Atypical Antipsychotics: Matching Receptor Profile to Individual Patient's Clinical Profile

By Darius K. Shayegan, BS, and Stephen M. Stahl, MD, PhD

FOCUS POINTS

- The mechanistic inner-workings thought to underlie both pharmacologic and clinical class actions possessed by atypical antipsychotics may ultimately owe to the inherent utility of each compound's 5-HT2A/D2 receptor-relative–binding affinity ratio.
- Rapid dissociation of atypical antipsychotics from D_2 receptors is also believed to contribute to overall antipsychotic efficacy and decreased incidence of extrapyramidal symptoms.
- Appropriate dosing remains a critical issue and ultimately a prerequisite for optimizing the therapeutic effects and tolerability profile of each atypical antipsychotic.

ABSTRACT

Understanding common pharmacologic and clinical "class" actions associated with atypical antipsychotics certainly reveals how these agents are alike, but what about unique differences from one agent to another? Atypical antipsychotics are also a heterogeneous group of agents that have complex pharmacologic entities, acting upon multiple dopamine receptors (D_2, D_1, D_3, and D_4) and multiple serotonin receptors (5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, and 5-HT_{1D}, among others). Atypical antipsychotics also interact with noradrenergic (α_1- and α_2-adrenergic receptor blockade), histaminergic (H_1-receptor blockade), and cholinergic (muscarinic M_1 blockade) neurotransmitter systems as well as with monoamine (D, 5-HT, and norepinephrine reuptake blockade) transporters. However, no two atypical antipsychotics possess the same portfolio of actions upon all of these additional neurotransmitter systems.

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INTRODUCTION

Atypical antipsychotics are the preferred first-line treatments for schizophrenia, owing to their ability to effectively manage the positive and negative symptoms of schizophrenia while minimizing extrapyramidal side effects (EPS). Furthermore, the utility of these agents as mood stabilizers with application for treatment within bipolar illness has also recently been recognized. Understanding individual differences among the various atypical antipsychotics may provide many of the answers to common clinical questions. Why does one patient respond to one agent, and not another? Why do some patients experience side effects with one agent, yet others do not? Are these drugs interchangeable in their antipsychotic or mood-stabilizing effects? How well do different agents address other independent symptom domains of disease? This review will examine the similarities and differences among atypical antipsychotics in terms of their mechanisms of action and clinical efficacy. The strategy of matching the best receptor profile to each individual patient's clinical profile as a means for obtaining a favorable treatment outcome will also be assessed.

BACKGROUND

Having now celebrated the 50th anniversary of the introduction of classical neuroleptics into clinical practice, these conventional antipsychotics very successfully demonstrated the relationship between dopamine (D_2) receptor blockade and clinically robust antipsychotic action. In fact, all available antipsychotic agents target the key hypothetical neurochemical disturbance in psychosis—excessive dopamine neurotransmission at D_2 receptors in the mesolimbic pathway of the brain—presumably responsible for the positive symptoms of schizophrenia. Building upon the classical model of mesolimbic D_2 antagonism, present day atypical antipsychotics extend upon this theme, offering comparable if not better control over positive symptoms of psychosis, while maintaining a dramatically reduced propensity for causing motor side effects typically associated with conventional agents.

This more clinically desirable therapeutic and tolerability profile of the five first-line atypical antipsychotics—aripiprazole, ziprasidone, quetiapine, olanzapine, and risperidone—is due largely to their serotonin

This article is based on information presented at the 157th Annual Meeting of the American Psychiatric Association, held May 1–6, 2004, in New York City. Since the data were presented, aripiprazole, quetiapine, and ziprasidone were approved by the US Food and Drug Administration for the treatment of acute bipolar mania. Other atypical antipsychotics previously approved for the treatment of acute bipolar mania include olanzapine and risperidone.

