-20). 5HT3 receptors regulate inhibitory interneurons in the cortex and mediate vomiting via the vagal nerve (Figure 10-20). 5HT6 receptors are under intense investigation, as they may be key in regulating the release of neurotrophic factors such as brain derived neurotrophic factor (BDNF), which in turn regulates the formation of long-term memory. Finally, the role of 5HT7 receptors is being clarified; these seem to be linked to circadian rhythms, sleep, and mood (Figure 10-20).

**5HT1A and 5HT2A receptors have opposite actions in regulating dopamine release**
Some serotonin receptors have a major influence on dopamine release; when serotonin acts on them, they can determine whether dopamine release is stimulated or inhibited. Specifically, 5HT1A receptors act as an accelerator for dopamine release, whereas 5HT2A receptors act as a brake on dopamine release (Figure 10-21). How does this happen?
**The 5HT2A receptor is a dopamine brake**

Serotonin neurons innervate dopamine neurons either directly via postsynaptic 5HT2A receptors on the dopamine neuron, or indirectly via 5HT2A receptors on GABA interneurons (Figure 10-21). When serotonin is released onto these postsynaptic 5HT2A receptors, the dopamine neuron is inhibited, providing a braking action on dopamine release (lower left of Figure 10-21).

**The 5HT1A receptor is a dopamine accelerator**

How does serotonin also act as an accelerator to stimulate dopamine release via 5HT1A receptors? Recall that 5HT1A receptors in the somatodendritic region of serotonin neurons are autoreceptors that act to inhibit serotonin release (Figure 10-19). When 5HT1A receptors inhibit serotonin release (Figure 10-19B), the 5HT2A postsynaptic receptors on dopamine neurons cannot be activated (lower right of Figure 10-21). In other words, the 5HT2A dopamine brake is not applied and dopamine neurons will lose the inhibitory action of serotonin via 5HT2A receptors. This lack of 5HT2A inhibition is also known as “disinhibition,” which is just a fancy way of saying “turned on.” Technically speaking,
FIGURE 10-18A and B 5HT1B/D autoreceptors. Presynaptic 5HT1B/D receptors are autoreceptors located on the presynaptic axon terminal. They act by detecting the presence of serotonin (5HT) in the synapse and causing a shutdown of further 5HT release. When 5HT builds up in the synapse (A), it is available to bind to the autoreceptor, which then inhibits serotonin release (B).
FIGURE 10-19A and B 5HT1A autoreceptors. Presynaptic 5HT1A receptors are autoreceptors located on the cell body and dendrites, and are therefore called somatodendritic autoreceptors (A). When serotonin (5HT) binds to these 5HT1A receptors, it causes a shutdown of 5HT neuronal impulse flow, depicted here as decreased electrical activity and a reduction in the release of 5HT from the synapse on the right (B).
FIGURE 10-20 Possible functions of postsynaptic serotonin receptors. Postsynaptic serotonin (5HT) receptors are G protein–linked receptors. 5HT binding to these receptors causes signal transduction and downstream events that regulate various neuronal circuits. In particular, postsynaptic 5HT1A receptors inhibit cortical pyramidal neurons, regulate hormones, and play a role in depression, anxiety, and cognition. 5HT2A receptors excite cortical pyramidal neurons, increase glutamate release, decrease dopamine release, and are involved in sleep and hallucinations. 5HT2C receptors regulate dopamine and norepinephrine release and play a role in obesity, mood, and cognition. 5HT3 receptors regulate inhibitory interneurons in the brain and also mediate vomiting via the vagal nerve. 5HT6 receptors may regulate release of neurotrophic factors (e.g., brain-derived neurotrophic factor, or BDNF), which could affect long-term memory. 5HT7 receptors may be involved in circadian rhythms, mood, and sleep.
5HT2A and 5HT1A Receptors: Opposite Actions on DA Release

- **5HT2A receptor**
  - DA brake: inhibits DA release

- **5HT1A receptor**
  - DA accelerator: stimulates DA release

**Legend**:
- 5HT2A
- 5HT1A
- 5HT
- GABA
- DA

**Color Code**:
- Red: overactivation
- Normal: normal
c- Baseline: baseline
- Cyan: hypoactivation
activation of 5HT1A autoreceptors disinhibits the dopamine neuron, and thus dopamine release is enhanced (Figure 10-21, lower right). Thus, the presynaptic somatodendritic 5HT1A autoreceptor is a DA accelerator.

**5HT2A antagonism makes an antipsychotic atypical**

**5HT2A antagonists stimulate dopamine release**

Many atypical antipsychotics are antagonists at the 5HT2A receptor as well as at the D2 receptor (Figure 10-14). Some research suggests that this antagonist action is actually more precisely described as inverse agonist action at 5HT2A receptors, but the clinical differences between antagonists and inverse agonists are not yet clear. The pharmacological distinctions between so-called “silent” antagonists and inverse agonists are discussed in Chapters 4 and 5 and illustrated in Figures 4-21 through 4-28 and in Figures 5-9 through 5-18. Here we will continue to refer to the actions of atypical antipsychotics at 5HT2A receptors as antagonist actions.

What is so important about 5HT2A antagonist actions of atypical antipsychotics? 5HT2A antagonism can cause dopamine release in certain brain areas (Figure 10-22), and this pharmacological action hypothetically explains the atypical clinical properties of these agents that distinguish them from conventional antipsychotics, namely “low EPS” and “good for negative symptoms.” Thus, the 5HT2A receptor “brake” on dopamine release shown in Figure 10-21 and on the left in Figure 10-22 is disrupted by a 5HT2A antagonist, essentially cutting the brake cable, disinhibiting the dopamine neuron, and stimulating dopamine release (Figure 10-22, the right).

**5HT2A antagonism reduces EPS**

So far, we have shown how serotonin neurons act on the somatodendritic regions of dopamine neurons (Figures 10-21 and 10-22). However, serotonin neurons may also act on the axon terminals of dopamine neurons (Figures 10-23 through 10-26). For example, serotonin actions on nigrostriatal dopamine neurons may occur both at the level of the brainstem in the substantia nigra, where the somatodendritic regions of these dopamine neurons are located, and also in the striatum, where the axon terminals of these dopamine neurons are located (Figure 10-23). In both cases, a 5HT2A receptor mediates the action of serotonin at the dopamine neuron, via either a direct connection between the serotonin neuron and the dopamine neuron or an indirect connection with a GABA interneuron (Figure 10-24A). Specifically, Figure 10-24B shows actions of 5HT2A receptors in the somatodendritic region of the dopamine neuron in the substantia nigra, inhibiting dopamine release in the striatum, as in Figure 10-21, lower left. In addition, the actions of 5HT2A receptors on dopamine axon terminals in the striatum are shown in Figure 10-24C, also inhibiting the release of dopamine in the striatum. A closeup depiction of these actions of 5HT at axon terminal 5HT2A receptors in the striatum is shown in Figure 10-25, where striatal

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**Figure 10-21** 5HT2A and 5HT1A receptors: opposite actions on DA release. Serotonin (5HT) 1A and 2A receptors influence dopamine (DA) release, either directly or via gamma aminobutyric acid (GABA) neurons. However, these receptors actually have opposite effects on DA release. Specifically, 5HT2A receptors act as a DA brake. When 5HT binds to 5HT2A receptors on postsynaptic DA neurons, this inhibits DA release (bottom left). Similarly, 5HT binding to 5HT2A receptors on GABA interneurons causes GABA release, which in turn inhibits DA release (also bottom left). 5HT1A somatodendritic autoreceptors, on the other hand, act as DA accelerators. That is, when 5HT binds to these receptors, it inhibits 5HT release; thus, 5HT is unable to inhibit DA release, and dopamine release is thus disinhibited, and therefore increased (bottom right).
**FIGURE 10-22 5HT2A antagonists stimulate DA release.** Serotonin (5HT) inhibits dopamine (DA) release via stimulation of 5HT2A receptors (left); when this action is blocked by a 5HT2A antagonist, this leads to an increase in DA release, either by blocking 5HT2A receptors on postsynaptic DA neurons or by blocking 5HT2A receptors on gamma aminobutyric acid (GABA) interneurons (on the right).

