01 - 5 Targeting Dopamine and Serotonin Receptors

5 Targeting Dopamine and Serotonin Receptors for Psychosis, Mood, and Beyond: So-Called “Antipsychotics”

Targeting Dopamine and Serotonin Receptors for Psychosis, Mood, and Beyond: So-Called “Antipsychotics” Targeting Mesolimbic/Mesostriatal Dopamine D2 Receptors Causes Antipsychotic Actions 161 Targeting Dopamine D2 Receptors in Mesolimbic/ Mesostriatal and Mesocortical Pathways Causes Secondary Negative Symptoms 162 Secondary Negative Symptoms Due to Targeting Mesolimbic Dopamine D2 Receptors 162 Secondary Negative Symptoms Due to Targeting Mesocortical Dopamine D2 Receptors 163 Targeting Tuberoinfundibular Dopamine D2 Receptors Causes Elevation of Prolactin 164 Targeting Nigrostriatal Dopamine D2 Receptors Causes Motor Side Effects 165 Drug-Induced Parkinsonism 166 Drug-Induced Acute Dystonia 169 Akathisia 169 Neuroleptic Malignant Syndrome 169 Tardive Dyskinesia 170 Drugs Targeting Dopamine D2 Receptors: So-Called First Generation or Conventional “Antipsychotics” 179 Drugs Targeting Serotonin 2A Receptors with or without Simultaneously Targeting Dopamine D2 Receptors 183 5HT2A Receptor Regulation of Dopamine Release in Three Downstream Pathways 184 Drugs Targeting Serotonin 1A Receptors and Dopamine D2 Receptors as Partial Agonists 189 D2 Partial Agonism 189 How Does D2 Partial Agonism Cause Fewer Motor Side Effects than D2 Antagonism? 192 5HT1A Partial Agonism 193 Links between Receptor Binding Properties of Drugs Used to Treat Psychosis and Other Therapeutic Actions and Side Effects 195 Mania 195 Antidepressant Actions in Bipolar and Unipolar Depression 195 Anxiolytic Actions 196 Agitation in

Dementia 197 Sedative Hypnotic and Sedating Actions 197 Cardiometabolic Actions 198 Pharmacological Properties of Selected Individual First-Generation D2 Antagonists 201 Chlorpromazine 201 Fluphenazine 202 Haloperidol 202 Sulpiride 202 Amisulpride 203 An Overview of the Pharmacological Properties of Individual 5HT2A/ D2 Antagonists and D2/5HT1A Partial Agonists: The Pines (Peens), Many Dones and a Rone, Two Pips and a Rip 204 The Pines (Peens) 222 Many Dones and a Rone 234 Two Pips and a Rip 239 Selective 5HT2A Antagonist 240 The Others 240 Future Treatments for Schizophrenia 241 Roluperidone (MIN-101) 241 D3 Antagonists 241 Trace Amine Receptor Agonists and SEP363856 241 Cholinergic Agonists 242 A Few Other Ideas 242 Summary 242 This chapter explores drugs that target dopamine receptors, serotonin receptors, or both, for the treatment of psychosis, mania, and depression. It also explores myriad additional neurotransmitter receptors that these agents engage. The drugs covered in this chapter have classically been called “antipsychotics,” but this terminology is now considered out of date and confusing since these same agents are used even more frequently for mood disorders than for psychosis, yet are not classified as “antidepressants.” As mentioned earlier, throughout this textbook we strive to utilize modern neurosciencebased nomenclature, where drugs are named for their pharmacological mechanism of action and not for their clinical indication. Thus, drugs discussed in this chapter have “antipsychotic action” but are not called “antipsychotics”; they also have “antidepressant action”

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY but are not called “antidepressants.” Instead, this chapter reviews one of the most extensively prescribed classes of psychotropic agents in psychiatry today, namely, those that target dopamine and serotonin receptors, and that began as drugs for psychosis, and later extended their use even more frequently as drugs for mania, bipolar depression, and treatment-resistant unipolar depression. On the horizon is the use of at least some of these agents in PTSD (posttraumatic stress disorder), agitation in dementia, and beyond. We discuss how the pharmacological properties of these agents form not only a single large class of many agents, but in many ways, how each individual agent has binding properties that render every agent unique from all the others. The reader is referred to standard reference manuals and textbooks for practical prescribing information because this chapter on drugs for psychosis and mood emphasizes basic pharmacological concepts of mechanism of action and not practical issues such as how to prescribe these drugs (for that information, see, for example, Stahl’s Essential Psychopharmacology: the Prescriber’s Guide, which is a companion to this textbook). The pharmacological concepts developed here should help the reader understand the rationale for how to use each of the different agents, based first and foremost upon their interactions with the dopamine and serotonin receptor systems, and secondarily with other neurotransmitter systems. Such interactions can often explain both the therapeutic actions and the side effects of the various drugs in this group. Understanding the full range of receptor interactions for each individual drug also sets the stage for differentiating one drug from another, and thus for tailoring the selection of a drug treatment by matching the pharmacological mechanisms of a specific drug to the therapeutic and tolerability needs of an individual patient. Figure 5-1 Therapeutic mechanisms of drugs for psychosis. The first mechanism identified to treat psychosis was dopamine-2 (D2) antagonism, and for several decades all available medications to treat psychosis were D2 antagonists. Today, there are many agents available with additional mechanisms, including D2 antagonism combined with serotonin (5HT) 2A (5HT2A) antagonism, D2 partial agonism (PA) combined with serotonin 1A (5HT1A) partial agonism, and 5HT2A antagonism alone. 5HT1A PA Therapeutic Mechanisms of Drugs for Psychosis D2 D2 antagonist 5HT2A/D2 antagonist 5HT2A

antagonist D2/5HT1A partial agonist 5HT2A D2 5HT2A D2 PA

Chapter 5: Targeting for Psychosis Figure 5-2 Mesolimbic/mesostriatal dopamine pathway and D2 antagonists. (A) In untreated schizophrenia, the mesolimbic/ mesostriatal 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. (B) Administration of a D2 antagonist or partial agonist blocks dopamine from binding to the D2 receptor, which reduces hyperactivity in this pathway and thereby reduces positive symptoms as well. However, because the mesolimbic/mesostriatal dopamine pathway also plays a role in regulating motivation and reward, blockade of D2 receptors can cause secondary negative symptoms such as apathy and anhedonia. overactivation positive symptoms A B reduced positive symptoms therapeutic side effect secondary negative symptoms (apathy, anhedonia) NORMAL normal HIGH normal Mesolimbic/Mesostriatal Pathway - D2 Antagonist/Partial Agonist Mesolimbic/Mesostriatal Pathway - Untreated Schizophrenia = D2 antagonist/ partial agonist (SIGH) TARGETING MESOLIMBIC/ MESOSTRIATAL DOPAMINE D2 RECEPTORS CAUSES ANTIPSYCHOTIC ACTIONS How do the drugs approved for treating psychosis, especially in schizophrenia, work? The earliest effective treatments for schizophrenia and other psychotic illnesses arose from serendipitous clinical observations approximately 70 years ago, rather than from scientific knowledge of the neurobiological basis of psychosis, or of the mechanism of action of effective drugs that empirically treated psychosis. Thus, the first truly effective drugs for psychosis other than sedating tranquilizers were discovered by accident in the 1950s when a drug with antihistamine properties (chlorpromazine) was observed to improve psychosis when this putative antihistamine was tested in schizophrenia 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 drug for treating psychosis out of proportion to its ability to cause sedation, it was tested experimentally to uncover its mechanism of antipsychotic action, which was identified as dopamine D2 receptor antagonism (Figures 5-1 and 5-2). Early in the testing process, chlorpromazine and other drugs for psychosis of this era were all found to cause “neurolepsis,” known as an extreme form of slowness

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY or absence of motor movements as well as behavioral indifference in experimental animals. The original drugs for psychosis in fact were first discovered largely by their ability to produce this effect in experimental animals, and thus sometimes drugs with antipsychotic properties are called “neuroleptics.” A human counterpart of neurolepsis is also caused by these drugs and is characterized by psychomotor slowing, emotional quieting, and affective indifference, sometimes also called “secondary” negative symptoms because they mimic the primary negative symptoms associated with the untreated illness itself (see Figures 4-56 through 4-59 and Tables 4-4 and 4-5). We know today that neurolepsis and secondary negative symptoms are likely caused at least in part by blocking D2 receptors that normally mediate motivation and reward (Figure 5-2B) as an undesired “cost of doing business” in order to simultaneously block D2 receptors that are thought to mediate the positive symptoms of psychosis due to excessive release of dopamine (see Figure 5-2A). By the 1970s it was widely recognized that the key pharmacological property of all “neuroleptics” with antipsychotic properties was their ability to block D2 receptors (Figure 5-1 and Figure 5-2B), specifically those in the mesolimbic/mesostriatal dopamine pathway (Figure 5-2B; see also Figure 4-15). This pharmacological property has been retained by many of the newer agents, some of which add

highly potent serotonin 2A (5HT2A) antagonism and/or 5HT1A partial agonism to D2 antagonism, others of which substitute D2 partial agonism for D2 antagonism, and, most recently, still others which only have 5HT2A antagonism and drop the D2 targeting entirely (Figure 5-1). The effects of serotonin-receptor-targeting of the newer agents and of partial agonism are discussed in detail below. Also explained in the following sections are how targeting serotonin and dopamine receptors in various brain circuits mediates not only therapeutic effects in psychosis and other conditions, but also side effects. These drugs are first classified into several general groups and then each individual drug is discussed. TARGETING DOPAMINE D2 RECEPTORS IN MESOLIMBIC/ MESOSTRIATAL AND MESOCORTICAL PATHWAYS CAUSES SECONDARY NEGATIVE SYMPTOMS Secondary Negative Symptoms Due to Targeting Mesolimbic Dopamine D2 Receptors Dopamine 2 (D2) receptors in the mesolimbic/mesostriatal dopamine pathway are postulated not only to mediate the positive symptoms of psychosis from excessive release of dopamine in the pathway (see Figures 4-14, 4-15, and 5-2A), but also to have a major role in regulating motivation and reward (Figures 4-14 and 5-2B). In fact, the nucleus accumbens, a major target of mesolimbic/ mesostriatal dopamine neurons in the ventral emotional striatum, is widely considered to be the “pleasure center” of the brain. The mesolimbic dopamine pathway to the nucleus accumbens is often considered the final common pathway of all reward and reinforcement (even if this is an oversimplification), including not only normal reward (such as the pleasure of eating good food, orgasm, listening to music) but also the artificial reward of substance abuse (see the discussion on drugs of abuse in Chapter 13). If normal mesolimbic D2 receptor stimulation is associated with the experience of pleasure (Figure 4-14) and excessive mesolimbic D2 receptor stimulation is associated with the positive symptoms of psychosis (Figure 5-2A), D2 antagonism/partial agonism may not only reduce the positive symptoms of schizophrenia, but at the same time block reward mechanisms (both shown in Figure 5-2B). When this happens, it can leave patients feeling apathetic, anhedonic, and lacking motivation, interest, or joy from social interactions, a state very similar to that of negative symptoms of schizophrenia. However, these negative symptoms are caused by the drug, not the illness and thus are termed “secondary” negative symptoms. When D2 blockers are administered, as has already been mentioned above, an adverse behavioral state can thus be simultaneously produced by D2 antagonist/partial agonists, sometimes called the “neuroleptic-induced deficit syndrome” because it looks so much like the negative symptoms produced by schizophrenia itself, and this is reminiscent of “neurolepsis” in animals. The near shut-down of the mesolimbic dopamine pathway, sometimes necessary to improve the positive symptoms of psychosis (Figure 5-2A), may exact a heavy “cost of doing business” to the patient by causing a worsening of anhedonia, apathy, and other negative symptoms (Figure 5-2B). Worsening negative symptoms with loss of pleasure caused by treatment with drugs for psychosis is a plausible partial explanation for the high incidence of smoking and drug abuse in schizophrenia as patients may attempt to overcome this anhedonia and lack of pleasurable experiences. The emotional flattening and worsening of negative symptoms may contribute to patients stopping their given D2 blockers. Treatment of negative symptoms includes reducing the dose of the D2 blocker or switching to a D2 blocker that is better tolerated; some adjunct medications can be helpful

Chapter 5: Targeting for Psychosis Figure 5-3 Mesocortical dopamine pathway and D2 antagonists. (A) In untreated schizophrenia, the mesocortical dopamine pathways to the dorsolateral prefrontal cortex (DLPFC) and to the ventromedial prefrontal cortex (VMPFC) are hypothesized to be hypoactive, indicated here by the dotted outlines of the pathway. 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). (B) Administration of a D2 antagonist or partial agonist could further reduce activity in this pathway and thus potentially worsen these symptoms. Mesocortical Pathway - Untreated Schizophrenia Mesocortical Pathway - D2 Antagonist/Partial Agonist = D2 antagonist/ partial agonist negative symptoms affective symptoms A B (SIGH)

negative symptoms affective symptoms (SIGH) cognitive symptoms symptoms worsen symptoms worsen LOW normal LOW normal in reducing negative symptoms, including drugs that treat depression. Several other agents are in various stages of development for negative symptoms and include 5HT2A antagonists as well as dopamine 3 (D3) partial agonists, as discussed below in the section on individual agents. Secondary Negative Symptoms Due to Targeting Mesocortical Dopamine D2 Receptors Negative symptoms (Figure 5-3A) can also be worsened by D2 antagonist/partial agonist actions in the mesocortical dopamine pathway (Figure 5-3B).

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY TARGETING TUBEROINFUNDIBULAR DOPAMINE D2 RECEPTORS CAUSES ELEVATION OF PROLACTIN Dopamine 2 receptors in the tuberoinfundibular dopamine pathway are also blocked when D2 antagonists are administered and this causes plasma prolactin concentrations to rise, a condition called Drugs for psychosis also block those D2 receptors that are present in the mesocortical dopamine pathway (Figure 5-3B) where dopamine is already hypothetically deficient in schizophrenia (see Figures 4-17 through 4-19). This can cause or worsen not only negative symptoms of schizophrenia, but also cognitive and affective symptoms related to dopamine action in the mesocortical dopamine pathway, even though there is only a low density of D2 receptors in the cortex (Figure 5-3B). Figure 5-4 Tuberoinfundibular dopamine pathway and D2 antagonists. (A) The tuberoinfundibular dopamine pathway, which projects from the hypothalamus to the pituitary gland, is theoretically "normal" in untreated schizophrenia. (B) 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). Tuberoinfundibular Pathway - Untreated Schizophrenia Tuberoinfundibular Pathway - D2 Antagonist prolactin levels rise NORMAL normal LOW normal = pure D2 antagonist A B

Chapter 5: Targeting for Psychosis TARGETING NIGROSTRIATAL DOPAMINE D2 RECEPTORS CAUSES MOTOR SIDE EFFECTS Motor side effects are caused by D2 antagonists/partial agonists blocking D2 receptors in the nigrostriatal motor pathway (Figure 5-5). When D2 receptors are blocked acutely in the nigrostriatal pathway – the same pathway that degenerates in Parkinson's disease – this can cause a condition known as drug-induced parkinsonism (DIP) because it looks similar to Parkinson's disease with tremor, muscular rigidity, and slowing of movements (bradykinesia) or loss of movement (akinesia) (Figure 5-5B). Often, any abnormal motor symptoms caused hyperprolactinemia (Figure 5-4). This can be associated with a condition called gynecomastia, or enlargement of the breasts, in men as well as women, and another condition called galactorrhea (i.e., breast secretions) and amenorrhea (i.e., irregular or lack of menstrual periods) in women. Hyperprolactinemia may thus interfere with fertility, especially in women. Hyperprolactinemia might lead to more rapid demineralization of bones, especially in postmenopausal women who are not taking 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. Figure 5-5 Nigrostriatal dopamine pathway and D2 antagonists.

(A) The nigrostriatal dopamine pathway is theoretically unaffected in untreated schizophrenia. (B) Blockade of D2 receptors prevents dopamine from binding there and can cause motor side effects such as drug-induced parkinsonism (tremor, muscle rigidity, slowing or loss of movement), akathisia (motor restlessness), and dystonia (involuntary twisting and contractions). Nigrostriatal Pathway - Untreated Schizophrenia Nigrostriatal Pathway - D2 Antagonist/Partial Agonist = D2 antagonist/ partial agonist DIP drug-induced parkinsonism akathisia dystonia NORMAL normal LOW normal A B

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY such as constant chewing, tongue protrusions, facial grimacing, but also limb movements that can be quick, jerky, or choreiform (dancing). Unfortunately, DIP and TD are often lumped together as EPS, leading to the failure to differentiate one versus the other despite the fact that they have essentially opposite pharmacologies and vastly different treatments, as discussed below. Now that treatments exist for both DIP and TD, it is more important than ever to make this differentiation so that proper treatment can be given. Inadequate relief of motor side effects of D2 blockers is a major reason why patients stop their medication. Drug-Induced Parkinsonism The most common side effect of drugs that target D2 receptors for psychosis is drug-induced parkinsonism, explained above as the presence of tremor, muscular rigidity, and slowing of movements (bradykinesia) or loss of movement (akinesia). Classic treatment for DIP is the use of "anticholinergics," namely drugs that block muscarinic cholinergic receptors, especially the postsynaptic M1 receptor. This approach exploits the normal reciprocal balance between dopamine and acetylcholine in the striatum (Figure 5-7A). Dopamine by D2 receptor blockers are lumped together and called collectively extrapyramidal symptoms (EPS), but EPS is an old-fashioned and relatively imprecise term for describing the motor side effects of D2 antagonists/ partial agonists. A practical consequence of lumping all D2-blocker-induced movements together as EPS is to miss the fact that different motor symptoms can have different clinical manifestations and – importantly – vastly different treatments. More precise terms than EPS include not only DIP but also akathisia (motor restlessness) and dystonia (involuntary twisting and contractions), which can also be caused by the acute administration of D2 antagonists/partial agonists and are discussed below. Yet another abnormal involuntary movement disorder can be caused by the chronic blockade of D2 receptors in the nigrostriatal dopamine pathway, namely tardive dyskinesia (TD) ("tardive" because, unlike the other motor symptoms caused by D2 blockade, these abnormal involuntary movements are late and delayed in onset, often after months to years of treatment) (Figure 5-6). TD emerges only after chronic treatment with D2 blockers, and can be irreversible. It consists of involuntary continuous movements, often about the face and tongue, Figure 5-6 Tardive dyskinesia. (A) Dopamine binds to D2 receptors in the nigrostriatal pathway. (B) Chronic blockade of D2 receptors in the nigrostriatal dopamine pathway can cause upregulation of those receptors, which can lead to a hyperkinetic motor condition known as tardive dyskinesia, characterized by facial and tongue movements (e.g., tongue protrusions, facial grimaces, chewing) as well as quick, jerky limb movements. chronic treatment A B tardive dyskinesia

Chapter 5: Targeting for Psychosis the other hand, there are many potential problems with administering anticholinergics (such as the commonly used benztropine); namely, peripheral side effects, such as dry mouth, blurred vision, urinary retention, and constipation, as well as central side effects including drowsiness and cognitive dysfunction, such as problems with memory, concentration, and slowing of cognitive processing (Figure 5-8). To compound matters, many drugs

for psychosis themselves have anticholinergic properties as will be discussed below for each individual agent. Furthermore, many patients are on concomitant psychotropic and nonpsychotropic medications that have anticholinergic properties. Thus, the clinician must be alert to the total anticholinergic burden for a given patient and also be wary of the side effects that can interfere with normal cognitive functioning and can lead to life-threatening decrease in bowel motility called paralytic ileus. On balance, today many patients administered D2 blockers are overmedicated with total anticholinergic burden. Alternatives to using these agents should often be sought, such as use of a different drug for psychosis that lacks anticholinergic properties, neurons in the nigrostriatal motor pathway make postsynaptic connections on cholinergic interneurons (Figure 5-7A). Dopamine acting at D2 receptors normally inhibits acetylcholine release from postsynaptic nigrostriatal cholinergic neurons (Figure 5-7A). When D2 blockers are given, dopamine can no longer suppress acetylcholine release, thus disinhibiting acetylcholine release from cholinergic neurons (see enhanced acetylcholine release in Figure 5-7B). This in turn leads to more excitation of postsynaptic muscarinic cholinergic receptors on medium spiny GABAergic neurons, which hypothetically leads in part to inhibition of movements and to the symptoms of DIP (akinesia, bradykinesia, rigidity, and tremor). However, when the enhanced downstream release of acetylcholine is blocked by anticholinergics at muscarinic cholinergic receptors, this hypothetically restores in part the normal balance between dopamine and acetylcholine in the striatum, and DIP is reduced (Figure 5-7C). Empirically, anticholinergics do work in clinical practice to reduce DIP, especially the DIP caused by some of the older D2 blockers that lack serotonergic actions. On Figure 5-7A 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 binding at D2 receptors suppresses acetylcholine activity (no acetylcholine being released from the cholinergic axon on the right). M1 receptor striatum cholinergic interneuron = acetylcholine (ACh) = dopamine (DA) D2 receptor nigrostriatal DA neuron DA inhibiting ACh release

