Receptor Pharmacology of Neuroleptics: Relation to Clinical Effects

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This article reviews the receptor pharmacology of neuroleptics, with a focus on newer drugs (e.g., risperidone, olanzapine, sertindole, quetiapine, and ziprasidone) in contrast to older compounds. All these newer compounds are considered to be atypical neuroleptics based upon certain criteria, which are reviewed. Several hypotheses about the molecular mechanisms that explain atypicality are considered. Finally, the in vitro receptor binding data presented for these compounds are related to the therapeutic and adverse effects of these drugs. *(J Clin Psychiatry 1999;60[suppl 10]:5–14)*

The decade of the 1990s is living up to its name as the Decade of the Brain in the field of psychopharmacology. Since the beginning of this decade, 5 new neuroleptics and 6 new antidepressants have been approved for use in the United States by the Food and Drug Administration (FDA) or are in the approval process. The new neuroleptics (also called antipsychotic drugs, major tranquilizers, and antischizophrenic drugs) in order of their date of FDA approval are risperidone, olanzapine, sertindole,* quetiapine, and ziprasidone (Figure 1). These drugs, along with the prototypical drug clozapine, marketed in 1989 in the United States, are all considered atypical neuroleptics.

What is an atypical neuroleptic? This is one question that this article will attempt to answer, along with the question of whether any of the older generation neuroleptics (e.g., thioridazine or loxapine) may also be classified as atypical.

Advances in molecular pharmacology in the past few decades have greatly increased our understanding of the actions of neuroleptics. Thus, molecular pharmacologic studies on the first generation of these compounds show that many of the older neuroleptics have numerous actions at many different sites in the nervous system. Rhône-Poulenc Rorer Pharmaceuticals, Inc., a French pharmaceutical company that marketed chlorpromazine, was well aware of the multitude of effects of this first neuroleptic, because it was given the trade name Largactyl, meaning "large number of actions." We now know that many of these actions relate to specific neurotransmitter receptor blocking effects of these drugs and that many of these actions produce unwanted effects. Thus, several newer generation neuroleptics have been selected in preclinical screening because they lack some of these properties (e.g., antimuscarinic effects).

In addition, many of the newer neuroleptics were selected on the basis of their having certain receptor binding properties, which are theoretically predictive of atypicality. These theories are based in part on animal studies and in part on new information that has come from the stellar progress in the molecular biology of neurotransmitter receptors.

This article presents an overview of the molecular pharmacologic actions of neuroleptics at the level of neurotransmitter receptors. Information on both newer and older generation compounds is presented. These data can be of use to the clinician to understand the basis of some adverse effects of neuroleptics and some of their drug interactions.

DRUGS AVAILABLE IN THE UNITED STATES

In the United States, neuroleptics for clinical use come in a multitude of chemical classes: phenothiazine, thioxanthene, butyrophenone, rauwolfia alkaloid, indolic derivative (indolone), dibenzoxazepine, dibenzodiazepine, diphenylbutylpiperidine, benzisoxazole, imidazolidinone, and benzisothiazole. Only the phenothiazine class has more than 2 derivatives clinically available. There are 2

*Although sertindole was approved by the FDA, it may never be marketed in the U.S. because of the drug's potential cardiovascular side effects and the attendant FDA requirement for prominent display of this information in the package insert.

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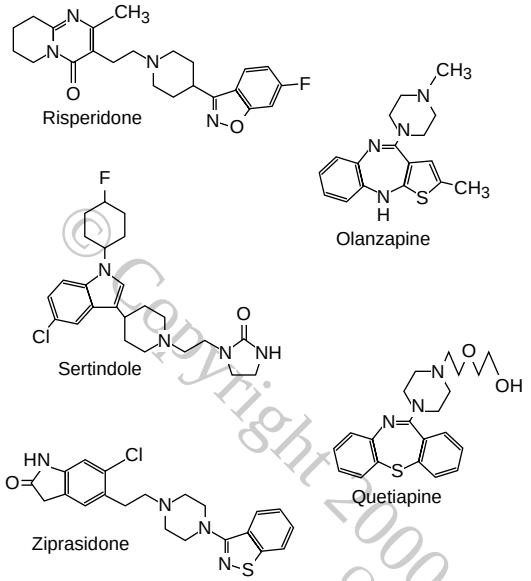
Figure 1. Structures of Some of the Newest Neuroleptics Approved for Marketing in the United States or in the Approval Process



thioxanthenes and 1 compound for each of the other classes.

Although the diphenylbutylpiperidine pimozide may be considered a new generation neuroleptic, it is not marketed in the United States for treating psychoses. Instead, it is approved for use in Tourette's disorder for those who do not respond to standard treatment. It also may be useful for treating delusional parasitosis.[1]

The newest neuroleptics marketed or approved for marketing in the United States are shown in Figure 1. These include the structurally similar drugs olanzapine (dibenzodiazepine) and quetiapine (dibenzothiazepine), both of which resemble clozapine (dibenzodiazepine), and the structurally distinct compounds sertindole (imidazolidinone), risperidone (benzisoxazole), and ziprasidone (benzisothiazole), which bears some structural similarity to risperidone.