Dopamine release (Figure 10-25A) is inhibited by serotonin actions at postsynaptic 5HT2A receptors located at an axoaxonic synapse of a serotonin neuron on a striatal dopamine nerve terminal (Figure 10-25B).

How does 5HT2A antagonist action reduce EPS? The answer to this is shown in Figure 10-26, where both the D2 and 5HT2A antagonist actions of an atypical antipsychotic are illustrated in the striatum. First, the D2 actions of an atypical antipsychotic are shown in Figure 10-26A. In this case, most of the D2 receptors in the striatum are occupied, and if this persisted, it would cause EPS, as this would be no different than the actions of a conventional antipsychotic with pure D2 antagonist actions (Figure 10-1). However, in Figure 10-26B, the additional action of the 5HT2A antagonist is shown. Adding this second action results in disinhibition of the dopamine neuron, which causes stimulation of dopamine release, just as has already been explained and illustrated in Figure 10-22. The result of this increased dopamine release is that dopamine competes with drug at D2 receptors and reduces binding there enough to eliminate EPS (Figure 10-26B).
These actions of an atypical antipsychotic with both D2 antagonist actions and 5HT2A antagonist actions are confirmed when imaging D2 receptors in the striatum of patients receiving antipsychotic drugs (Figure 10-27). In the case of a conventional antipsychotic given at clinically effective doses, it is estimated that up to 90 percent of D2 receptors are blocked in every dopamine pathway in the brain. This degree of blockade of D2 receptors in the nucleus accumbens of the mesolimbic dopamine pathway is presumably necessary to reduce positive symptoms of psychosis, but this degree of simultaneous blockade of D2 receptors in the striatum causes EPS and eventually, tardive dyskinesia. An artist's conception of occupancy of 90 percent of D2 receptors by a conventional antipsychotic drug is shown in Figure 10-27A. Real neuroimaging scans with positron emission tomography (PET) ligands are much more complicated, but we know that if we could selectively label the D2 receptors in the striatum after a clinically effective dose of a conventional antipsychotic, a high proportion of D2 receptors in the striatum would be occupied (Figure 10-27A).

However, in the case of an atypical antipsychotic, the number of D2 receptors that are occupied in the striatum is notably less at clinically effective doses (Figure 10-27B). How can this be? Presumably it is due to the actions of drug blocking 5HT2A receptors and leading to increased striatal dopamine release (as shown in Figure 10-26B), which in turn causes dopamine to knock enough drug off D2 receptors that the occupancy drops below the threshold for producing EPS (i.e., presumably less than 70 to 80 percent of D2 receptor occupancy).
**5HT2A antagonism reduces negative symptoms**

There is a debate as to how robustly atypical antipsychotics compared to conventional antipsychotics reduce negative symptoms. Some experts believe that atypical antipsychotics do not really reduce negative symptoms but that conventional antipsychotics increase them, presumably due to the induction of secondary negative symptoms related to EPS. If conventional antipsychotics cause EPS and thus secondary negative symptoms but atypical antipsychotics do not (as explained in the section above and illustrated in Figures 10-26 and 10-27), this could explain some of the apparent differences in the severity of negative symptoms in patients taking conventional antipsychotics versus atypical antipsychotics.

However, the lack of production of secondary negative symptoms does not appear to be an adequate explanation for all the reduction in severity of negative symptoms by atypical antipsychotics compared to conventional antipsychotics. Another mechanism that could explain this apparent reduction is that atypical antipsychotics, working through their 5HT2A antagonist properties, may increase dopamine release in hypoactive mesolimbic...
pleasure centers. If this were the case to any great extent, one might expect to see an activation of positive symptoms by atypical antipsychotics as well, but this is not observed. Apparently, dopamine release by 5HT2A receptor antagonism in the nucleus accumbens is not as robust as in other brain areas.

What, then, is the mechanism whereby atypical antipsychotics improve the negative, cognitive, and affective symptoms of schizophrenia in those patients in whom these actions are observed? The answer is illustrated in Figure 10-28 where the 5HT2A antagonist actions of atypical antipsychotics are shown to be increasing DA release in prefrontal cortex. Note that no blockade of D2 receptors in the prefrontal cortex is shown, since D2 receptors are not very dense in this part of the brain. Note also that dopamine deficiency can be primary, due to hypoactive mesocortical dopamine neurons (Figure 10-28A), or secondary, due to
Inhibition of DA Release by 5HT2A Axon Terminal Postsynaptic Receptors

FIGURE 10-24C Serotonin regulation of dopamine release from nigrostriatal dopamine neurons, part 3. Here, serotonin is being released from a synaptic connection projecting from axoaxonal contacts or by volume neurotransmission between serotonergic axon terminals and dopamine axon terminals, resulting in serotonin occupying postsynaptic serotonin 2A (5HT2A) receptors on dopamine and gamma aminobutyric acid (GABA) neurons (bottom red circle). Because of this, dopamine release from its axonal terminal is inhibited (top red circle).

high levels of serotonin acting at 5HT2A receptors, causing inhibition of dopamine release (Figure 10-28B). Secondary dopamine deficiency in mesocortical dopamine pathways is sometimes seen in patients taking serotonin selective reuptake inhibitors (SSRIs), which boost the action of serotonin at 5HT2A receptors on mesocortical dopamine neurons, thus producing the side effect of cognitive dulling and affective flattening. Figure 10-28C shows what happens when a 5HT2A antagonist occupies 5HT2A receptors on mesolimbic dopamine neurons: namely, dopamine release is increased. Thus, affective, cognitive, and negative symptoms in schizophrenia may be reduced (Figure 10-28C).

These actions of atypical antipsychotics are confirmed when 5HT2A receptors in the cortex of a patient receiving antipsychotic drugs are imaged (Figure 10-29). In the case of a conventional antipsychotic given at clinically effective doses, essentially no 5HT2A
FIGURE 10-25A and B Enlarged view of serotonin (5HT) and dopamine (DA) interactions in the nigrostriatal DA pathway at axon terminals in the striatum. Normally, 5HT inhibits DA release. (A) DA is being released because no 5HT is stopping it. Specifically, no 5HT is present at its 5HT2A receptor on the nigrostriatal DA neuron. (B) Now DA release is being inhibited by 5HT in the nigrostriatal dopamine pathway. When 5HT occupies its 5HT2A receptor on the DA neuron (lower red circle), this inhibits DA release, so there is no DA in the synapse (upper red circle).

