

# The Psychopharmacology of Ziprasidone: Receptor-Binding Properties and Real-World Psychiatric Practice

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Schizophrenia is a highly complex disorder characterized by a diversity of symptoms, psychotic and nonpsychotic, that most likely arise from heterogeneous neuroanatomical and neurochemical malfunctions. As with all antipsychotic agents, ziprasidone targets the key hypothetical neurochemical disturbance in psychosis—excessive dopamine neurotransmission at dopamine D<sub>2</sub> receptors in the mesolimbic pathway of the brain—presumably responsible for the positive symptoms of schizophrenia. Like other atypical antipsychotic agents, ziprasidone is a serotonin-2A (5-HT<sub>2A</sub>)/dopamine D<sub>2</sub> antagonist; however, its in vitro 5-HT<sub>2A</sub>/D<sub>2</sub> receptor affinity ratio is higher than that of the other first-line atypical antipsychotic agents (namely, risperidone, olanzapine, quetiapine, and aripiprazole). Ziprasidone also exhibits potent interaction with 5-HT<sub>2C</sub>, 5-HT<sub>1D</sub>, and 5-HT<sub>1A</sub> receptors in human brain tissue, characteristics that predict heightened negative symptom relief, enhanced modulation of mood, cognitive improvement, and reduced motor dysfunction. Ziprasidone has moderate affinity for serotonin and norepinephrine reuptake sites, predicting antidepressant/anxiolytic activity. On the other hand, ziprasidone's low affinity for α<sub>1</sub>-adrenoceptors, as well as histamine H<sub>1</sub> and muscarinic M<sub>1</sub> receptors, suggests that patients should experience relatively little orthostatic hypotension, sedation, cognitive disturbance, weight gain, or dysregulation of prolactin levels. Efficacy and tolerability data from trials to date indicate that ziprasidone's clinical activity is consistent with its receptor profile.

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The cardinal features of an ideal antipsychotic include overall safety, low liability for extrapyramidal symptoms (EPS), efficacy against the positive and negative symptoms of schizophrenia, and amelioration of cognitive dysfunction and affective symptoms. Key to understanding the clinical utility of atypical antipsychotic agents is an evolving theory of schizophrenia as a polygenic illness encompassing multiple, interacting symptoms—positive and negative, cognitive and affective, behavioral and functional—that limit the capacity of affected individuals to participate in meaningful social engagement.<sup>1</sup> According to this theory, the earlier and more globally these symptoms are arrested, the better the long-term prospect that patients will become meaningfully engaged in community and family life. If schizophrenia is a neurodegenerative disease, stemming the progressive loss of social functioning through appropriate pharmaco-

therapy would be essential to providing the framework for improved long-term outcomes.

Atypical antipsychotics are now the preferred first-line treatments for schizophrenia, owing to their ability to manage effectively the positive and negative symptoms of schizophrenia with minimized EPS. However, even as use of these agents increases, many psychiatrists still ponder the distinctions among the various atypical agents. Are these drugs interchangeable in their antipsychotic effects? How well do different agents target the multitude of other symptoms associated with schizophrenia? Are their associated side effect profiles similar to one another? In the absence of a critical mass of comparative data, the most relevant hypotheses for providing answers to these questions may be found through consideration of the psychopharmacology and clinical trial results of individual atypical antipsychotic agents.

Ziprasidone is an atypical antipsychotic chemically unrelated to any other currently marketed antipsychotic drug, possessing a multireceptor-binding profile unique from that of any other antipsychotic agent in its class. Insofar as neurochemical activity predicts clinical efficacy and tolerability, the receptor-binding profile of ziprasidone may explain its performance in clinical studies and psychiatric practice. This article summarizes the neurochemical basis of antipsychotic activity, describes the psychopharmacol-

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ogy of ziprasidone, and, finally, constructs a conceptual framework for ziprasidone's observed effects in clinical trials.

### KEY NEUROTRANSMITTER SYSTEMS

Trials of atypical antipsychotics have reported significant improvement in cognitive and affective symptoms, although clinical effects vary with the agent. Satisfactory treatment of these symptoms requires a neurobiologically informed appreciation of current hypotheses linking neurochemistry and neurocircuitry to the manifestations of psychosis, since it may very well be the case that the secondary receptor-binding properties of different agents contribute to their efficacy.