THE DEFINITION OF AN ATYPICAL NEUROLEPTIC

Each of these new antipsychotic drugs is presently classified as an atypical neuroleptic. Although there is no unanimous agreement about the criteria to define a neuroleptic as atypical, there are certain features derived from preclinical and clinical studies that can be used as a general guideline. For example, Meltzer et al.[2] defined an atypical neuroleptic on the basis of both clinical and preclinical criteria. More recently, Kinon and Lieberman[3] have defined it solely on the basis of clinical criteria. On these latter criteria, an atypical neuroleptic is a drug that has antipsychotic efficacy, has a low propensity to cause extrapyramidal side effects with short-term treatment, and does not cause tardive dyskinesia with long-term treatment or (in the absence of long-term studies) causes a small elevation of serum prolactin levels. In addition, clozapine has apparent efficacy for treating the negative signs and symptoms (e.g., social withdrawal, flattened affect) of schizophrenia in some[4] but not all studies.[5] As a result, the additional criterion of efficacy in treating the negative signs and symptoms of schizophrenia, along with treating the positive signs and symptoms, is sometimes added to the definition of an atypical neuroleptic.[3]

In the early stages of drug development, when few or no clinical data are available, the finding of no or weak potential to cause catalepsy in preclinical studies is also a criterion to classify a neuroleptic as atypical.[2] In addition, as discussed below, the relative affinity of a neuroleptic for serotonin-2A (5-HT_{2A}) receptors over dopamine D_2 receptors also has some predictive value for classifying drugs as atypical neuroleptics.[2,6] The affinity of a drug for a receptor is a measure of how tightly it binds to that receptor and has units of the inverse of molarity (mol/L).

HYPOTHESES TO EXPLAIN WHY A NEUROLEPTIC IS ATYPICAL

In the past 15 years, several basic research findings have provided hypotheses about what makes a neuroleptic atypical. This research, which spans many different disciplines, includes studies of the receptor pharmacology of neuroleptics at dopamine, serotonin,[2,7–9] and muscarinic[10–12] receptors, electrophysiologic studies with rats treated chronically with drugs,[13,14] and molecular biological studies measuring the expression of immediate early genes.[15] From this basic research comes the reasonable conclusion that no single hypothesis explains why a particular drug behaves as an atypical neuroleptic. In other words, it is likely that different drugs are atypical for different reasons. However, for several of the atypical drugs presently available, atypicality may derive from their relative potencies for blocking dopamine D_2 and 5-HT_{2A} receptors. Reduction in brain serotonergic function, which can be achieved in part by blocking serotonin receptors (Figure 2), has long been known to reduce extrapyramidal effects of neuroleptics in animal studies.[16,17]

Blockade of Dopamine and Serotonin Receptors

There is general agreement that in vitro binding affinity of neuroleptics for dopamine D_2 receptors (Figure 3) predicts efficacy, daily dosage, and likelihood of causing extrapyramidal side effects.[18–20] This relationship, which is based on in vitro binding data, has been supported by in vivo radioligand binding studies with positron emission tomography (PET).[21,22] These PET studies show that the therapeutic effects of neuroleptics, with the exception of

Figure 2. Mitigation of Dopamine D_2 Receptor Blockade by Blockade of Serotonin 5-HT_{2A}

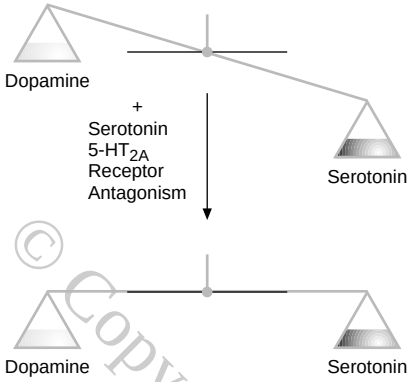
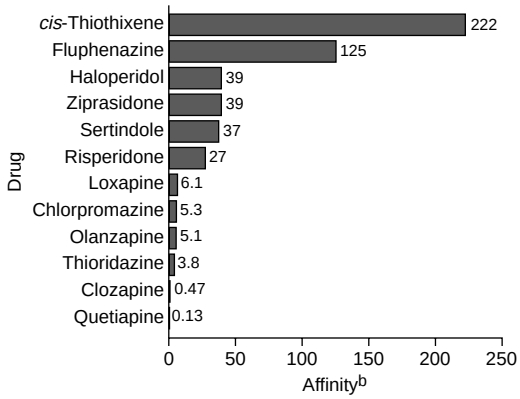


Figure 3. Neuroleptics and Dopamine D_2 Receptor Blockade[a]



[a]Affinity data from references 68 and 69.
[b]$10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

clozapine and, possibly, olanzapine, are achieved beginning at about 70% dopamine D_2 receptor occupancy, while extrapyramidal side effects are generally seen at higher D_2 receptor occupancies.[21–23] In addition, from these types of PET studies, some atypical neuroleptics at usual clinical dosages cause greater than 80% 5-HT_{2A} receptor occupancy in conjunction with less than 80% D_2 receptor occupancy.[24]

Thus, although dopamine D_2 receptor occupancy is related to extrapyramidal side effects, blockade of 5-HT_{2A} receptors with high affinity, in addition, appears to mitigate against the extrapyramidal side effects of neuroleptics (see Figure 2).[2,25,26] This serotonergic receptor blockade (Figure 4) may also be the underlying mechanism for the efficacy of an atypical neuroleptic to treat the negative signs and symptoms of schizophrenia.