FIGURE 10-26A and B Serotonin 2A antagonists in nigrostriatal pathway. In panel A postsynaptic dopamine 2 (D2) receptors are being blocked by a serotonin-dopamine antagonist (SDA) in the nigrostriatal dopamine pathway. This shows what would happen if only the D2 blocking action of an atypical antipsychotic were active—namely, the drug would only bind to postsynaptic D2 receptors and block them. In contrast, panel B shows the dual action of the SDAs, in which both D2 and serotonin 2A (5HT2A) receptors are blocked. The interesting thing is that the second action of 5HT2A antagonism actually reverses the first action of D2 antagonism. This happens because dopamine is released when serotonin can no longer inhibit its release. Another term for this is disinhibition. Thus, blocking a 5HT2A receptor disinhibits the dopamine neuron, causing dopamine to pour out of it. The consequence of this is that dopamine can then compete with the SDA for the D2 receptor and reverse the inhibition there. As D2 blockade is thereby reversed, SDAs cause little or no extrapyramidal symptoms (EPS) or tardive dyskinesia.
receptors are occupied in the cortex because conventional antipsychotic drugs do not have high affinity for 5HT2A receptors (Figure 10-29A). However, at clinically effective doses of an atypical antipsychotic, a very high proportion of 5HT2A receptors are occupied (Figure 10-29B). Areas where a 5HT2A antagonist is binding to 5HT2A receptors on mesolimbic dopamine neurons represent areas where dopamine release is presumably enhanced as well. The increased availability of dopamine to areas with hypoactive dopamine release in schizophrenia may lead to improvement in the negative, cognitive, and affective symptoms thought to be mediated by these areas of the brain.

Theoretically, the ideal treatment of schizophrenia would be a drug with actions at clinical doses that fully saturate 5HT2A receptors in the prefrontal cortex (Figure 10-29B) while blocking enough D2 receptors in the mesolimbic area to reduce positive symptoms but not abolish reward; also, the drug would block too few D2 receptors in the nigrostriatal pathway to cause EPS (Figure 10-27B). The atypical antipsychotics with 5HT2A antagonist properties at least as potent as their D2 antagonist properties seem to fulfill that role (see Figures 10-27B and 10-29B).
FIGURE 10-28A, B and C Mesocortical pathway and serotonin-dopamine antagonism. The mesocortical dopamine (DA) pathway may mediate affective, cognitive, and negative symptoms in schizophrenia because of a relative deficiency in DA, due either to a primary deficiency (A) or to various secondary causes, such as serotonin (5HT) excess (B). In either case, blockade of 5HT2A receptors with an atypical antipsychotic should lead to DA release (C), which could compensate for the DA deficiency and improve affective, cognitive, and negative symptoms.

5HT2A antagonism may improve positive symptoms

We have already discussed how 5HT1A receptors and 5HT2A receptors regulate dopamine release (Figure 10-21). These same receptors also regulate glutamate release, with 5HT1A receptors acting as brakes to inhibit glutamate release and 5HT2A receptors acting as accelerators to stimulate glutamate release (Figure 10-30). This is the opposite of their regulatory actions on dopamine release (illustrated in Figures 10-21 and 10-22).

The regulatory effects of seroton in glutamate may play a role in schizophrenia, since it is possible that the stimulatory effects of 5HT2A receptors on glutamate release may be linked to the causation of hallucinations. That is, most hallucinogens are partial agonists at 5HT2A receptors, implicating possible abnormal activation of 5HT2A receptors on cortical glutamate neurons not only in hallucinogen abuse but also in schizophrenia. The role of 5HT2A receptors in the mechanism of action of drugs of abuse is discussed in the chapter on substance abuse.

Furthermore, in schizophrenia, the action of 5HT2A receptors in enhancing cortical glutamate output (Figure 10-30) can be linked to the pathophysiology of positive symptoms such as hallucinations within a three-neuron circuit: one utilizing serotonin, one utilizing dopamine, and one utilizing glutamate (Figure 10-31). That is, glutamate input via projections to mesolimbic dopaminergic neurons in the VTA can be direct (as shown in Figure 10-31) or indirect (the predominant circuit already shown in Figure 9-39). The direct excitatory input of glutamate descending to the VTA shown in Figure 10-31 is hypothetically
controlled by serotonin projections ascending to glutamatergic cortical pyramidal neurons (as shown in Figure 10-31).

In schizophrenia, activation of 5HT2A receptors in the prefrontal cortex may contribute to positive symptoms of hallucinations by enhancing the excitation of this descending glutamate neuron, which in turn further excites the mesolimbic dopamine neuron it innervates downstream (Figure 10-31A). The take-away message here is that understanding the pharmacology of this three-neuron circuit shows why 5HT2A antagonist actions could reduce positive symptoms such as hallucinations (Figure 10-31B). That is, when 5HT2A antagonists block the serotonergic excitation of cortical pyramidal cells, their glutamate release is reduced, and this lowers the hyperactive drive on the mesolimbic dopamine pathway downstream, thus reducing hallucinations and other positive symptoms.

This idea suggests that the ideal atypical antipsychotic would have not only 5HT2A antagonist actions but also more potent such actions than D2 antagonist actions in order to optimize antipsychotic therapeutic efficacy and reduce the risk of D2-mediated side effects. In fact, this idea has led to proposals that adding a pure 5HT2A antagonist to either a conventional or atypical antipsychotic drug could result in better control of positive symptoms without producing unwanted side effects. The goal would be to achieve perhaps...
FIGURE 10-30 Effects of 5HT1A and 5HT2A on glutamate release. Serotonin (5HT) 2A and 5HT1A receptors have opposing actions on glutamate release from cortical pyramidal neurons. Specifically, 5HT2A receptors act as glutamate accelerators, stimulating glutamate release when 5HT binds to them (top right). 5HT1A receptors, on the other hand, act as glutamate brakes. That is, when 5HT binds to cortical 5HT1A receptors, this inhibits glutamate release (bottom right). Thus, the regulatory actions of 5HT2A and 5HT1A on glutamate release are the opposite of their actions on dopamine release, where 5HT2A acts as a brake and 5HT1A acts as an accelerator.
FIGURE 10-31A and B Possible reduction of positive symptoms by 5HT2A antagonists. Ascending serotonin (5HT) projections from the raphe to the cortex stimulate release of glutamate from descending glutamatergic cortical pyramidal neurons via postsynaptic 5HT2A receptors. Because descending cortical pyramidal neurons synapse directly with dopaminergic neurons in the ventral tegmental area (VTA), serotonergic actions at 5HT2A receptors can indirectly modulate activity of the mesolimbic dopamine pathway. Thus stimulation of 5HT2A receptors increases glutamate release, which in turn increases dopamine release in the mesolimbic pathway, possibly leading to positive symptoms of psychosis (A). On the other hand, blockade of 5HT2A receptors would reduce glutamate release, which in turn would reduce mesolimbic dopamine release (B). 5HT2A antagonism is therefore a possible mechanism for reducing positive symptoms of psychosis.

only about 70 to 80 percent blockade of D2 receptors in the mesolimbic dopamine pathway but essentially complete blockade of mesocortical 5HT2A receptors and to do this by “topping up” the antipsychotic with pure 5HT2A antagonism in a second drug. Several selective 5HT2A antagonists and inverse agonists are in testing as add-on treatments to antipsychotics to improve the balance of 5HT2A antagonism to D2 antagonism and thus improve both the efficacy and the tolerability of an antipsychotic. Recently one of these selective 5HT2A agents, actually an inverse agonist at 5HT2A receptors and known as ACP 103, has been reported to enhance the efficacy of risperidone in schizophrenia.