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$(5\text{-HT})_{2A}/D_2$ antagonist or D_2 receptor partial agonist actions—properties that contribute to improved antipsychotic efficacy, reduced motor side effects, and a variety of potential mood-stabilizing effects.[1-5] In fact, in addition to having properties of $5\text{-HT}_{2A}/D_2$ antagonism/partial agonism, atypical antipsychotics also exert substantial blockade of D_2 receptors with concomitant comparable or greater functional blockade of 5-HT_{2A} receptors at clinically therapeutic doses. It is predominantly these features that are considered pharmacologic actions shared by all atypical antipsychotics as a class; they are thought to account for the universal ability of these agents to mitigate the positive symptoms of schizophrenia and other disorders of psychosis and potentially exert a variety of other mood-stabilizing effects. The mechanistic inner-workings thought to underlie both pharmacologic and clinical class actions possessed by atypical antipsychotics may ultimately owe to the inherent utility of each compound's $5\text{-HT}_{2A}/D_2$ receptor-relative–binding affinity ratio (Figure 1).[6-8]

When maximized through optimal dosing of each agent, it is the fundamental binding affinity relationship between drug and receptor that allows atypical antipsychotics to leverage and apply their associated class properties of D_2 and 5-HT_{2A} antagonism or partial agonism within key neurocircuits involved in the pathophysiology of disease.

WHAT IS SO GREAT ABOUT 5-HT_{2A} ANTAGONISM?

Although 5-HT_{2A} antagonism alone has been associated with the potential for antipsychotic activity, by itself this property does not appear to confer antipsychotic effects comparable to those attributed to classical D_2 antagonism.[9,10] Rather, 5-HT_{2A} antagonism functions to reduce dopamine D_2 antagonism in key pathways, which can help to avoid motor symptoms without reversing antipsychotic activity. In the mesolimbic dopamine pathway, 5-HT_{2A} antagonism does not reverse D_2 antagonism to the extent that it would interfere with antipsychotic actions. In the mesocortical pathway, 5-HT_{2A} antagonism may help to increase dopamine release enough to improve negative and cognition symptoms mediated in this pathway. In the nigrostriatal dopamine pathway, the opposition of dopamine release by serotonin would act to decrease the likelihood of causing motor side effects. Thus, the superimposition of 5-HT_{2A} antagonism on D_2 antagonism in this pathway reduces D_2 binding sufficiently that enough D_2 receptor blockade in the striatum is reversed, ultimately reducing liability for EPS.

This concert of $5\text{-HT}_{2A}/D_2$ antagonist/partial agonist actions has been previously analogized as a kind of seesaw that "teeters" and "totters" until achieving balance in the distressed circuits outlined above.[11] Rapid dissociation of atypical antipsychotics from D_2 receptors is also believed to contribute to overall antipsychotic efficacy and decreased incidence of EPS.[12] These agents—clozapine and quetiapine, in particular—are thought to exhibit a "hit-and-run" action at the dopamine D_2 receptor, hitting this receptor with sufficient force (binding affinity) to result in antipsychotic effects, yet binding weakly enough to run (dissociate) off the receptor before causing EPS.[13]

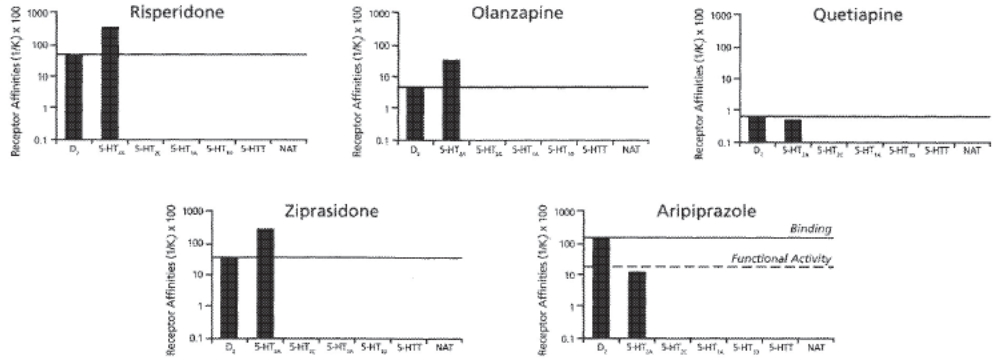

FIGURE 1. All Atypical Antipsychotics Have Relevant 5-HT_{2A} and D_{2A} Binding[6-8]