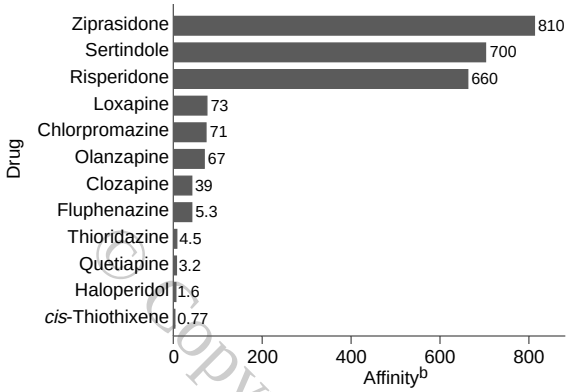
Reduced dopaminergic function in the nigrostriatal pathway leads to parkinsonism and other extrapyramidal problems. Increased serotonergic tone in this area similarly can reduce dopaminergic neurotransmission (an explanation for the extrapyramidal side effects sometimes seen with antidepressants that block transport of serotonin), while reduced serotonergic function in this pathway has the opposite effect.[16,17,25–27] Thus, blockade of brain 5-HT_{2A} receptors, which clinically is a way to reduce serotonergic function, biochemically opposes and, therefore, moderates the reduction in dopaminergic function resulting from blockade of dopamine D_2 receptors (see Figure 2).

Increased dopamine function in the mesolimbic pathway may be responsible for the positive clinical manifestations of schizophrenia, while decreased dopamine function in the prefrontal cortex may be responsible for the negative signs and symptoms.[28] Animal studies suggest that antagonism of 5-HT_{2A} receptors increases dopamine and serotonin levels in the limbic system.[29] This enhancement may also occur in the prefrontal cortex. These results would predict efficacy of an antagonist of 5-HT_{2A} receptors to treat the negative signs and symptoms of schizophrenia. This hypothesis is supported by a well-controlled trial with ritanserin,[30] which blocks 5-HT_{2A} and 5-HT_{2C} receptors. In that study, ritanserin was effective in reducing negative signs and symptoms. It is also possible, of course, that serotonin plays a more direct role in schizophrenia than just modulating levels of dopamine.[31]

The correlation is reasonably strong, but not perfect, for predicting that a drug is atypical if the logarithm of its affinity for 5-HT_{2A} receptors (Figure 4) divided by the logarithm of its affinity for dopamine D_2 receptors (see Figure 3) is greater than 1 (Figure 5).[2,6] For example, by this criterion loxapine and its metabolite amoxapine, as well as chlorpromazine and thioridazine, would be classified as atypical neuroleptics (Figure 5). However, PET studies with loxapine show that in vivo it is equipotent at blocking dopamine D_2 and 5-HT_{2A} receptors.[32] On the other hand, similar studies with amoxapine suggest that this antidepressant drug fits the criteria for being an atypical neuroleptic, since its in vivo blockade of 5-HT_{2A} receptors was much greater than its blockade of dopamine D_2 receptors at usual clinical dosages.[33]

Both loxapine and amoxapine are metabolized into 7-hydroxy and 8-hydroxy derivatives.[34–37] For patients taking oral loxapine, blood levels of both 8-hydroxyloxapine and 8-hydroxyamoxapine are higher than that for loxapine (by 2- to 4-fold and 2- to 3-fold, respectively).[35,37] Levels of the 7-hydroxy derivatives are generally low. An occasional patient, however, will have relatively high levels of 7-hydroxyloxapine,[35] which is the most active at human dopamine D_2 and serotonin 5-HT_{2A} receptors, relative to loxapine, amoxapine, 7-hydroxyamoxapine, and the respective 8-hydroxy metabolites (Figures 6A and 6B). The logarithm of the affinity for 5-HT_{2A} receptors divided by the logarithm of the affinity for dopamine D_2 receptors for loxapine and metabolites is presented in Figure 7. Whether clinical response and adverse effects are different depend-

Figure 4. Neuroleptics and Serotonin 5-HT$_{2A}$ Receptor Blockade[a]



[a]Affinity data from references 68 and 69.
[b]$10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

Figure 5. Neuroleptics: Ratio of the Logarithm of the Affinity for Serotonin 5-HT$_{2A}$ Receptors Over the Logarithm of the Affinity for Dopamine D$_2$ Receptors