5HT2A antagonist actions reduce hyperprolactinemia

Serotonin and dopamine have reciprocal roles in the regulation of prolactin secretion from the pituitary lactotroph cells. That is, dopamine inhibits prolactin release by stimulating D2 receptors (Figure 10-32), whereas serotonin promotes prolactin release by stimulating 5HT2A receptors (Figure 10-33).

Thus, when D2 receptors are blocked by a conventional antipsychotic, dopamine can no longer inhibit prolactin release, so prolactin levels rise (Figure 10-34). However, in the case of an atypical antipsychotic, there is simultaneous inhibition of 5HT2A receptors, so serotonin can no longer stimulate prolactin release (Figure 10-35). This tends to mitigate the hyperprolactinemia of D2 receptor blockade. Although this is interesting theoretical
FIGURE 10-32 Dopamine inhibits prolactin. Dopamine inhibits prolactin release from pituitary lactotroph cells in the pituitary gland when it binds to D2 receptors (red circle).

FIGURE 10-33 Serotonin stimulates prolactin. Serotonin (5HT) stimulates prolactin release from pituitary lactotroph cells in the pituitary gland when it binds to 5HT2A receptors (red circle). Thus, serotonin and dopamine have a reciprocal regulatory action on prolactin release.
FIGURE 10-34 Conventional antipsychotics and prolactin. Conventional antipsychotic drugs are D2 antagonists and thus oppose dopamine's inhibitory role on prolactin secretion from pituitary lactotrophs. Thus, these drugs increase prolactin levels (red circle).

FIGURE 10-35 Atypical antipsychotics and prolactin. This figure shows how serotonin (5HT) 2A antagonism reverses the ability of D2 antagonism to increase prolactin secretion. As dopamine and serotonin have reciprocal regulatory roles in the control of prolactin secretion, one cancels the other. Thus, stimulating 5HT2A receptors reverses the effects of stimulating D2 receptors. The same thing works in reverse, namely, blockade of 5HT2A receptors (shown here) reverses the effects of blocking D2 receptors (shown in Figure 10-34).
pharmacology, in practice, not all serotonin dopamine antagonists reduce prolactin secretion to the same extent and others do not reduce prolactin elevations at all.

“Tuning” dopamine output with serotonin 2A/dopamine 2 antagonists

The actions of antipsychotics can be conceptualized as agents that “tune” dopamine output in malfunctioning neuronal circuits. Schizophrenia is probably not as simple as just “too much” or “too little” dopamine activity in various brain regions. Instead, therapeutic agents must target inefficient information processing in various brain regions by optimizing function. In some cases this may mean increasing dopamine activity, but in others it may mean decreasing dopamine activity. Although a conventional antipsychotic can only decrease dopamine and will do this at D2 receptors throughout the brain (Figure 10-7), antipsychotics with 5HT2A antagonist properties have much more complicated net actions on dopamine activity since they can not only decrease dopamine activity by blocking D2 receptors but also increase dopamine release and thus increase dopamine activity at both D1 and D2 receptors (Figures 10-22 and 10-26 through 10-29).

Which action predominates and in which part of the brain is the subject of intense current investigation, but it is already clear that the addition of 5HT2A antagonist properties to D2 antagonist properties yields a very different type of drug – namely, an atypical antipsychotic agent with therapeutic actions not only on positive symptoms but also on negative, cognitive, and affective symptoms with a significant reduction in the incidence of extrapyramidal side effects and hyperprolactinemia (Figures 10-26 through 10-36).

Clinicians can exploit these properties of atypical antipsychotics by individualizing drug selection and dosage to individual patients, since the exact balance of 5HT2A antagonism versus D2 antagonism differs with different drugs in different parts of the brain, and the ideal balance will be different in individual patients. The trick is to exploit these pharmacological mechanisms to get the best clinical results, often by simultaneous blockade of D2 receptors and 5HT2A receptors with a single drug, which causes nearly the opposite things in different areas of the same brain at the same time! Although there are obviously many other factors at play here and this is an overly simplistic explanation, it is a useful starting point for beginning to appreciate the pharmacological actions of serotonin-2A/dopamine-2 antagonists as a class of atypical antipsychotic drugs.

Numerous therapeutic agents available on the worldwide market have the pharmacological properties of full antagonism of D2 receptors plus antagonism (or inverse agonism) of 5HT2A receptors (Figure 10-37). Each of these will be discussed individually in a later section of this chapter. In addition, several other agents with serotonin-dopamine antagonism (SDA) pharmacology are in clinical development and may become available in the future (Figure 10-38).

Rapid dissociation from D2 receptors makes an antipsychotic atypical

A second pharmacological mechanism that hypothetically makes an antipsychotic act in an atypical manner is the way in which it binds to D2 postsynaptic receptors: that is, whether it binds “tightly” with long times on the receptor, like a conventional antipsychotic (Figure 10-1), or whether it binds “loosely” and slips off the receptor quickly, with what is termed a rapid “off” time, like some atypical antipsychotics (Figure 10-39). Conventional antipsychotics are known for long-lasting binding to D2 receptors and for this reason are indicated with an icon that has “teeth” in Figures 10-1 and 10-40. Once a conventional antipsychotic binds to the D2 receptor (indicated with grooves for the teeth of the conventional antipsychotic in Figure 10-40), the drug stays for a long time. The consequence of long receptor occupancy
Dopamine Output - Untreated Schizophrenia

- **Mesolimbic Pathway**
  - normal (HIGH)
  - positive symptoms
- **Mesocortical Pathway to DLPFC**
  - normal (LOW)
  - cognitive symptoms
- **Mesocortical Pathway to VMPFC**
  - normal (LOW)
  - affective symptoms
- **Nigrostriatal Pathway**
  - normal (NORMAL)
- **Tuberoinfundibular Pathway**
  - normal (NORMAL)
  - negative symptoms

Dopamine Output - After Serotonin Dopamine Antagonist

- **Mesolimbic Pathway**
  - normal (LOW)
  - reduced positive symptoms
- **Mesocortical Pathway to DLPFC**
  - normal (NORMAL)
- **Mesocortical Pathway to VMPFC**
  - normal (NORMAL)
- **Nigrostriatal Pathway**
  - normal (NORMAL)
  - no parkinsonism
- **Tuberoinfundibular Pathway**
  - normal (NORMAL)
  - no elevated prolactin
  - lack of pleasure or reward
FIGURE 10-37 Serotonin-dopamine antagonists on the market. Which antipsychotics are SDAs (serotonin 2A/dopamine 2 antagonists)? There are several pharmacological agents available with the dual properties of D2 antagonism and serotonin (5HT) 2A antagonism. These include clozapine, risperidone, paliperidone, olanzapine, quetiapine, and ziprasidone in the United States as well as perospirone, zotepine, and sertindole outside of the United States. In addition, at low doses the conventional antipsychotics loxapine and cyamemazine may be serotonin-dopamine antagonists.

is that conventional antipsychotics outlive their welcome: that is, they don't just stay on the D2 receptor long enough to relieve the positive symptoms of psychosis but instead actually stay too long and thus cause extrapyramidal side effects (Figure 10-41).