ACh release inhibited A

Figure 5-7B Dopamine, acetylcholine, and D2 antagonism. Since dopamine normally suppresses acetylcholine activity, removal of dopamine inhibition causes an increase in acetylcholine activity. As shown here, if D2 receptors are blocked on the cholinergic dendrite on the left, then acetylcholine release from the cholinergic axon on the right is enhanced. This is associated with the production of druginduced parkinsonism. striatum = D2 antagonist/ partial agonist B D2 blocker reversing DA inhibition

enhanced ACh release Figure 5-7C D2 antagonism and anticholinergic agents. One compensation for the overactivity that occurs when D2 receptors are blocked is to block the muscarinic cholinergic receptors with an anticholinergic agent (M1 receptors being blocked by an anticholinergic on the far right). This hypothetically restores in part the normal balance between dopamine and acetylcholine and can reduce symptoms of drug-induced parkinsonism. striatum C = anticholinergic

blockade of enhanced ACh action at M1 receptors

Chapter 5: Targeting for Psychosis this condition and can even make this form of dystonia worse. Akathisia Akathisia is a syndrome of motor restlessness seen commonly after treatment with D2 blockers. Akathisia has both subjective and objective features. Subjectively, there is a sense of inner restlessness, mental unease, or dysphoria. Objectively, there are restless movements, most typical being lower-limb movements such as rocking from foot to foot, walking or marching in place when standing, or pacing. Sometimes drug-induced akathisia can be difficult to distinguish from the agitation and repetitive restless movements that are part of the underlying psychiatric disorder. Akathisia is not particularly effectively treated with anticholinergic medication, but instead is often more effectively treated with either β-adrenergic blockers or benzodiazepines. Serotonin 2A antagonists can also be helpful. Neuroleptic Malignant Syndrome A rare but potentially fatal complication can occur with D2 receptor blockade, possibly due in part to D2 receptor blockade specifically in the nigrostriatal motor pathway. This is called the “neuroleptic malignant syndrome,” associated with extreme muscular rigidity, high fevers, coma, and even death. Some consider neuroleptic malignant syndrome to be the most extreme form of DIP; others theorize that this is a toxic complication of D2 blocking drugs on cell membranes, including muscle. It constitutes a medical emergency that requires withdrawal of the D2 blocker, muscle-relaxing agents such or stopping anticholinergic medications, or use of amantadine, which lacks anticholinergic properties but can mitigate the symptoms of DIP. Amantadine’s mechanism of action is thought to be weak antagonism of NMDA (N-methyl-D-aspartate) glutamate receptors, possibly leading to downstream changes in the activity of dopamine in both the direct and indirect striatal motor pathways. No matter what its actual mechanism of action, amantadine can be useful for improving DIP and also has some evidence of being useful in TD and levodopa-induced dyskinesias caused by levodopa treatment of Parkinson’s disease. Drug-Induced Acute Dystonia Occasionally, exposure to D2 blockers, especially those with neither serotonergic nor anticholinergic properties, can cause a condition called dystonia, often upon first exposure to the D2 blocker. Dystonia is intermittent spasmodic or sustained involuntary contraction of the muscles in the face, neck, trunk, pelvis, extremities, or even the eyes. Drug-induced dystonias can be frightening and severe; fortunately, administration of an intramuscular injection of an anticholinergic is nearly always effective within 20 minutes. The cause and the treatment of this condition are other examples of the clinical significance of the balance between dopamine and acetylcholine in the motor striatum for the regulation of movements (Figures 5-7A, 5-7B, and 5-7C). Chronic treatment with D2 blockers can also cause late-onset dystonia as a manifestation of tardive dyskinesia, sometimes also called tardive dystonia. This requires TD treatment, as anticholinergics rarely work for Figure 5-8 Side effects of muscarinic cholinergic receptor blockade. Blockade of muscarinic cholinergic receptors can reduce druginduced parkinsonism, but can also induce side effects such as constipation, blurred vision, dry mouth, drowsiness, and cognitive dysfunction (problems with memory and concentration, slowed cognitive processing). dry mouth constipation blurred vision M1 Inserted LAXATIVE E Q PEE PP QQ drowsiness cognitive dysfunction M1 receptor cholinergic neuron ACh

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY as dantrolene and dopamine agonists, as well as intensive supportive medical treatment. Tardive Dyskinesia Pathophysiology Overall, about 5% of patients maintained on D2 antagonists that have little or no serotonin receptor action will develop TD every year (i.e., about 25% of patients by 5 years), not a very encouraging prospect for an illness starting in the early 20s and requiring lifelong treatment. The risk of developing TD in elderly subjects may be as high as 25% within the first year of exposure to D2 antagonists.

Estimates for the newer D2 drugs for psychosis that have serotonergic receptor action are more difficult to obtain since many patients taking them have taken the older drugs as well in the past. Nevertheless, for those likely to have taken only newer D2 antagonists/5HT2A antagonists or D2/5HT1A partial agonists, the rate of TD may be about half the rate of the older drugs. These newer agents may mitigate DIP as well by the mechanisms discussed in detail below. Those mechanisms are both 5HT2A antagonism and 5HT1A partial agonism. Perhaps these mechanisms by which they mitigate DIP serve also to mitigate the chances of getting TD. Who amongst all those who receive drugs for psychosis will get TD and how does this happen? Some evidence suggests that those who are most vulnerable to having DIP with acute D2 blockade may also be those who are the most vulnerable to getting TD with chronic D2 blockade. One theory is that nigrostriatal D2 receptors most sensitive to blockade trigger a form of undesirable neuroplasticity called supersensitivity in reaction to D2 receptor blockade (Figures 5-6). If D2 receptor blockade is removed early enough, TD may reverse. This reversal is theoretically due to a “resetting” of supersensitive D2 receptors by an appropriate return to normal in the number or sensitivity of D2 receptors in the nigrostriatal pathway once the antipsychotic drug that had been blocking these receptors is removed. However, after long-term treatment, sometimes the D2 receptors apparently cannot reset back to normal, even when D2 blocking drugs are discontinued. This leads to TD that is irreversible, persisting whether or not D2 blockers are administered. Interestingly, D2 receptors in the motor striatum also appear to react in much the same way to chronic stimulation by levodopa in Parkinson’s disease as they do to chronic blockade by D2 antagonists/partial agonists in schizophrenia. That is, chronic levodopa administration in Parkinson’s disease can lead to levodopa-induced dyskinesias that look very similar to TD, and may share a similar pathophysiology of aberrant striatal plasticity and abnormal neuronal “learning.” Perhaps the lesson here is not to mess with your dopamine receptors in the motor striatum or consequences may ensue! A more detailed view of D2 antagonist/partial agonist effects in the nigrostriatal dopamine system is shown in Figures 5-9A, 5-9B, and 5-9C. This view was introduced in Chapter 4 and illustrated in Figures 4-13B, 4-13C, 4-13D, 4-13E, and 4-13F. Some fibers of the nigrostriatal dopamine pathway, particularly those projecting medially to the associative striatum, may be hyperactive as part of the limbic (emotional) system and contribute to the positive symptoms of psychosis (see Figure 4-16B). Other nigrostriatal dopamine projections, particularly those projecting to the sensorimotor striatum, are part of the extrapyramidal nervous system and control motor movements and those are the nigrostriatal dopaminergic neurons depicted in Figures 5-9A, 5-9B, and 5-9C. Normally, dopamine acts at D2 receptors in the indirect motor pathway, which is the receptor subtype present in this pathway. The so-called indirect pathway is also the pathway for “stop” actions (Figures 4-13F and 5-9A). Since D2 receptors are inhibitory, dopamine causes inhibition of the stop pathway; a fancy way for dopamine to say “go” in this pathway (Figures 4-13B and 5-9A). Thus, dopamine at D2 receptors in the indirect pathway triggers a “go” signal. What happens when this action of dopamine is blocked? When acute D2 antagonists/partial agonists are administered, this blocks the ability of dopamine to say “go” because these drugs inhibit dopamine’s action in the “stop” pathway. Another way to say this is that D2 antagonists say “stop” in the indirect pathway (Figure 5-9B). If there is too much “stop,” this can result in DIP (Figure 5-9B). In technical terms, when “stop” is not inhibited by dopamine action at D2 receptors in the indirect pathway because of the presence of a D2 blocker, then movements are “stopped” – sometimes so much so that the slow, rigid movements of DIP are produced (Figure 5-9B). If this situation is allowed to persist, D2 receptors in the indirect pathway of the motor striatum

hypothetically react to the acute D2 receptor blockade shown in Figure 5-9B by “learning” to have TD when D2 blockade becomes chronic (Figure 5-9C). The theoretical mechanism for this is a proliferation of excess numbers

Chapter 5: Targeting for Psychosis Figure 5-9A D2 receptor inhibition of the stop pathway. Dopamine released from the nigrostriatal pathway binds to postsynaptic D2 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus externa. This causes inhibition of the indirect (stop) pathway, thus instead telling it to “go.” STN= subthalamic nucleus r c e i SN = substantia nigra reticulata SN = substantia nigra compacta GP =

globus pallidus externa GP = globus pallidus interna glu = glutamate GABA = γ-aminobutyric acid DA = dopamine D2 = dopamine 2 receptor Thalamus Cortex STN Striatum SNc DA GABA glu D2 G

-

g+ D2 Inhibition of Stop Pathway Inhibition of stop or “GO” normally GP /SNr e i GP dopamine inhibiting the “STOP” pathway makes you “GO” normally D2 D2 of D2 receptors in the indirect motor pathway (Figure 5-9C). Perhaps the dopamine system becomes engaged in a futile attempt to overcome drug-induced blockade by making more D2 receptors (Figure 5-9C). The result is supersensitivity of the indirect pathway to dopamine. It has been difficult to prove, but animal models and positron emission tomography (PET) scans in patients with schizophrenia do indeed suggest that chronic D2

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-9B D2 receptor blockade activates the stop pathway. Dopamine released from the nigrostriatal

pathway is blocked from binding to postsynaptic D2 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus externa. This prevents inhibition of the indirect (stop) pathway; in other words, D2 antagonists activate the indirect (stop) pathway. Too much stop can result in drug-induced parkinsonism. SNc Thalamus Cortex STN GABA glu D2 antagonist/ partial agonist G

GABA G

- D2 Blocker Activates “STOP” Pathway and Causes Drug-Induced Parkinsonism GP /SNr e i GP D2 antagonist blocks DA from inhibiting the “stop” pathway - makes you stop - i.e. DIP STOP: don’t go Striatum blockade in the motor striatum causes upregulated, supersensitive D2 receptors, and this happens to the greatest extent in patients with TD. Whatever is happening, it leads to the opposite situation (Figure 5-9C) to what was just described for acute blockade of D2 receptors (Figure 5-9B).

Chapter 5: Targeting for Psychosis

Figure 5-9C Chronic D2 receptor blockade and overinhibition of the stop pathway. Dopamine released from the nigrostriatal pathway is blocked from binding to postsynaptic D2 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus externa. Chronic blockade of these receptors can lead to their upregulation; the upregulated receptors may also be “supersensitive” to dopamine. Dopamine can now exert its

inhibitory effects in the indirect (stop) pathway, and in fact cause so much inhibition of the “stop” signal that the “go” signal is overactive, leading to the hyperkinetic involuntary movements of tardive dyskinesia. Thalamus Cortex STN Striatum SNc DA GABA glu D2 ST GABA

-

glu +

Chronic D2 Blockade Causes Upregulation of D2 Receptors, Enhanced Inhibition of “STOP” Pathway, and Tardive Dyskinesia Major Inhibition of stop or “GO” “GO” “GO” GP /SNr e i GP upregulated D2 receptors from chronic blockade cause major inhibition of the “stop” pathway and tardive dyskinesia D2 D2 antagonist/ partial agonist upregulated supersensitive D2 receptors D2 D2 inhibition of stop signals from acute D2 blockade (Figure 5-9B), there is now too much inhibition of stop signals from chronic D2 blockade (Figure 5-9C). The situation has flipped from slow rigid movements of DIP (Figure 5-9B) to rapid hyperkinetic involuntary movements of TD (Figure 5-9C).

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY What is the mechanism that causes the indirect pathway to flip from too much stop to too much go? The answer may be abnormal neuronal plasticity causing the proliferation of too many and too sensitive D2 receptors in the indirect pathway (Figure 5-9C). Now, all of a sudden, instead of not enough dopamine at D2 receptors (Figure 5-9B), there is too much dopamine at too many D2 receptors (Figure 5-9C). The motor striatum translates this into excessive inhibition of the “stop” signal; thus, “not enough stop” and “too much go.” Therefore, neuronal impulse traffic out of the striatum no longer has an enforced speed limit, and thus, the involuntary hyperkinetic movements of TD emerge. The emergence of abnormal involuntary movements of TD should be specifically monitored, using a neurological

examination and a rating scale such as the AIMS (Abnormal Involuntary Movement scale) periodically. Best practices are to monitor movements in anyone taking any of these drugs, although it is frequently not done, and especially not done in patients being treated for depression, unfortunately. If anything, patients with mood disorders may be at greater risk for TD. Remember, these are the same drugs no matter in whom they are used. Treatment If the brain has literally "learned" to have TD in an aberrant attempt to compensate for chronic D2 blockade and this has resulted in unwanted dopamine overstimulation in the indirect pathway, then TD would seem to be a disorder ideally set up to respond to interventions that lower dopamine neurotransmission. How can this be done? One way is to raise the dose of D2 antagonist to block those numerous new upregulated and supersensitive D2 receptors. Although this might work short-term in some patients, it is done at the expense of more immediate side effects and the prospects of making TD even worse down the road. Another treatment possibility is to stop the offending D2 antagonist with the hope that the motor system will readjust back to normal on its own and that the movement disorder will reverse. Many patients who do not have an underlying psychotic disorder may be able to tolerate the discontinuation of their D2 antagonist/ partial agonist, but most patients with psychosis may not be able to tolerate D2 antagonist/partial agonist discontinuation. Furthermore, it does not seem that the TD brain can "forget" its aberrant neuroplastic learning very well, and only some patients – particularly those who discontinue D2 blockade soon after the onset of their TD movements – will likely enjoy reversal of their TD. In fact, most patients experience an immediate worsening of their movements when D2 blockade is eliminated, due to the completely unblocked actions of dopamine in the absence of any D2 antagonist therapy at all. Thus, D2 antagonist drug discontinuation is often not an option in the treatment of TD. Recent developments show that TD can now be successfully treated by inhibiting the vesicular monoamine transporter type 2 (VMAT2). Presynaptic transporters for neurotransmitters released into the synapse were discussed in Chapter 2 (see Table 2-3 and Figures 2-2A and 2-2B). These transporters are localized on the presynaptic axon terminal and are well known as "reuptake pumps" targeted by many drugs for depression (Figures 2-2A and 2-2B; see also discussion of monoamine reuptake blockers in Chapter 6 on drugs for depression). Transporters also exist for neurotransmitters that are inside neurons; these intraneuronal transporters are located on synaptic vesicles and called vesicular transporters. Several types of vesicular transporters have been identified, including different ones for GABA (γ-aminobutyric acid), glutamate, glycine, acetylcholine, monoamines, and others (see Chapter 2 and Figures 2-2A and 2-2B). The specific transporter known as VMAT2 is located on synaptic vesicles inside dopamine, norepinephrine, serotonin, and histamine neurons. VMAT2 acts to store intraneuronal neurotransmitters until they are needed for release during neurotransmission (Figure 5-10A). VMAT2 can also transport certain drugs as "false" substrates, such as amphetamine and "Ecstasy" (MDMA; 3,4-methylenedioxymethamphetamine), and these false substrates can compete with the "true" natural neurotransmitter and block it from being transported. This is discussed in further detail in Chapter 11 on stimulant treatment for attention deficit hyperactivity disorder, and in Chapter 13 on substance abuse. Synaptic vesicles create low pH in their lumens (interiors) with an energy-requiring proton pump there (Chapter 2 and Figures 2-2A and 2-2B). Low pH in turn serves as the driving force to sequester neurotransmitter in synaptic vesicles. There are actually two types of VMATs: VMAT1 localized on synaptic vesicles of neurons in both the peripheral and central nervous system, and VMAT2, located only on synaptic vesicles within central nervous system neurons. There are also two known types of VMAT inhibitors: reserpine, which irreversibly inhibits

Storage of Dopamine by VMAT2 E E VMAT2 VMAT2 VMAT2 DA release Figure 5-10A Vesicular monoamine transporter 2 (VMAT2) and dopamine. The VMAT2 is an intraneuronal transporter located on synaptic vesicles. VMAT2 takes intraneuronal monoamines, including dopamine, up into the synaptic vesicles so that they can be stored until they are needed for release during neurotransmission. both VMAT1 and VMAT2; and tetrabenazine-related drugs, which reversibly inhibit only VMAT2. That is why reserpine, but not tetrabenazine-related drugs, is associated with frequent peripheral side effects, such as orthostatic hypotension (reserpine was once used for hypertension), stuffy nose, itching, and gastrointestinal side effects. Although VMAT2 transports multiple neurotransmitters into synaptic vesicles (dopamine, norepinephrine, serotonin, and histamine), tetrabenazine preferentially affects dopamine transport at clinical doses (Figure 5-10B). When tetrabenazinerelated drugs block the transport of dopamine into presynaptic vesicles, dopamine is rapidly degraded by monoamine oxidase (MAO) within the presynaptic neuron, leading to depletion of presynaptic dopamine proportional to the degree of VMAT2 inhibition (Figure 5-10B). Tetrabenazine itself is actually an inactive prodrug converted into four active dihydro metabolites by the enzyme carbonyl reductase, and all four are inactivated by CYP450 2D6 (Figure 5-11A). Most of the inhibition of VMAT2 by tetrabenazine is ultimately done by the Chapter 5: Targeting for Psychosis Dopamine Depletion by VMAT2 Inhibition E E VMAT2 VMAT2 VMAT2 VMAT2 inhibitor DA depletion Figure 5-10B Dopamine depletion by VMAT2 inhibition. Inhibition of VMAT2 prevents dopamine from being taken up into synaptic vesicles. The intraneuronal dopamine is therefore metabolized, leading to depletion of dopamine stores. +β-dihydro enantiomer because it has the greatest potency for VMAT2 of those metabolites that inhibit VMAT2 (Figure 5-11A). Tetrabenazine is not approved for the treatment of TD, but is approved for the treatment of a related hyperkinetic movement disorder, namely, the chorea of Huntington’s disease. Tetrabenazine’s disadvantages are its short half-life and thus need for three times a day dosing; its peak-dose side effects, including sedation and drug-induced parkinsonism; the need to do genetic testing for poor metabolizers of CYP450 2D6 in order to go to higher doses; and the risk of depression and even suicide when used to treat Huntington’s disease. A clever trick called deuteration has recently been discovered that converts a drug that is a good substrate for CYP450 2D6 into a poorer substrate for CYP450 2D6; this allows for a longer half-life, less frequent dosing, and lower peak plasma levels. Deuteration is the process of substituting some of the hydrogen atoms in a drug with deuterium, also called heavy hydrogen. Deuterium is a stable isotope of hydrogen with a nucleus consisting of one proton and one neutron, which is double the mass of the nucleus of ordinary hydrogen that contains only one proton. This substitution causes the drug to be a less favorable substrate for CYP450 2D6, 175

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY have substantial concentrations of the –α- and the –β-dihydro enantiomers, which carry additional receptor actions, especially antagonism of 5HT7 receptors and to a lesser extent antagonism of D2 receptors (Figures 5-11A and 5-11B). Another form of tetrabenazine is called valbenazine, named because the amino acid valine is linked to the +α enantiomer of tetrabenazine. When swallowed, valbenazine is hydrolyzed into valine and +α-tetrabenazine, which is rapidly converted by carbonyl reductase to just the +α dihydro enantiomer of tetrabenazine, the most selective and potent inhibitor of VMAT2 amongst the four active enantiomers (Figure 5-11C). The slow hydrolysis of valbenazine results in a long half-life and once-daily administration. Valbenazine is approved for the treatment of TD, has no need for genetic testing, no need for dosing with food, once-daily dosing, and no suicide warning. resulting in the predicted increased half-life, decreased dosing frequency (twice rather than three times a day),

and reduced peak-dose side effects, all problems with non-deuterated tetrabenazine mentioned above. For commercial considerations, deuteration can also restart the patent life of the non-deuterated drug, creating incentives for drug development. Other advantages of deuterated tetrabenazine, also called deutetrabenazine, are specific regulatory approval for the treatment of TD as well as Huntington's disease, no longer needing to do genetic testing in order to administer the full dose range, and the lack of a suicide warning for treatment of TD. Disadvantages include need for twice daily administration and dosing with food. The metabolites of deutetrabenazine (Figure 5-11B) are the same as those of nondeuterated tetrabenazine (Figure 5-11A). In addition to the +β-dihydro enantiomer, both tetrabenazine and deutetrabenazine Figure 5-11A Tetrabenazine potency. Tetrabenazine is an inactive prodrug; its metabolism by carbonyl reductase results in four active dihyro metabolites, all of which are converted into inactive metabolites by CYP450 2D6. Of the four active metabolites, the +β-dihydro enantiomer has the greatest potency for VMAT2 and thus is responsible for most of tetrabenazine's therapeutic effects. The other active metabolites have additional receptor actions, as shown. tetrabenazine - inactive prodrug carbonyl reductase inactive metabolites dihydro active metabolites c2D6 E tetrabenazine VMAT2 VMAT2 +α +ß D2 5HT7 VMAT2 -ß E D2 5HT7 VMAT2 -α

Chapter 5: Targeting for Psychosis Figure 5-11B Deutetrabenazine potency. Deuteration is the process of substituting some of the hydrogen atoms in a drug with deuterium. Deuterium has one proton and one neutron and is thus double the mass of hydrogen. The substitution of deuterium for hydrogen makes it a less favorable substrate for CYP450 2D6 (shown with the smaller c2D6 enzyme compared to Figure 5-11A). This allows for a longer half-life, decreased dosing frequency, and reduced peak-dose side effects. D2 5HT7 D2 5HT7 Deuterated tetrabenazine - inactive prodrug carbonyl reductase inactive metabolites c2D6 E E Deutetrabenazine VMAT2 VMAT2 VMAT2 VMAT2 Deu +α Deu -α Deu +ß Deu -ß dihydro deuterated active metabolites D D D D D D D D D D Figure 5-11C Valbenazine potency. Valbenazine is tetrabenazine with the amino acid valine linked to the +α enantiomer of tetrabenazine. When swallowed, valbenazine is hydrolyzed into valine and +α tetrabenazine and then rapidly converted by carbonyl reductase into +α-dihydrotetrabenazine. The slow hydrolysis results in a long half-life and once-daily dosing. inactive metabolites 2D6 carbonyl reductase hydrolysis E E valine tetrabenazine +α valine tetrabenazine +α +α dihydro tetrabenazine E VMAT2 A more detailed explanation of the mechanism of action of VMAT2 inhibition on TD is shown in Figures 5-12A through 5-12D within both the direct and indirect pathways. The state of normal movements condition is shown in Figure 5-12A, where dopamine at the bottom left is enhancing "go" in the direct pathway at

where dopamine is inhibiting “stop” in the indirect pathway at D2 receptors. The striatum regulates normal motor movements by facilitating or diminishing dopamine release at the direct and indirect pathways as it orchestrates the smooth execution of movements and postures that require muscles to go or to stop, often in sequence and in changing ways over time (Figure 5-12A). Figure 5-12B shows the situation when TD develops, with the upregulation of D2 receptors on the bottom right in

the indirect pathway causing far too much inhibition of stop, and thus the message “go, go, go,” with the result being the hyperkinetic involuntary movements of TD. This was also explained above and shown in Figure 5-9C. Figures 5-12C and 5-12D show the mechanism of action of VMAT2 inhibition in TD. No matter what form Normal Regulation of Motor Movements by Dopamine: Enhancing “Go” at D1 Receptors in the Direct Pathway and Inhibiting “Stop” at D2 Receptors in the Indirect Pathway

motor output glu + Cortex GABA

Thalamus glu + GABA GABA

-

STN GP /SNr i GABA direct pathway “go” indirect pathway “stop”

-

GP e

D1 D2 +

DA DA Striatum inhibiting “stop” enhancing “go” SNc of tetrabenazine is chosen to block VMAT2 in order to treat TD, it appears that a high degree, perhaps >90%, of VMAT2 inhibition may often be required for the best balance between efficacy for TD and tolerability. VMAT2 inhibition is a mechanism that reduces dopamine stimulation without blocking D2 receptors. Thus, this action reduces the overstimulation of D2 receptors in the indirect pathway (bottom right in Figure 5-12C), resulting in less inhibition of the stop signal there. However, there is also a benefit of VMAT2 inhibition in the direct pathway, where “go” signals are being amplified normally by dopamine at D1 receptors (Figure 5-12A). Even though these D1 receptors and this direct extrapyramidal pathway (Figure 5-12A) may not be the site of pathology in TD (see Figures 5-9C and 5-12B), they do drive “go” signals for movement normally (Figure 5-12A), and thus lowering dopamine there by Figure 5-12A Normal regulation of motor movements by dopamine. Dopamine regulates motor movements through both the direct (go) and indirect (stop) pathways. In the direct pathway (shown on the left), dopamine released into the striatum binds to D1 receptors on GABA neurons. This stimulates GABA release, which ultimately leads to glutamate release in the cortex and thus enhances motor output. In the indirect pathway (shown on the right), dopamine released into the striatum binds to D2 receptors on GABA neurons. This inhibits GABA release, thus inhibiting the “stop” pathway, and therefore also enhancing motor output.

