

Describing an Atypical Antipsychotic: Receptor Binding and Its Role in Pathophysiology

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All antipsychotics have actions at dopamine-2 receptors, but the atypical agents behave differently than the conventional antipsychotics at those receptors. In addition, the atypical antipsychotics block serotonin-2 receptors. These differences in receptor-binding profiles provide the basis for 2 theories that explain why the 2 classes of antipsychotics are similar in efficacy but different in side effect profile, especially in their propensity to cause motor side effects such as extrapyramidal symptoms and tardive dyskinesia. (*Primary Care Companion J Clin Psychiatry* 2003;5[*suppl* 3]:9-13)

The atypical antipsychotics—clozapine, risperidone, olanzapine, quetiapine, and ziprasidone—have improved treatment for schizophrenia but have confused the terminology. These antipsychotics have been grouped into a new therapeutic class often referred to as *atypical*¹⁻⁴ (Table 1). Grouping these new agents together, despite some dissimilarities, helps to distinguish them as a class from most of the older conventional antipsychotics, which are clearly less tolerable and possibly less effective for negative symptoms.¹⁻⁵ Clinical characteristics, such as propensity for or lack of motor side effects such as extrapyramidal side effects (EPS) and tardive dyskinesia, can separate the atypical agents from the conventional drugs. Underlying the different clinical profiles are differences in receptor binding, especially at dopamine-2 (D₂) and serotonin-2A (5-HT_{2A}) receptors. While these drugs are bound to a receptor, that receptor is blocked from the naturally occurring substance, in this case, dopamine or serotonin. The improved tolerability of atypical antipsychotics is linked to reduced D₂ receptor blockade in parts of the brain where side effects are mediated. This reduced blockade, in turn, may be linked to antagonism of 5-HT_{2A} receptors, a drug's ability to quickly dissociate from D₂ receptors, or both.

DOPAMINE PATHWAYS AND THEIR FUNCTIONS

Four dopamine pathways in the brain play a role in the pathophysiology of schizophrenia as well as the therapeutic effects and side effects of antipsychotic agents (Figure 1).⁴ Activity in each of them has a unique set of physical, cognitive, and psychological effects. For example, dopamine hyperactivity in the mesolimbic dopamine pathway is thought to induce psychosis, so reducing dopamine activity in that pathway, such as by blocking receptors with an antipsychotic drug, will theoretically alleviate psychotic symptoms. Although D₂ receptor blockade may have a beneficial outcome in one pathway, it may cause problems in another.

Nigrostriatal Dopamine Pathway

The nigrostriatal dopamine pathway, as part of the extrapyramidal nervous system, controls movements.⁴ This pathway degenerates in Parkinson's disease, and blockade of D₂ receptors in this pathway causes the drug-induced movement disorders EPS and, eventually, tardive dyskinesia. Dopamine deficiency as well as receptor blockade in this pathway can also cause akathisia and dystonia.

Mesolimbic Dopamine Pathway

Hyperactivity in the mesolimbic dopamine pathway is thought to cause psychosis and the positive symptoms of schizophrenia such as hallucinations and delusions. This pathway is also thought to be involved in emotion and sensations of pleasure—stimulants and cocaine increase dopamine activity here. In fact, the paranoia and psychosis that can be induced by constant, long-term stimulant abuse are virtually indistinguishable from schizophrenia. Blocking hyperactivity in this pathway should reduce or eliminate positive symptoms.⁴

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Table 1. Types of Antipsychotics

Atypical antipsychotics ^a	
	Clozapine
	Risperidone
	Olanzapine
	Quetiapine
	Ziprasidone
Examples of conventional (typical) antipsychotics	
Phenothiazines	
	Chlorpromazine
	Fluphenazine
	Mesoridazine
	Perphenazine
	Pimozide
	Thioridazine
	Trifluoperazine
Butyrophenones	
	Haloperidol
	Droperidol
Thioxanthenes	
	Thiothixene

^aAripiprazole is not included in this list because of differences in mechanism of action from the atypical antipsychotics listed here.