By contrast, atypical antipsychotics, even if they also have the 5HT2A antagonist properties discussed above, also have the ability to rapidly dissociate from D2 receptors. This is indicated by a smooth icon for the binding property of an atypical antipsychotic at D2 receptors (Figures 10-14, 10-39, and 10-42). Rapid dissociation from the D2 receptor, or "hit and run" binding, is indicated in Figure 10-42, with the smooth D2 binding surface of the atypical antipsychotic fitting into the D2 receptor (the "hit") but not getting caught in the grooves and thus slipping off (the "run"). Theoretically, such an agent is able to stay at D2 receptors long enough to exert an antipsychotic action but then

FIGURE 10-36 Integrated theory of schizophrenia and serotonin-dopamine antagonists. In untreated schizophrenia, dopamine output is high in the mesolimbic pathway, causing positive symptoms; it is low in the mesocortical pathway to dorsolateral prefrontal cortex (DLPFC), causing cognitive and negative symptoms; it is low in the mesocortical pathway to ventromedial prefrontal cortex (VMPFC), causing affective and negative symptoms; and it is normal in the nigrostriatal and tuberoinfundibular pathways (top panel). With administration of a D2-serotonin 2A antagonist, dopamine output is decreased in the mesolimbic pathway, which can reduce the positive symptoms of psychosis, although it may also reduce the experience of pleasure or reward, since these are mediated by the mesolimbic pathway (bottom panel). Any potential decrease in mesocortical dopamine with D2 antagonism may be offset by serotonin 2A antagonism; in fact, the net effect may actually be that dopamine in the cortex is increased, which could reduce cognitive, negative, or affective symptoms. In the nigrostriatal and tuberoinfundibular pathways, the net effect of serotonin-dopamine antagonism may be that dopamine output is unchanged, thus reducing the risk of extrapyramidal symptoms (EPS) or prolactin elevation (bottom panel).
leaves prior to producing an extrapyramidal side effect, elevation of prolactin, or worsening of negative symptoms (Figure 10-43). The hit-and-run theory is summarized in Figure 10-44.

One of the interesting clinical aspects of atypical antipsychotics is the observation that they need to be administered less frequently than would be required to keep D2 receptors occupied 24 hours a day. Drugs with short half-lives therefore often need to be administered only once a day. Why is this? It seems possible that continuous receptor occupancy is not
FIGURE 10-40A and B D2 binding of conventional antipsychotics. (A) Shown here is an icon for conventional antipsychotic drugs. Because of the biochemical properties of these drugs, their binding to postsynaptic D2 receptors is tight and long-lasting, as shown by the teeth on the binding site of the conventional antipsychotic. The D2 receptor has grooves at which the teeth of the drug can bind tightly. (B) Here, the conventional antipsychotic is binding to the postsynaptic D2 receptor, with its teeth locking the drug into the receptor binding site to block it in a long-lasting manner.

FIGURE 10-41 Hypothetical action of a conventional antipsychotic over time. This figure shows a curve of D2 receptor blockade after two doses of a conventional antipsychotic as well as the concomitant clinical effects. Prior to dosing a schizophrenic patient with a conventional antipsychotic (far left), there is no D2 receptor blockade, and the schizophrenic patient has positive symptoms of psychosis such as delusions and hallucinations. Also, since there is no drug present, there will be no EPS. Following a dose of a conventional antipsychotic (middle), D2 receptors are blocked so tightly that they both cause antipsychotic actions and induce EPS. Following another dose of a conventional antipsychotic (far right), the D2 receptors stay persistently blocked, so that antipsychotic actions are always associated with EPS and eventually tardive dyskinesia may even occur.
required for the desired antipsychotic actions but may in fact contribute to the undesired side effects. Indeed, what may be required for antipsychotic efficacy may be akin to “ringing a bell” by clanging the D2 receptor just once a day. The D2 receptor continues to resonate with antipsychotic actions long after the atypical antipsychotic hits it.

These observations suggest that antipsychotics are atypical because they stay around D2 receptors long enough to cause an antipsychotic action but not long enough to cause side effects. One of the consequences of fast dissociation is that the drug is gone from the receptor until the next dose arrives (Figure 10-43). This means that natural dopamine can bathe the receptor for a while before the next pulse of drug. Perhaps a bit of real dopamine in the nigrostriatal dopamine system is all that is needed to prevent motor side effects. If this happens while there is yet insufficient dopamine in the mesolimbic dopamine system to reanimate psychosis between doses, the drug has atypical antipsychotic clinical properties (Figures 10-42 through 10-44).

The idea of rapid D2 receptor dissociation as a pharmacological property that can explain atypical clinical actions of some antipsychotic drugs is supported by the observation that rapid dissociation from the D2 receptor in vitro is a good predictor of low extrapyramidal side-effect potential in patients. Since rapid dissociation generally also means low potency, this also means that low-potency agents (i.e., those requiring higher milligram doses, such as clozapine and quetiapine) have faster dissociation from the D2 receptor than high-potency agents (i.e., those requiring lower milligram doses, such as risperidone), with
FIGURE 10-43 Hypothetical action of atypical antipsychotic over time. This figure shows a curve of D2 receptor blockade after two doses of an atypical antipsychotic as well as the concomitant clinical effects. Prior to dosing a schizophrenic patient with an atypical antipsychotic (far left), there is no D2 receptor blockade, and the schizophrenic patient has positive symptoms of psychosis, just as in Figure 10-41. Also, since there is no drug present, there will be no extrapyramidal symptoms (EPS). Following a dose of an atypical antipsychotic (middle), D2 receptors are blocked initially, but then the drug slides off the receptor and they are no longer blocked. Theoretically, antipsychotic actions require only initial blockade of D2 receptors, whereas EPS require persistent blockade of D2 receptors. Since the nature of atypical antipsychotic binding is such that the drugs rapidly dissociate from D2 receptors after binding to them, these drugs can have antipsychotic actions without inducing EPS by hitting the D2 receptor hard enough to cause antipsychotic effects and then running before they cause EPS. Since this happens dose after dose (far right), there are persistent and long-lasting antipsychotic actions, but EPS do not develop over time.

intermediate-potency agents such as olanzapine in the middle. This roughly correlates with the abilities of these drugs to cause motor side effects within the group of atypical antipsychotics and also sets them all apart from the conventional antipsychotics. It may also help explain some of the atypical clinical actions of benzamide antipsychotics, such as sulpiride and amisulpride, discussed in the following section, which have low potency at D2 receptors and lack serotonin 2A-antagonist properties yet have some atypical clinical properties.