Tardive Dyskinesia: Upregulated D2 Receptors in the Indirect Pathway and Too Much “GO”

motor output glu + Cortex Thalamus GABA GABA

•

STN GP /SNr i GP e D1 D2 +

DA DA Striatum SNc VMAT2 inhibition would be expected to lower the “go” signals arising from the direct pathway (Figure 5-12D). Combined with more “stop” signals from the indirect pathway (Figure 5-12C), motor output to drive abnormal involuntary hyperkinetic movements is therefore robustly reduced by this combination of effects of dopamine depletion in both pathways (Figures 5-12C and 5-12D). So, it appears that VMAT2 inhibition “trims” the “go” drives of dopamine in both direct and indirect motor pathways (Figures 5-12C and 5-12D) to compensate for the abnormal “learning” just in the indirect pathway after chronic D2 receptor blockade (Figures 5-9C and 5-12B). Whether this will be disease modifying in the long run, and reverse rather than only treat movements Chapter 5: Targeting for Psychosis Figure 5-12B Upregulation of dopamine 2 receptors in the indirect pathway. Chronic blockade of D2 receptors can lead to their upregulation; the upregulated receptors may also be supersensitive to dopamine. In the indirect (stop) pathway, this can lead to so much inhibition of the “stop” signal that the “go” signal is overactive, leading to the hyperkinetic involuntary movements of tardive dyskinesia. D2 too much inhibition of “stop” causing tardive dyskinesia symptomatically, must be determined by long-term studies of VMAT2 inhibition in TD. DRUGS TARGETING DOPAMINE D2 RECEPTORS: SOCALLED FIRST GENERATION OR CONVENTIONAL “ANTIPSYCHOTICS” A list of many of the earliest agents used to treat psychosis is given in Table 5-1. Several of these remain in clinical use today. Although not generally used first line, conventional D2 antagonists are still used in patients who do not respond to the newer drugs for psychosis and 179

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY VMAT2 Inhibition in the Indirect Pathway Causes Less D2 Inhibition of “Stop,” so TD Movements are Stopped motor output glu + Cortex GABA

Thalamus glu + GABA

STN GP /SNr i GABA

GP e D1 + DA Striatum SNc in patients requiring injections, both immediate-onset and long-acting injections. Several of the first-generation drugs for psychosis are available both orally and as injections and many clinicians still have experience with them, even preferring them in treatment-resistant and difficult cases. Although these original drugs for psychosis (Table 5-1) are often called “conventional,” “classic,” or “first-generation” antipsychotics, we will continue to refer to drugs as “having antipsychotic actions” and not as “antipsychotics,” to reduce confusion, since many of these same agents are used to treat many other conditions, including bipolar mania, psychotic mania, psychotic depression, Tourette syndrome, Figure 5-12C VMAT2 inhibition in the indirect (stop) pathway. VMAT2 inhibition reduces dopaminergic output; thus, it can reduce the overstimulation of inhibitory D2 receptors in the indirect (stop) pathway. This disinhibits the indirect (stop) pathway and therefore can reduce the hyperkinetic movements of tardive dyskinesia. VMAT2 inhibition in aberrant indirect pathway reduces “go” and even for gastrointestinal problems including gastroesophageal reflux, gastroparesis from diabetes, and to prevent/treat nausea and vomiting including from cancer chemotherapy. So, not just antipsychotic actions! Modern nomenclature for the drugs in this group of original agents for psychosis is “D2 antagonists” because this is the common pharmacological mechanism for all uses, not just for

antipsychotic actions. D2 antagonists have various other pharmacological properties, including muscarinic cholinergic antagonism (discussed above, see Figure 5-8), antihistaminic actions (H1 antagonism), and α1-adrenergic antagonism (Figure 5-13). These additional pharmacological

VMAT2 Inhibition in the Direct Pathway Causes Less D1 Stimulation of “GO,” so TD Movements are Stopped motor output glu + GABA

glu + GABA

GP /SNr i

VMAT inhibited D1 + DA Striatum VMAT2 inhibition in normal direct pathway also reduces “go” SNc properties are linked much more to side effects than to therapeutic effects. Blockade of muscarinic

cholinergic receptors is associated with dry mouth, blurred vision, and risk of paralytic ileus as discussed earlier (Figure 5-8); blocking H1 histamine receptors is associated with weight gain and sedation (Figure 5-13A); and blockade of α1-adrenergic receptors is associated with sedation as well as cardiovascular side effects such as orthostatic hypotension (Figure 5-13B). As many D2 antagonists have all three actions, anticholinergic, antihistaminic, and α1 antagonist, they can combine to contribute to a great deal of

sedation by simultaneously blocking several of the neurotransmitters in the arousal pathway; namely, acetylcholine, histamine, and norepinephrine (Figure 5-14). Agents with particularly strong binding at these three receptors (such as chlorpromazine) are sometimes administered when sedation is needed on top of antipsychotic action. However, even if sedation

Figure 5-12D VMAT2 inhibition in the direct (go) pathway. VMAT2 inhibition reduces dopaminergic

output; thus, it can reduce activation of excitatory D1 receptors in the direct (go) pathway. This inhibits the direct (go) pathway and therefore can reduce the hyperkinetic movements of tardive dyskinesia. Cortex Thalamus GABA

STN GABA

GP e is needed in some clinical situations, it is not always desirable. Conventional D2 antagonists (Table 5-1) differ in terms of their ability to block muscarinic, histaminic, and α1-adrenergic receptors. For example, the popular conventional antipsychotic haloperidol has relatively little anticholinergic or antihistaminic binding activity. Because of this, conventional D2 antagonists differ somewhat in their side-effect profiles, even if they do not differ overall in their therapeutic profiles. That is, some D2 blockers are more sedating than others; some have more ability to cause cardiovascular side effects than others, some have more ability to cause DIP and other movement disorders than others. Differing degrees of muscarinic cholinergic blockade may explain why some D2 antagonists have a lesser propensity to produce DIP than others. That is, those D2 antagonists that are more likely to cause DIP are generally the agents that have only weak anticholinergic properties, whereas those D2 181

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY H1 Inserted histamine neuron HA drowsiness weight gain H1 receptor A α 1 Inserted norepinephrine neuron NE dizziness α receptor B Cortical Arousal T HA BF ACh Hy NE Figure 5-13 Blockade of histamine 1 and α1-adrenergic receptors. The majority of D2 antagonists have additional pharmacological properties; the specific receptor profiles differ for each agent and contribute to divergent side-effect profiles. Many of the early D2 antagonists also block H1 receptors (A), which can contribute to weight gain and drowsiness, and/or α1-adrenergic

receptors (B), which can contribute to dizziness, drowsiness, and decreased blood pressure. decreased blood pressure drowsiness Figure 5-14 Neurotransmitters of cortical arousal. The neurotransmitters acetylcholine (ACh), histamine (HA), and norepinephrine (NE) are all involved in arousal pathways connecting neurotransmitter centers with the thalamus (T), hypothalamus (Hy), basal forebrain (BF), and cortex. Thus, pharmacological actions at their receptors could influence arousal. In particular, antagonism of muscarinic M1, histamine H1, and α1-adrenergic receptors are all associated with sedating effects. alpha1 receptors M1 receptors H1 receptors

Table 5-1 Earliest agents used to treat psychosis Generic name Trade name Comment Chlorpromazine Thorazine Low potency Cyamemazine Tercian Popular in France; not available in the US Flupenthixol Depixol Depot; not available in the US Fluphenazine Prolixin High potency; depot Haloperidol Haldol High potency; depot Loxapine Loxitane Mesoridazine Serentil Low potency; QTc issues; discontinued Perphenazine Trilafon High potency Pimozide Orap High potency; Tourette syndrome; QTc issues; second line Pipothiazine Piportil Depot; not available in the US Sulpiride Dolmatil Not available in the US Thioridazine Mellaril Low potency; QTc issues; second line Thiothixene Navane High potency Trifluoperazine Stelazine High potency Zuclopenthixol Clopixol Depot; not available in the US blockers that cause DIP less frequently are the agents that have stronger anticholinergic properties. These latter agents have a sort of “inbuilt” anticholinergic property that accompanies their D2 antagonist property. Although DIP may occur less frequently with such agents, the risk of constipation and potential for life-threatening paralytic ileus is higher, especially when combined with other drugs with anticholinergic properties, and requires more monitoring of gastrointestinal status and bowel movements. A few selected agents from the firstgeneration class of D2 antagonists are discussed in more detail below. Chapter 5: Targeting for Psychosis DRUGS TARGETING SEROTONIN 2A RECEPTORS WITH OR WITHOUT SIMULTANEOUSLY TARGETING DOPAMINE D2 RECEPTORS In an attempt to improve the efficacy and the tolerability of the first-generation classic drugs for psychosis with D2 antagonist properties, a newer class of drugs with antipsychotic action combines D2 antagonism with serotonin (5HT) 2A antagonism, so-called secondgeneration antipsychotics or atypical antipsychotics. We will refer to them as 5HT2A antagonists/D2 antagonists with antipsychotic properties, and not as “antipsychotics” or “atypical antipsychotics.” An even newer class of drugs with antipsychotic properties are agents with 5HT2A antagonism without any D2 antagonism. Some preclinical studies suggest that all known 5HT2A antagonists may actually be inverse agonists (see Chapter 2 and Figures 2-9 and 2-10) rather than antagonists at 5HT2A receptors (Figure 5-15). Since it is not clear what clinical distinction there is between an inverse agonist (Chapter 2 and Figures 2-9 and 2-10) and an antagonist (Figures 2-6 and 2-10) at 5HT2A receptors, we will continue to refer to these agents using the simpler term “antagonist.” Antagonism of serotonin 5HT2A receptors appears to improve both the efficacy and the side effects of D2 antagonism: Schizophrenia. Clinical trials show that adding selective 5HT2A antagonists to drugs with D2 antagonism/partial agonism may improve positive symptoms of psychosis in schizophrenia. Also, there is some indication that the more potent a 5HT2A/D2 antagonist is for 5HT2A receptors compared to potency for D2 receptors, the lower the degree of D2 antagonism that may be necessary to treat positive symptoms, and also the better tolerated the drug might be. More research is necessary on this possibility. Parkinson’s disease psychosis and dementiarelated psychosis. Antagonism of serotonin 5HT2A receptors alone appears to provide sufficient antipsychotic action to be useful as monotherapy for other causes of psychosis, such as Parkinson’s disease psychosis and dementia-related psychosis, allowing D2 antagonism and its side effects to be avoided entirely. 183

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-15 Agonist spectrum for drugs to treat psychosis. Drugs used to treat psychosis may fall along a spectrum, with some having actions closer to a silent antagonist and others having actions closer to a full agonist. For dopamine 2 (D2) binding, agents with too much agonism may be psychotomimetic and thus not ideal for treating psychosis, but may be useful within Parkinson's disease. D2 partial agonists that are closer to the antagonist end of the spectrum may be preferred for treating psychosis, as are D2 antagonists. Many drugs used to treat psychosis are serotonin 5HT2A antagonists, either in conjunction with D2 binding or without D2 binding. Some preclinical data suggest that they may actually be inverse agonists, but the clinical significance of this distinction is unclear. 5HT1A partial agonism is also a common property of many drugs used to treat psychosis, in particular many D2 partial agonists. full agonist D2 partial agonists for psychosis 5HT2A antagonist inverse agonist inverse agonist antagonist Where on the Agonist Spectrum Do Drugs for Psychosis Lie? neurotransmitters 5HT1A partial agonists D2 partial agonists for Parkinson's disease partial agonist D2 antagonist Negative symptoms of psychosis in schizophrenia. Clinical trials show that administering selective 5HT2A antagonists by themselves, or adding selective 5HT2A antagonists to drugs with D2 antagonism/partial agonism, may improve negative symptoms in schizophrenia. Motor side effects. Adding 5HT2A antagonist actions to D2 antagonism has also proven to lessen unwanted motor side effects such as drug-induced parkinsonism. Hyperprolactinemia. Adding 5HT2A antagonist actions to D2 antagonism lessens the elevation of prolactin caused by D2 receptor blockade. Why would adding 5HT2A antagonism improve side effects of D2 blockade and enhance the antipsychotic efficacy of D2 blockade? The short answer may be that 5HT2A antagonism opposes D2 antagonism in some pathways by causing more dopamine release in these sites and thus reversing some of the unwanted D2 antagonism that causes side effects. On the other hand, because of the differing configuration of other brain circuits, 5HT2A antagonism can enhance the efficacy of D2 antagonism in another circuit and thus improve positive symptoms. Let's now explain this. 5HT2A Receptor Regulation of Dopamine Release in Three Downstream Pathways The key to understanding why adding 5HT2A antagonism creates entirely new classes of drugs to treat psychosis with reduced side-effect burden is to grasp the pharmacology of 5HT2A receptors, where they are located, and what happens to dopamine when 5HT2A receptors are blocked. All 5HT2A receptors are postsynaptic and excitatory. The 5HT2A receptors critical to this discussion are the ones located on three separate populations of cortical glutamatergic pyramidal neurons that are all naturally stimulated by serotonin at their 5HT2A receptors to release glutamate downstream. These three separate populations of descending glutamate neurons regulate three distinct dopamine pathways (Figure 5-16). One population of glutamatergic pyramidal neurons directly innervates mesolimbic/mesostriatal dopamine neurons projecting to the emotional striatum that mediates the positive symptoms of psychosis (Figure 5-16A). This very same pathway was discussed extensively in Chapter 4 and illustrated in Figures 4-29A–C through 4-45. The glutamate neuron depicted in Figure 5-16A is that same glutamate neuron in the final common pathway of positive symptoms of psychosis (Figures 4-29B, 4-52C, 4-52D, 4-54, and 4-55). Specifically, this neuron is the hypothetical final common pathway downstream from all causes of positive symptoms of psychosis, whether in schizophrenia from hypofunctioning glutamate receptors on GABA interneurons (Figure 4-29B), in dementia-related psychosis from loss of these same GABA interneurons (Figure 4-52D and Figure 4-55), in Parkinson's disease

Chapter 5: Targeting for Psychosis PFC PFC PFC SN /VTA m emotional striatum 5HT2A 5HT2A 5HT Glu Glu DA low DA low DA GABA GABA Glu hallucinations A B C lu VTA 5HT Glu SNl motor striatum

5HT2A 5HT u ABA emotional blunting, flattening of affect emotional blunting, flattening of affect lack of mental sharpness DIP Figure 5-16 5HT2A receptor regulation of downstream dopamine (DA) release. 5HT2A receptors, which are postsynaptic and excitatory, are relevant to the treatment of psychosis because of their presence on three separate populations of descending glutamate neurons. (A) 5HT2A receptors are located on descending glutamatergic pyramidal neurons that directly innervate mesolimbic/mesostriatal dopamine neurons projecting to the emotional striatum. Excessive activity in this pathway can lead to the positive symptoms of psychosis. (B) 5HT2A receptors are located on descending glutamatergic pyramidal neurons that indirectly innervate nigrostriatal dopamine neurons via a GABAergic interneuron in the substantia nigra. Excessive stimulation of these 5HT2A receptors leads to a reduction in dopamine release in the motor striatum and can cause side effects such as drug-induced parkinsonism. (C) 5HT2A receptors are located on descending glutamatergic pyramidal neurons that indirectly innervate mesocortical dopamine neurons via a GABAergic interneuron in the ventral tegmental area. Excessive stimulation of these 5HT2A receptors leads to a reduction in dopamine release in the prefrontal cortex (PFC), which could lead to cognitive dysfunction as well as negative symptoms such as emotional blunting and flattened affect. SNm, medial substantia nigra; VTA, ventral tegmental area; SNl, lateral substantia nigra.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-17 5HT2A receptor antagonism and downstream dopamine release. 5HT2A antagonism can modulate downstream dopamine release via three key pathways. (A) 5HT2A antagonism reduces glutamatergic output from a descending neuron that directly innervates mesolimbic/mesostriatal dopamine neurons. This in turn reduces dopamine output in the emotional striatum and can therefore decrease the positive symptoms of psychosis. (B) 5HT2A antagonism reduces glutamatergic output in the substantia nigra, leading to reduced activity of the GABA interneuron and therefore disinhibition of the nigrostriatal dopamine pathway. The increased dopamine release in the motor striatum can reduce motor side effects caused by D2 antagonism because there is more dopamine to compete with the D2 antagonist. (C) 5HT2A antagonism reduces glutamatergic output in the ventral tegmental area, leading to reduced activity of the GABA interneuron and therefore disinhibition of the mesocortical dopamine pathway. Increased dopamine release in the prefrontal cortex (PFC) can potentially reduce cognitive and negative symptoms of psychosis. SNm, medial substantia nigra; VTA, ventral tegmental area; SNl, lateral substantia nigra. reduction in DIP PFC PFC PFC SN /VTA m emotional striatum 5HT2A 5HT2A 5HT2A antagonist decreased positive symptoms VTA SNl motor striatum 5HT2A emotional blunting, flattening of affect emotional blunting, flattening of affect lack of mental sharpness 5HT2A antagonist 5HT2A antagonist 5HT2A antagonist A B C psychosis from excessive actions of serotonin (Figure 4-52C and Figure 4-54), or in hallucinogen psychosis from excessive stimulation of serotonin receptors (Figure 4-52B and Figure 4-53). In all cases, anything that increases the activity of this population of glutamate neurons will hypothetically lead to downstream release of dopamine from mesolimbic/mesostriatal dopamine neurons to cause the positive symptoms of psychosis (Figure 5-16A). The most common treatment of course is to block excessive dopamine release at the end of this circuit, namely at D2 receptors in the emotional striatum. However, one can also reduce the excitatory tone of serotonin at 5HT2A receptors at the beginning of

this circuit (Figure 5-17A, top left) by blocking them here with a 5HT2A antagonist, using either an agent having both D2 and 5HT2A antagonist properties or an agent selective for just 5HT2A antagonist properties (Figure 5-1). When this happens at the specific glutamate neurons shown in

Figure 5-16A, this theoretically reduces release of dopamine in the emotional striatum (Figure 5-17A, right) and this in turn causes a mechanistically independent antipsychotic action, different from direct D2 receptor blocking. In the case of schizophrenia being treated with agents that have combined 5HT2A/D2 antagonism, any simultaneous D2 antagonism would theoretically become even more effective in treating positive symptoms of psychosis. Clinical trials are in progress adding a selective 5HT2A antagonist to the other agents with antipsychotic properties to determine if ramping up 5HT2A antagonism will consistently improve positive symptoms of psychosis or if it will allow reduction of dose, to lower D2 antagonism, in order to improve side effects without losing therapeutic effects. There are indeed suggestions that drugs with very potent 5HT2A antagonism might require less D2 antagonism to treat positive symptoms of psychosis (see discussion of lumateperone, clozapine, quetiapine, and others below). In the case of psychosis in dementia or in Parkinson's disease, where D2 antagonism can cause problematic side effects or even be dangerous, 5HT2A antagonist action alone can produce a sufficiently robust antipsychotic effect even in the absence of any D2 antagonism. A second population of glutamatergic pyramidal neurons indirectly innervate those nigrostriatal dopamine neurons that project to the motor striatum and mediate the motor side effects of D2 antagonism (Figure 5-16B). This is a parallel pathway to the pathway just discussed in Figure 5-16A, and involves a different population of glutamate neurons that not only project to the substantia nigra rather than to the ventral tegmental area (VTA)/ mesostriatum/integrative hub, but do so indirectly, namely, first to a GABA interneuron in the substantia nigra and then to the nigrostriatal dopamine motor pathway (compare Figure 5-16A and B). This has the effect of changing the polarity of upstream glutamate release from stimulating dopamine release (Figure 5-16A) to inhibiting dopamine release downstream (Figure 5-16B). Therefore, blocking 5HT2A receptors on the specific glutamate neurons shown in Figure 5-16B (upper left) leads to disinhibiting (i.e., increasing) dopamine release downstream in the motor striatum Chapter 5: Targeting for Psychosis (Figure 5-17B, right). That is precisely what is needed to reduce motor side effects! Namely, more dopamine is available to compete with a D2 antagonist in the motor striatum that otherwise would cause motor side effects. And that is exactly what is observed with 5HT2A antagonist/D2 antagonist drugs: i.e., fewer motor side effects compared to D2 antagonists without 5HT2A antagonism. This has indeed been repeatedly observed for 5HT2A/D2 antagonists, and has reduced the need for anticholinergic medication administration to treat motor side effects compared to D2 antagonists without 5HT2A antagonist actions (see Figure 5-1 and compare icons on the top with the bottom left). A third population of glutamatergic pyramidal neurons indirectly innervate those mesocortical dopamine neurons that project to the prefrontal cortex and mediate in part the negative, cognitive, and affective symptoms of schizophrenia (Figure 5-16C). This is yet another parallel pathway to the pathways just discussed, and involves yet different glutamate neurons that project indirectly via a GABA interneuron to those dopamine neurons in the VTA destined to innervate the prefrontal cortex. As discussed above for the nigrostriatal pathway (Figure 5-16B), this arrangement in Figure 5-16B also has the effect of upstream glutamate release leading to inhibiting dopamine release downstream (see Figure 5-16C). Thus, blocking 5HT2A receptors on these specific glutamate neurons (Figure 5-17C, top left) will lead to disinhibiting (i.e., increasing) dopamine release in the prefrontal cortex (Figure 5-17C, top right). This is just what you need to improve negative symptoms of schizophrenia, and that is what has been observed in trials of 5HT2A selective agents, either alone or augmenting other D2 antagonist and 5HT2A/D2 antagonist drugs. Increasing dopamine release in the prefrontal cortex also has the potential of improving cognitive and affective/depressive symptoms (Figure 5-17C). This effect is not consistent or robust across all