Mesocortical Dopamine Pathway

The role of the mesocortical dopamine pathway, especially in schizophrenia, is still open to debate. This pathway is thought to control cognitive function, and dopamine deficiency in this pathway may be responsible for the negative and cognitive symptoms of schizophrenia. If this is the case, it presents a therapeutic challenge, since dopamine receptor blockade in this pathway would theoretically lead to a worsening of negative and cognitive symptoms. In other words, an agent would have to decrease dopamine in the mesolimbic pathway to alleviate positive symptoms but increase it in the mesocortical pathway to treat negative and cognitive symptoms.⁴

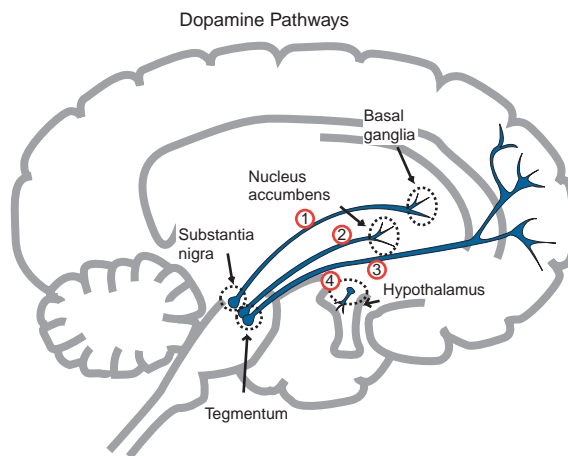
Tuberoinfundibular Dopamine Pathway

Normal function of the tuberoinfundibular dopamine pathway inhibits prolactin release. In postpartum women, activity in this pathway decreases, allowing lactation. If normal function of this pathway is disrupted, for example, by D₂-blocking drugs, hyperprolactinemia can occur, with side effects such as galactorrhea, amenorrhea, and sexual dysfunction.⁴

HYPOTHESES OF ATYPICALITY

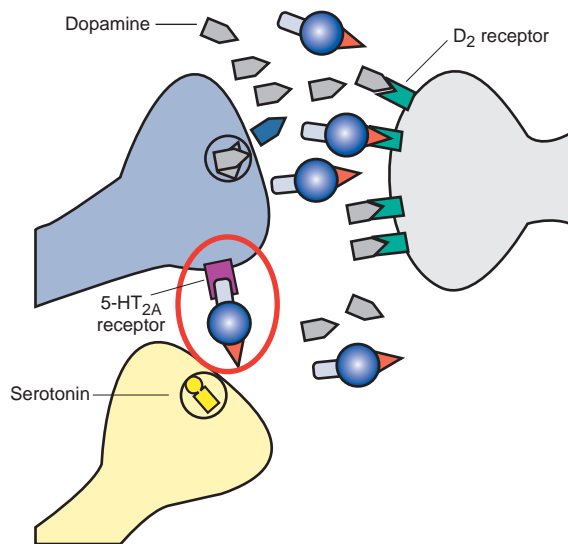
All antipsychotics have actions at D₂ receptors in the brain. One way to distinguish the atypical antipsychotics from the conventional agents is that they block 5-HT_{2A} receptors as well as D₂ receptors and have fewer motor side effects such as EPS than the conventional antipsychotics have at standard doses.¹⁻⁹ One atypical antipsychotic (quetiapine) has no more EPS than placebo.⁸ Additionally, at least 2 antipsychotics (olanzapine and risperidone) have shown greater efficacy than a conventional antipsychotic for negative symptoms, and 3 (olanzapine, ziprasidone,

Figure 1. Four Dopamine Pathways in the Brain^a



^aReprinted with permission from Stahl.⁴ The pathways are (1) the nigrostriatal pathway, (2) the mesolimbic pathway, (3) the mesocortical pathway, and (4) the tuberoinfundibular pathway.