The mechanism of action of atypical antipsychotics is related directly to 2 crucial neurotransmitter systems, dopamine and serotonin, that interact at various sites in the central nervous system to orchestrate a variety of physiologic effects. Additionally, dopamine controls the release of acetylcholine, and serotonin controls the release of dopamine.<sup>2</sup> Several major categories of serotonin (5-HT) receptors have been identified, including the presynaptic receptors 5-HT<sub>1D</sub>, 5-HT<sub>1A</sub>, and several postsynaptic receptors (5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, and others). Serotonin is responsible for wide-ranging regulatory actions, including those modulating obsessive-compulsive behavior, depression, anxiety, appetite, sexual functioning, and memory.

Psychosis hypothetically occurs when too much dopamine exists in the synapses of the mesolimbic pathway. All conventional and atypical antipsychotics readily block the dopamine D<sub>2</sub> receptor, an action that accounts for their universal ability to mitigate the positive symptoms of schizophrenia and other psychotic disorders. As a group, however, conventional antipsychotic agents are largely devoid of activity against 5-HT<sub>2A</sub> receptors.

The properties that distinguish atypical from conventional antipsychotic drugs—little or no propensity for EPS or tardive dyskinesia, minimal elevation of prolactin over the long term, and improved control of negative symptoms<sup>1</sup>—derive in large part from their shared antagonism of 5-HT<sub>2A</sub>/D<sub>2</sub> receptors.<sup>3</sup> Since serotonin opposes the release of dopamine in the nigrostriatal pathway, antipsychotic agents that block 5-HT<sub>2A</sub> receptors will reverse D<sub>2</sub> blockade in the striatum. This action is thought to explain why atypical antipsychotics are associated with a lower liability for movement disorders than are conventional antipsychotics. In other words, antipsychotics are “atypical” when superimposition of their 5-HT<sub>2A</sub> antagonism on their D<sub>2</sub> antagonism reduces their D<sub>2</sub> binding sufficiently to reverse motor side effects (in the nigrostriatal pathway) but not enough to reverse antipsychotic action (in the mesolimbic pathway), a kind of see-saw that ultimately achieves balance. Fast dissociation from D<sub>2</sub> receptors, i.e.,

after antipsychotic action occurs but before motor side effects are induced, may also contribute to atypicality.<sup>1</sup> Either way, pure 5-HT<sub>2A</sub> antagonism alone does not produce robust antipsychotic action. However, by reducing D<sub>2</sub> antagonism, 5-HT<sub>2A</sub> antagonism can temper or prevent motor symptoms without diminishing antipsychotic effects.

Clearly, all 5-HT<sub>2A</sub>/D<sub>2</sub> antagonists share the same clinically ambitious goals: to quiet hyperactive dopamine neurons that mediate psychosis (mesolimbic pathway), to trigger 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)—all in the same brain at the same time.

That said, atypical antipsychotics are also a heterogeneous group of agents. Beyond 5-HT<sub>2A</sub>/D<sub>2</sub> antagonism, these complex pharmacologic entities act, to a greater or lesser degree, on multiple dopamine receptors (not just D<sub>2</sub> but also D<sub>1</sub>, D<sub>3</sub>, and D<sub>4</sub>) and multiple serotonin receptors (not just 5-HT<sub>2A</sub> but also 5-HT<sub>1A</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub>). Aside from the inhibition of serotonin and norepinephrine reuptake, other neurotransmitter receptors are also affected by atypical antipsychotics, including the noradrenergic ( $\alpha_1$ - and  $\alpha_2$ -adrenergic receptor blockade), histaminergic (H<sub>1</sub>-receptor blockade), and cholinergic systems (muscarinic M<sub>1</sub> blockade). However, no 2 atypical antipsychotics have the same portfolio of actions on all of these additional neurotransmitter receptors.

Thus, putting these agents into a single category (atypical) obscures important clinical differences among them—differences that psychiatrists witness patient by patient in the real world. The receptor-binding profile of ziprasidone differs substantially from that of other atypical agents. Insofar as receptor activity predicts pharmacologic efficacy and tolerability, ziprasidone's receptor-binding profile may explain its performance in clinical trials and psychiatric practice.