Represented here for comparison are individual receptor-binding–affinity profiles for five first-line atypical antipsychotic agents. Binding affinity of these agents for the D2, and 5-HT2A receptors are plotted on a logarithmic scale for the purpose of relative comparison. Each of the agents has binding affinity for the 5-HT2A receptor, which approaches or exceeds its binding affinity for the D2 receptor. A dashed line labeled "Functional Activity" has been added to the receptor affinity plot for aripiprazole in an effort to illustrate the hypothetical functional activity of this compound at various dopamine receptor subtypes, consistent with the hypothesis proposed by Lawler and colleagues[8] that aripiprazole maintains functionally selective activation of D2 (and possibly D3)-dopamine receptors expressed in human tissue.

D=dopamine; 5-HT=serotonin; NAT=noradrenaline transporter.

Shayegan DK, Stahl SM. *CNS Spectr.* Vol 9, No 10 (Suppl 11). 2004.

Undoubtedly, all 5-HT_{2A}/D_2 antagonists share the same treatment targets: to quiet hyperactive dopamine neurons that mediate psychosis (mesolimbic pathway); to spark underactive dopamine neurons that mediate negative and cognitive symptoms (mesocortical pathway); and to preserve physiologic function in dopamine neurons that regulate movement (nigrostriatal pathway) and prolactin secretion (tuberoinfundibular pathway)—accomplishing each of these goals concurrently in the brain.

CLASS ACTIONS ARE IMPORTANT: WHAT DOSE IS NEEDED TO ENLIST THEM?

As mentioned previously, how favorably a clinician is able to take advantage of the pharmacologic and associated clinical class actions of atypical antipsychotics depends largely on how each agent is dosed in practice. However, each of the five first-line agents entered the market with dosing recommendations that did not necessarily provide the best aim toward establishing both maximal antipsychotic efficacy and tolerability of these agents in patients treated within our own clinical practice. The discrepancies between effective doses of these agents determined within earlier clinical trials, and the optimal therapeutic dosing models we have now refined, given the benefit of time and clinical experience, are possibly due to the notion that the subpopulation of patients studied in trials may not precisely represent the whole of patients seen in real-world practice. In any event, we have now learned that it is a good idea to dose risperidone less than what was initially predicted (16 mg/day), namely within 2–6 mg/day to help avoid unwanted EPS without sacrificing antipsychotic efficacy.

Similarly, olanzapine 10 mg/day was initially thought to be the most effective dose; however, widespread clinical experience suggests that 15–20 mg/day may be more efficacious. Even higher doses may be more effective for patients refractory to antipsychotic treatment. Olanzapine also appears to share a dose-response curve for efficacy, but not necessarily for weight gain, suggesting that more efficacy might potentially be gained with higher doses without necessarily incurring more side effects.[14]

Quetiapine, though, historically has not been dosed correctly. This atypical was initially expected to work between 200–300 mg/day, but nearly every clinician in practice now knows it takes ≥500 mg/day to optimize antipsychotic efficacy, tolerability, and mood-stabilizing effects. Dosing quetiapine up to ≥750 mg/day may potentially be useful in treating difficult cases.[15]

To date, ziprasidone has been gloriously underdosed in clinical practice. Initial studies of D_2 receptor occupancy data predicted antipsychotic efficacy of ziprasidone at doses of 20–40 mg.[16-18] However, more recent assessments of D_2 and 5-HT_2 receptor occupancy across multiple doses of ziprasidone indicate that doses of at least 120 mg/day are required to optimize antipsychotic action.[19] These findings perhaps also explain empiric limitations in clinical response reported by clinicians to occur when ziprasidone is administered in the lower end of the dosing range. In light of this information and recent data showing an apparent lack of a dose-response curve for QTc interval prolongation, ziprasidone is even beginning to be utilized at doses of 160–320 mg/day in difficult cases.[20]