D2 partial agonism (DPA) makes an antipsychotic atypical
A new class of antipsychotics is emerging that stabilizes dopamine neurotransmission in a state between silent antagonism and full stimulation. This is due to partial agonist actions at the D2 receptor (Figure 10-45). Partial agonist actions are explained in Chapters 4 and 5 and illustrated in Figures 4-21 through 4-28 and Figures 5-9 through 5-18. Dopamine partial agonists (DPAs) theoretically bind to the D2 receptor in a manner that is neither too antagonizing, like a conventional antipsychotic ("too cold," with antipsychotic actions but also EPS, as in Figure 10-46A), nor too stimulating, like a stimulant or dopamine itself ("too hot," with positive symptoms of psychosis, as in Figure 10-46B). Instead, a partial
Dopamine Output - Untreated Schizophrenia

Mesolimbic Pathway
- normal
- HIGH
- positive symptoms

Mesocortical Pathway to DLPFC
- normal
- LOW
- cognitive symptoms

Mesocortical Pathway to VMPFC
- normal
- LOW
- affective symptoms

Nigrostriatal Pathway
- normal
- NORMAL
- negative symptoms

Tuberoinfundibular Pathway
- normal
- NORMAL

Hit-and-Run Theory

Mesolimbic Pathway
- normal
- LOW
- reduced positive symptoms

Mesocortical Pathway to DLPFC
- normal
- LOW
- no elevated prolactin

Mesocortical Pathway to VMPFC
- normal
- NORMAL
- lack of pleasure or reward

Nigrostriatal Pathway
- normal
- NORMAL
- no parkinsonism

Tuberoinfundibular Pathway
- normal
- NORMAL
agonist binds in an intermediary manner ("just right," with antipsychotic actions but no EPS, as in Figure 10-46C). For this reason, partial agonists that get the balance "just right" between full agonism and complete antagonism are sometimes called "Goldilocks" drugs. However, as we will see, this explanation is an oversimplification.

Partial agonists have the intrinsic ability to bind receptors in a manner that causes signal transduction from the receptor to be intermediate between full output and no output (Figure 10-47). The naturally occurring neurotransmitter generally functions as a full agonist and causes maximum signal transduction from the receptor it occupies (Figure 10-47, top), whereas antagonists essentially shut down all output from the receptor they occupy and make them "silent" in terms of communicating with downstream signal transduction cascades (Figure 10-47, middle). Partial agonists cause receptor output that is more than the silent antagonist but less than the full agonist (Figure 10-47, bottom). Thus many degrees of partial agonism between these two extremes are possible.

Partial agonist actions have unique functional and clinical consequences. Dopamine partial agonists (DPAs) used to treat schizophrenia reduce D2 hyperactivity in mesolimbic dopamine neurons to a degree that is sufficient to exert an antipsychotic action on positive symptoms, even though they do not completely shut down the D2 receptor, as a conventional

**FIGURE 10-44 Integrated theory of schizophrenia and hit-and-run actions.** In untreated schizophrenia, dopamine output is high in the mesolimbic pathway, causing positive symptoms; is low in the mesocortical pathway to dorsolateral prefrontal cortex (DLPFC), causing cognitive and negative symptoms; is low in the mesocortical pathway to ventromedial prefrontal cortex (VMPFC), causing affective and negative symptoms, and is normal in the nigrostriatal and tuberoinfundibular pathways (upper panel). With administration of an agent that rapidly dissociates from D2 receptors, dopamine output is decreased in the mesolimbic pathway, which can reduce the positive symptoms of psychosis, although it may also reduce the experience of pleasure or reward since these are mediated by the mesolimbic pathway (lower panel). Theoretically, decreased dopamine in mesocortical pathways may require persistent blockade of D2 receptors, and thus worsening of affective, cognitive, or negative symptoms may not occur with agents that dissociate rapidly. Similarly, decreased dopamine in the nigrostriatal and tuberoinfundibular pathways may require persistent blockade of D2 receptors; thus, agents that dissociate rapidly may have reduced risk for extrapyramidal symptoms (EPS) and prolactin elevation, respectively (lower panel).
FIGURE 10-46A, B and C Spectrum of dopamine neurotransmission. Simplified explanation of actions on dopamine. **(A)** Conventional antipsychotics bind to the D2 receptor in a manner that is "too cold"; that is, they have powerful antagonist actions while preventing agonist actions and thus can reduce positive symptoms of psychosis but also cause extrapyramidal symptoms (EPS). **(B)** D2 receptor agonists, such as dopamine itself, are "too hot" and can therefore lead to positive symptoms. **(C)** D2 partial agonists bind in an intermediary manner to the D2 receptor and are therefore "just right" with antipsychotic actions but no EPS.

antipsychotic does (Figure 10-48). At the same time, DPAs reduce dopamine activity in the nigrostriatal system to a degree that is insufficient to cause EPS (Figure 10-49). Only a small amount of signal transduction through D2 receptors in the striatum seems to be necessary for a DPA to avoid EPS, and this seems to be the property of DPAs used to treat
FIGURE 10-47 Dopamine receptor output. Dopamine itself is a full agonist and causes full receptor output (top). Conventional antipsychotics are full antagonists and allow little if any receptor output (middle). The same is true for atypical antipsychotics that are serotonin dopamine antagonists. However, D2 partial agonists can partially activate dopamine receptor output and cause a stabilizing balance between stimulation and blockade of dopamine receptors (bottom).

schizophrenia (Figure 10-49). Full agonists, antagonists, and partial agonists may cause different changes in receptor conformation, which lead to a corresponding range of signal transduction output from the receptor (Figure 10-50). The effects of DPAs on dopamine output are summarized in Figure 10-51.

Antipsychotics that act as DPAs include not only aripiprazole but also a new agent called bifeprunox (Figure 10-52). Older agents that may have DPA actions include amisulpride and possibly even low doses of sulpiride, but the partial agonist properties of amisulpride or sulpiride are not well characterized with modern techniques. Many new DPAs are in development (Figure 10-53), and several others have been tested and dropped from further development (Figure 10-54). Bifeprunox is in late stage development in several countries, and related compounds SLV313 and SLV314 are early in clinical testing (Figure 10-53). ACP-104 is a clozapine metabolite that may have DPA actions, but it is still in early testing, and many other compounds shown in Figure 10-53 are also in early testing.

The plethora of new DPAs establishes the point that there is a spectrum of partial agonist action, and clinical testing has shown that too much agonism is not acceptable for a DPA in the treatment of schizophrenia (Figure 10-54). This is perhaps best demonstrated by the successful development of aripiprazole, compared to the failure of a related compound from the same laboratory, OPC 4293. That is, OPC 4293 is a partial agonist that is closer to a full agonist on the DPA spectrum than is aripiprazole (Figure 10-54). This compound did show the ability to improve negative symptoms of schizophrenia, but it caused worsening of positive symptoms, similar to the psychotomimetic actions of a stimulant. Aripiprazole was then developed with a DPA profile closer to the antagonist part of the spectrum and...
has proven to be an atypical antipsychotic without psychotomimetic actions and without significant EPS in most patients.