### UNIQUE RECEPTOR-BINDING PROFILE OF ZIPRASIDONE

#### Highest 5-HT<sub>2A</sub>/D<sub>2</sub> Receptor Affinity Ratio

The receptor-binding properties of ziprasidone (Table 1), depicted schematically in Figure 1, have been extensively studied in vitro, in animal models, and more recently in human tissue.<sup>4</sup> In vitro, all first-line agents, except aripiprazole, have 5-HT<sub>2A</sub> affinity roughly equal to or greater than D<sub>2</sub> affinity; ziprasidone has the highest 5-HT<sub>2A</sub>/D<sub>2</sub> receptor affinity ratio (Figure 2).<sup>4</sup> The potential clinical benefits of serotonergic action would be realized at any level of D<sub>2</sub> receptor occupancy in the brain for agents with 5-HT<sub>2A</sub> affinity higher than D<sub>2</sub> affinity. Using positron emission tomography, Fischman and colleagues<sup>7</sup> showed that a clinically relevant dose of ziprasidone

**Table 1. Selected Binding Affinities for Ziprasidone, Clozapine, Olanzapine, and Haloperidol in Human Brain Tissue Receptors<sup>a</sup>**

Drug	Receptor			
	D <sub>2</sub>	5-HT <sub>2A</sub>	5-HT <sub>1A</sub>	α <sub>1</sub>
Ziprasidone	3.1	0.39	2.5	13
Aripiprazole	0.34	3.4	1.7	57
Clozapine	130	8.9	140	4.0
Olanzapine	20	3.3	2100	54
Quetiapine	180	220	230	15
Risperidone	2.2	0.29	210	1.4
Haloperidol	1.4	120	3600	4.7

<sup>a</sup>Aripiprazole data from reference 5; all other data from Schmidt et al.<sup>4</sup>

Data shown as mean pK<sub>i</sub> (nanomolar) values.  
Abbreviations: D = dopamine, 5-HT = serotonin.

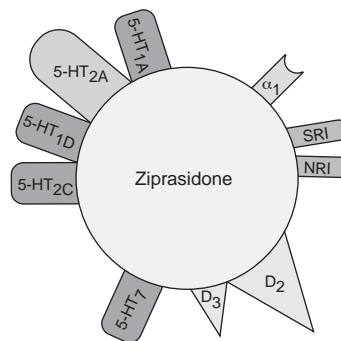
(40 mg) was highly potent in blocking 5-HT<sub>2A</sub> receptors in healthy male volunteers. A high 5-HT<sub>2A</sub>/D<sub>2</sub> receptor ratio has been correlated with a lower propensity for EPS and may also signify activity against the negative symptoms of schizophrenia.<sup>4,8</sup> Thus, to the extent that 5-HT<sub>2A</sub> antagonism contributes to atypical clinical properties of ziprasidone and other atypical antipsychotics, potent action at 5-HT<sub>2A</sub> receptors relative to D<sub>2</sub> receptors is indicative of a favorable pharmacologic profile.

#### Highest 5-HT<sub>2C</sub>/D<sub>2</sub> Receptor Affinity Ratio

Ziprasidone also has the highest ratio of 5-HT<sub>2C</sub> receptor binding to D<sub>2</sub> receptor binding among the first-line atypical antipsychotics (Figure 2).<sup>4</sup> To the extent that blockade of 5-HT<sub>2C</sub> receptors may disinhibit both dopamine and norepinephrine neurons in the cortex, this blockade would lead to a desirable enhancement of dopamine and norepinephrine release in these sites, i.e., the cortex.<sup>9,10</sup> That is, enhancement of dopaminergic and noradrenergic neurotransmission may contribute to improvement in cognitive symptoms when it occurs in dorsolateral prefrontal cortex<sup>11,12</sup> and to improvement in affective symptoms when it occurs in medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex.<sup>13,14</sup> With agents that have considerable affinity for the 5-HT<sub>2C</sub> receptor, and thus high ratios of 5-HT<sub>2C</sub>/D<sub>2</sub> affinities, this desirable pharmacologic action would occur simultaneously when D<sub>2</sub> receptors are blocked. Those agents with the higher ratios would have more 5-HT<sub>2C</sub> antagonism occurring with equivalent degrees of D<sub>2</sub> blockade. Thus, at clinically effective doses, ziprasidone would have considerable 5-HT<sub>2C</sub> antagonism concomitant with its 5-HT<sub>2A</sub> and D<sub>2</sub> antagonism. Such actions coincide theoretically with observations that ziprasidone can improve cognition and mood in schizophrenic patients.