5HT2A/D2 antagonist drugs that treat psychosis, in part because of different potencies of 5HT2A antagonism compared to D2 antagonism, and because of the presence of additional interfering pharmacological properties in some agents, such as anticholinergic and antihistaminic actions. A better approach may ultimately prove to be adding a selective 5HT2A antagonist to drugs with D2 antagonist action. How Do 5HT2A Antagonist Actions Reduce Hyperprolactinemia? The pituitary lactotroph is responsible for secretion of prolactin and both D2 receptors and 5HT2A receptors 187

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY are located on the membranes of these cells. Serotonin and dopamine have reciprocal roles in the regulation of prolactin secretion, with dopamine inhibiting prolactin release via stimulation of D2 receptors (Figure 5-18A) and serotonin promoting prolactin release via stimulation of 5HT2A receptors (Figure 5-18B). Thus, when D2 receptors alone are blocked by D2 antagonism, dopamine can no longer inhibit prolactin release, so prolactin levels rise (Figure 5-18C). However, in the case of a drug that has 5HT2A receptor pituitary lactotroph prolactin D2 receptor dopamine serotonin A serotonin 5HT2A receptor pituitary lactotroph prolactin B both D2 antagonism and 5HT2A antagonism, there is simultaneous inhibition of 5HT2A receptors, so serotonin can no longer stimulate prolactin release (Figure 5-18D). This mitigates the hyperprolactinemia of D2 receptor blockade. Although this is interesting theoretical pharmacology, in practice, not all 5HT2A/D2 antagonists reduce prolactin secretion to the same extent, and others do not reduce prolactin elevations at all, possibly due to other off-target receptor properties. Figure 5-18A, B Dopamine and serotonin regulate prolactin release, part 1. (A) Dopamine binding at inhibitory D2 receptors (red circle) prevents prolactin release from pituitary lactotroph cells in the pituitary gland. (B) Serotonin (5HT) binding at excitatory 5HT2A receptors (red circle) stimulates prolactin release from pituitary lactotroph cells in the pituitary gland. Thus, dopamine and serotonin have a reciprocal regulatory action on prolactin release.

pituitary lactotroph p D2 antagonist C pituitary lactotroph 5HT2A/D2 antagonist D DRUGS TARGETING SEROTONIN 1A RECEPTORS AND DOPAMINE D2 RECEPTORS AS PARTIAL AGONISTS Another attempt to improve first-generation drugs for psychosis with D2 antagonist properties substitutes D2 partial agonism for D2 antagonism, and adds serotonin 5HT1A partial agonism. Chapter 5: Targeting for Psychosis Figure 5-18C, D Dopamine and serotonin regulate prolactin release, part 2. (C) D2 antagonism (red circle) blocks dopamine's inhibitory effect on prolactin secretion from pituitary lactotrophs. Thus, these drugs increase prolactin levels. (D) As dopamine and serotonin have reciprocal regulatory roles in the control of prolactin secretion, one cancels the other. Thus, 5HT2A antagonism reverses the ability of D2 antagonism to increase prolactin secretion. D2 Partial Agonism Some antipsychotics act to stabilize dopamine neurotransmission at D2 receptors in a state between complete silent antagonism (see Chapter 2, Figures 2-6 and 2-10) and full stimulation/agonist action (Chapter 2, Figures 2-5 and 2-10). This intermediate position is illustrated here in Figures 5-19 through 5-22 and is called partial agonism. This was also discussed and illustrated in Chapter 2 (see Figures 2-7 and 2-10). 189

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-19 Spectrum of dopamine neurotransmission. Simplified explanation of actions on dopamine. (A) Full D2 antagonists 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 drug-induced parkinsonism (DIP) and prolactin elevation. (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 without DIP or prolactin elevation. full D2 antagonist: deficiency of agonist A B C too cold DIP DIP antipsychotic prolactin prolactin antipsychotic dopamine stimulant excess of full agonist too hot dopamine partial agonist dopamine stabilizer: balance between agonist and antagonist actions just right psychosis

An oversimplified explanation of partial agonist action at the D2 receptor is illustrated in Figure 5-19. Namely, D2 antagonist action is “too cold,” with antipsychotic actions but elevated prolactin and motor symptoms such as DIP (Figure 5-19A). On the other hand, maximally stimulating full agonist actions of dopamine itself (or amphetamine, which releases dopamine) are “too hot” with positive symptoms of psychosis (Figure 5-19B). Instead, a partial agonist binds in an intermediary manner, hopefully “just right,” with antipsychotic actions but lower DIP and lesser prolactin elevations (Figure 5-19C). For this reason, partial agonists are sometimes called “Goldilocks” drugs if they get the balance “just right” between full agonism and complete antagonism. However, as we shall see, this explanation is an oversimplification; the balance is slightly different for receptor output D2R DA D2 antagonist D2 partial agonist Chapter 5: Targeting for Psychosis each drug in the D2 partial agonist class and there is no perfect “Goldilocks” solution. A more sophisticated explanation is that partial agonists have the intrinsic ability to bind to receptors in a manner that causes signal transduction from the receptor to be intermediate between full output and no output (Figure 5-20). The naturally occurring neurotransmitter generally functions as a full agonist, and causes maximum signal transduction from the receptor it occupies (volume blaring in Figure 5-20, 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 (volume essentially turned off in Figure 5-20, middle). By contrast, partial agonists (Figure 5-20, bottom) cause receptor output that is more than Figure 5-20 Dopamine receptor output. Dopamine (DA) itself is a full agonist and causes full receptor output (top). D2 antagonists allow little if any receptor output (middle). However, D2 partial agonists can partially activate dopamine receptor output and cause a stabilizing balance between stimulation and blockade of dopamine receptors (bottom).

 very close to the agonist end of the spectrum (Figure 5-15). They are almost full agonists. Using these agents at the full agonist end of the spectrum for the treatment of psychosis would make the psychosis worse, just as using agents at the other end of the spectrum near to antagonist for the treatment of Parkinson’s disease would make their motor movements worse. Thus, it is important not to lump all partial agonists together and to understand where on the spectrum a given agent lies in order to understand its pharmacological mechanism of action because very small changes in the amount of partial agonism and placement on this spectrum (Figure 5-15) can have profound clinical effects. How Does D2 Partial Agonism Cause Fewer Motor Side Effects than D2 Antagonism? It seems that it takes only a very small amount of signal transduction through D2 receptors in the striatum in the silent antagonist (Figure 5-20, middle), but less than the full agonist (Figure 5-20, top). Thus, many degrees of partial agonism are possible between these two extremes. Full agonists, silent antagonists, and partial agonists may all cause different changes in receptor conformation that lead to a corresponding range of signal transduction output from the receptor (Figure 5-21). Where on the agonist spectrum

do D2 partial agonists for psychosis lie? This is illustrated in Figure 5-15, showing that the D2 partial agonists under discussion here for the treatment of psychosis are very close to the antagonist end of the spectrum, where all the D2 antagonists discussed so far lie (Figure 5-15). That is because these D2 partial agonists for the treatment of psychosis are “almost” antagonists with just a whiff of intrinsic agonist activity. By contrast, other dopamine partial agonists useful for the treatment of Parkinson’s disease and classified as dopamine partial agonists lie Figure 5-21 Agonist spectrum and receptor conformation. This figure shows an artist’s depiction of changes in receptor conformation in response to full agonists versus antagonists versus partial agonists. With full agonists, the receptor conformation is such that there is robust signal transduction through the G-protein-linked second-messenger system of D2 receptors (left). Antagonists, on the other hand, bind to the D2 receptor in a manner that produces a receptor conformation that is not capable of any signal transduction (middle). Partial agonists, such as a dopamine partial agonist, cause a receptor conformation such that there is an intermediate amount of signal transduction (right). However, the partial agonist does not induce as much signal transduction (right) as a full agonist (left). full agonist antagonist D2 partial agonist

order for a D2 partial agonist to have reduced propensity to cause motor side effects, especially drug-induced parkinsonism. Thus, a very slight degree of agonism, sometimes called “intrinsic activity,” can have a very different set of clinical consequences compared to a fully silent and completely blocked D2 receptor, which is what D2 antagonists and 5HT2A/D2 antagonists do. D2 partial agonists capable of treating psychosis lie very close to antagonists on the agonist spectrum (Figure 5-15), as more dopamine antagonism than agonist action is what is needed for the treatment of psychosis. What is so interesting is how very small movements up and down the partial agonist spectrum (Figure 5-15) can have profound effects upon the clinical properties. Just slightly too close to a pure agonist and such agents may have reduced motor side effects and prolactin elevations and be sufficiently activating to improve negative symptoms but be too activating so that there is lessened efficacy for positive symptoms, or even worsening of positive symptoms, as well as nausea and vomiting. Fairly extensive testing has been made of several D2 partial agonists in schizophrenia and three of these are approved. OPC4392 (structurally and pharmacologically related to both aripiprazole and brexpiprazole, which were tested later) turned out to be too much of an agonist; it had relatively little intrinsic activity and improved negative symptoms of schizophrenia, with little in the way of motor side effects, but its intrinsic activity was nevertheless too great because this drug also activated and worsened positive symptoms of schizophrenia, so it was never marketed. Another D2 partial agonist, bifeprunox, is less of an agonist than OPC4392 but turned out to be still too much of an agonist since it caused nausea and vomiting; although it did have some efficacy for positive symptoms and did not cause motor side effects, it was less robust in improving positive symptoms than other agents and also had more gastrointestinal side effects, so the US Food and Drug Administration (FDA) did not approve it. Next, investigators threw another dart closer to the antagonist end of the spectrum and it landed as aripiprazole (the original “pip” – see below). This agent indeed improves positive symptoms without severe motor side effects, but does cause some akathisia and some clinicians question if it is as efficacious as D2 antagonists for the most severely psychotic patients, although this has never been proven. Finally, two more D2 partial agonists have been approved: a second “pip” called brexpiprazole and a “rip” called cariprazine. Both are similar on the D2 partial agonist Chapter 5: Targeting for Psychosis spectrum to aripiprazole, have antipsychotic efficacy and low motor side effects but some akathisia, and differ mostly in secondary binding properties of

receptors other than the D2 receptor, as will be discussed in detail in the section on individual drugs below. How Does D2 Partial Agonist Action Reduce Hyperprolactinemia? The pituitary lactotrophs' D2 receptors have proven to be more sensitive to the intrinsic activity of D2 partial agonists than the other dopamine pathways and targets. Specifically, the three partial agonists in clinical use all actually reduce prolactin levels, rather than raise them. It is hypothesized that this is due to the D2 receptors on the lactotrophs detecting these drugs more as agonists than as antagonists, and thus these drugs shut down prolactin secretion rather than stimulate it. In fact, co-administration of one of the D2 partial agonists to a patient who is experiencing hyperprolactinemia while taking one of the D2 antagonists can actually reverse that hyperprolactinemia. 5HT1A Partial Agonism Why would adding 5HT1A partial agonism to D2 partial agonism improve the side effects and enhance efficacy for affective and negative symptoms compared to D2 blockade? There is a simple answer, easy to understand if you have grasped the reason why 5HT2A antagonism does much the same thing. That is, 5HT1A partial agonism, especially if closer to full agonism than to antagonism on the partial agonist spectrum (Figure 5-15), has similar effects to those of 5HT2A antagonism. Just like 5HT2A antagonism shown in Figure 5-17, 5HT1A partial agonism/full agonism also opposes D2 antagonism in side-effect pathways by causing more dopamine release in these sites, reversing some of the unwanted effects of D2 antagonism/partial agonism and improving negative and affective symptoms (Figure 5-22). How does this happen? 5HT1A receptors are always inhibitory and they can be both presynaptic on serotonin neurons and postsynaptic on many neurons, including the same glutamatergic pyramidal neurons that have 5HT2A receptors (compare the glutamate neurons upper left in both Figure 5-16A and 5-22A). One can think of the situation as the pyramidal neuron having both an accelerator (5HT2A receptors) and a brake (5HT1A receptors). Taking your foot off the accelerator (5HT2A antagonism) should have a similar effect as stepping on the brake (5HT1A partial agonism), especially if they are done at the same time. Thus, 5HT1A partial agonism 193

 partial agonism could potentially reduce motor side effects and improve mood, affective, negative, and cognitive symptoms by enhancing downstream release of dopamine. 5HT1A partial agonist has actions at glutamatergic neurons indirectly innervating nigrostriatal dopamine neurons projecting to the motor striatum (Figure 5-22A). Recall that blocking 5HT2A receptors on these same glutamate neurons disinhibits dopamine release to reduce motor side effects (Figure 5-17B). That is exactly what happens with 5HT1A partial agonism at these same neurons, namely disinhibition of dopamine release and improvement in motor side effects (Figure 5-22A). As explained above, more dopamine release competes with D2 blocking agents for the receptors in the motor striatum has many of the same effects on dopamine release as 5HT2A antagonism. As will be discussed later, some drugs used to treat psychosis and mood have both 5HT2A antagonist and 5HT1A partial agonist properties, which should theoretically enhance the actions on downstream dopamine even further compared to either of these mechanisms alone. So, just as explained above for 5HT2A antagonism, 5HT1A partial agonism opposes D2 antagonism/partial agonism in some pathways by causing more dopamine release in these sites and thus reversing some of the unwanted D2 antagonism/partial agonism that causes motor side effects. There is less evidence that 5HT1A partial agonism can enhance the efficacy of D2 antagonism/partial agonism to improve positive symptoms of psychosis. Let's now explain how 5HT1A Figure 5-22 5HT1A receptor partial agonism and downstream dopamine release. 5HT1A receptors are inhibitory and can be located both presynaptically on serotonin neurons and postsynaptically on other neurons. (A) 5HT1A receptors are located on descending glutamatergic

pyramidal neurons that indirectly innervate nigrostriatal dopamine neurons via a GABAergic interneuron in the substantia nigra (SN). Partial agonism of these 5HT1A receptors reduces glutamatergic output in the substantia nigra, leading to reduced activity of the GABA interneuron and therefore disinhibition of the nigrostriatal dopamine pathway. The increased dopamine release in the motor striatum can reduce motor side effects caused by D2 antagonism/partial agonism because there is more dopamine to compete with the D2 binding agents. (B) 5HT1A receptors are located on descending glutamatergic pyramidal neurons that indirectly innervate mesocortical dopamine neurons via a GABAergic interneuron in the ventral tegmental area (VTA). 5HT1A partial agonism reduces glutamatergic output in the VTA, leading to reduced activity of the GABA interneuron and therefore disinhibition of the mesocortical dopamine pathway. Increased dopamine release in the prefrontal cortex (PFC) can potentially reduce cognitive, negative, and affective symptoms of psychosis. PFC PFC A B (SIGH) VTA SN motor striatum 5HT1A improved negative, cognitive, and affective symptoms reduction in DIP 5HT1A agonist 5HT1A agonist

to reverse motor side effects. Since D2 partial agonists are also 5HT1A partial agonists, these two properties can combine to reduce many motor side effects, although akathisia can still commonly occur. 5HT1A partial agonist also has actions at glutamatergic neurons indirectly innervating mesocortical dopamine neurons projecting to the prefrontal cortex (Figure 5-22B). Recall that blocking 5HT2A receptors on these specific glutamate neurons disinhibits dopamine release in the prefrontal cortex (Figure 5-17C). This is just what you need to improve negative, cognitive, and affective/ depressive symptoms. That is also what happens with 5HT1A partial agonism at these same neurons (Figure 5-22B). These clinical actions may be particularly robust in bipolar and unipolar depression where these serotonin/ dopamine partial agonists are frequently used. LINKS BETWEEN RECEPTOR BINDING PROPERTIES OF DRUGS USED TO TREAT PSYCHOSIS AND OTHER THERAPEUTIC ACTIONS AND SIDE EFFECTS So far in this chapter we have discussed the antipsychotic mechanisms and side effects of drugs for psychosis that are hypothetically linked to interactions at dopamine D2, serotonin 5HT2A, and serotonin 5HT1A receptors. The reality is that these same drugs bind to many other neurotransmitter receptors, and are used for many other therapeutic applications. In fact, many more prescriptions for D2 blockers are written for indications other than psychosis than are written for psychosis, a key reason why they are not called “antipsychotics” here and in international nomenclature. These additional receptor actions are likely relevant to other therapeutic actions and side effects (Figures 5-23 through 5-26). The entire known panoply of receptors that are bound by drugs in this class are discussed in the sections below. Mania Essentially all drugs with D2 antagonist/partial agonist properties are effective in the treatment of acute bipolar mania and in preventing recurrences of mania. Some agents are better studied than others, and the therapeutic effects in acute bipolar mania are present whether the mania is psychotic or nonpsychotic. There is an old saying about drugs that treat psychosis in schizophrenia: “you Chapter 5: Targeting for Psychosis get mania treatment for free.” That is, essentially any drug that can treat the positive symptoms of psychosis can probably also treat the symptoms of mania. That could be because mania is thought to be due to excessive dopamine release from mesolimbic/mesostriatal neurons, just as for the positive symptoms of schizophrenia (Figures 4-15 and 4-16). Thus, it is not surprising that agents that reduce dopamine overactivity in this pathway are effective when the patient is in a manic state as well as in a psychotic state. Further discussion of mania will follow in Chapter 6 and of treatments for mania in Chapter 7. Antidepressant Actions in Bipolar and Unipolar Depression The most common use for 5HT2A/D2 antagonists and D2/5HT1A partial agonists is not the treatment of psychosis in

schizophrenia or mania in bipolar disorder. Rather, the treatment of unipolar major depressive disorder and bipolar depression is where these agents are most commonly prescribed and at lower doses, especially the newer agents with fewer side effects but higher costs. Almost all drugs treating psychosis have to be dosed so that 80% or so of D2 receptors are blocked in the emotional striatum, whereas the doses of these same drugs for depression are lower and likely insufficient to robustly block D2 receptors. So, how do they work in depression? 5HT2A antagonism and 5HT1A partial agonism, and the resultant increase in dopamine release in the prefrontal cortex, are thought to be potentially key antidepressant mechanisms. Looking over the vast panoply of receptor actions of the individual drugs in this class (see discussion below and Figures 5-27 through 5-62), one can readily see many additional potential antidepressant mechanisms. These will be discussed and illustrated in detail in Chapters 6 and 7 on mood disorders and their treatments; here we will just mention several of those key mechanisms. Binding properties accompanying D2 blockade that are candidates for explaining antidepressant actions are shown for all the individual D2 blockers in the many figures in the sections that follow in this chapter and include: monoamine reuptake blocking properties α2 antagonism D3 partial agonism 5HT2C antagonism 5HT3 antagonism 5HT7 antagonism others including possibly 5HT1B/D antagonism No two agents in this group have exactly the same binding characteristics and maybe that explains in part 195

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Where on the Metabolic Highway Should Psychopharmacologists Monitor Antipsychotics? premature death and loss of 20-30 years of normal life span metabolic highway

> “ 25 diabetes monitor antipsychotic action beta cell failure insulin muscle adipose liver pancreas insulin resistance hyperinsulinemia monitor antipsychotic action obesity and increased BMI H O O C H C O O C H C O O C H C H triglycerides monitor antipsychotic action increased appetite BEWARE: cardiometabolic risk ahead weight gain why some patients can have an antidepressant response to one agent in this group and not another. Please see the discussion of individual drugs below for which of these actions are part of the mechanisms of those specific drugs. Anxiolytic Actions A somewhat controversial use of drugs normally used to treat psychosis is for the treatment of various Figure 5-23 Monitoring on the metabolic highway. Monitoring for cardiometabolic side effects is necessary for any patient taking a medication to treat psychosis, although risk can vary by individual agent. First, increased appetite and weight gain can lead to elevated body mass index (BMI) and ultimately obesity. Thus, weight and BMI should be monitored here. Second, some agents can cause insulin resistance by an unknown mechanism; this can be detected by measuring fasting plasma triglyceride levels. Finally, hyperinsulinemia may advance to pancreatic β-cell failure, prediabetes, and then diabetes. Diabetes increases the risk for cardiovascular events and premature death. RIP cardiovascular events sugar prediabetes anxiety disorders. Some studies suggest efficacy of these agents as monotherapy for generalized anxiety disorder and to augment other agents for other anxiety disorders. Another controversial use of these agents is for posttraumatic stress disorder (PTSD). It is possible that the antihistamine and

> anticholinergic sedative properties of some of these agents are calming in some patients and responsible for anxiolytic/anti-PTSD action in them. If so, why are these uses controversial? There are both