Several other DPAs that are “too hot” on the spectrum are shown in Figure 10-54. Although there has not been sufficient head-to-head testing of the agents listed as DPAs in Figure 10-52 to determine how they may be distinguishable from each other or exactly where they should be placed along the partial agonist spectrum, hints from both preclinical and clinical investigations suggest that bifeprunox may be closer to the full agonist part of the spectrum than aripiprazole, whereas amisulpride and sulpiride may be closer to the silent antagonist part of the spectrum than aripiprazole. Although it does appear that sulpiride is too close to a silent antagonist to have an ideal clinical profile, it is not clear what the clinical differences are for agents within the effective portion of the DPA spectrum. Perhaps different patients will have better responses to one of these agents versus another, but establishing where different agents may lie on the DPA spectrum and what clinical significance this may have will require much further testing.
**FIGURE 10-49** Dopamine partial agonist and nigrostriatal pathway. Dopaminergic tone in nigrostriatal neurons must be maintained for optimal motor functioning. Conventional antipsychotics reduce this tone so much that extrapyramidal symptoms (EPS) are produced (lower left). On the other hand, dopamine partial agonists allow continuing dopaminergic tone in these neurons, so that EPS are not present (lower right).

**5HT1A partial agonist (SPA) actions make an antipsychotic atypical**

The fourth pharmacological mechanism that may contribute to the atypical clinical properties of an antipsychotic is the ability of some of these agents to act at 5HT1A receptors either as full agonists or partial agonists (serotonin partial agonist, or SPA) (Figure 10-55). We have already discussed the 5HT2A antagonist actions of some atypical antipsychotics, and have also contrasted the regulatory influence of 5HT1A receptors with 5HT2A receptors on dopamine release (Figure 10-21) and on glutamate release (Figure 10-30). Thus, agonist actions at 5HT1A receptors would be expected to increase dopamine release (Figure 10-21) and reduce glutamate release (Figure 10-30). Enhanced dopamine release by SPA action in the striatum would theoretically improve extrapyramidal actions; enhanced dopamine release by SPA action in the pituitary would theoretically reduce the risk of hyperprolactinemia; and enhanced dopamine release by SPA action in the prefrontal cortex would theoretically improve negative, cognitive, and affective symptoms of schizophrenia.
Reduced glutamate release by SPA action in prefrontal cortex could theoretically reduce positive symptoms. Thus, 5HT1A agonist action has similar net effects to 5HT2A antagonism. Some drugs have both 5HT1A agonist actions and 5HT2A antagonist actions, an action that could be additive or synergistic (Figure 10-56). Other drugs have SPA actions without 5HT2A antagonist actions; furthermore SPA actions can be combined either with D2 antagonism or with DPA to create an atypical antipsychotic drug (Figure 10-56).

Receptor binding properties and pharmacokinetics of antipsychotics

Over two dozen antipsychotic drugs are in clinical use; and so far in this chapter we have discussed pharmacological properties that are shared among some drugs in this class and how those actions are linked to therapeutic efficacy and certain side effects. Many
drugs in the antipsychotic class have additional binding properties at receptors other than the dopamine and serotonin receptors discussed above, and many of these drugs also have additional side effects, such as cardiometabolic risk and sedation. In many cases, there is good evidence to link pharmacological actions with clinical actions, but in other cases these links are only hypothetical or even tenuous. In the following section, we will review a number of receptor interactions for antipsychotic drugs and show where there may be
FIGURE 10-54 Spectrum of dopamine partial agonists. Dopamine partial agonists may themselves fall along a spectrum, with some having actions closer to a silent antagonist and others having actions closer to a full agonist. Agents with too much agonism (such as failed agent OPC 4293) may be psychotomimetic and thus not effective antipsychotics. Instead, partial agonists that are closer to the antagonist end of the spectrum (such as aripiprazole or bifeprunox) seem to have favorable profiles. Amisulpride and sulpiride may be very partial agonists, with their partial agonist clinical properties more evident at lower doses.

FIGURE 10-55 5HT1A full/partial agonism. A fourth property that may contribute to the atypicality of an antipsychotic is full or partial agonism of serotonin 1A receptors. Agonism of serotonin 1A receptors can increase dopamine release, which could improve affective, cognitive, and negative symptoms while also reducing the risk of extrapyramidal symptoms (EPS) and prolactin elevation. Serotonin 1A agonism can also decrease glutamate release, which could indirectly reduce positive symptoms of psychosis.
Which Antipsychotics are SPAs?
(Serotonin 1A Partial Agonists)

FIGURE 10-56 5HT1A partial agonists. Ziprasidone, quetiapine, and clozapine are all partial agonists at serotonin (5HT) 1A receptors, in addition to being antagonists at 5HT1A receptors. Aripiprazole is not only a partial agonist at D2 receptors but also an antagonist at 5HT2A receptors and a partial agonist at 5HT1A receptors. Bifeprunox is partial agonist at both D2 and 5HT1A receptors.

potential links between pharmacology and clinical actions. Wherever there is evidence of differentiation among the many members of the antipsychotic class, we will emphasize potential pharmacological explanations for clinical distinctions. Pharmacokinetic properties as well as neurotransmitter receptor binding actions and clinical effects are discussed for antipsychotics in general and for fifteen important antipsychotics in particular.

Links between antipsychotic binding properties and clinical actions
Antipsychotics have perhaps the most complicated pattern of binding to neurotransmitter receptors of any drug class in psychopharmacology. So far, we have concentrated on just three receptors: the D2 dopamine receptor, the 5HT2A receptor, and the 5HT1A receptor. In reality, there are at least a dozen more receptors to which one or another of the antipsychotic drugs also bind (Figure 10-57A). Scientists are just beginning to unravel the clinical significance of these receptor actions, but it is clear that many of them are clinically relevant, contributing to therapeutic actions (Figure 10-57B), side effects (Figure 10-57C), and the clinical differentiation between one agent in this class and another (discussed later in this section and illustrated in Figures 10-90 through 10-104).

Although the actions of these drugs on the various receptors are fairly well established, the link of this receptor binding to clinical actions remains hypothetical, with some
links better established than others. We have already discussed the side effects mediated by unwanted D2 receptor blockade, namely extrapyramidal side effects, tardive dyskinesia, hyperprolactinemia, and worsening of negative, cognitive, and affective symptoms in schizophrenia. Here we tackle the possible pharmacological mechanisms involved in mediating two other important side effects: cardiometabolic risk and sedation (Figures 10-57A, 10-58, and 10-66). Later, we will attempt to link other pharmacological properties to both the efficacy and differential side effects of individual atypical antipsychotics (Figures 10-90 through 10-104).

Cardiometabolic risk and antipsychotics

Atypical antipsychotics have been on the market for over a decade, and only now is it becoming clear that some of these agents are associated with significant cardiometabolic risk (Tables 10-2 through 10-4) and with pharmacological actions that may mediate this cardiometabolic risk (Figure 10-58). At first, weight gain and obesity were clearly linked to atypical antipsychotics (Table 10-2 and Figure 10-59), but more recently, increased risk for dyslipidemia, diabetes, accelerated cardiovascular disease, and premature death have been linked to certain drugs in this class as well (Tables 10-3 and 10-4; Figures 10-60 through 10-65).

All of us in western civilization and particularly in the United States, live in a society experiencing an epidemic of obesity and diabetes. The “metabolic highway” begins with increased appetite and weight gain and progresses to obesity, insulin resistance, and dyslipidemia with increases in fasting triglyceride levels (Figure 10-60). Ultimately, hyperinsulinemia advances to pancreatic beta cell failure, prediabetes, and then diabetes. Once diabetes is established, risk for cardiovascular events is further increased, as is the risk of premature death (Figure 10-60).