Figure 2. Dopamine Receptor Blockade Reversed by Serotonin Receptor Blockade in the Nigrostriatal Dopamine Pathway^a



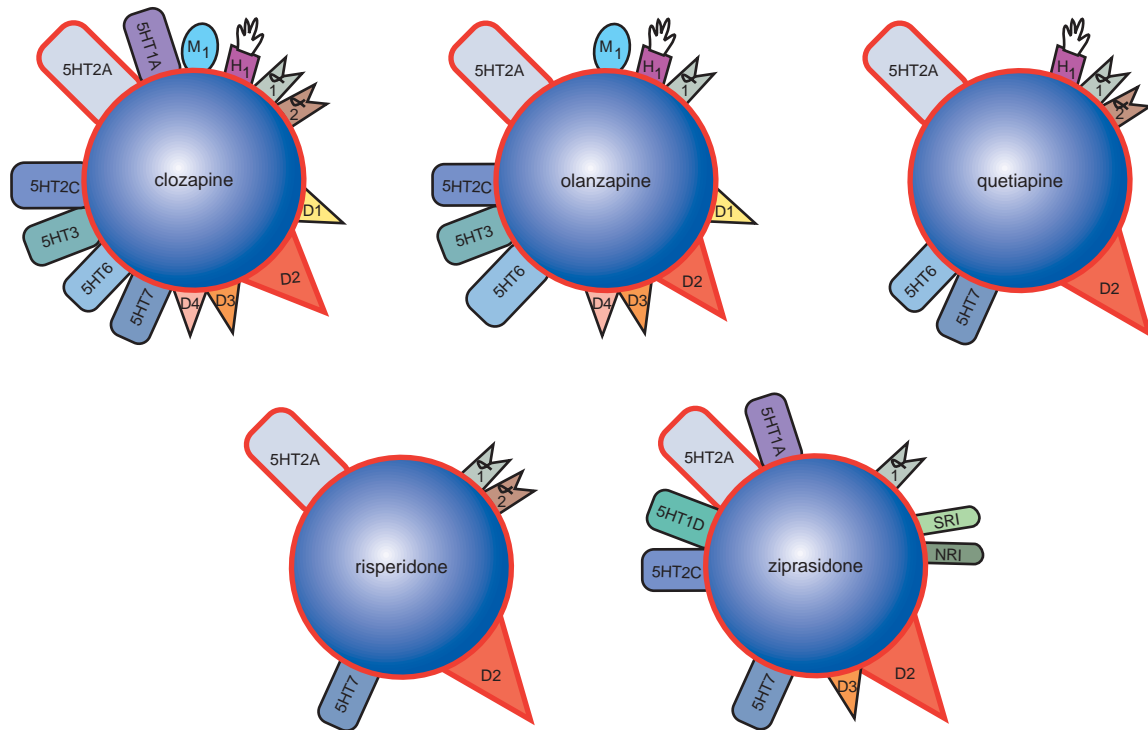
^aReprinted with permission from Stahl.⁴ Abbreviations: D₂ = dopamine-2, 5-HT_{2A} = serotonin-2A.

and quetiapine) do not raise prolactin levels like the conventional drugs do.⁶⁻⁸ Ziprasidone is associated with less weight gain compared with conventional and other atypical antipsychotics.¹⁻³

Serotonin

Atypical antipsychotics have antipsychotic actions with much reduced or no motor side effects like EPS and tardive dyskinesia.⁴ Theoretically, this effect could be the result of blockade of 5-HT_{2A} receptors in addition to D₂ receptors.^{4,5} Serotonin regulates dopamine release: the pres-