Chapter 5: Targeting for Psychosis positive and negative studies of efficacy for anxiety and PTSD indications; also, given the side effects of many agents used to treat psychosis, the risk:benefit ratio is not necessarily favorable compared to alternative treatments for anxiety and PTSD. A promising exception may be a positive study of one of these agents (brexpiprazole) in combination with a selective serotonin reuptake inhibitor (SSRI), specifically sertraline. This is also mentioned in Chapter 8 on anxiety and traumatic disorders. Agitation in Dementia Treating a problematic condition known as agitation in patients with dementia is another controversial use of drugs for psychosis because there is no clear efficacy signal in most studies, and also because there is a safety warning for cardiovascular complications and deaths in elderly dementia patients taking these drugs. Although there is promise for drugs acting by different mechanisms and currently in testing (see Chapter 12 on dementia), there are also positive results for agitation in dementia for one agent that is in the class of drugs for psychosis, namely brexpiprazole, and it may be that it has a satisfactory risk:benefit profile. This is discussed in further detail in Chapter 12 on dementia. Sedative Hypnotic and Sedating Actions A long debate exists as to whether sedation is a good or a bad property for antipsychotic action. The answer seems Figure 5-24 Insulin resistance and elevated triglycerides: caused by tissue actions at an unknown receptor? Some drugs used to treat psychosis may lead to insulin resistance and elevated triglycerides, independently of weight gain, although the mechanism is not yet established. This figure depicts a hypothesized mechanism in which an agent binds to receptor X at adipose tissue, liver, and skeletal muscle to cause insulin resistance. A B Insulin Resistance / Elevated Triglycerides and Drugs for Psychosis: Caused by Tissue Actions at an Unknown Receptor? adipose liver skeletal muscle receptor X insulin serotonindopamine blocker X X X X X X

 to be that sedation is both good and bad in the treatment of psychosis. In some cases, particularly for short-term treatment, sedation is a desired therapeutic effect, especially early in treatment, during hospitalization, and when patients are aggressive, agitated, or needing sleep induction. In other cases, particularly for longterm treatment, sedation is generally a side effect to be avoided because diminished arousal, sedation, and somnolence can lead to cognitive impairment. When cognition is impaired, functional outcomes are compromised. The pharmacology of sedation is discussed above and illustrated in Figures 5-8, 5-13, and 5-14 for anticholinergic, antihistamine, and α1 antagonist actions. Sedative hypnotics are discussed in Chapter 10 on sleep, and aggression and violence are discussed in Chapter 13 on impulsivity. Cardiometabolic Actions Although all D2/5HT2A/5HT1A drugs for treating psychosis share a class warning for causing weight gain and risks for obesity, dyslipidemia, and hyperglycemia/ diabetes mellitus, there is actually a spectrum of risk among the various agents: high metabolic risk: clozapine, olanzapine moderate metabolic risk: risperidone, paliperidone, quetiapine, asenapine, iloperidone low metabolic risk: lurasidone, cariprazine, lumateperone, ziprasidone, pimavanserin, aripiprazole, brexpiprazole The “metabolic highway” shown schematically in Figure 5-23 passes by weight gain, dyslipidemia, and hyperglycemia/diabetes mellitus and ends with the sad destination of premature death. The point

of discussing the metabolic highway is to monitor the patient along their journey of taking one of the moderate- or high-risk agents, and to intervene when possible to prevent predictable adverse outcomes. The onramp to the metabolic highway is increased appetite and weight gain, with progression to obesity, insulin resistance, and dyslipidemia with increases in fasting triglyceride levels (Figure 5-23). Ultimately, hyperinsulinemia advances to pancreatic β-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 5-23). The pharmacological mechanisms for what propels a patient taking a drug with antipsychotic properties along the metabolic highway to these risks and beyond are only beginning to be understood. Increased weight gain associated with some agents may be due to actions at the H1 histamine receptor and the 5HT2C serotonin receptor. When these receptors are blocked, particularly at the same time, patients can experience weight gain. Since weight gain can lead to obesity, and obesity to diabetes, and diabetes to cardiac disease along the metabolic highway (Figure 5-23), it seemed feasible at first that weight gain might explain all the other cardiometabolic complications associated with treatment with those drugs used for psychosis that cause moderate or high amounts of weight gain. This may be true, but only in part, and perhaps mostly for those agents that have both potent antihistamine properties as well as potent 5HT2C antagonist properties; notably, clozapine, olanzapine, and quetiapine, as well as the antidepressant mirtazapine (discussed in Chapter 7). However, it now appears that the cardiometabolic risk cannot simply be explained by increased appetite and weight gain, nor by antagonist actions at these two receptors, even though they certainly do represent the first steps down the slippery slope towards cardiometabolic complications for some of the higher-risk agents. However, many drugs that block one or another of these two receptors do not have a great deal of appetite or weight gain associated with use, and many other drugs that cause weight gain lack actions at these two receptors. It appears that there may be a second mechanism acting to cause weight gain, dyslipidemia, and diabetes; namely, immediate increase in insulin resistance. This can be measured in part by elevation of fasting triglyceride levels and cannot be explained by weight gain alone, because this occurs prior to gaining significant weight; it is as if there is an acute receptor-mediated action of these drugs on insulin regulation. We still do not know what that receptor might be, but it is hypothesized as receptor “X” on the drug icon in Figure 5-24. So, there appears to be a second mechanism of metabolic dysfunction other than that which causes increased appetite and weight gain of the H1/5HT2Cmediated mechanism. This outcome was unexpected when these drugs were all developed, and some drugs seem to have this second mechanism (high- and moderate-risk agents) while others seem to lack it (lowrisk agents). 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 upon initiation of some D2/5HT2A antagonists, and the rapid fall of fasting triglycerides upon discontinuation of such drugs, is highly suggestive that an unknown

pharmacological mechanism causes these changes, although this remains speculative. The hypothetical actions of agents with this postulated receptor action are shown in Figure 5-24, where adipose tissue, liver, and skeletal muscle all develop insulin resistance in response to administration of certain drugs (e.g., high-risk drugs but not “metabolically friendly” low-risk drugs), 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 D2/5HT2A antagonists, that this enhances cardiometabolic risk and moves such patients

along the metabolic highway (Figure 5–23), and that this functions as another step down the slippery slope towards the diabolical destination of cardiovascular events and premature death. This does not happen in all patients taking any D2/5HT2A antagonist, but the development of this problem can be detected by monitoring (Figure 5-25) and it can be managed when it does occur (Figure 5-26). Another rare but life-threatening cardiometabolic problem is known to be associated with serotonin/ dopamine agents that treat psychosis: namely, an association with the sudden occurrence of diabetic ketoacidosis (DKA) or the related condition hyperglycemic hyperosmolar syndrome (HHS). The mechanism of this complication is under intense investigation, and is probably complex and multifactorial. In some cases, it may be that patients with undiagnosed insulin resistance, prediabetes, or diabetes, who are in a state of compensated hyperinsulinemia on the metabolic highway (Figure 5-23), when given certain serotonin/ dopamine antagonists, become decompensated because of some unknown pharmacological action. Because of the risk of DKA/HHS, it is important to know the patient's location along the metabolic highway prior to prescribing drugs for psychosis, particularly if the patient has hyperinsulinemia, prediabetes, or diabetes. It is thus important to monitor (Figures 5-23 and 5-25) and manage (Figure 5-26) these risk factors. Specifically, there are at least three stops along the metabolic highway where a psychopharmacologist should monitor a patient taking a drug for psychosis (or using these same drugs for other indications, particularly depression) and manage their cardiometabolic risks (Figure 5-23). This starts with monitoring weight, body mass index, and fasting glucose to detect the development of diabetes (Figures 5-23 and 5-25). It also means getting a baseline of fasting triglyceride levels and determining whether there is a family history of Chapter 5: Targeting for Psychosis Psychopharmacologist's Metabolic Monitoring Tool Kit 5 BMI chart + scale + fasting TGs fasting glu BP FLOW CHART John Doe wt/BMI baseline visit 1 visit 2 fasting TGs fasting glu BP Figure 5-25 Metabolic monitoring tool kit. The psychopharmacologist's metabolic monitoring tool kit includes items for tracking four major parameters: weight/body mass index (BMI), fasting triglycerides (TGs), fasting glucose (glu), and blood pressure (BP). These items are simply a flowchart that can appear at the beginning of a patient's chart, with entries for each visit. diabetes. The second action to monitor is whether or not these drugs are causing dyslipidemia and increased insulin resistance by measuring fasting triglyceride levels before and after starting a serotonin/dopamine agent (Figure 5-25). If body mass index or fasting triglycerides 199

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Insulin Resistance: What Can a Psychopharmacologist Do? psychopharmacologist no options modest chance of success genes/aging lifestyle/diet insulin resistance increase significantly, a switch to a different drug in this class, especially a low-metabolic-risk drug, should be considered. In patients who are obese, with dyslipidemia, and either in a prediabetic or diabetic state, it is especially important to monitor blood pressure, fasting glucose, and waist circumference before and after initiating a serotonin/dopamine agent. Best practices are to monitor these parameters in anyone taking any of these drugs, although it is frequently not done, especially not in patients being treated for depression, unfortunately. Too often these same patients are not monitored for other side effects in this class either, such as tardive dyskinesia. If there is one lesson to be learned about knowing the pharmacology of drugs it is that the mechanism dictates not only efficacy but also safety. Too often these drugs are Figure 5-26 Insulin resistance: what can a psychopharmacologist do? Several factors influence whether or not an individual develops insulin resistance, some of which are manageable by a psychopharmacologist and some of which are not. Unmanageable factors include genetic makeup and age, while items that are modestly manageable include lifestyle (e.g., diet,

exercise, smoking). Psychopharmacologists exert their greatest influence on managing insulin resistance through the selection of medication treatments that either do or do not cause insulin resistance. most manageable option choice of drug for psychosis monitored one way when used for psychosis, frequently in inpatient settings, and another way, much less rigorously, when used for depression, often in outpatient settings. Guess what? These are the same drugs no matter where or in whom they are used. In high-risk patients, it is especially important to be vigilant for DKA/HHS, and possibly to reduce that risk by maintaining the patient on a drug for psychosis (or mood) with lower cardiometabolic risk. In high-risk patients, especially those with pending or actual pancreatic β-cell failure, as manifested by hyperinsulinemia, prediabetes, or diabetes, fasting glucose and other chemical and clinical parameters can be monitored to detect early signs of rare but potentially fatal DKA/HHS.

The psychopharmacologist's metabolic toolkit is quite simple (Figure 5-25). It involves a flow chart that tracks perhaps as few as four parameters over time, especially before and after switches from one agent to another, or as new risk factors evolve. These four parameters are weight (as body mass index), fasting triglycerides, fasting glucose, and blood pressure. The management of patients at risk for cardiometabolic disease can be quite simple as well, although patients who already have developed dyslipidemia, hypertension, diabetes, and heart disease will likely require management of these problems by a medical specialist. However, the psychopharmacologist is left with a very simple set of options for managing patients with cardiometabolic risk who are prescribed one of these drugs with any amount of metabolic risk (Figure 5-26). The major factors that determine whether a patient progresses along the metabolic highway to premature death include: those that are unmanageable (genetic makeup and age) those that are modestly manageable (change in lifestyle such as diet, exercise, and stopping smoking) those that are most manageable, namely the selection of medication and perhaps switching from one that is causing increased risk in a particular patient, to one that monitoring demonstrates reduces that risk Other options for managing the metabolic syndrome and dyslipidemia in patients taking serotonin/dopamine antagonists is the promising possibility that co-therapy with other agents may prevent weight gain and possibly dyslipidemia. That is, the anti-diabetes drug metformin has been shown in several studies to cause weight loss after drug-induced weight gain and, perhaps even more impressively, to reduce weight gain when starting a high- or moderate-metabolic-risk agent. Less consistent results have also been reported for the anticonvulsant topiramate. A new agent on the horizon that can reduce olanzapine-induced weight gain is the combination of the μ-opioid antagonist samidorphan with olanzapine. PHARMACOLOGICAL PROPERTIES OF SELECTED INDIVIDUAL FIRST-GENERATION D2 ANTAGONISTS The original D2 antagonists launched approximately 70 years ago are still used to treat psychosis and a few of the most commonly prescribed agents are selected Chapter 5: Targeting for Psychosis for individual discussion here. To characterize all the receptor binding properties of all the various drugs that treat psychosis, we show these properties both by simplified icons and by binding strips that represent all the known receptors that drug binds as one box per receptor, in rank order from most potent on the far left to least potent on the far right (see Figures 5-27 through 5-31 for some of the original D2 antagonists, and see subsequent figures for the other drugs to treat psychosis). Specifically, the pharmacological binding properties of each drug can be represented as a row of semiquantitative and rank-order relative binding potencies at numerous neurotransmitter receptors. These figures are conceptual and not precisely quantitative, can differ from one laboratory to another, species to species, method to method, and the consensus values for binding properties evolve over time.

More potent binding (higher affinity) is shown to the left of the value for the D2 receptor, which is indicated by a vertical dotted line; less potent binding (lower affinity) is shown to the right. Drugs used to treat psychosis are arguably the most complicated medicines in psychopharmacology, if not indeed in all of medicine, and this method should hopefully give the reader a rapid semi-quantitative grasp of the individual pharmacological properties of two dozen different drugs used to treat psychosis, and how these compare to all the other drugs that treat psychosis, and to do it in a glance. Dopamine 2 antagonists/partial agonists are generally dosed for antipsychotic action so that at least 60–80% of D2 receptors are occupied. Thus, all receptors to the left of D2 in the various figures of these drugs are occupied at the level of 60% or more at antipsychotic dosing levels. The receptors shown to the right of D2 in these individual drug figures are occupied at a level of less than 60% at antipsychotic dosing levels. Only those receptors that are bound by a drug within an order of magnitude of potency of D2 affinity are likely to have clinically relevant actions at antipsychotic doses, and maybe no relevant actions at lower doses such as doses used to treat depression. Chlorpromazine One of the very first agents with D2 antagonist properties used to treat psychosis is chlorpromazine, in the chemical class of phenothiazine. It was originally branded as “Largactil” meaning it had a large number of actions, but none of its actions were known to be linked to any specific receptor at that time. Those “large actions” are shown in Figure 5-27, and in addition to therapeutic D2 antagonism, chlorpromazine has numerous receptor actions 201

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY + + + + + + + chlorpromazine α2 +++ D3 α1 +++ D2 H1 ++ 5HT2A ++ D4 ++ 5HT2C ++ 5HT6 ++ 5HT7 ++ M5 ++ M1 ++ M3 ++ M4 ++ D1 D5 5HT5A M2 H2 5HT1E 5HT1D +++ +++ 5HT2A D2 5HT2C 5HT6 5HT7 D4 D3 H1 M1 M3 M4 M5 α D1 Figure 5-27 Chlorpromazine’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of chlorpromazine. In addition to the D2 receptor, chlorpromazine binds potently to α1-adrenergic receptors, D3 receptors, and H1 receptors, and also has actions at numerous other receptors as shown. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. associated with sedation (muscarinic, α1, and histamine antagonism), as well as other side effects (see Figures 5-8 and 5-13). Chlorpromazine is often prescribed to exploit its sedation in patients who do well with sedation, particularly short-term orally or as a short-acting intramuscular injection when needed to treat agitation or a sudden worsening in psychosis, often administered on top of another drug in the same class that is given daily. Fluphenazine This agent is another phenothiazine, although more potent than chlorpromazine and less sedating (Figure 5-28). It has both short-acting and long-acting formulations for convenient use, and it is one of the agents for which monitoring plasma drug levels may be useful. Haloperidol Haloperidol (Figure 5-29) is one of the most potent D2 antagonists, and less sedating than some others. It also has both short- and long-acting formulations for convenient use and it, too, is one of the agents for which monitoring plasma drug levels may be useful. Sulpiride Sulpiride (Figure 5-30) has D2 antagonist properties and, as expected, generally causes motor side effects

Chapter 5: Targeting for Psychosis + + + + + + + + fluphenazine α1 α2C α2B +++ 5HT7 +++ ++ D5 ++ 5HT2A 5HT6 ++ ++ H1 ++ ++ D4 ++ D1 ++ α2A 5HT1B 5HT1D M5 5HT1E 5HT1A 5HT2C H2 D2 ++++ D3 ++++ 5HT2A D2 5HT6 5HT7 D4 D5 D3 H1 α D1 α2C α2B Figure 5-28 Fluphenazine’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of fluphenazine. Along with D2 antagonism,

fluphenazine has potent actions at D3, 5HT7, and α1-adrenergic receptors, and binds at numerous other receptors as well. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. and prolactin elevation at usual antipsychotic doses. However, particularly at lower doses, it may be a bit activating, and have efficacy for negative symptoms of schizophrenia and for depression for unclear reasons. Dopamine 3 antagonist/partial agonist actions in depression are discussed in Chapter 7 on treatments for mood disorders, and this is a candidate explanation (see Figure 5-30). Sulpiride remains a popular option for treating psychosis in countries outside the US such as the UK, as it may be better tolerated than some of the other original D2 agents. Amisulpride Amisulpride (Figure 5-31) is structurally related to sulpiride (Figure 5-30) and was developed and marketed outside the US. Some early preclinical data suggest that it might be more selective for mesolimbic/mesostriatal dopamine receptors than for nigrostriatal dopamine receptors, and thus might have a lower propensity for motor side effects at antipsychotic doses. There are reports of amisulpride's efficacy for the negative symptoms of schizophrenia and for depression at doses lower than those used to treat positive symptoms of psychosis. Amisulpride has some D3 antagonist actions and some weak 5HT7 antagonist actions, which may explain some of its negative symptom and antidepressant actions (Figure 5-31). Antidepressant actions of D3 antagonism/partial agonism and 5HT7 antagonism are discussed in Chapter 7. The active isomer of amisulpride is in early clinical testing for possible development in the US.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-29 Haloperidol's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of haloperidol. Haloperidol binds potently to D2 receptors as well as to omega, D3, and α1-adrenergic receptors. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. + + + + + + + + σ σ haloperidol α2C α2B α2A α1 +++ D3 +++ D2 +++ ++ D4 D1 5HT2A M5 5HT7 5HT1B +++ 5HT2A D2 D4 D3 α AN OVERVIEW OF THE PHARMACOLOGICAL PROPERTIES OF INDIVIDUAL 5HT2A/D2 ANTAGONISTS AND D2/5HT1A PARTIAL AGONISTS: THE PINES (PEENS), MANY DONES AND A RONE, TWO PIPS AND A RIP We have established that D2 antagonist/partial agonist properties can explain the antipsychotic efficacy for positive symptoms as well as many side effects of drugs used to treat psychosis. The 5HT2A antagonist and/or 5HT1A partial agonist properties can help to explain the reduced propensity for motor side effects and prolactin elevation and potential therapeutic enhancement of positive, negative, depressive, and cognitive symptoms. However, the contributions of these properties to each individual agent used to treat psychosis are quite variable. As mentioned above for the original D2 antagonists, we also characterize all the receptor binding properties of the D2/5HT2A/5HT1A drugs by binding strips that represent all the known receptors that each drug binds to as one box per receptor, in rank order from most potent on the far left to least potent on the far right (see Figures 5-32

sulpiride D2 D3 ++ ++ amisulpride D3 D2 D3 5HT7 5HT2B +++ +++ ++ + Figure 5-30 Sulpiride's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of sulpiride. At usual antipsychotic doses, sulpiride is a D2 antagonist and also has D3 antagonist/partial agonist actions. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. D2 D3 Figure 5-31 Amisulpride's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding

properties of amisulpride. In addition to its actions at D2 receptors, amisulpride has some D3 antagonist actions and some weak 5HT7 antagonist actions. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. D2 205

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY 5HT2A binding by pines 5HT2A clozapine 5HT2A olanzapine 5HT2A quetiapine 5HT2A asenapine 5HT2A zotepine A 5HT2A binding by dones and a rone 5HT2A risperidone 5HT2A paliperidone 5HT2A ziprasidone 5HT2A iloperidone 5HT2A lurasidone 5HT2A lumateperone B 5HT2A binding by two pips and a rip 5HT2A aripiprazole 5HT2A brexpiprazole 5HT2A cariprazine C more potent than D2 less potent than D2 Figure 5-32 5HT2A binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the D2 receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Interestingly, D2 binding is not the most potent property for any of the agents shown here. (A) The "pines" (i.e., clozapine, olanzapine, quetiapine, asenapine, and zotepine) all bind much more potently to the 5HT2A receptor than they do to the D2 receptor. (B) The "dones" and "rone" (i.e., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone, and lumateperone) also bind more or as potently to the 5HT2A receptor as they do to the D2 receptor. (C) Aripiprazole and cariprazine both bind more potently to the D2 receptor than to the 5HT2A receptor, while brexpiprazole has similar potency at both receptors.