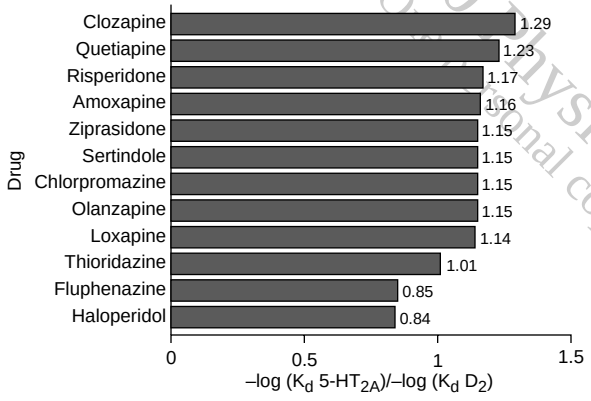
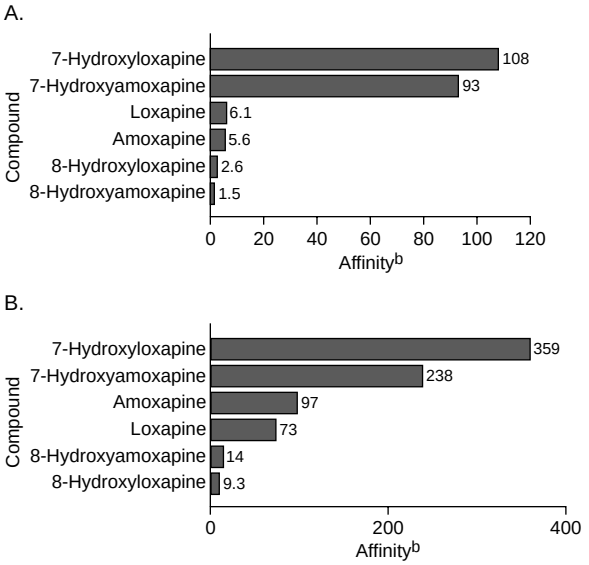
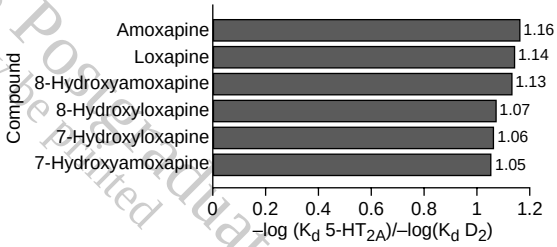


Figure 6. Loxapine, Amoxapine, and Metabolites at (A) Dopamine D$_2$ Receptor Blockade and (B) Serotonin 5-HT$_{2A}$ Receptor Blockade[a]



[a]Affinity data from E.R., unpublished data, 1999.
[b]$10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

Figure 7. Loxapine, Amoxapine, and Metabolites: Ratio of the Logarithm of the Affinity for Serotonin 5-HT$_{2A}$ Receptors Over the Logarithm of the Affinity for Dopamine D$_2$ Receptors[a]



[a]Affinity data from E.R., unpublished data, 1999.

ing on the levels of these metabolites are questions for future research.

One caution in focusing on one serotonin receptor subtype as the key to atypicality is that to date researchers have molecularly cloned 13 subtypes of the human serotonin receptor (more have been cloned in nonhuman species).[38] As receptors are molecularly cloned, subtypes are almost invariably also discovered. From biochemical pharmacologic studies, researchers knew that there were several subtypes of receptors for serotonin. However, certainly no one imagined that there were so many. Similar statements may be made for muscarinic and dopamine receptors. With all these and other receptors, the pharmacology is decades behind the molecular biology. So, sorting out the physiologic roles and pharmacologic relevance of the various subtypes of receptors will be a long time in coming.

Nonetheless, recent studies with the molecularly cloned serotonin 5-HT$_6$ receptor[9,39] suggest that clozapine's high-affinity binding to this site explains the pharmacologic uniqueness of this neuroleptic and, possibly, some others as well. One can imagine now that a selective serotonin 5-HT$_6$ receptor antagonist is being designed for clinical trials in schizophrenia.

Similarly, several years ago, with the molecular cloning of the dopamine D$_4$ receptor,[7] clozapine was found to bind with high affinity to this dopamine receptor subtype. Therefore, it was hypothesized that this property of clozapine, which more recently has been shown to be a property of other neuroleptics,[8] explained its atypicality. However, the excitement generated about the role of this dopamine receptor subtype in the pathophysiology of schizophrenia was dampened by a clinical trial showing no efficacy of a selective D$_4$ receptor antagonist in acutely psychotic schizophrenic patients.[40]

Figure 8. Mitigation of Dopamine D_2 Receptor Blockade by Muscarinic m1 Receptor Blockade

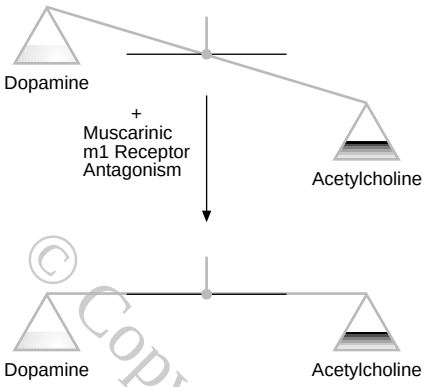
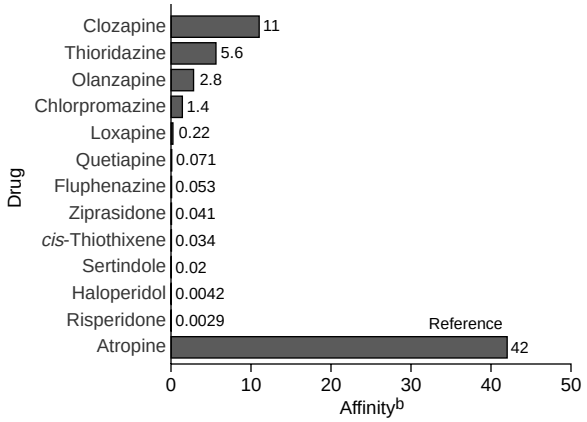