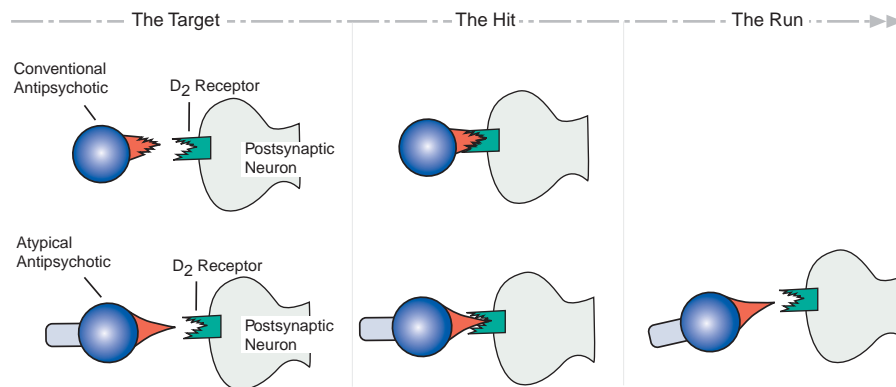
Figure 3. Receptor Binding Profiles of the Atypical Antipsychotics^a



^aReprinted with permission from Stahl.¹¹

Abbreviations: α_1 = α_1 -adrenergic, α_2 = α_2 -adrenergic, D = dopamine, 5HT = serotonin, H = histamine, M = muscarinic, NRI = norepinephrine reuptake inhibitor, SRI = serotonin reuptake inhibitor.

Figure 4. “Hit-and-Run” Actions at Dopamine Receptors: Conventional vs. Atypical Antipsychotics^a



^aReprinted with permission from Stahl.¹⁴

Abbreviation: D₂ = dopamine-2.

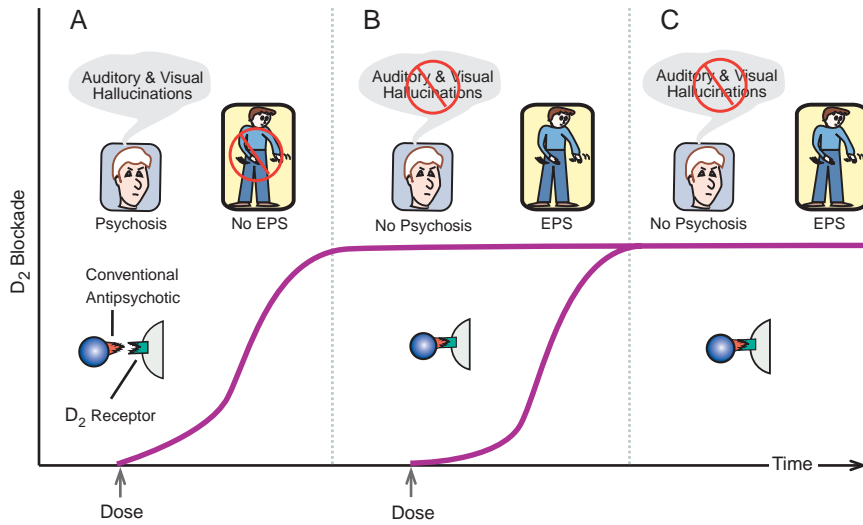
ence of serotonin in some dopamine pathways, such as the nigrostriatal pathway, inhibits the release of dopamine, whereas in the mesolimbic dopamine pathway, serotonin has little or no effect.

In other words, when 5-HT_{2A} receptors are blocked, dopamine is released in the nigrostriatal dopamine pathway but is not released in the mesolimbic dopamine pathway.

In the nigrostriatal pathway, this reaction may reverse some of the D₂ blockade by atypical antipsychotics through a process called *disinhibition*. When serotonin receptors are blocked in this pathway, dopamine levels increase. The naturally occurring dopamine is then “disinhibited” and fills D₂ receptors, preventing blockade by the antipsychotic agent. With less D₂ blockade in nigrostriatal pathways, motor side effects are reduced (Figure 2).