5HT1A binding by pines 5HT1A clozapine olanzapine 5HT1A quetiapine asenapine 5HT1A zotepine A 5HT1A binding by dones and a rone risperidone paliperidone 5HT1A ziprasidone 5HT1A iloperidone 5HT1A lurasidone lumateperone B 5HT1A binding by two pips and a rip 5HT1A aripiprazole 5HT1A brexpiprazole 5HT1A cariprazine C more potent than D2 less potent than D2 Chapter 5: Targeting for Psychosis Figure 5-33 5HT1A binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine and quetiapine both bind more potently to the 5HT1A receptor than they do to the D2 receptor, while asenapine and zotepine bind less potently to the 5HT1A receptor and olanzapine does not bind to it at all. (B) All of the "dones" (i.e., risperidone, paliperidone, ziprasidone, iloperidone, and lurasidone) bind to the 5HT1A receptor with less potency than they do to the D2 receptor; lumateperone does not bind the 5HT1A receptor. (C) Aripiprazole, brexpiprazole, and cariprazine each have similar relative potency for the D2 and 5HT1A receptors. 5HT1A binding is actually the most potent property of brexpiprazole. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the D2 receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. 5HT1A 5HT1A 5HT1A 207

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Monoamine reuptake inhibition by pines clozapine olanzapine NET quetiapine asenapine NET SERT zotepine A Monoamine reuptake inhibition by

dones and a rone risperidone paliperidone NET ziprasidone iloperidone lurasidone SERT lumateperone B Monoamine reuptake inhibition by two pips and a rip aripiprazole brexpiprazole cariprazine C more potent than D2 less potent than D2 Figure 5-34 Monoamine transporter binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Of the “pines,” quetiapine is the only one with any relevant monoamine reuptake inhibition. Specifically, it binds to the norepinephrine transporter (NET) with similar potency as it does to the 5HT2A receptor, and greater potency than to the D2 receptor. (B) Ziprasidone binds to NET and the serotonin transporter (SERT), though with less potency than to the D2 receptor. Lumateperone binds to SERT with similar potency as to the D2 receptor. (C) Aripiprazole, brexpiprazole, and cariprazine do not bind to any of the monoamine transporters. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. SERT

Alpha2 binding by pines α2C α2B α2A clozapine α2C α2B olanzapine α2C α2B α2A quetiapine asenapine α2 zotepine A Alpha2 binding by dones and a rone α2C risperidone α2C α2A α2B paliperidone ziprasidone α2C iloperidone α2C α2A lurasidone lumateperone B Alpha2 binding by two pips and a rip α2C aripiprazole α2C brexpiprazole α2A cariprazine C more potent than D2 less potent than D2 Chapter 5: Targeting for Psychosis Figure 5-35 Alpha-2 binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) All of the “pines” (i.e., clozapine, olanzapine, quetiapine, asenapine, zotepine) bind to α2 receptors to varying degrees. Clozapine and quetiapine in particular bind to some α2 receptor subtypes with greater potency than they do to the D2 receptor. (B) All of the “dones” (i.e., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone) bind to α2 receptors to varying degrees. Risperidone and paliperidone bind to the α2C receptor with similar potency as to the D2 receptor. Lumateperone does not bind to any α2 receptors. (C) Aripiprazole binds to α2 receptors with less potency than it does to the D2 receptor. Brexpiprazole binds to α2C receptors, and cariprazine has some affinity for α2A receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. α2A α2B α2A α2C α2A α2B α2C α2B α2A α2A α2B α2A α2B 209

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY D3 binding by pines D3 clozapine D3 olanzapine D3 quetiapine D3 asenapine D3 zotepine A D3 binding by dones and a rone D3 risperidone D3 paliperidone D3 ziprasidone D3 iloperidone D3 lurasidone lumateperone B D3 binding by two pips and a rip D3 aripiprazole D3 brexpiprazole D3 cariprazine C more potent than D2 less potent than D2 Figure 5-36 D3 binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) All of the “pines” bind to D3 receptors, but

with varying degrees of potency. (B) Likewise, all of the “dones” bind to D3 receptors, again with varying degrees of potency. Lumateperone, however, does not bind to D3 receptors at all. (C) D3 receptor partial agonism is actually the most potent binding property of cariprazine. Aripiprazole and brexpiprazole also bind to D3 receptors, less potently than they do to D2 receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box.

5HT2C binding by pines 5HT2C clozapine 5HT2C olanzapine 5HT2C quetiapine 5HT2C asenapine 5HT2C zotepine A 5HT2C binding by dones and a rone risperidone 5HT2C paliperidone 5HT2C ziprasidone iloperidone 5HT2C lurasidone 5HT2C lumateperone B 5HT2C binding by two pips and a rip 5HT2C aripiprazole brexpiprazole cariprazine C more potent than D2 less potent than D2 Chapter 5: Targeting for Psychosis Figure 5-37 5HT2C binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) All of the “pines” (i.e., clozapine, olanzapine, quetiapine, asenapine, zotepine) bind more potently to the 5HT2C receptor than they do to the D2 receptor. (B) All of the “dones” (i.e., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone) as well as lumateperone have some affinity for the 5HT2C receptor, although only ziprasidone binds with comparable potency as at the D2 receptor. (C) Aripiprazole, brexpiprazole, and cariprazine all have relatively weak affinity for the 5HT2C receptor. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. 5HT2C 5HT2C 5HT2C 5HT2C 211

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY 5HT3 binding by pines 5HT3 clozapine 5HT3 olanzapine 5HT3 quetiapine asenapine 5HT3 zotepine A 5HT3 binding by dones and a rone risperidone paliperidone ziprasidone iloperidone lurasidone lumateperone B 5HT3 binding by two pips and a rip aripiprazole brexpiprazole cariprazine C more potent than D2 less potent than D2 Figure 5-38 5HT3 binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) All of the “pines” bind to 5HT3 with less affinity than they have for the D2 receptor. (B) None of the “dones” or “rone” have any binding activity at 5HT3 receptors. (C) Aripiprazole binds weakly to 5HT3 receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. 5HT3 5HT3

5HT6 and 5HT7 binding by pines 5HT6 5HT7 clozapine 5HT6 olanzapine 5HT7 5HT6 quetiapine 5HT7 5HT6 asenapine 5HT6 5HT7 zotepine A 5HT6 and 5HT7 binding by dones and a rone 5HT7 risperidone 5HT7 paliperidone 5HT7 ziprasidone 5HT6 iloperidone 5HT7 lurasidone lumateperone B 5HT6 and 5HT7 binding by two pips and a rip 5HT7 aripiprazole brexpiprazole cariprazine C more potent than D2 less potent than D2 Chapter 5: Targeting for Psychosis Figure 5-39 5HT6 and 5HT7 binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine, quetiapine, asenapine, and zotepine each have greater or similar potency for the 5HT7 receptor compared to the D2 receptor, while clozapine, olanzapine, asenapine, and zotepine each have greater or similar potency for the 5HT6 receptor compared to the D2 receptor. (B) Risperidone, paliperidone, ziprasidone, and lurasidone all bind potently to the 5HT7 receptor. In fact, lurasidone has greater affinity for the 5HT7 receptor than for the D2 receptor. Ziprasidone and iloperidone also bind to the 5HT6 receptor. (C) Aripiprazole, brexpiprazole, and cariprazine all bind to the 5HT7 receptor, though none with more potency than for the D2 receptor. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. 5HT7 5HT6 5HT7 5HT6 5HT7 5HT6 5HT7 213

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY 5HT1B/D binding by pines 5HT1B 5HT1D clozapine olanzapine 5HT1D quetiapine 5HT1B asenapine 5HT1B 5HT1D zotepine A 5HT1B/D binding by dones and a rone risperidone 5HT1B 5HT1D paliperidone 5HT1B 5HT1D ziprasidone 5HT1B 5HT1D iloperidone lurasidone lumateperone B 5HT1 B/D binding by two pips and a rip 5HT1D aripiprazole brexpiprazole cariprazine C more potent than D2 less potent than D2 Figure 5-40 5HT1B/D binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine, olanzapine, asenapine, and zotepine all bind relatively weakly to the 5HT1B and 5HT1D receptors, while quetiapine binds relatively weakly only to the 5HT1D receptor. (B) Risperidone, paliperidone, ziprasidone, and iloperidone all have some affinity for the 5HT1B and 5HT1D receptors. In particular, ziprasidone binds with similar potency to these two receptors as it does to the D2 receptor. Lurasidone and lumateperone do not bind to 5HT1B/D receptors. (C) Aripiprazole and brexpiprazole each bind weakly to the 5HT1B receptor; aripiprazole also binds to the 5HT1D receptor. Cariprazine does not bind to 5HT1B/D receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. 5HT1B 5HT1D 5HT1D 5HT1B 5HT1D 5HT1B 5HT1B

Antihistamine/Anticholinergic binding by pines H1 M1 M3 M4 M2 clozapine H1 M1 M3 M4 M2 olanzapine H1 M1 M3 M2 M4 quetiapine asenapine H1 M1 M2 zotepine A Antihistamine/Anticholinergic binding by dones and a rone risperidone H1 paliperidone ziprasidone H1 iloperidone lurasidone lumateperone B Antihistamine/Anticholinergic binding by two pips and a

rip H1 aripiprazole brexpiprazole cariprazine C more potent than D2 less potent than D2 Chapter 5: Targeting for Psychosis Figure 5-41 Antihistamine/ anticholinergic binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine, olanzapine, quetiapine, and zotepine all have strong potency for histamine 1 receptors; clozapine, olanzapine, and quetiapine also have strong potency for muscarinic receptors. Asenapine has some affinity for histamine H1 receptors and weak affinity for muscarinic receptors. (B) None of the “dones” or “rones” have anticholinergic properties. Risperidone, paliperidone, ziprasidone, and iloperidone all have some potency for H1 receptors. (C) Aripiprazole, brexpiprazole, and cariprazine all bind at the H1 receptor with less potency than they do to the D2 receptor, and do not bind to muscarinic receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. H1 M1 M2 H2 H1 H1 H1 H1 215

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Alpha1 binding by pines α1A α1B clozapine α1A olanzapine α1A α1B quetiapine α1B α1A asenapine α1 zotepine A Alpha1 binding by dones and a rone α1B α1A risperidone α1B α1A paliperidone α1B α1A ziprasidone α1 iloperidone α1 lurasidone α1 lumateperone B Alpha1 binding by two pips and a rip α1A α1B aripiprazole α1B α1D brexpiprazole α1A α1B α1D cariprazine C more potent than D2 less potent than D2 Figure 5-42 Alpha-1 binding by drugs used to treat psychosis. Shown here is a visual depiction of the binding profiles of drugs used to treat psychosis. (A) Clozapine, quetiapine, and zotepine each have greater potency for α1 receptors than for the D2 receptor, while asenapine binds with similar potency to the α2 and the D2 receptors. (B) All of the “dones” (i.e., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone) as well as lumateperone bind to the α1 receptor. In particular, paliperidone and iloperidone bind with greater potency than they do to the D2 receptor. (C) Aripiprazole, brexpiprazole, and cariprazine each have some binding potency at α1 receptors. Description of graphic: Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug). The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right. Binding at 5HT2A (see Figure 5-32) is indicated by an orange outline around the box. α1B α1A

Chapter 5: Targeting for Psychosis Figure 5-43 Clozapine’s pharmacological icon and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of clozapine. In addition to 5HT2A/D2 antagonism, numerous other binding properties have been identified for clozapine, most of which are more potent than its binding at the D2 receptor. It is unknown which of these contribute to clozapine’s special efficacy or to its unique side effects. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. D2 + + + + + + + + + + clozapine +++ α1B α2C α2B α2A α1A +++ M1 5HT2B 5HT2A 5HT2C 5HT6 ++ ++ ++ H1 ++ ++ ++ ++ M4 5HT7 M2 5HT1A 5HT3 5HT1B D1 D3 5HT1D 5HT1E ++ ++ M3 D4 ++ +++ +++

5HT2A D2 5HT2C 5HT2B 5HT6 5HT7 D4 H1 M1 M2 M3 M4 5HT1A 2C α 2B α 2A α 1A α 1B α through 5-63). These pharmacological binding properties are again represented as a row of semi-quantitative and rank-order relative binding potencies at numerous neurotransmitter receptors, with each figure highlighting a specific receptor so the relative binding potencies of all these drugs can be compared at a glance. More potent binding (higher affinity) is shown to the left of the value for the D2 receptor, which itself is indicated by a vertical dotted line; less potent binding (lower affinity) is shown to the right. Determining whether all drugs for psychosis should be in a single class, or a small number of classes, or whether each drug should be treated uniquely, is a bit like the famous quote of baseball great Yogi Berra, when he was once asked if he and his son were a lot the same. He paused, pondered for a bit, then answered, “Yes, but our similarities are different.” The same could be said for all these drugs used to treat psychosis (and mood, see Chapter 7). In some ways they are a lot the same, but in many ways their similarities are different! So, how are they similar? Beginning with the relative potencies of each of these agents for 5HT2A receptors compared to D2 receptors, the reader can see at a glance in Figure 5-32 that almost all agents show 5HT2A binding to the left of D2 binding, meaning these drugs with 5HT2A to the left all have higher affinity for 5HT2A receptors than for D2 receptors and would be expected to bind even more to 5HT2A receptors than to D2 receptors. The

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY α1A + α2B α2A α1B + + + + + + + + + olanzapine +++ H1 5HT2A 5HT2C 5HT6 ++ ++ 5HT2B ++ ++ ++ ++ 5HT3 5HT7 M2 M4 5HT1B 5HT1D M1 D4 ++ ++ D3 D1 ++ M3 ++ D2 α2C +++ 5HT2A D2 D3 D1 5HT2C 5HT2B 5HT6 D4 H1 M1 M3 α2C Figure 5-44 Olanzapine’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of olanzapine. Olanzapine binds at several receptors more potently than it does at the D2 receptor; in fact, it has strongest potency for the H1 and 5HT2A receptors. Olanzapine’s 5HT2C antagonist properties may contribute to its efficacy for mood and cognitive symptoms, although together with its H1 antihistamine properties they could also contribute to its propensity to cause weight gain. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. exceptions are the D2 partial agonists, but these drugs all show comparable potency for 5HT1A receptors and D2 receptors (Figure 5-33). However, D2 antagonists with potent 5HT2A properties generally do not have high affinity for 5HT1A receptors (compare drugs in Figure 5-32 with the same drugs in Figure 5-33 for their 5HT2A versus their 5HT1A properties). Maybe that does not really matter. Recall that many of the same downstream actions of 5HT2A antagonism are also caused by 5HT1A partial agonism (see discussion above and Figures 5-17 and 5-22). Yet, no two drugs are exactly the same and it can be expected that their clinical properties linked to 5HT2A and 5HT1A receptors may also differ, even though essentially all drugs listed have 5HT2A antagonism, 5HT1A partial agonism, or both, at least to some degree. One example of how drugs that all have potent 5HT2A antagonist properties nevertheless differ from each other is the observation that the greater the separation of 5HT2A binding from D2 binding (i.e., the further 5HT2A is to the left of D2), the less D2 receptor occupancy may be

Chapter 5: Targeting for Psychosis Figure 5-45 Quetiapine’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of quetiapine. Quetiapine does not actually have particularly potent binding at D2 receptors. Quetiapine’s prominent H1 antagonist properties probably contribute to its ability to enhance

sleep, and this may contribute as well to its ability to improve sleep disturbances in bipolar and unipolar depression as well as in anxiety disorders. However, this property can also contribute to daytime sedation, especially combined with M1 antimuscarinic and α1-adrenergic antagonist properties. A potentially important active metabolite of quetiapine, norquetiapine, may contribute additional actions at receptors, as noted in the binding profile with an asterisk. 5HT1A partial agonist actions, norepinephrine transporter (NET) inhibition, and 5HT2C, α2, and 5HT7 antagonist actions may all contribute to mood-improving properties of quetiapine. However, 5HT2C antagonist actions combined with H1 antagonist actions may contribute to weight gain. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. quetiapine M3*

- Binding primarily due to norquetiapine (a metabolite of quetiapine) ++ M1* ++ NET* ++ ++ α1A ++ α1B +++ H1* 5HT2B* ++ 5HT2A* ++ 5HT7* ++ 5HT1E* 5HT2C* 5HT5* 5HT6* M4* D2* D1*

-

5HT1A* + + + + + + + + D3* M2* + α2C 5HT1D* + + 5HT3* + α2B* α2A* NET H1 5HT2A 5HT1E D2 D1 5HT2C 5HT2B 5HT7 M1 M3 M4 1B 1A 2A 2C 5HT1A α α α α various agents have many, many pharmacological properties other than just dopamine and serotonin receptor binding, and these additional pharmacological properties are shown in the next nine figures (Figures 5-34 through 5-42). The first seven of these allow visual comparisons of putative antidepressant mechanisms mentioned above and that will be discussed in detail in Chapter 7. For example, the various receptor properties linked to postulated antidepressant actions are shown in the following figures: needed for an antipsychotic effect, explaining why studies show that those with the widest separation (namely, lumateperone, quetiapine, and clozapine) also have the lowest D2 occupancy at antipsychotic doses, in fact lower than 60%. Perhaps all this discussion is just a fancy way of saying that the drugs to treat psychosis are all the same but their similarities are different. If what is the same about these drugs is D2 binding and some degree of binding to either 5HT2A or 5HT1A receptors, that is where the similarities stop. These

Figure 5-46 Binding profile of quetiapine at different doses. The binding properties of quetiapine vary depending on the dose used. At antipsychotic doses (i.e., up to 800 mg/day), quetiapine has a relatively wide binding profile, with actions at multiple serotonergic, muscarinic, and α-adrenergic receptors. Histamine 1 receptor blockade is also present. At antidepressant doses (i.e., approximately 300 mg/day), the binding profile of quetiapine is more selective and includes norepinephrine reuptake inhibition, 5HT1A partial agonism, and 5HT2A, α2, 5HT2C, and 5HT7 antagonism. At sedative hypnotic doses (i.e., 50 mg/day), the most prominent pharmacological property of quetiapine is H1 antagonism. Papa Bear 800 mg antipsychotic 300 mg antidepressant Mama Bear 50 mg hypnotic Baby Bear NET H1 5HT2A 5HT1E D2 D1 5HT2C 5HT2B 5HT7 M1 M3 M4 1B 1A 2A 2C 5HT1A α α α α NET H1 5HT2A 5HT1E D2 D1 5HT2C 5HT2B 5HT7 M1 M3 M4 1B 1A 2A 2C 5HT1A α α α α H1 Figure 5-47 Asenapine’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of asenapine. Asenapine has a complex binding profile, with potent binding at multiple serotonergic and dopaminergic receptors, α1 and α2 receptors, and H1 histamine receptors. In particular, 5HT2C antagonist properties may contribute to its efficacy for mood and cognitive symptoms, while 5HT7 antagonist properties may contribute to its efficacy for mood, cognitive, and sleep symptoms. As

with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. asenapine 5HT2A 5HT1B 5HT1D 5HT2B D2 D3 D4 D1 5HT2C 5HT6 5HT5 5HT7 H1 2B α 2A α 1A α 1B α 5HT7 ++++ 5HT2A ++++ 5HT2C ++++ D3 5HT6 D2 +++ D4 +++ +++ D1 +++ +++ 5HT1A ++ ++ ++ 5HT1E 5HT3 + M1 + M2 + α2C α1B α2B α2A +++ 5HT5 +++ 5HT1B +++ H1 +++ 5HT2B +++ +++ +++ 5HT1D +++ α1A +++

Chapter 5: Targeting for Psychosis zotepine +++ H1 +++ D3 +++ 5HT2C +++ 5HT6 5HT7 +++ +++ 5HT2A +++ ++ D2 ++ M1 ++ D4 ++ D1 ++ 5HT1B 5HT1D + M2 + + 5HT1A + 5HT3 + 5HT1E + H2 + NET + SERT + α1 α2 5HT2A M1 5HT1B D2 D1 D4 D3 5HT2C 5HT6 5HT7 H1 α Figure 5-48 Zotepine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of zotepine. Zotepine is a 5HT2C antagonist, an α2 antagonist, and a 5HT7 antagonist, suggesting potential antidepressant effects. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. monoamine reuptake blocking properties (Figure 5-34) α2 antagonism (Figure 5-35) D3 partial antagonism/partial agonism (Figure 5-36) 5HT2C antagonism (Figure 5-37) 5HT3 antagonism (Figure 5-38) 5HT6 and 5HT7 antagonism (Figure 5-39) 5HT1B/D antagonism (Figure 5-40) Also, the various receptor binding properties theoretically linked to side effects are shown in these figures: antihistamine and anticholinergic (Figure 5-41), α1 antagonism (Figure 5-42). The point of these figures showing all these binding properties is to be able to see the differences amongst these drugs as well as the similarities. Individual agents have quite different mechanisms theoretically linked to antidepressant actions that may help explain why some are indicated for unipolar or bipolar depression and others are not, and also why one patient's depression may respond to one drug in this group but not to another. Another way to help the reader take this tour de force through two dozen complicated drugs a bit more easily,

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-49 Risperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of risperidone. Alpha-2 antagonist properties may contribute to efficacy for depression, but this can be diminished by simultaneous α1 antagonist properties, which can also contribute to orthostatic hypotension and sedation. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. risperidone +++ D4 +++ D3 D2 5HT2A +++ +++ +++ +++ 5HT7 +++ +++ 5HT2A D2 D3 5HT7 D4 1A 2C α α 1B α α2C α1A α1B α2B α2A ++ H1 ++ 5HT2C ++ 5HT1B ++ 5HT2B ++ 5HT1D ++ ++ 5HT5 D1 5HT1A + + + and for a bit of fun, is to organize all of them into three whimsical groups: the pines (peens) many dones and a rone two pips and a rip The members of each of the three groups have already been organized this way in Figures 5-32 through 5-42 and now we provide a brief description of each individual agent clustered into each of these three groups to try to make learning their distinctions easier and memorable. The Pines (Peens) Clozapine Clozapine (Figure 5-43) is widely recognized as being particularly effective when other drugs for psychosis fail, and is thus the "gold standard" for efficacy in

Chapter 5: Targeting for Psychosis Figure 5-50 Paliperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of paliperidone, the active metabolite of risperidone. Paliperidone shares many pharmacological

properties with risperidone. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. paliperidone +++ ++++ +++ 5HT2A +++ D3 +++ D2 +++ 5HT7 ++ H1 ++ ++ ++ D1 ++ ++ 5HT1B ++ 5HT2C 5HT2B 5HT1D ++ D4 ++ α1B α1A +++ α2A α2C α2B 5HT2A 5HT7 D3 D2 5HT1A + 5HT5 + 1B α 1A α 2C α schizophrenia. Clozapine is also the only antipsychotic that has been documented to reduce the risk of suicide in schizophrenia and may have a particular niche in treating aggression and violence in psychotic patients. It is unknown what pharmacological property accounts for this gold standard enhanced efficacy of clozapine, but it is unlikely to be D2 antagonism since at therapeutic doses, clozapine occupies fewer D2 receptors than the other drugs that treat psychosis. Likely, it works by an unknown but non-D2 mechanism. Patients treated with clozapine may occasionally experience an “awakening” (in the Oliver Sachs sense), characterized by a return to a nearnormal level of cognitive, interpersonal, and vocational functioning, and not just significant improvement in positive symptoms of psychosis, but this is unfortunately rare. The fact that awakenings can be observed at all, however, gives hope to the possibility that a state of wellness might some day be achieved in schizophrenia by the right mix of pharmacological mechanisms. In terms of side effects, clozapine causes little in the way of motor symptoms, does not seem to cause tardive dyskinesia and may even be effective in treating tardive dyskinesia, and also does not elevate prolactin. That’s the good news. The bad news is that clozapine has some unique side effects (Table 5-2), and prescribing clozapine effectively means the ability to manage these side effects