In the case of aripiprazole, it may be too early to define optimal dosing in schizophrenia, bipolar illness, and special patient populations. While doses of 10, 20, and 30 mg/day have been proven efficacious in patients treated within clinical trials, it is not yet clear whether these same doses provide the best combined antipsychotic efficacy and tolerability profile with respect to treating antipsychotic-naïve patients and children, for example, or if lower doses of aripiprazole may be more clinically desirable.[15] It is through trial and error of both on- and off-label uses that clinicians are helping to fine-tune aripiprazole dosing in regard to optimizing treatment not only in schizophrenia, but in acute mania and softer indications, such as bipolar II and in children.

Appropriate dosing remains a critical issue and ultimately a prerequisite for optimizing the therapeutic effects and tolerability profile of each individual atypical antipsychotic. Although the dosing tips summarized both above and in the Table can certainly help clinicians obtain positive and acute manic symptom efficacy, not every patient responds to the same agent at the same dose, nor does each patient necessarily have the same flavor of response to each agent at the same dose. Clarification on this issue requires the identification of other potential clinically relevant receptor actions of atypical antipsychotics, beyond the 5-HT_{2A}/D_2 antagonist/partial agonist properties shared by the class.

WHAT IS SO GREAT ABOUT ALL OF THE OTHER BINDING PROPERTIES OF ATYPICAL ANTIPSYCHOTICS?

Understanding common pharmacologic and clinical "class" actions associated with atypical antipsychotics certainly reveals how these agents are alike, but what about unique differences from one agent to another? It turns out that atypical antipsychotics are also a heterogeneous group of agents that have complex pharmacologic entities, acting upon multiple dopamine receptors (not just D_2 but also D_1, D_3, and D_4) and multiple serotonin receptors (not just 5-HT_{2A} but also 5-HT_{2C}, 5-HT_{1A}, and 5-HT_{1D}, among others). Atypical antipsychotics also interact with noradrenergic (α_1- and α_2-adrenergic receptor blockade), histamin-

ergic (H_1-receptor blockade), and cholinergic (muscarinic M_1 blockade) neurotransmitter systems as well as with monoamine (DA, 5-HT, and NE reuptake blockade) transporters. However, no two atypical antipsychotics possess the same portfolio of actions upon all of these additional neurotransmitter systems.

The path to unveiling the clinical usefulness of unique secondary pharmacologic actions of atypical antipsychotic agents begins with understanding the candidate models of polygenic illness for selective affective disorders such as schizophrenia and bipolar disorder. The framework underlying these models encompasses multiple interacting symptom domains (positive, negative, cognitive, affective, behavioral, and functional symptoms of schizophrenia) and phases (acute mania, hypomania, depression, and mixed states associated with bipolar illness) that limit the capacity of affected individuals to participate in meaningful social engagement or achieve their desired quality of life.[21] In the case of schizophrenia and schizoaffective disorder, such theories suggest that the earlier and more globally these symptoms are bombarded with treatment, the better the long-term prospect that patients will become meaningfully reintegrated into the workplace, community, and family life. These same models might also be expected to predict similar trends with regard to mood stabilization, as various areas of overlap in the genetics, neurocircuitry, and neurochemistry underlying schizophrenia and bipolar illness have now been identified.[22] To date, however, the effects of early atypical antipsychotic-based therapeutic intervention in bipolar disorders are considerably less well-understood in terms of their impact upon long-term patient outcomes.

Now equipped with a neurobiologically informed appreciation of current hypotheses linking genes, neurocircuitry, and neurochemistry to the manifestations of psychotic illness, the strategy of selectively leveraging pharmacologic actions which function to stabilize and reduce symptom domains most closely correlated with best treatment outcomes—cognitive and affective symptoms in schizophrenia—will ultimately serve to maximize the chances of these benefits, and thus of a favorable outcome.