Figure 9. Neuroleptics and Muscarinic Receptor Blockade[a]



[a]Affinity data are from references 68 and 69 and were determined with a radioligand that is not specific for the different subtypes of muscarinic receptors.
[b]$10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

The dopamine D_4 receptor is but 1 of at least 5 subtypes of the dopamine receptor. They are classified as D_1-like (D_1 and D_5 subtypes) or D_2-like (D_2, D_3, and D_4).[41] The dopamine D_2 subtype exists in a short (D_{2S}) and a long (D_{2L}) form. These 2 forms result from variations in the splicing of the mRNA, when the gene is transcribed ("splice variants"). There appears to be little pharmacologic difference between these 2 forms of the D_2 subtype. In addition, the clinical significance of blocking D_1, D_3, D_4, and D_5 receptors is uncertain.

Although probably the least abundant of all the dopamine receptor subtypes in brain, the dopamine D_4 receptor has attracted considerable interest because of clozapine's higher affinity for this receptor than for dopamine D_2 receptors[41]; it exists in alternate forms (polymorphisms) in the population,[42] which are not associated with schizophrenia,[43,44] and there is a report of a 6-fold higher level of this receptor in brains of patients with schizophrenia.[45] This last result is controversial, because an indirect binding assay is needed to measure these sites, which recently have been called "D_4-like" in a follow-up study.[46] In this recent study, there was a 3-fold elevation of "D_4-like" sites in brains of schizophrenic patients. However, using the unequivocal assay for dopamine D_4 receptors, namely, mRNA levels for this protein, researchers have found no increased expression of this dopamine receptor subtype in brains of schizophrenic patients.[47]

Interactions With Muscarinic Receptors

For neuroleptics, there is an inverse relationship between their affinity for muscarinic receptors and their incidence of causing extrapyramidal side effects, a fact that has been in the literature for well over 2 decades.[48,49] This relates, in part, to the mitigating effects on dopamine receptor blockade by blocking muscarinic receptors in the extrapyramidal system (Figure 8). Thus, clozapine, one of the neuroleptics least likely to cause extrapyramidal side effects, is one of the most potent neuroleptics at blocking muscarinic receptors (Figure 9). With the molecular cloning of 5 subtypes of the muscarinic receptor,[50,51] it became possible to study clozapine and other neuroleptics for their affinities for the various muscarinic receptor subtypes.

Clozapine has high affinity and selectivity for the m1* subtype of the muscarinic receptor.[10,52] Data for olanzapine[53] are similar to those for clozapine. The m1 subtype is the most abundant and the m5 the least abundant in most areas of the human brain.[54]

Does high affinity and selectivity for muscarinic m1 receptors make a neuroleptic atypical? It is possible that this is one of the properties needed. However, since putative atypical drugs like quetiapine, ziprasidone, and sertindole are weak muscarinic antagonists (see Figure 9), blockade of muscarinic receptors is not necessary to be atypical. In addition, adding a muscarinic antagonist to a typical neuroleptic does not make it behave biochemically as an atypical one.[55]

In light of the potent antimuscarinic effects of clozapine, this drug has a very curious side effect, namely, sialorrhea. Decreased salivation, not increased salivation, would be expected of a muscarinic antagonist. Yet the hypersalivation produced by clozapine can be treated with a muscarinic antagonist.[56,57]

That sialorrhea is caused by clozapine suggests that it is a muscarinic agonist, which in fact has been shown to be the case.[11,58] Working with the molecularly cloned human muscarinic receptors expressed in Chinese hamster ovary cells, Zorn and colleagues[11] showed that clozapine was able to activate the m4 genetic subtype of the muscarinic

*The genetic subtype of the muscarinic receptor is denoted with a lowercase "m" and a number, which is not subscripted. The pharmacologic subtype is denoted by an uppercase "M" and a subscripted number.

receptor. My colleagues and I have confirmed and extended these findings.[58] Although this property can explain the uniqueness of clozapine and some other atypical drugs, such as olanzapine,[58] we could not demonstrate this effect in rat brain tissue.

Effects on Dopaminergic Neuronal Electrical Activity

Depolarization block and *depolarization inactivation* are the phrases used to describe the occurrence of a dramatic decrease in the number of spontaneously active A9 (substantia nigra pars compacta) and A10 (ventral tegmental area) dopaminergic neurons when rats are treated chronically with neuroleptics.[13,14,59] A9 neurons are involved with the extrapyramidal side effects of neuroleptics, and A10 neurons may be involved with the therapeutic effects of these drugs. Thus, depolarization inactivation of dopaminergic neurons in the A9 and A10 areas by neuroleptics has important clinical implications. However, the significant finding is that atypical neuroleptics, unlike typical neuroleptics, affected only the A10 neurons. These results suggest why atypical neuroleptics cause few, if any, extrapyramidal side effects.