Because of its very high affinity for 5-HT<sub>2C</sub> receptors relative to D<sub>2</sub> receptors, however, ziprasidone may cause 5-HT<sub>2C</sub> antagonism without substantial D<sub>2</sub> antagonism when administered at low doses (e.g., < 120 mg/day). Experienced clinicians know that another potent 5-HT<sub>2C</sub> an-

**Figure 1. Receptor-Binding Properties of Ziprasidone<sup>a</sup>**



<sup>a</sup>Reprinted with permission from Stahl.<sup>2</sup>

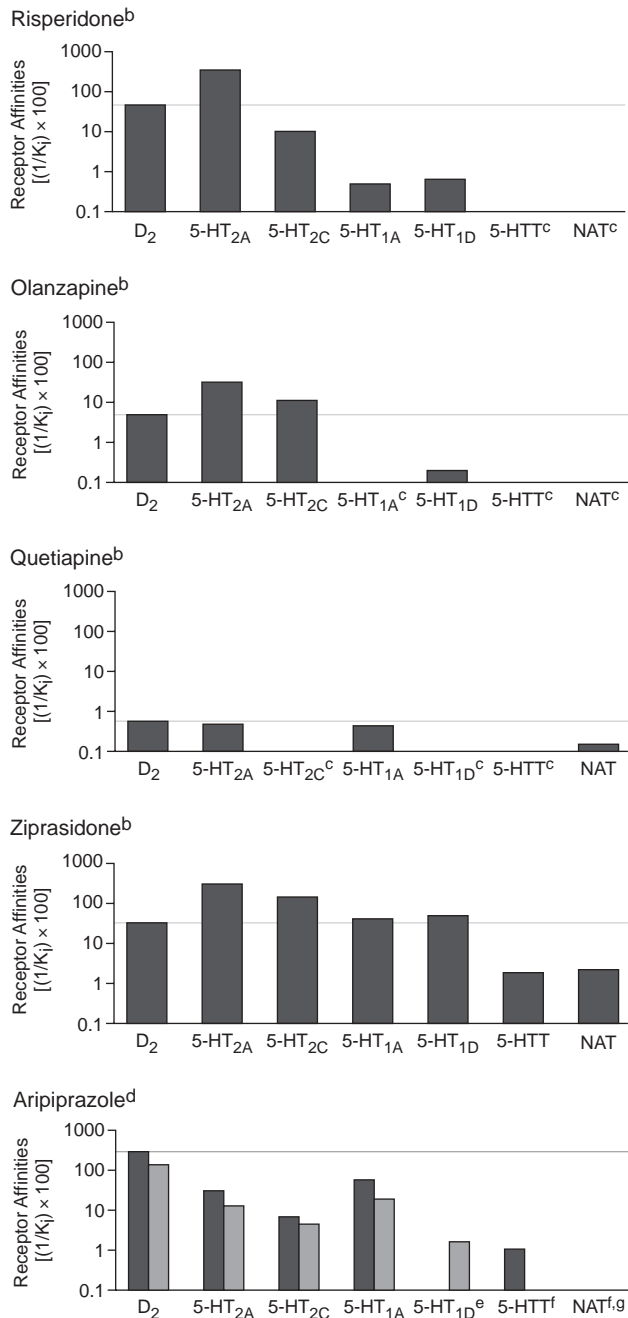
Abbreviations: α<sub>1</sub> = noradrenergic α<sub>1</sub>-blockade, D = dopamine, 5-HT = serotonin, NRI = norepinephrine reuptake inhibition, SRI = serotonin reuptake inhibition.