TABLE. ADJUSTING THE DOSE OF ATYPICAL ANTIPSYCHOTICS IN CLINICAL PRACTICE

Attaining The Goal of Substantial D_2 and 5-HT_{2A} Blockade

- Risperidone (original dosing of 16 mg reduced to 2–6 mg)
- Olanzapine (original dosing of 10 mg increased to 15–20+ mg)
- Quetiapine (original dosing of 200–300 mg needs to be adjusted to >500 mg and up to 800+ mg)
- Ziprasidone (average dose still often <80 mg; >50% of use is below 120 mg; dose needs to be >120 mg for optimal efficiency)
- Aripiprazole (who knows yet? 20–30 mg may be too high for children, mood disorders and those without prior antipsychotic dosing; 5mg?)

D=dopamine; 5-HT=serotonin.

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WHAT RECEPTOR-BINDING PROPERTIES MIGHT ENHANCE THE ABILITY OF AN ATYPICAL ANTIPSYCHOTIC TO IMPROVE MOOD AND COGNITION?

5-HT_{2A} and 5-HT_{2C} antagonist properties

5-HT_{2A} receptors are most highly concentrated on pyramidal neurons (and to a lesser extent γ-aminobutyric acid [GABA]ergic interneurons) residing in the cortex.[23,24] More specifically, these receptors are found densely populated about the apical dendrite and somal portions of cortical pyramidal cells (Figure 2a).[25] Current theories suggest that both dopaminergic and serotonergic input to cortical pyramidal cells—potentially mediated through D_1/D_5, and 5-HT_{2A} receptor mechanisms—are thought to play an important role in the endogenous modulation of cognitive processes. Furthermore, deficits in executive cognition and working memory are associated with hypothesized alterations in local prefrontal information-processing circuits that involve cortical pyramidal neurons—the same neurons implicated in the pathogenesis of schizophrenia.[26,27] Such developments have led many who study 5-HT_{2A} receptors to believe that the salutatory effects of 5-HT_{2A} antagonism are conferred via effects on cortical pyramidal neurons. Blocking 5-HT_{2A} receptors in these neurons appears to enhance aspects of working memory, whereas activation of the 5-HT_{2A} receptor in this context impairs cognition.[28] Whether or not clinically relevant, pro-cognitive effects associated with atypical antipsychotics are mediated (either entirely or in part) through actions upon 5-HT_{2A} receptors located on cortical pyramidal neurons. Although not fully understood, the role of 5-HT_{2A} receptor signaling in cortical processes remains an important therapeutic target for future drug discovery, and perhaps may be compelling enough for the neurobiologically informed clinician to consider when tailoring individual pharmacologic treatments to individual patients.

Another possibility to explain the potential importance of 5-HT_{2A} antagonist properties in the enhancement of cognition and mood through the dopaminergic and noradrenergic pathways is illustrated in Figure 2b. Serotonin neurons projecting from the raphe provide inhibitory control over dopamine neurons in the ven-

tral tegmental area (VTA).[29] These dopamine neurons project from the VTA to the cortex and are inhibited directly via 5-HT_{2A} receptors located on the dopamine neurons themselves. Similarly, serotonin neurons projecting from the raphe may also provide inhibitory control over noradrenaline (NA) neurons in the locus coeruleus (LC) via a 5-HT_{2A} receptor mechanism.[30,31] Noradrenaline neurons which project from the LC to the cortex may be inhibited directly via 5-HT_{2A} receptors located on the noradrenaline neurons themselves, and possibly indirectly via 5-HT_{2A} receptors located on GABA inhibitory interneurons.

5-HT_{2A} antagonist actions that block binding of serotonin to these receptors in these (and perhaps other) pathways might theoretically be expected to "disinhibit" both dopaminergic and noradrenergic output to cortex.[32,33] That is, enhancing dopaminergic and noradrenergic neurotransmission may contribute to improvement of cognitive symptoms when this occurs in dorsolateral prefrontal cortex[34,35] and to improvement of affective symptoms, such as the reduction of apathy and anhedonia, when this occurs in medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex.[36,37] Although specific circuitry and pathways are not as well-characterized, similar enhancement of dopamine and noradrenaline release in the cortex by way of antagonist actions at 5-HT_{2C} receptor sites, may also theoretically be expected to produce desirable clinical effects, including improvements in both cognition and mood (Figure 2c).