However, Mereu et al.,[60–62] who have brought attention to the inconsistencies in the literature on this topic, presented data to suggest that depolarization inactivation is an artifact brought about by the use of general anesthetics. These researchers suggest that the dopaminergic neuronal stimulation produced by these anesthetics in combination with increased excitability of these neurons from chronic treatment with neuroleptics produces this phenomenon. Nonetheless, this model system remains a good predictor of atypicality.

SIDE EFFECTS AND DRUG INTERACTIONS OF NEUROLEPTICS CAUSED BY RECEPTOR BLOCKADE

As is already apparent, neuroleptics are antagonists of several different neurotransmitter receptors. Some of this antagonism may relate to therapeutic properties, including atypicality, and some to adverse effects. Thus, the affinity of a neuroleptic for a particular receptor may be predictive of the likelihood that the drug will cause certain unwanted effects in patients (Table 1). The higher the affinity of a drug, the more likely it is to cause these problems, unless there is a mitigating influence from blockade of another receptor related to a particular adverse effect (see Table 1). The following will correlate potential adverse effects and drug interactions that may occur as a result of this receptor blockade.

Blockade of Dopamine D_2 Receptors

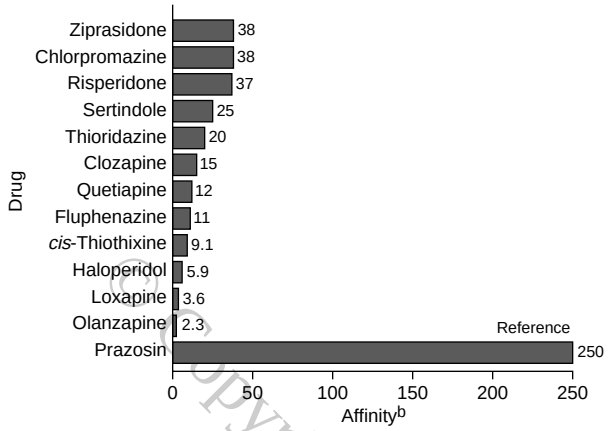
When a selected list of neuroleptics is rank ordered from the most potent to the least potent (see Figure 3), *cis*-thiothixene is the most potent. This drug is about 1700-fold more potent than the weakest compound, quetiapine, which is a putative atypical neuroleptic. The rank order of neuroleptics is predictive of the likelihood that these compounds will cause certain endocrinologic and extrapyramidal side effects. For example, *cis*-thiothixene will more likely cause a parkinsonian-like picture and galactorrhea than will chlorpromazine. Thus, low neuroleptic affinity at the dopamine D_2 receptor suggests low propensity to cause these extrapyramidal and endocrine problems.

Elevated serum levels of prolactin, which result from neuroleptic blockade of the dopamine receptors in the pituitary, can subsequently cause galactorrhea, menstrual changes and, in males, sexual dysfunction (impotence).[63] The galactorrhea that results in some patients from neuroleptic-induced elevation of prolactin can be especially

Table 1. Possible Therapeutic and Adverse Effects of Receptor Blockade by Neuroleptics

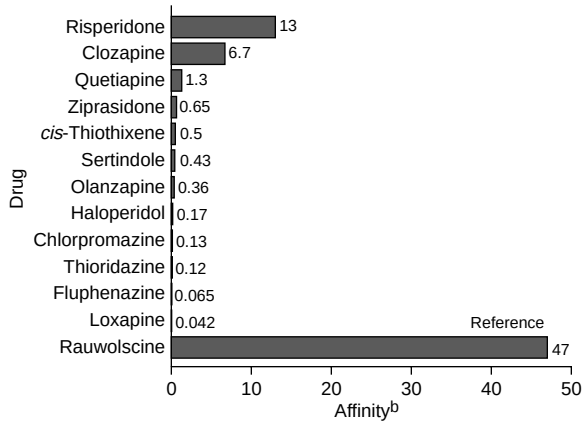
Blockade of dopamine D_2 receptors
Therapeutic effects
Amelioration of the positive signs and symptoms of psychosis
Adverse effects
Extrapyramidal movement disorders: dystonia, parkinsonism, akathisia, tardive dyskinesia, rabbit syndrome
Endocrine effects: prolactin elevation (galactorrhea, gynecomastia, menstrual changes, sexual dysfunction in males)
Blockade of α_1-adrenoceptors
Therapeutic effects
Unknown
Adverse effects
Potentiation of the antihypertensive effect of prazosin, terazosin, doxazosin, and labetalol
Postural hypotension, dizziness
Reflex tachycardia
Blockade of α_2-adrenoceptors
Therapeutic effects
Unknown
Adverse effects
Blockade of the antihypertensive effects of clonidine hydrochloride, guanabenz acetate, and methyldopa
Blockade of histamine H_1 receptors
Therapeutic effects
Sedation
Adverse effects
Sedation
Drowsiness
Weight gain
Potentiation of central depressant drugs
Blockade of muscarinic receptors
Therapeutic effects
Mitigation of extrapyramidal side effects
Adverse effects
Blurred vision
Attack or exacerbation of narrow-angle glaucoma
Dry mouth
Sinus tachycardia
Constipation
Urinary retention
Memory dysfunction
Blockade of serotonin 5-HT_{2A} receptors
Therapeutic effects
Amelioration of the negative signs and symptoms of psychosis
Mitigation of extrapyramidal side effects
Adverse effects
Unknown