tagonist without substantial D<sub>2</sub> antagonism, fluoxetine, can also have activating actions in some patients that range from desirable relief of fatigue to undesirable dysphoria, hypomania, and panic. Low doses of ziprasidone could potentially have such activating behavioral effects without substantial antipsychotic actions if dopamine and norepinephrine are disinhibited in cortex but dopamine is not blocked in limbic areas. The tendency of clinicians to underdose ziprasidone may lead to substantial 5-HT<sub>2C</sub> antagonist action without substantial D<sub>2</sub> antagonist actions. However, given the pharmacologic theory discussed thus far—D<sub>2</sub> antagonist actions are a necessary part of an atypical antipsychotic's desirable binding portfolio—this suggests that real-world use of ziprasidone would be greatly optimized if it is adequately dosed, most likely at dosages > 120 mg/day. Activation resulting from 5-HT<sub>2C</sub> antagonist actions that are unopposed by D<sub>2</sub> antagonist actions at low doses would thus diminish as ziprasidone dose is raised and substantial D<sub>2</sub> receptor antagonism begins to occur.

#### Highest 5-HT<sub>1A</sub>/D<sub>2</sub> Receptor-Binding Ratio

Ziprasidone is also unique among atypical agents in its potent interaction at 5-HT<sub>1A</sub> receptors, leading to receptor-binding affinities for these serotonin receptors comparable to its D<sub>2</sub> receptor-binding affinity (Figure 2).<sup>4</sup> Richelson and Souder<sup>15</sup> have found ziprasidone to be the most potent of 12 antipsychotics, including both typical and atypical agents and 1 metabolite (9-OH-risperidone), in blocking 5-HT<sub>1A</sub>, 5-HT<sub>1D</sub>, and 5-HT<sub>2A</sub> in postmortem normal human brain tissue subjected to radioligand-binding assays to determine equilibrium dissociation constants. These findings indicate that ziprasidone will occupy human 5-HT<sub>1A</sub> and 5-HT<sub>1B/1D</sub> receptors, as well as 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, to a far greater extent than any other first-line atypical antipsychotic at doses sufficient to achieve therapeutic

**Figure 2. Receptor Actions of Second- and Third-Generation Antipsychotics: Affinities for Dopamine D<sub>2</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>1A</sub>, and 5-HT<sub>1D</sub> Receptors and Inhibition of Synaptosomal Uptake (5-HT and norepinephrine transporters [5-HTT and NAT])<sup>a</sup>**



<sup>a</sup>Receptor affinity data shown as [(1/K<sub>i</sub>) × 100]. All receptors are human except for 5-HT<sub>1D</sub> (bovine) and 5-HTT and NAT (rat synaptosomes).

<sup>b</sup>Data from Schmidt et al.<sup>4</sup>

<sup>c</sup>[(1/K<sub>i</sub>) × 100] < 0.1.

<sup>d</sup>Data shown in black bars are from reference 5 (methods not stated), and data shown in gray bars are from Shapiro et al.<sup>6</sup> (cloned human cDNA).

<sup>e</sup>Reference 5 reported that [(1/K<sub>i</sub>) × 100] < 0.1.

<sup>f</sup>Shapiro et al. reported that [(1/K<sub>i</sub>) × 100] < 0.1.

<sup>g</sup>No data were available from reference 5.

blockade of dopamine D<sub>2</sub> receptors (Figure 2). This predicts a favorable clinical profile, not only for positive symptoms and low motor side effect liability, but also for improvement of mood, anxiety, and cognition in schizophrenia. That is, cognitive improvements in schizophrenia observed with atypical antipsychotic treatment have been linked to actions at 5-HT<sub>1A</sub> receptors.<sup>16,17</sup>

Not only is there evidence to suggest that 5-HT<sub>1A</sub> agonism, interacting with dopamine neurotransmission, may relieve negative symptoms and reduce motor side effects,<sup>18,19</sup> but activity at the 5-HT<sub>1A</sub> receptor may also be critical to tempering many of the nonpsychotic features of schizophrenia,<sup>20</sup> such as anxiety, depression, hostility, problems with cognition and working memory and attention, and inadequate social interactions.<sup>21</sup> 5-HT<sub>1A</sub>-receptor agonism has been shown to foster ziprasidone-induced dopamine release in the prefrontal cortex of rats,<sup>18</sup> a potentially desirable pharmacologic action for treatment of cognitive and mood symptoms in schizophrenia. Of note, ziprasidone's 5-HT<sub>1A</sub> agonist activity is similar to that of buspirone, which has proven antidepressant and anxiolytic activity.<sup>4</sup>