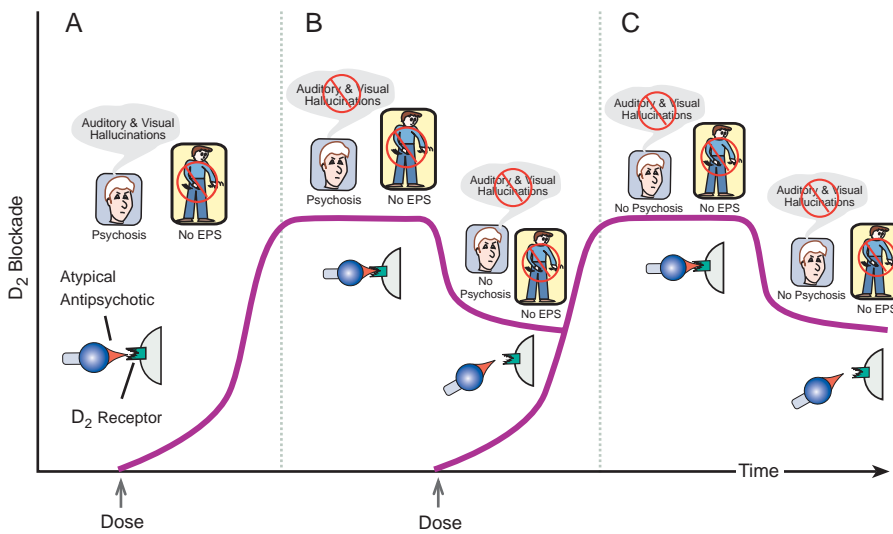
However, disinhibition in the nigrostriatal pathway does not affect the blockade of D₂ binding in the mesolimbic dopamine pathway, since few 5-HT_{2A} receptors are in the mesolimbic dopamine pathway; thus antipsychotic actions are preserved. According to this hypothesis, antipsychotics are atypical when their 5-HT_{2A} antagonism superimposed on their D₂ antagonism reduces their D₂ binding enough to reverse motor side effects but not enough to reverse antipsychotic effects.^{4,5,10}

Figure 5. Hypothetical Action of a Conventional Antipsychotic Over Time^a



^aReprinted with permission from Stahl.¹⁴ Section A is prior to dosing, when the patient experiences psychosis but no EPS. In sections B and C, the patient has received a dose of a conventional antipsychotic and is no longer psychotic, but does experience EPS due to the tight and persistent blockade of D₂ receptors. Abbreviations: D₂ = dopamine-2, EPS = extrapyramidal symptoms.

Figure 6. Hypothetical Action of an Atypical Antipsychotic Over Time^a



^aReprinted with permission from Stahl.¹⁴ Section A is prior to dosing, when the patient experiences psychosis but no EPS. After a dose of an atypical antipsychotic in section B, the drug initially blocks but then slides off the D₂ receptor; the amount of D₂ blockade decreases somewhat until another dose in section C. Antipsychotic actions are persistent, but EPS do not have the chance to develop. Abbreviations: D₂ = dopamine-2, EPS = extrapyramidal symptoms.

How many, if any, of the atypical properties are due to serotonin antagonism remains open to debate. There are at least 16 receptors where 1 or more of the new drugs interact.¹⁻³ In addition, no 2 atypical agents have an identical receptor-binding profile, providing a possible explanation for some of the differences clinicians observe from one

drug to another and from one patient to another (Figure 3).¹¹ These ancillary pharmacologic properties, in addition to 5-HT₂ and D₂ antagonism, include binding to D₁, D₃, and D₄ receptors; to 5-HT_{1A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, and 5-HT₇ receptors; to α₁-adrenergic, α₂-adrenergic, histamine H₁, and muscarinic cholinergic receptors; and to serotonin and norepinephrine reuptake pumps.¹⁻⁹

Many of the old antipsychotics bind to α₁-adrenergic, muscarinic, and histaminic receptors in addition to D₂ receptors⁴; however, a few traditional antipsychotics also bind to the 5-HT_{2A} receptor just like the new antipsychotics. These include loxapine, chlorpromazine, and thioridazine.^{9,12}

Dopamine

Another hypothesis of atypicality is that, although all antipsychotics have actions at D₂ receptors, the dopamine blockade with atypical agents lasts only long enough to cause an antipsychotic action but not long enough to cause the side effects associated with conventional agents.¹³ Theoretically, it takes only a quick blockade of the D₂ receptor to cause an antipsychotic action, but a longer-lasting action to cause motor side effects such as EPS. Thus, if the antipsychotic has “hit-and-run” actions, also called *rapid dissociation*, it dissociates from D₂ receptors after antipsychotic actions are established but before motor side effects are induced. In Figure 4, the conventional antipsychotic’s teeth fit tightly with the grooves in the receptor, representing the tight and long-lasting blockade with those agents.¹⁴ The atypical antipsychotic, however, fits neatly in the receptor, but is smooth and able to slide back out, to hit and then run, so to speak.