Cardiovascular disease and diabetes are illnesses determined by both the environment and genetics. Lifestyle factors such as poor diet, lack of exercise, stress, and smoking interact with genetic risk factors such as family history of cardiovascular disease and diabetes associated with genes coding for subtle molecular abnormalities that appear to “bias” the body towards developing cardiovascular disease and diabetes. In the twenty-first century, the schizophrenic patient thus comes to treatment with the same environmental cardiometabolic risk factors that affect all of us. In addition, there is some indication that whatever genes add risk for serious mental illness may also add incremental risk for cardiometabolic disorders. For these reasons, it was not recognized early following the introduction of atypical antipsychotics that some of these agents enhanced cardiometabolic risk beyond these background factors of genes and environment (see Tables 10-2 through 10-4 and Figures 10-58 through 10-65).

As already mentioned, the first indication that certain atypical antipsychotics are associated with increased cardiometabolic risk was the recognition that weight gain, sometimes profound, is associated with some antipsychotics (Table 10-2). Receptors associated with increased weight gain are the H1 histamine receptor and the 5HT2C serotonin receptor; when these receptors are blocked, particularly at the same time, patients can experience weight gain (Table 10-2 and Figures 10-58 and 10-59). Such weight gain is at least in part due to enhanced appetite in hypothalamic eating centers (Figure 10-59), although peripheral factors unrelated to appetite may also be involved in antipsychotic-induced weight gain. Antipsychotics associated with the greatest degree of weight gain are those that have the most potent antagonist actions simultaneously at H1 and 5HT2C receptors (Table 10-2 and Figures 10-58 and 10-59; see also Figures 10-90 through 10-104). Since weight gain
FIGURE 10-58 Receptors mediating cardiometabolic risk. Which receptors hypothetically mediate cardiometabolic risk? Serotonin-2C, muscarinic-3, and histamine-1 receptors as well as receptors yet to be identified (signified here as receptor X), are all hypothetically linked to cardiometabolic risk. In particular, antagonism of serotonin-2C and histamine-1 receptors is associated with weight gain, while antagonism at muscarinic-3 receptors can impair insulin regulation. An unknown receptor X may be involved in the rapid production of insulin resistance and may also rapidly cause elevated fasting plasma triglyceride levels in some patients who experience increased cardiometabolic risk on certain atypical antipsychotics.

can lead to obesity, obesity to diabetes, and diabetes to cardiac disease along the metabolic highway (Figure 10-60), it seemed feasible at first that weight gain might explain all the other cardiometabolic complications linked to treatment with those atypical antipsychotics that cause weight gain (Table 10-2).

However, it now appears that the cardiometabolic risk of certain atypical antipsychotics cannot simply be explained by increased appetite and weight gain, even though they certainly do represent the first steps down the slippery slope toward cardiometabolic complications (Figure 10-61). That is, some atypical antipsychotics can elevate fasting triglyceride levels and cause increased insulin resistance in a manner that cannot be explained by weight gain alone (Tables 10-3 and 10-4; Figures 10-62 and 10-63; see also Figures 10-90 through 10-104). When dyslipidemia and insulin resistance occur, this moves a patient along the

FIGURE 10-57A, B and C Pharmacological properties of atypical antipsychotics. Atypical antipsychotics have some of the most complex mixtures of pharmacological properties in psychopharmacology. (A) Beyond antagonism of serotonin (5HT) 2A and D2 receptors, agents in this class interact with multiple other receptor subtypes for both dopamine and serotonin, including 5HT1A, 5HT1D, 5HT2C, 5HT3, 5HT6, 5HT7, the 5HT transporter, and D1, D3, and D4. Atypical antipsychotics may have effects on other neurotransmitter systems as well, with inhibition of the norepinephrine transporter as well as muscarinic-1, muscarinic-3, histamine-1, alpha-1 adrenergic, and alpha-2 adrenergic receptors. In addition, some atypical antipsychotics may have actions that alter cellular insulin resistance and increase fasting plasma triglyceride levels, hypothetically due to action at receptors that are not yet well understood, signified by receptor X in this picture. Some of these multiple pharmacological properties can contribute to the therapeutic effects of atypical antipsychotics (B), whereas others can contribute to their side effects (C). No two atypical antipsychotics have identical binding properties, which probably helps to explain why they all have distinctive clinical properties.
### TABLE 10-2 Atypical antipsychotics and risk of weight gain: FDA and experts agree on three tiers of risk

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Risk for Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone*</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
</tr>
</tbody>
</table>

*Risperidone’s active metabolite paliperidone likely poses the same risk of weight gain as risperidone itself.
FDA, US Food and Drug Administration.

### TABLE 10-3 Atypical antipsychotics and cardiometabolic risk: FDA and experts disagree on one versus three tiers of risk

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Cardiometabolic/Dyslipidemia/Diabetes Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expert consensus</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Definite risk</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Definite risk</td>
</tr>
<tr>
<td>Risperidone*</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/- limited data</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/- limited data</td>
</tr>
</tbody>
</table>

*Risperidone’s active metabolite paliperidone likely poses the same cardiometabolic risk as risperidone itself.
ND, not done (clozapine and aripiprazole not studied in early phases of this trial).
CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness.
FDA, US Food and Drug Administration.

### TABLE 10-4 Are there “metabolically friendly” atypical antipsychotics? Low-risk agents for weight gain and cardiometabolic illness

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Cardiometabolic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>Low</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Low</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Possibly low but not well studied</td>
</tr>
<tr>
<td>Bifeprunox</td>
<td>Possibly low, studies in progress</td>
</tr>
</tbody>
</table>
metabolic highway toward diabetes and cardiovascular disease (Figure 10-60). Although this happens in many patients with weight gain alone, it also occurs in some patients who take atypical antipsychotics prior to gaining weight, as though there were an acute receptor-mediated action of these drugs on insulin regulation.

This hypothesized mechanism is indicated as receptor X on the drug icon in Figures 10-57 and 10-58 and on the icons for those agents hypothesized to have this action on insulin resistance and fasting triglycerides (see Tables 10-3 and 10-4 and Figures 10-90 through 10-104). To date, the mechanism of this increased insulin resistance and elevation of fasting triglycerides has been vigorously pursued but has not yet been identified. The rapid elevation of fasting triglycerides on initiation of some antipsychotics and the rapid fall of fasting triglycerides on discontinuation of such drugs (Table 10-3) is highly suggestive that an unknown pharmacological mechanism causes these changes, although this remains speculative. The hypothetical actions of atypical antipsychotics with this postulated receptor action are shown in Figure 10-62, where adipose tissue, liver, and skeletal muscle all develop insulin resistance in response to administration of certain antipsychotic drugs (e.g., high-risk drugs listed in Table 10-3 but not metabolically friendly drugs listed in Table 10-4), at least in certain patients.

Whatever the mechanism of this effect, it is clear that fasting plasma triglycerides and insulin resistance can be elevated significantly in some patients taking certain antipsychotics (Tables 10-3 and 10-4) and that this enhances cardiometabolic risk, moves such patients along the metabolic highway (Figure 10-60), and functions as a second step down the slippery slope toward the diabolical destination of cardiovascular events and premature death (Figure 10-63). This does not happen in all patients taking an antipsychotic (Tables 10-3 and 10-4), but the development of this problem can be detected by monitoring