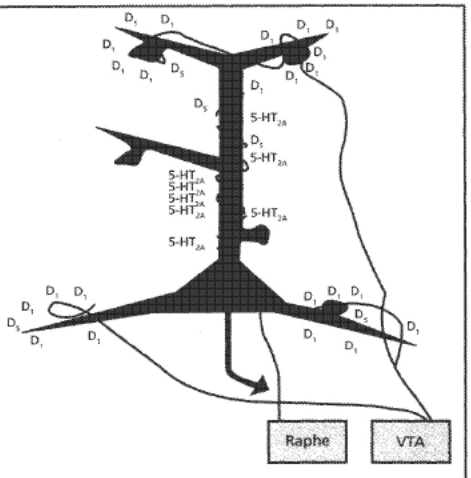

FIGURE 2A. Cortical Pyramidal Neuron[25]

Artist's representation of cortical pyramidal neuron physiology.

D=dopamine; 5-HT=serotonin; VTA=ventral tegmental area.

Adapted from: Goldman-Rakic PS.The "psychic" neuron of the cerebral cortex. *Ann N Y Acad Sci.* 1999;868:13-26.

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Each of the five first-line atypical antipsychotics have binding affinity for the 5-HT_{2A} receptor, which approaches or exceeds their binding affinity for the D_2 receptor (Figure 1). Risperidone, olanzapine, and ziprasidone each possess binding affinity for the 5-HT_{2C} receptor, which approaches or exceeds their affinity for the dopamine D_2 receptor (Figure 4). These agents, having considerable affinity for the 5-HT_{2C} receptor, likewise have high 5-HT_{2C}/D_2 affinity ratios. Thus, these agents possess the desirable pharmacologic action of 5-HT_{2C} antagonism in the presence of concomitant D_2 receptor and 5-HT_{2A} receptor blockade—all at

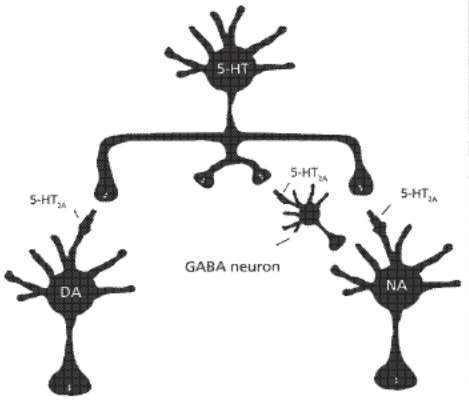

FIGURE 2B. 5-HT_{2A} Antagonist Properties[25]

5-HT=serotonin; DA=dopamine; NA=noradrenaline; GABA=γ-aminobutyric acid.

Shayegan DK, Stahl SM. *CNS Spectr.* Vol 9, No 10 (Suppl 11). 2004.

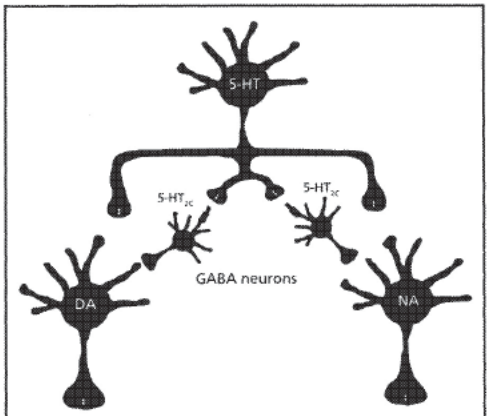

FIGURE 2C. 5-HT_{2C} Antagonist Properties[25]

5-HT=serotonin; DA=dopamine; NA=noradrenaline; GABA=γ-aminobutyric acid.

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