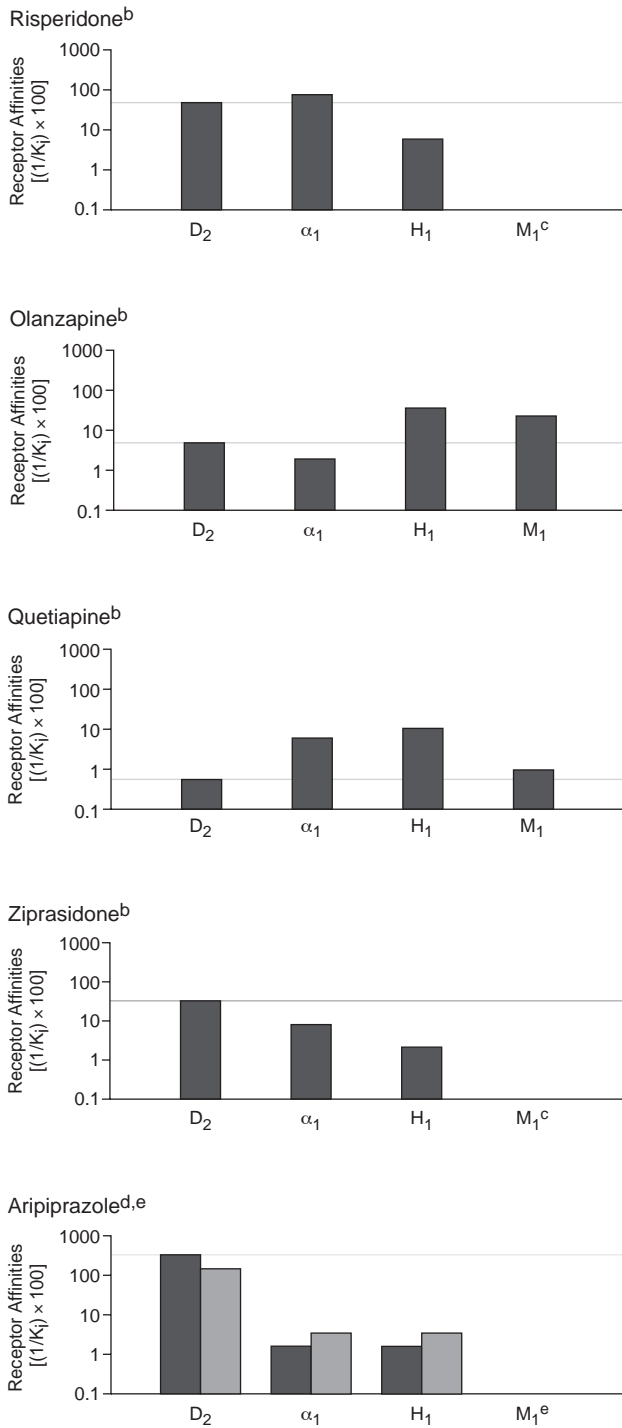
### Unique and Potent 5-HT<sub>1D</sub> Antagonism

The unique and very potent antagonism of the 5-HT<sub>1D</sub> receptor by ziprasidone—the only atypical antipsychotic with this pharmacologic property (Figure 2)—also suggests potential utility in treating mood and affective symptoms in schizophrenic patients.<sup>22</sup> The 5-HT<sub>1D</sub> receptor is a presynaptic autoreceptor that inhibits serotonin release, so blocking this receptor disinhibits serotonin release, which would theoretically have both antidepressant and anxiolytic effects.<sup>23</sup> Early unpublished studies of 5-HT<sub>1D</sub> antagonists indeed show preliminary evidence of efficacy in major depressive disorder.