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-51 Ziprasidone’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of ziprasidone. This compound seems to lack the pharmacological actions associated with weight gain and increased cardiometabolic risk such as increasing fasting plasma triglyceride levels or increasing insulin resistance. Ziprasidone also lacks many of the pharmacological properties associated with significant sedation. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. ziprasidone 5HT2A 5HT1B 5HT1D 5HT2C 5HT7 D2 +++ ++++ 5HT2A 5HT1B +++ 5HT2C +++ D2 +++ 5HT1D +++ 5HT7 +++ D3 +++ ++ α1B α1B α1A α2B α2A ++ 5HT1A ++ 5HT2B ++ NET ++ H1 ++ ++ 5HT6 α2C ++ ++ D1 + D4 + + + 5HT5 SERT 5HT1E + D3 if they arise. One life-threatening and occasionally fatal complication of clozapine treatment is neutropenia, requiring patients to have their blood counts monitored for as long as they are treated. Clozapine also has an increased risk of seizures, especially at high doses (Table 5-2). It can be very sedating, has an increased risk of myocarditis, and is associated with the greatest degree of weight gain and possibly the greatest cardiometabolic risk among the drugs for psychosis. Clozapine can also cause excessive salivation, which can be mitigated by pro-cholinergic treatment or even by localized botulinum toxin injections for severe cases. Thus, clozapine may have the greatest efficacy but also the most side effects among the atypical antipsychotics. Table 5-2 Side effects of clozapine requiring expert management Neutropenia Constipation/paralytic ileus Sedation, orthostasis, tachycardia Sialorrhea Seizures Weight gain, dyslipidemia, hyperglycemia Myocarditis, cardiomyopathy, interstitial nephritis DRESS (drug reaction with eosinophilia and systemic symptoms), serositis

5HT1B iloperidone 5HT2A D2 α1 ++++ ++ ++ ++ ++ ++ ++ ++ ++ D3 H1 α2C α2A + 5HT2C D4 5HT1D 5HT6 5HT1A 5HT1B +++ +++ Because of these side-effect risks, clozapine is not

considered to be a first-line treatment, but is used when other antipsychotics fail. The mechanisms of clozapine's ability to cause neutropenia and myocarditis are entirely unknown; its weight gain may be partially associated with its potent blockade of both H1 histamine and 5HT2C receptors (Figure 5-43). Sedation is probably linked to clozapine's potent antagonism of muscarinic M1, H1, and α1-adrenergic receptors (Figures 5-8, 5-14, and 5-43). Profound muscarinic blockade can also cause excessive salivation, especially at higher doses, as well as severe constipation that can lead to bowel obstruction, especially if administered concomitantly with other anticholinergic agents, such as benztropine, or other drugs for psychosis with potent anticholinergic properties, such as chlorpromazine. Because of these side effects and the hassle of arranging for blood counts, the use of clozapine is low in clinical practice, and probably too low given the great number of patients with inadequate responses to the other drugs for psychosis. To reduce one logistical and pragmatic barrier to clozapine use, a point-ofChapter 5: Targeting for Psychosis Figure 5-52 Iloperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of iloperidone. Among the medications discussed here, iloperidone has one of the simplest pharmacological profiles and comes closest to a serotonin dopamine antagonist (SDA). Its other prominent pharmacological property is potent α1 antagonism, which may be responsible for the risk of orthostatic hypotension but also may contribute to its low risk of drug-induced parkinsonism (DIP). As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. α1A D2 α2B 5HT7 D1 + + + + care blood-count-monitoring system is now available with a finger stick rather than a blood draw and local assay rather than sending away to a distant laboratory. It is important not to lose the art of how to prescribe clozapine and for whom, and how to mitigate and manage side effects, as clozapine remains a powerful and unfortunately underutilized therapeutic intervention for many patients. Therapeutic drug monitoring of plasma drug levels can be of great assistance in finding the right dose of clozapine. This specific drug is a subject all to itself and for this reason the author has co-written a handbook on how to use clozapine that the reader may wish to consult for details (Meyer and Stahl, The Clozapine Handbook). Olanzapine Olanzapine (Figure 5-44) is an antagonist at both 5HT2A and D2 receptors, and although not proven as effective as clozapine for psychosis, it is widely considered (by clinical experience rather than by definitive clinical trials) to be the next most effective agent, with at least a bit more efficacy than the others in this class except 225

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY 5HT1A 5HT2A lurasidone 5HT7 D4 D4 5HT7 D2 5HT2A 5HT1A ++++ ++++ ++ ++ α2C +++ +++ +++ ++ clozapine. It also has a higher risk for metabolic side effects. Olanzapine tends to be used in higher doses than originally studied and approved for marketing, especially when guided by plasma drug levels, since clinical use suggests that higher doses may have greater efficacy, especially in patients who have not responded to other drugs for psychosis or to olanzapine at lower doses. Olanzapine is approved for schizophrenia and for maintaining response in schizophrenia (age 13 or older), for agitation associated with schizophrenia or with bipolar mania (intramuscular), acute bipolar mania/ mixed mania and maintenance (age 13 or older), and in combination with fluoxetine for both bipolar depression and treatment-resistant unipolar depression (in the US). Figure 5-53 Lurasidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of lurasidone. Lurasidone has a relatively simple pharmacological profile. It binds most potently to the D4 receptor, the effects of which are not well understood, and to the 5HT7 receptor, which may contribute to efficacy for mood, cognitive, and sleep symptoms. As with all agents

discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. D2 α2A α1 D3 5HT2C ++ + Perhaps the 5HT2C antagonist properties, with weaker α2 antagonist properties (see Figures 5-35 and 5-37 and also Figure 5-44), especially when combined with the 5HT2C antagonist properties of the antidepressant fluoxetine (see Chapter 7 on treatments for mood disorders), may explain some aspects of olanzapine's apparent efficacy in unipolar and bipolar depression. Olanzapine is available as an oral disintegrating tablet, as an acute intramuscular injection, and as a long acting 4-week intramuscular depot. An inhaled formulation for rapid onset use is in late clinical development. As mentioned earlier, olanzapine is also in late-stage clinical testing with the μ-opioid antagonist samidorphan to mitigate weight gain and metabolic disturbances.

Chapter 5: Targeting for Psychosis Figure 5-54 Lumateperone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of lumateperone. Lumateperone has very high affinity for the 5HT2A receptor and moderate affinity for the D2, D1, and α1 receptor. It also has moderate affinity for the serotonin transporter. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. lumateperone 5HT2A D2 D1 ++++ 5HT2A D2 D1 SERT SERT α1 ++ ++ ++ ++ + 5HT2C α1 Quetiapine Quetiapine (Figure 5-45) is an antagonist at both serotonin 5HT2A and dopamine D2 receptors, but has several differentiating pharmacological properties, especially at different doses. The net pharmacological actions of quetiapine are actually due to the combined pharmacological actions not only of quetiapine itself, but also of its active metabolite, norquetiapine (Figure 5-45 adds together the net actions of quetiapine and norquetiapine). Norquetiapine has unique pharmacological properties compared to quetiapine, especially norepinephrine transporter (NET) inhibition (i.e., norepinephrine reuptake inhibition) (Figure 5-34), but also, combined with the parent drug quetiapine, it has 5HT7 (Figure 5-39), 5HT2C (Figure 5-37), and α2 antagonism (Figure 5-35), and 5HT1A partial agonist actions (Figure 5-33), all of which may contribute to quetiapine's overall clinical profile, especially its robust antidepressant effects. Thus, quetiapine has an overall very complex set of binding properties to many neurotransmitter receptors, many of which have higher potency than to the D2 receptor, and this may account for why this drug appears to be far more than simply a drug for psychosis. In fact, like the others in this class, quetiapine is far more often prescribed for indications other than psychosis, including frequently as a hypnotic for insomnia, a drug for depression, for anxiety, for Parkinson's disease psychosis, or as an adjunct for psychosis with other 5HT2A/5HT1A/D2 drugs. Different Drug at Different Doses? The story of quetiapine dosing can be told as Goldilocks and the three bears (Figure 5-46).
For psychosis, quetiapine is an 800 mg Papa Bear. For depression, quetiapine is a 300 mg Mama Bear. For insomnia, quetiapine is a 50 mg Baby Bear. Starting with Baby Bear, only the most potent binding properties of quetiapine to the far left in the strip at the bottom of Figure 5-45 are relevant, especially H1 antihistamine properties (see also Figure 5-41). Baby Bear doses are not approved for use as a hypnotic, and this can be an option with metabolic risks, so is not considered a first-line option for sleep. At this dose, hypothetically there are insufficient numbers of 5HT2C receptors or NETs blocked for antidepressant efficacy; also, there is insufficient occupancy of D2 receptors for antipsychotic efficacy.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-55 Pre- and postsynaptic dopamine 2 receptor binding. (A) D2 receptors are present both pre- and postsynaptically; dopamine binding at

these receptors is inhibitory. (B) In psychosis, dopamine synthesis and release are enhanced, leading to excessive stimulation of postsynaptic D2 receptors. (C) Most D2 antagonists block both pre- and postsynaptic D2 receptors. Blockade of presynaptic D2 receptors disinhibits presynaptic dopamine release, thus further enhancing dopamine release. Full blockade of postsynaptic D2 receptors, however, can counter the effect of presynaptic D2 blockade. (D) Lumateperone is unusual among D2 antagonists in that it seems to be an antagonist at postsynaptic D2 receptors but a partial agonist at presynaptic D2 receptors. This would mean that less postsynaptic D2 antagonism would be necessary to achieve an antipsychotic effect, because dopamine release would already be diminished. D2 presynaptic antagonist D2 presynaptic agonist D2 Normal D2 presynaptic and postsynaptic antagonist D2 presynaptic agonist and postsynaptic antagonist Psychosis D2 postsynaptic antagonist D2 postsynaptic antagonist A C B D D2 D2 D2 D2 D2 D2 D2

Chapter 5: Targeting for Psychosis Figure 5-56 Aripiprazole’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of aripiprazole. Aripiprazole is a partial agonist at D2 receptors rather than an antagonist. Additional important pharmacological properties that may contribute to its clinical profile include 5HT2A antagonist actions, 5HT1A partial agonist actions, 5HT7 antagonist actions, and 5HT2C antagonist actions. Aripiprazole lacks or has weak binding potency at receptors usually associated with significant sedation. Aripiprazole also seems to lack the pharmacological actions associated with weight gain and increased cardiometabolic risk, such as increasing fasting plasma triglyceride levels or increasing insulin resistance. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. aripiprazole 5HT2B 5HT1A D2 D3 5HT7 5HT2C 5HT2A5HT1D D4 5HT6 5HT3 5HT1B H1 ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ + + + + + +++ +++ ++++ 5HT2A 5HT1D D2 D3 5HT2B 5HT7 5HT2C H1 2A 1A 2C 5HT1A α α α 1B α α1A α1B α2C α2A α2B Mama Bear at 300 mg range has robust antidepressant effects in depression by combining several simultaneous known antidepressant mechanisms discussed above. Thus, the combination of these antidepressant mechanisms would enhance dopamine and norepinephrine release (via norepinephrine reuptake inhibition, 5HT1A partial agonism, and 5HT2A, α2, and 5HT2C antagonism) and serotonin release (by 5HT7 antagonism) (see Chapter 7 for explanation and illustrations for all these antidepressant mechanisms). Especially when combined with selective serotonin reuptake inhibitors (SSRIs)/serotonin–

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-57 Brexpiprazole’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of brexpiprazole. Brexpiprazole is a partial agonist at D2 receptors rather than an antagonist, and also binds potently to 5HT2A, 5HT1A, and α1 receptors. Brexpiprazole also seems to lack actions at receptors usually associated with significant sedation, weight gain, and increased cardiometabolic risk, although it is too early to evaluate the clinical profile of this medication. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. brexpiprazole D2 D3 5HT2B 5HT7 D4 5HT2A 5HT1A 5HT2C H1 5HT1B 5HT6 D1 + ++++ ++++ ++++ ++++ ++++ 5HT2A D2 2C 5HT1A α 1B α α1B ++ ++ ++ ++ +++ +++ +++ α2C α1D +++ +++ +++ α1A norepinephrine reuptake inhibitors (SNRIs) there would be triple monoamine actions of increasing serotonin as well as norepinephrine and dopamine while simultaneously treating symptoms of insomnia and anxiety by antihistaminic action (Figure 5-45). Quetiapine is approved both for

bipolar depression and as an augmenting agent to SSRIs/SNRIs in unipolar depression that fails to respond sufficiently to those agents (in the US). Finally, Papa Bear is 800 mg quetiapine, which completely saturates both H1 histamine and 5HT2A receptors continuously in both cases, but has more inconsistent occupancy above 60% for D2 receptors, especially between doses. Quetiapine is approved both for schizophrenia/ schizophrenia maintenance (ages 13 and above) and for mania/mixed mania and maintenance (ages 10 and above). The pharmacology of quetiapine suggests why it is used more often in depression and insomnia than in

Chapter 5: Targeting for Psychosis Figure 5-58 Cariprazine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of cariprazine. Cariprazine has potent actions at D3, 5HT2B, D2, and 5HT1A receptors, with relatively weaker affinity for 5HT2A and H1 receptors. Cariprazine actually has higher affinity for the D3 receptor than dopamine does. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. cariprazine D2 ++++ 5HT2B ++++ D3 +++++ +++ +++ +++ +++ +++ 5HT1A 5HT2A ++ ++ H1 + α1B α1D α2A α1A 5HT7 + 5HT2C 1B α 1D α 2A α 1A α 5HT2A D2 5HT2B 5HT1A D3 Figure 5-59 Pimavanserin's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of pimavanserin. Pimavanserin is the only known drug with proven antipsychotic efficacy that does not bind to D2 receptors. Instead, it has potent 5HT2A antagonism (sometimes called inverse agonism) with lesser 5HT2C antagonist actions. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. pimavanserin 5HT2A ++++ +++ 5HT2C 5HT2A 5HT2C

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY additional serotonin receptor subtypes (Figure 5-47). This suggests that asenapine would have antidepressant actions, but only antipsychotic/antimanic actions have been proven. Asenapine is unusual in that it is given as a sublingual formulation, because it is not absorbed if it is swallowed. The surface area of the oral cavity for oral absorption limits the size of the dose, so asenapine is generally taken twice a day despite a long half-life. Since asenapine is rapidly absorbed sublingually with rapid peak drug levels, unlike other formulations that simply dissolve rapidly in the mouth but are followed psychosis. Quetiapine causes virtually no motor side effects nor prolactin elevations. However, quetiapine has at least moderate risk for weight gain and metabolic disturbances. Asenapine Asenapine (Figure 5-47) has a chemical structure related to the antidepressant mirtazapine and shares several of mirtazapine's pharmacological binding properties, especially 5HT2A, 5HT2C, H1, and α2 antagonism, plus many other properties that mirtazapine does not have, especially D2 antagonism, as well as actions upon many Figure 5-60 Sertindole's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of sertindole. Potent antagonist actions at α1 receptors may account for some of sertindole's side effects. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. sertindole 5HT2A 5HT2C 5HT6 D2 ++++ 5HT2A +++ 5HT2C +++ 5HT6 +++ +++ D2 ++ α1 α1 α2B α2C α2A ++ D1 D4 ++ 5HT7 5HT1D 5HT1B ++ ++ + DAT + + + + 5HT1A + M1 + 5HT1F 5HT1E +

5HT1A 5HT2A perospirone D4 D2 5HT2A 5HT1A ++++ ++++ ++++ +++ by delayed absorption (e.g., orally dissolving olanzapine preparations), asenapine can be used as rapid-acting oral PRN

(as needed) antipsychotic to “top up” patients without resorting to an injection. One side effect of sublingual administration in some patients is oral hypoesthesia; also, patients may not eat or drink for 10 minutes following sublingual administration to avoid the drug being washed into the stomach where it will not be absorbed. Asenapine can be sedating, especially upon first dosing, and has a moderate propensity for weight gain, metabolic disturbances, or motor side effects. It is approved for schizophrenia/maintenance in adults and Chapter 5: Targeting for Psychosis Figure 5-61 Perospirone’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of perospirone. 5HT1A partial agonist actions may contribute to efficacy for mood and cognitive symptoms. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. D2 D4 α2 α1 D1 ++ ++ + in the US for bipolar mania (ages 10 or older). It is also available in a transdermal formulation. Zotepine Zotepine (Figure 5-48) is available in Japan and Europe, but not the US. Zotepine has 5HT2A and D2 antagonist properties and is not as popular as other drugs for psychosis because it has to be administered three times a day. There may be an elevated risk of seizures. Zotepine is a 5HT2C antagonist, an α1 antagonist, a 5HT7 antagonist, and a weak partial agonist of 5HT1A receptors as well as a weak inhibitor of norepinephrine reuptake (NET), 233

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY 5HT2A blonanserin D3 D2 ++++ ++++ suggesting potential antidepressant effects that have not been well established yet in clinical trials. Many Dones and a Rone Risperidone Risperidone (Figure 5-49) is the original “done” and has a different chemical structure and a different pharmacological profile than the pines (compare pines and dones in Figure 5-32). Risperidone has favored uses in schizophrenia/maintenance (age 13 and older) and bipolar mania/maintenance (ages 10 and older). Some prefer this agent for children and adolescents in particular where it is also approved for treatment of Figure 5-62 Blonanserin’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of blonanserin. Blonanserin has high affinity for D3 receptors; in fact, it has higher affinity for D3 receptors than does dopamine itself. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. D2 D3 5HT2A ++++ irritability associated with autistic disorder, including symptoms of aggression towards others, deliberate self-injury, tantrums, and quickly changing moods (ages 5–16). Low-dose risperidone is occasionally used “off-label” for the controversial – due to a “black box” safety warning – treatment of agitation and psychosis associated with dementia. This practice may lessen as other drugs in the pipeline get approved for this indication. Risperidone is available in long-term depot injectable formulations lasting for 2 or 4 weeks and it can be useful to monitor plasma drug levels of risperidone and its active metabolite paliperidone, especially to guide dosing for patients receiving long-term depot

5HT2A σ roluperidone 5HT2A σ ++++ injections and who are treatment-resistant. There is also an orally disintegrating tablet and liquid formulation of risperidone. Although risperidone does have somewhat reduced motor side effects at lower doses, it raises prolactin levels even at low doses. Risperidone has a moderate amount of risk for weight gain and dyslipidemia. Weight gain can be particularly a problem in children. Paliperidone Paliperidone, the active metabolite of risperidone, is also known as 9-hydroxy-risperidone and like risperidone has 5HT2A and D2 receptor antagonism (Figure 5-50). One pharmacokinetic difference, however, between risperidone and paliperidone is that paliperidone, unlike risperidone, is not hepatically metabolized, but its elimination is based

upon urinary excretion and thus it has few pharmacokinetic drug interactions. Another pharmacokinetic difference is that the oral form of paliperidone is provided in a sustained-release oral formulation, which risperidone is not, and this actually changes some of the clinical characteristics of paliperidone compared to risperidone, a fact that is not Chapter 5: Targeting for Psychosis Figure 5-63 Roluperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of roluperidone. Still in clinical testing, roluperidone is a 5HT2A antagonist with additional σ2 antagonism. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. ++++ always well recognized and can lead to underdosing of oral paliperidone. Oral sustained release means that paliperidone only needs to be administered once a day, whereas risperidone, especially when treatment is initiated, and especially in children or the elderly, may need to be given twice daily to avoid sedation and orthostasis. Side effects of risperidone may be related in part to the rapid rate of absorption and higher peak doses with greater drug-level fluctuation leading to shorter duration of action, properties that are eliminated by the controlled release formulation of paliperidone. Despite the similar receptor binding characteristics of paliperidone and risperidone, paliperidone tends to be more tolerable, with less sedation, less orthostasis, and fewer motor side effects, although this is based upon anecdotal clinical experience and not head-to-head clinical studies. Paliperidone has moderate risk for weight gain and metabolic problems. Paliperidone is approved specifically for schizophrenia/maintenance (ages 12 and older).The main advantage of paliperidone over risperidone is that the long-acting injectable for paliperidone is easier to load, easier to dose, and has both a 1-month and a 3-month formulation, with studies in progress for a 6-month 235

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 5-64 Localization of trace amine-associated receptor type 1 (TAAR1). A new potential mechanism of antipsychotic action is agonism of the trace amine-associated receptor type 1 (TAAR1). TAAR1 is widely expressed throughout the brain, including in monoamine brainstem centers (dorsal raphe nucleus, ventral tegmental area) and in monoamine projection areas. amygdala hippocampus ventral tegmental area pituitary dorsal raphe nucleus TAAR1 prefrontal cortex hypothalamus bed nucleus stria terminalis formulation. It can be useful to monitor plasma drug levels to guide dosing, especially for patients receiving long-term depot injections and who are treatment-resistant. Ziprasidone Ziprasidone (Figure 5-51) is a 5HT2A/D2 antagonist with the major differentiating feature being that it has little or no propensity for weight gain or metabolic disturbances. However, it is short acting, requires more than once a day dosing, and must be taken with food. Earlier concerns about dangerous QTc prolongation by ziprasidone now appear to be exaggerated. Unlike iloperidone, zotepine, sertindole, and amisulpride, ziprasidone does not cause dose-dependent QTc prolongation, and few drugs have the potential to increase ziprasidone's plasma levels. Ziprasidone has an intramuscular dosage formulation for rapid use in urgent circumstances. Ziprasidone is approved in schizophrenia/maintenance and in bipolar mania/ maintenance. Iloperidone Iloperidone (Figure 5-52) also has 5HT2A/D2 antagonist properties. Its most distinguishing clinical properties include a very low level of motor side effects, low level of dyslipidemia, and moderate level of weight gain associated with its use. Its most distinguishing pharmacological property is its potent α1 antagonism (Figure 5-52). As discussed earlier in this chapter, α1 antagonism is generally associated with the potential for orthostatic hypotension and sedation, especially if rapidly dosed. Although iloperidone has an 18- to 33-hour half-life that theoretically supports once daily dosing, it is generally dosed twice daily and titrated over several days when initiated in order to avoid both

orthostasis and sedation. Slow dosing can delay onset of antipsychotic effects, so iloperidone is often used as a switch agent in non-urgent situations. It is approved in the US for schizophrenia/maintenance. Lurasidone Lurasidone is a 5HT2A/D2 antagonist (Figure 5-53) approved for use in schizophrenia and much more popular for use in bipolar depression. This compound exhibits high affinity for both 5HT7 receptors (Figure 5-39) and 5HT2A receptors (Figure 5-32), moderate affinity for 5HT1A (Figure 5-33) and α2 receptors (Figure 5-35), yet minimal affinity for H1 histamine and M1 cholinergic receptors (Figure 5-41), properties that may explain some of lurasidone's antidepressant profile, with low risk of weight gain or metabolic dysfunction. Risk of motor side effects or sedation are reduced if lurasidone is dosed at night. Due perhaps to the synergism amongst the several potential antidepressant properties accompanied by good tolerability, especially lack of weight gain, it is a highly effective agent for bipolar depression (ages 10 and older) and one of the preferred agents for this use in the countries where it is approved for this use such as in the US. Lurasidone is approved