The receptor is then available, briefly, to naturally occurring dopamine before the next dose.

According to this hypothesis, lack of motor side effects comes from low D₂ binding due to rapid dissociation, not reversal by 5-HT_{2A} antagonism. Support for the hit-and-run hypothesis of atypical antipsychotic action is based in part

on evidence from positron emission tomography scans of patients taking antipsychotics, which shows that when D₂ binding in the striatum is high, even in the presence of high 5-HT_{2A} binding in the cortex, motor side effects still occur.¹⁵

Also, rapid dissociation from the D₂ receptor in vitro is a good predictor of low potential for motor side effects.¹⁶ Since rapid dissociation occurs more readily when the drug has low potency, low-potency agents (i.e., those requiring higher milligram doses such as clozapine and quetiapine) have faster dissociation from the D₂ receptor than high-potency agents (i.e., those requiring lower milligram doses such as risperidone), with intermediate-potency agents such as olanzapine in the middle. This hierarchy roughly correlates with the tendencies of these drugs to cause motor side effects within the group of atypical antipsychotics and also sets all of them apart from the conventional antipsychotics. This difference between low- and high-potency atypical antipsychotics also points to the need for careful dosing, especially with the high-potency agents, to maximize antipsychotic action but minimize side effects such as movement disorders.

One of the consequences of fast dissociation is that the drug is gone from the receptor until the next dose. Natural dopamine can then bathe the receptor for a while before the next dose of the drug. It is possible that a bit of real dopamine in the nigrostriatal dopamine system is all that is needed to prevent motor side effects. If enough natural dopamine is available in the nigrostriatal pathway to minimize these side effects but not enough is available in the mesolimbic dopamine system to reactivate psychosis between doses, the drug will have atypical antipsychotic clinical properties (Figures 5 and 6).

CONCLUSION

Either 5-HT_{2A} antagonism or fast dissociation from D₂ receptors may define the atypicality of an antipsychotic. To have little or no motor symptoms from an antipsychotic, it is clear that D₂ receptor binding in the striatum must be less than that caused by conventional antipsychotics. Pure 5-HT_{2A} antagonism by itself does not result in robust antipsychotic actions. However, 5-HT_{2A} antagonism can reduce D₂ antagonism and thereby reduce motor symptoms without reversing antipsychotic actions. If, however, this 5-HT_{2A} antagonism is overwhelmed by too much D₂ antagonism, it cannot result in such atypical antipsychotic actions.

Another route to reducing D₂ receptor binding appears to be a shorter binding time, also known as rapidly dissociating from the D₂ receptor. Many of the agents with atypical antipsychotic clinical properties “hit” the D₂ receptor hard enough to cause antipsychotic effects and then “run” before they cause motor side effects like EPS.

Although these agents are classified as antipsychotics, the nomenclature should not intimidate clinicians interested in using these agents. Instead, one can demystify them by

calling them *serotonin-dopamine antagonists*, or, by seeing the similarities with antiparkinsonian agents, *dopamine modulators*. Hopefully, with a basic understanding of the mechanism of action of these agents, clinicians in both psychiatry and primary care will be able to recognize their benefits and manage their side effects more effectively.

Drug names: aripiprazole (Abilify), chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril and others), droperidol (Inapsine and others), fluphenazine (Permitil, Prolixin, and others), haloperidol (Haldol and others), loxapine (Loxitane and others), mesoridazine (Serentil), olanzapine (Zyprexa), perphenazine (Trilafon and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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