Figure 10. Neuroleptics and α_1-Adrenoceptor Blockade[a]



[a]Affinity data from references 68 and 69.
[b]$10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

Figure 11. Neuroleptics and α_2-Adrenoceptor Blockade[a]



[a]Affinity data from references 68 and 69.
[b]$10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

bothersome and can be treated with a switch to a drug with lower affinity for the dopamine D_2 receptors or with cautious use of bromocriptine.

The extrapyramidal side effects of neuroleptics can be divided into those of early onset (acute dyskinesia, akathisia, and parkinsonism) and those of late onset (tardive dyskinesia and, rarely, the rabbit syndrome). The early-onset problems occur within the first 10 weeks of therapy and are always reversible. The only relatively common late-onset extrapyramidal side effect is tardive dyskinesia, which is by definition caused by neuroleptics and is not always reversible. Tardive dyskinesia is characterized by abnormal involuntary, persistent movements of the tongue, lips, and facial, and sometimes trunk, muscles. The rabbit syndrome, a rare extrapyramidal side effect occurring late, although clinically similar to tardive dyskinesia, is distinguished from this disorder by its responsiveness to treatment with antimuscarinic agents. Again, the available clinical data seem to suggest that neuroleptics with low affinity for the dopamine D_2 receptor (or high affinity for the $5\text{-}HT_{2A}$ or muscarinic m1 receptor) will have low propensity to cause these extrapyramidal problems.

Blockade of α-Adrenoceptors

There are 2 major subclassifications of α-adrenergic receptors—α_1 and α_2—and neuroleptics competitively antagonize each (Figures 10 and 11). These receptors are located both in the central and in the peripheral nervous systems, where they are involved with presynaptic and postsynaptic effects of norepinephrine. An important role is played by these receptors in the regulation of blood pressure. In addition, norepinephrine has been implicated in the pathophysiology of depression and psychosis. Further, it has been suggested that blockade of these receptors (especially the α_2 subtype) with high affinity confers atypical properties on a neuroleptic.[64]

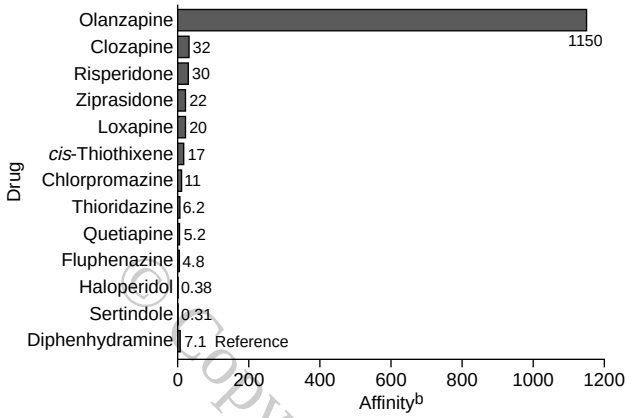
In general, neuroleptics are much more potent at blocking α_1- than α_2-adrenoceptors (see Figures 10 and 11). Few (e.g., risperidone and clozapine) are potent at α_2-adrenoceptor blockade (see Figure 11). Thus, most neuroleptics in clinical practice will likely cause significant blockade at the α_1-adrenoceptor. This may cause postural hypotension, dizziness, and a reflex form of tachycardia (see Table 1). In addition, nasal congestion is likely a side effect due to potent α_1-adrenoceptor blockade. If any of these side effects become very bothersome and tolerance to these effects does not occur, then the patient should be given a trial with a drug with lower affinity at the α_1-adrenoceptor (see Figure 10).

At the α_2-adrenoceptor of human brain, risperidone is the most potent and loxapine is the least potent of the neuroleptics shown as antagonists of this receptor in Figure 11. In general, most of these drugs are absolutely weak at these receptors, so that their effects on the α_2-adrenoceptor in clinical practice should be minimal, except, perhaps, for a few drugs at the top of the list (see Figure 11). However, a therapeutic or side effect associated with blockade of the α_2-adrenoceptor is unknown. Such an effect would not likely be related to the atypical effects of neuroleptics,[64] since α_2-adrenoceptor blockade is a weak property of many of the atypical drugs (see Figure 11 and reference 65). Nonetheless, α_2-adrenoceptor blockade may reduce the effectiveness of those antihypertensive agents thought to work by ultimately stimulating the α_2-adrenoceptor (see Table 1).