Chapter 5: Targeting for Psychosis Figure 5-65 Agonism of trace amine-associated receptor type 1 (TAAR1). Trace amines are formed from amino acids when either the tyrosine hydroxylase (TYR) step or the tryptophan hydroxylase (TOH) step is omitted during production of dopamine or serotonin, respectively. (A) Dopamine is produced and packaged into synaptic vesicles, then released into the synapse. Dopamine binding at both pre- and postsynaptic D2 receptors can either trigger the inhibitory G (Gi) protein signal transduction cascade or the β-arrestin 2 signal transduction cascade. The β-arrestin 2 cascade leads to production of glycogen synthase kinase 3 (GSK-3); too much GSK-3 activation may be associated with mania or psychosis. (B) When TAAR1 receptors are bound by an agonist, they translocate to the synaptic membrane and couple with D2 receptors (heterodimerization). This biases the D2 receptor toward activating the Gi signal transduction cascade instead of the β-arrestin cascade. Presynaptically, amplification of the Gi pathway leads to inhibition of the synthesis and release of dopamine, which would be beneficial in cases of psychosis. Postsynaptically, amplification of the Gi pathway can lead to reduced production of GSK-3. D2 D2 TAAR1 TAAR1 -arrestin GSK-3 overstimulation and psychosis Gi -arrestin Gi D2 D2 TAAR1 TAAR1 TAAR1 agonist -arrestin Gi -arrestin Gi TOH TYR TYR DOPA DA E E TOH TYR TYR DOPA receptor dimerization receptor dimerization A B DA E E worldwide for schizophrenia/maintenance (ages 10 and higher) and because of its good tolerability it is often preferred for the treatment of children. A glutamate modulator D-cycloserine combined with lurasidone, called NRX101 (Cyclurad), combines antagonism of the glycine site of the NMDA receptor (see Figures 4-21, 4-22, 4-26, 4-27) with lurasidone, for the potential treatment of acute suicidal ideation and behavior, as well as for bipolar depression, with early positive findings. Lumateperone Lumateperone (Figure 5-54) is a more recently approved 5HT2A/D2 antagonist for schizophrenia. It has very high affinity for the 5HT2A receptor (Figure 5-32) and moderate affinity for D2, D1 (Figure 5-54), and α1 receptors (Figure 5-42), and low affinity for histamine H1 receptors (Figure 5-41). Unusually, lumateperone also has moderate affinity for the serotonin transporter (Figure 5-34). Early clinical experience suggests efficacy for schizophrenia without dose titration and good tolerability in terms of little or no weight gain or metabolic disturbances. Two key points on its mechanism of action include a wide separation between its 5HT2A antagonist and its D2 antagonist binding, perhaps explaining why it has antipsychotic actions at doses that have relatively low occupancy of D2 receptors, and maybe also why there are low D2-type side effects (e.g., little or no drug-induced parkinsonism

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY SEP-363856 5HT1D 5HT1A 5HT7 TAAR1 TAAR1 5HT1D 5HT1A 5HT7 Figure 5-66 SEP-363856’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of SEP-363856. A new potential mechanism of antipsychotic action is agonism of the trace amine-associated receptor type 1 (TAAR1). SEP363856 is an agonist at TAAR1 receptors; it also has 5HT1D, 5HT1A, and 5HT7 receptor binding properties. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. Figure 5-67 Xanomeline’s pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of xanomeline. Xanomeline is being studied for its potential use in psychosis because of its agonism at central muscarinic cholinergic receptors; specifically, the M4 and M1 receptors. Xanomeline also binds to multiple serotonin receptor subtypes. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated. xanomeline 5HT1B 5HT2B 5HT2C 5HT1A 5HT2A M1 M4 M3 +++ 5HT1D M3 M4 ++ ++ 5HT2B 5HT2C 5HT1B ++ ++ ++ 5HT1A M1 ++ ++ + + + 5HT7 5HT2A M2 + + + 5HT1E 5HT4 D3 5HT1D

or akathisia). The presence of moderate affinity for serotonin reuptake inhibition suggests antidepressant potential and indeed early studies in bipolar depression show promising efficacy. Although not yet clarified completely, preclinical evidence suggests a novel mechanism of action of lumateperone at D2 receptors. Recall that PET findings show enhanced presynaptic dopamine synthesis and release (Figures 4-15 and 4-16; also compare Figure 5-55A and B). Dopamine 2 blockers generally do not discriminate between presynaptic D2 receptors and postsynaptic D2 receptors (Figure 5-55C). When these D2 blockers are administered, they block presynaptic D2 receptors, causing disinhibition of presynaptic dopamine release, making things worse! Although that might be the last thing you want in treating schizophrenia psychosis, the solution is to so fully block the D2 receptors postsynaptically that this extra dopamine release does not matter (Figure 5-55C). However, in the case of lumateperone, preclinical evidence suggests that it may have presynaptic agonist actions and postsynaptic antagonist actions, a unique combination of mechanisms. How this may occur as an action potentially differentiating it from other D2 blocking drugs for psychosis is suggested by preclinical data showing potentially unique actions to reduce dopamine synthesis by either presynaptic tyrosine hydroxylase and other presynaptic protein phosphorylation or changes in glutamate-mediated ionic currents (Figure 5-55D). Whatever the mechanism, if presynaptic D2 agonism is caused by lumateperone rather than presynaptic antagonism characteristic of the other drugs in this class, lumateperone would theoretically turn off dopamine synthesis presynaptically to reduce the oversupply of dopamine present in presynaptic dopamine synapses in psychosis (Figure 5-55D). That would mean less postsynaptic D2 antagonism would be necessary to have an antipsychotic effect because dopamine release is already diminished. If lumateperone can be proven to have such a mechanism of presynaptic partial agonism of D2 receptors, combined with its well-established highly potent 5HT2A antagonism, this could account for why lumateperone has antipsychotic efficacy in schizophrenia with low amounts of postsynaptic D2 antagonism compared to most other drugs in this class (and low amounts of motor and metabolic side effects). Further investigations are needed to clarify this possible explanation. Lumateperone is also in clinical trials for bipolar depression. Chapter 5: Targeting for Psychosis Two Pips and a Rip Aripiprazole Aripiprazole is the original “pip” and is a D2/5HT1A partial agonist (see Figure 5-56). Because of its D2 partial agonist actions, aripiprazole has

relatively low motor side effects, mostly akathisia, and actually reduces prolactin rather than elevating it. It has only moderate affinity for 5HT2A receptors (Figure 5-32), but higher affinity for 5HT1A receptors (Figure 5-33). Aripiprazole is effective in treating schizophrenia/maintenance (age 13 and older) and also agitation (intramuscular) and bipolar mania/maintenance (ages 10 and older), and is also approved for use in various other child and adolescent groups, including autismrelated irritability (ages 5 to 17) and Tourette syndrome (ages 6 to 18). It is approved for adjunctive treatment to SSRIs/SNRIs for major depressive disorder, and this is by far its major use in clinical practice in the US. It is not approved for bipolar depression but commonly used off-label for that. How aripiprazole works in depression compared to how it works in schizophrenia is of course unknown, but its potent 5HT1A partial agonist (Figure 5-33) and 5HT2C and 5HT7 antagonist properties (Figures 5-37 and 5-39) are theoretical explanations for potential antidepressant actions, as these would be active at the low doses generally used to treat depression. Aripiprazole lacks the pharmacological properties normally associated with sedation, namely, muscarinic cholinergic and H1 histamine antagonist properties (Figure 5-41), and thus is not generally sedating. A major differentiating feature of aripiprazole is that it has, like ziprasidone and lurasidone, little or no propensity for weight gain, although weight gain can be a problem for some, including some children and adolescents. An intramuscular dosage formulation of aripiprazole for short-term use is available as an orally disintegrating tablet and a liquid formulation. One long-acting 4-week injectable and another 4- to 6- to 8-week long-acting injectable, the latter with a loading injection on the first day not requiring continuing oral loading, are available. These formulations are commonly used options for assuring compliance, especially in early-onset psychosis where aripiprazole’s favorable tolerability profile may be particularly well received. Brexpiprazole The second “pip” is brexpiprazole (Figure 5-57). Just as its name suggests, brexpiprazole is chemically and pharmacologically related to aripiprazole. However, it does differ pharmacologically from aripiprazole in that 239

 it has more potent 5HT2A antagonism (Figure 5-32), 5HT1A partial agonism (Figure 5-33), and α1 antagonism (Figure 5-42) relative to its D2 partial agonism (Figure 5-57) than aripiprazole (Figure 5-56), which should theoretically reduce its propensity to cause motor side effects and akathisia. There is some indication that there may be reduced akathisia with brexpiprazole compared to aripiprazole, but this has not been proven in head-to-head trials. Like aripiprazole, brexpiprazole is approved for the treatment of schizophrenia, but unlike aripiprazole, is not indicated for the treatment of acute bipolar mania. Brexpiprazole (Figure 5-57) has 5HT1A partial agonist (Figure 5-33) and relatively higher potency for α1 (Figure 5-42) and α2 (Figure 5-35) binding than aripiprazole. These properties could theoretically contribute to antidepressant actions (mechanisms further explained and illustrated in Chapter 7 on treatments for mood disorders). Alpha-1 actions in particular could theoretically help explain the efficacy brexpiprazole has demonstrated in some of its potential novel indications. Specifically, brexpiprazole is in late-stage clinical development with positive studies for the treatment of agitation in dementia (discussed further in Chapter 12 on dementia). There are also promising preliminary data for brexpiprazole when combined with the SSRI sertraline for the treatment of PTSD. Cariprazine Cariprazine (Figure 5-58) is the “rip” of this group and is another D2/5HT1A partial agonist approved for schizophrenia and also for acute bipolar mania. Cariprazine with its potent 5HT1A partial agonist actions (Figure 5-33) despite lesser 5HT2A antagonism (Figure 5-32) exhibits low incidence of drug-induced parkinsonism, but some akathisia, which can be much reduced by slow-dose titration. Cariprazine has two longto very long-lasting active metabolites with

the novel and interesting potential for development as a weekly or biweekly or even monthly “oral depot,” which takes longer to reach steady state but has less reduction in plasma drug levels as a dose is skipped. Cariprazine has proven to be a highly effective and well-tolerated agent for the treatment of bipolar depression in lower doses. Like lurasidone, which is also approved for bipolar depression, cariprazine has a very low propensity for weight gain or metabolic disturbance. Like other drugs in this class, cariprazine has both 5HT1A and α1 and α2 actions, suggesting antidepressant efficacy, but it is the very potent D3 partial agonist actions that are perhaps the most distinguishing and novel pharmacological characteristics. The role of D3 receptors is just now being clarified in humans since preclinical studies suggest therapeutic potential of D3 partial agonism for cognition, mood, emotions, and reward/substance abuse, as well as negative symptoms. In fact, cariprazine has been shown to be superior to D2/5HT2A antagonist treatment for the improvement of negative symptoms in schizophrenia. The mechanism of action of D3 partial agonism will be illustrated and explained in further detail in Chapter 7 on treatments for mood disorders. In brief, D3 antagonist/ partial agonist action may block key postsynaptic D3 receptors in limbic areas to reduce dopamine overactivity in emotional striatum and key somatodendritic presynaptic D3 receptors in the ventral tegmental area/ mesostriatal/integrative hub to increase dopamine release in the prefrontal cortex and improve negative, affective, and cognitive symptoms. For this reason, clinical trials and clinical experience suggest robust efficacy of cariprazine across the mood-disorder spectrum for all mixtures of mania and depression, as will be illustrated and described in Chapter 7. Selective 5HT2A Antagonist Pimavanserin Pimavanserin (Figure 5-59) is the only known drug with proven antipsychotic efficacy that does not have D2 antagonist/partial agonist actions. This agent has potent 5HT2A antagonist with lesser 5HT2C antagonist actions, sometimes called inverse agonism, as explained earlier in this chapter and as illustrated in Figure 5-15. The role if any of 5HT2C antagonism in the treatment of psychosis is not clear but 5HT2C antagonist actions would theoretically improve dopamine release in both depression and in the negative symptoms of schizophrenia. Indeed, pimavanserin is in testing as an augmenting agent to SSRIs/SNRIs, with some positive preliminary results in major depressive disorder, and as an augmenting agent to D2/5HT2A/5HT1A agents in negative symptoms of schizophrenia, also with positive results from early trials. It is approved for the treatment of psychosis in Parkinson’s disease and in late-stage testing for psychosis in dementia. The Others Sertindole Sertindole (Figure 5-60) is a 5HT2A/D2 receptor antagonist originally approved in some European countries, then withdrawn for further testing of its

cardiac safety and QTc-prolonging potential, and then reintroduced into certain countries as a second-line agent. It may be useful for some patients in whom other antipsychotics have failed, and who can have close monitoring of their cardiac status and drug interactions. Perospirone Perospirone (Figure 5-61) is another 5HT2A and D2 antagonist available in Asia to treat schizophrenia. 5HT1A partial agonist actions may contribute to its efficacy and/or tolerability. Its ability to cause weight gain, dyslipidemia, insulin resistance, and diabetes is not well investigated. It is generally administered three times a day, with more experience in the treatment of schizophrenia than in the treatment of mania. Blonanserin Blonanserin (Figure 5-62) is also a 5HT2A/D2 antagonist, available in Asia to treat schizophrenia, and is administered twice a day. Blonanserin has the unique property of higher affinity for the D3 receptor than dopamine has for the D3 receptor (like cariprazine), suggesting possible utility for the negative symptoms of schizophrenia and for bipolar depression, but it is not yet well studied in these indications. FUTURE TREATMENTS FOR SCHIZOPHRENIA Roluperidone (MIN-101) Roluperidone (Figure 5-63) is a 5HT2A

antagonist with additional σ2 antagonist actions, which is in study for schizophrenia. Early studies suggest possibly efficacy for negative symptoms, and trials are ongoing. D3 Antagonists In addition to cariprazine and blonanserin (both of which are unique in their highly potent D3 antagonist/ partial agonist properties), other D3 antagonists/partial agonists are in clinical trials. One is F17464, which has higher selectivity for D3 than for D2 or 5HT1A receptors, and which has shown efficacy in schizophrenia in early studies. Trace Amine Receptor Agonists and SEP-363856 An exciting new potential mechanism of antipsychotic action is trace amine agonism specifically acting at the trace amine-associated receptor type 1 (TAAR1). What is a trace amine and why would targeting its receptors have antipsychotic action? There are five principal trace Chapter 5: Targeting for Psychosis amines in humans and six human trace amine-associated receptors, but the most important receptor is TAAR1 (Table 5-3). Trace amines are formed from amino acids when the tyrosine hydroxylase (see Figure 4-2) step is omitted or the tryptophan hydroxylase (see Figure 4-36) step is omitted. Trace amines have long been a mystery as they are only present in trace amounts, are not stored in synaptic vesicles, and are not released upon nerve firing. The fact that TAAR1 receptors are localized in monoamine brainstem centers and in monoamine projection areas (Figure 5-64) has long made psychopharmacologists think that trace amines might be involved in regulating monoamine action even though trace amines are not neurotransmitters in their own right. Instead, trace amines have been called “the rheostat of dopaminergic, glutamatergic, and serotonergic neurotransmission,” maintaining central neurotransmission within defined physiological limits. The current hypothesized mechanism of antipsychotic action for TAAR1 agonists is that they act tonically both presynaptically and postsynaptically to prevent the dopaminergic hyperactivity of psychosis and mania (Figures 4-15 and 4-16). Thus, TAAR1 agonists are potentially a novel way to prevent dopamine overactivity at D2 receptors. How do they do this? TAAR1 receptors theoretically prevent dopamine overactivity after occupancy by an agonist through translocation to the synaptic membrane, where they couple with D2 receptors (called heterodimerization), which makes the second-messenger system decide to go with the inhibitory G (Gi) protein Table 5-3 Trace amines and their receptors Five principal trace amines in humans β-Phenylethylamine (PEA) p-Tyramine Tryptamine p-Octopamine p-Synephrine Six human trace amine-associated receptors (TAARs) TAAR1 (main TAAR in humans) TAAR2 TAAR5 TAAR6 TAAR8 TAAR9 241

 signal transduction cascade rather than the β-arrestin 2 pathway (Figure 5-65A, B). TAAR1 receptors can be said to “bias” D2 receptors away from β-arrestin 2 and towards Gi-protein-regulated second messengering (Figure 5-65B). Why does this matter? When heterodimerization with TAAR1 happens to presynaptic D2 receptors, the downstream consequences of the Gi pathway are amplified and those include inhibiting the synthesis and release of dopamine (presynaptic area of Figure 5-65B). That would be a good thing if dopamine is in excess presynaptically, as it seems to be in psychosis and in mania. When D2 receptor signaling postsynaptically is also shunted away from the β-arrestin 2 pathway to the Gi pathway by “biased” and heterodimerized postsynaptic D2 receptors, this theoretically mitigates the consequences of excessive signals through β-arrestin to excessive GSK-3 (glycogen synthase kinase 3) activation that results from postsynaptic D2 receptor overstimulation (postsynaptic area of Figure 5-65B). The bottom line of all this is that TAAR1 agonists may enhance presynaptic D2 autoreceptors (thus turning off dopamine synthesis and release) while simultaneously reducing some of the unwanted downstream functions of overly active postsynaptic D2 receptors (thus mitigating the effects of excessive dopamine release in psychosis and mania). Furthermore, TAAR1

agonism does both pre- and postsynaptic actions without actually directly pharmacologically blocking the D2 receptor! (Figure 5-65B). SEP-363856 (Figure 5-66) is an example of a TAAR1 agonist with weak affinity for the TAAR1 receptor as well as weaker affinities for the 5HT1D and 5HT7 receptors as antagonist and for the 5HT1A receptor as agonist. This drug surprisingly showed preclinical behavioral evidence of efficacy serendipitously for psychosis, and only then did its pharmacological and molecular mechanism of action on TAAR1 receptors get discovered. Already, an early study in patients with schizophrenia has confirmed antipsychotic action with few side effects, and the drug has been given breakthrough status by regulators. Further trials are ongoing. Cholinergic Agonists Activation of central muscarinic cholinergic receptors, either directly or by allosteric modulation, is under investigation as a novel antipsychotic mechanism. Preclinical and postmortem studies in patients with schizophrenia suggest that central cholinergic receptor alterations may be key to the pathophysiology of schizophrenia. M4 receptor agonism may reduce psychotic symptoms whereas M1 receptor agonism may be most relevant to improving the cognitive deficits of schizophrenia. Xanomeline (Figure 5-67), as an M4/M1 central agonist, decreases dopamine cell firing in the ventral tegmental area. This would theoretically reduce positive psychotic symptoms. Xanomeline also increases extracellular levels of dopamine in the prefrontal cortex, which theoretically would improve cognitive, negative, and affective symptoms. Xanomeline combined with tropsium, an anticholinergic that does not penetrate into the brain and that blocks M2 and M3 activated side effects in the periphery, has shown promising efficacy and tolerability for the psychotic symptoms of schizophrenia with improved side effects and is progressing as a potential breakthrough into advanced clinical trials. The known binding profile of xanomeline at muscarinic cholinergic receptors as well as serotonin receptors is shown in Figure 5-67. A Few Other Ideas Although several agents targeting glutamate neurotransmission have been studied in schizophrenia, most have not had consistently positive or robust efficacy findings. A novel idea still being pursued is to inhibit the enzyme DAO (D-amino acid oxidase) as a way to boost glutamate function (see Figure 4-22). Another novel approach to blocking the effects of hyperactive dopamine is to block the action of the enzyme phosphodiesterase type 9/10; several potential drugs are in clinical development. This mechanism alters the second-messenger signal transduction cascade of dopamine at D1 and D2 receptors and may have downstream effects similar to blocking D2 receptors, and do it more selectively in the dopamine neurons thought to be hyperactive in schizophrenia. SUMMARY This chapter reviews drugs used to treat psychosis, but has avoided the term “antipsychotics,” since these same agents are used more frequently for other indications such as unipolar and bipolar depression. Instead, the hypothetical mechanism of “antipsychotic action” is explored in detail. Specifically, this chapter reviews the pharmacology of drugs that treat psychosis, including those with predominantly D2 antagonist properties, those

with 5HT2A antagonist/D2 antagonist properties, those with D2/5HT1A partial agonist properties, and those with 5HT2A selective antagonist properties. These agents are compared and contrasted across these various dopamine and serotonin receptor subtypes and their receptor actions linked to hypothetical therapeutic actions as well as side effects. Multiple additional receptor binding properties at other neurotransmitter receptor sites that are hypothesized to be linked to additional clinical Chapter 5: Targeting for Psychosis actions of these agents, especially to their antidepressant actions, are presented and discussed. Still other receptor actions hypothetically linked to additional side effects are also presented. The pharmacological and clinical properties of two dozen specific drugs either marketed or in late-stage clinical trials are discussed in detail, including exciting new potential mechanisms of action at trace amine-associated receptors and at muscarinic cholinergic receptors. 243

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