Blockade of Histamine H_1 Receptors

Neuroleptics also antagonize the histamine H_1 receptor (Figure 12). Histamine is a neurotransmitter in brain where, like elsewhere in the body, it has at least 3 types of receptors, histamine H_1, H_2, and H_3.[66] In brain, histamine receptors are thought to be involved with a number of

Figure 12. Neuroleptics and Histamine H_1 Receptor Blockade[a]



[a]Affinity data from references 68 and 69.
[b]$10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

functions including arousal (H_1) and the regulation of appetite (H_1). Outside the nervous system, classically, histamine H_1 receptors are involved with allergic reactions, and histamine H_2 receptors are involved with gastric acid secretion. Histamine H_3 receptors affect release of histamine and other neurotransmitters from nerve endings.

Many neuroleptics are more potent than the classical antihistamine diphenhydramine (see Figure 12) at blocking histamine H_1 receptors. Among the selected group of neuroleptics (see Figure 12), olanzapine and clozapine are the most potent. In fact, olanzapine is by far the most potent of all neuroleptics and may be the most potent histamine H_1 antagonist known.

The antihistaminic (H_1) property of these drugs likely relates to their ability to cause sedation and drowsiness. Because sedation is the most common side effect of histamine H_1 antagonists, they are used clinically as sedative-hypnotics. In addition, neuroleptics with high affinity for the histamine H_1 receptor will potentiate the actions of central depressant drugs, which also cause sedation and drowsiness (in most cases by other mechanisms).

Finally, histamine H_1 receptor blockade by neuroleptics and other compounds may play a role in the appetite-stimulating effects of these drugs. A switch to a drug that is less potent as an antihistamine (see Figure 12) may alleviate this problem. Consistent with these predictions is the fact that olanzapine commonly causes somnolence and weight gain.[67]

Blockade of Muscarinic Acetylcholine Receptors

The vast majority of acetylcholine receptors are muscarinic in brain, where they are thought to be involved with memory and motor functions, among other things. In the periphery, some important functions of this receptor are the control of gastrointestinal motility and micturition. The rank order of potency of these drugs based upon their affinities in binding assays with a nonselective muscarinic antagonist (3-quinuclidinyl benzilate) shows that clozapine is the most potent and risperidone is the least potent at blocking the muscarinic receptor (see Figure 9).

Although no antipsychotic drug is more potent than the classic antimuscarinic drug atropine at blocking the muscarinic receptor, clinically significant muscarinic receptor blockade will occur in patients given the drugs at the top of the list in Figure 8 owing to the high doses and, therefore, high receptor levels achieved in clinical practice. Atropine is used at 1 mg or less, reflecting its high affinity for the muscarinic receptor, whereas a drug such as clozapine is used at 100 or more times that amount. Receptor pharmacology predicts that the percentage of receptors occupied (bound) by a drug is dependent on the affinity *and* the concentration of the drug at the receptor site. Thus, a drug with a relatively low affinity for a receptor can achieve the same degree of receptor blockade as a drug of relatively high affinity, but to do so the drug with lower affinity needs to be present at a higher concentration at the receptor site.

The antimuscarinic property of these drugs may result in several different types of side effects (see Table 1). For example, it may cause memory dysfunction or urinary retention. Again, low affinity for the muscarinic receptor suggests a low propensity to cause antimuscarinic side effects. Thus, by choosing a drug low on the list (see Figure 9), these side effects should be minimized. On the other hand, this property mitigates against the extrapyramidal effects due to dopamine D_2 receptor blockade (see Figure 8).

SUMMARY

From this review of the pharmacology of neuroleptics, one could speculate about some of the pharmacologic criteria for the ideal neuroleptic. This ideal drug might be a much more potent antagonist of the serotonin 5-HT_{2A} and muscarinic m1 receptors than of dopamine D_2 receptors. It would also have little or no affinity for histamine H_1 and α-adrenergic receptors. Although pharmacokinetics was not discussed here, this ideal neuroleptic would also have an elimination half-life allowing once-per-day dosing. Meeting this later criterion are olanzapine, sertindole, and risperidone (when its active metabolite, 9-hydroxy-risperidone, is considered). A review of the receptor binding data presented here suggests that we do not yet have the ideal neuroleptic, but we do have in the newer generation compounds those that may be closer to that ideal than the older generation compounds.

Nonetheless, data presented here should allow the physician to anticipate certain adverse effects and drug interactions of the older as well as the newer compounds, as these latter drugs become available. Thus, the clinician is given a rational basis for understanding these unwanted effects and for selecting neuroleptics to minimize these effects in their patients.

Drug names: amoxapine (Asendin), bromocriptine (Parlodel), chlorpromazine (Thorazine and others), clonidine (Catapres), clozapine (Clozaril), diphenhydramine (Benadryl and others), doxazosin (Cardura), droperidol (Inapsine), fluphenazine (Prolixin and others), guanabenz (Wytensin and others), haloperidol (Haldol and others), labetalol (Normodyne, Trandate), loxapine (Daxolin, Loxitane), methyldopa (Aldomet and others), olanzapine (Zyprexa), pimozide (Orap), prazosin (Minipress), quetiapine (Seroquel), risperidone (Risperdal), terazosin (Hytrin), thioridazine (Mellaril and others), thiothixene (Navane).

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