### Unique Blockade of Monoamine Transporters

There are still other unique dimensions of ziprasidone's neurotransmitter receptor-binding profile. Ziprasidone is the only first-line atypical antipsychotic to block serotonin, norepinephrine, and dopamine reuptake sites at clinically relevant dosing (Figure 2).<sup>24,25</sup> In a study of 38 antipsychotic agents, Tatsumi and colleagues<sup>25</sup> showed that ziprasidone was the only one of all first-line atypical antipsychotics tested with potent binding properties at the human serotonin transporter, norepinephrine transporter, and dopamine transporter. In each of these binding assays, ziprasidone was several orders of magnitude more potent than olanzapine, quetiapine, and risperidone, which exhibited only weak activity at the monoamine transporters under study. These investigators<sup>25</sup> suggested that blockade of dopamine transporters and 5-HT<sub>2A</sub> receptors in the striatum and prefrontal cortex may boost dopaminergic function there, thereby contributing to the avoidance of motor side effects while improving the negative symptoms of schizo-

**Figure 3. Receptor Actions of Second- and Third-Generation Antipsychotics: Affinities for Dopamine D<sub>2</sub>, α<sub>1</sub>-Adrenoceptor, Histamine H<sub>1</sub> Receptors, and Muscarinic M<sub>1</sub> Receptors<sup>a</sup>**



<sup>a</sup>Receptor affinity data shown as [(1/K<sub>i</sub>) × 100] (derived from human receptors).

<sup>b</sup>Data from Schmidt et al.<sup>4</sup>

<sup>c</sup>[(1/K<sub>i</sub>) × 100] < 0.1.

<sup>d</sup>Data shown in black bars are from reference 5 (methods not stated), and data shown in gray bars are from Shapiro et al.<sup>6</sup> (cloned human cDNA).

<sup>e</sup>Both references<sup>5,6</sup> reported that [(1/K<sub>i</sub>) × 100] < 0.1.

phrenia. Similar to those of antidepressants, which block monoamine transport to varying degrees, ziprasidone's activity at these transporter sites would appear to confer mood-modulating effects, as well. Ziprasidone inhibits both norepinephrine and serotonin reuptake with a potency akin to those of imipramine and amitriptyline.<sup>4</sup>

**Lack of Potent α<sub>1</sub>, Muscarinic Cholinergic M<sub>1</sub>, and Histamine H<sub>1</sub> Antagonism**

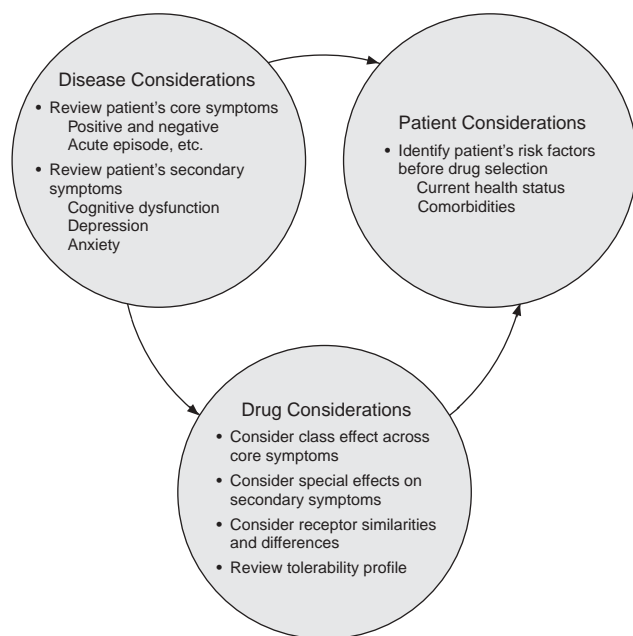
In addition to the presence of many unique receptor-binding actions described here, it may also be important that ziprasidone has an absence of or a low affinity for other relevant receptor-binding properties compared with its potency at D<sub>2</sub> receptors (Figure 3).<sup>4</sup> This may relate more to an advantageous tolerability profile than to efficacy for schizophrenia. These properties include low relative affinity for α<sub>1</sub>-adrenoceptors compared with affinity for D<sub>2</sub> receptors and even lower relative affinity for histamine H<sub>1</sub> and muscarinic M<sub>1</sub> receptors.<sup>4</sup> Lower affinity for α<sub>1</sub>-adrenoceptors than for dopamine D<sub>2</sub> receptors suggests that ziprasidone is less likely to induce orthostatic hypotension and sedation than agents with the reverse binding profile.<sup>4</sup> A low affinity for muscarinic M<sub>1</sub> receptors (Figure 3) predicts a low propensity for anticholinergic side effects, including cognitive dysfunction and gastrointestinal disturbances, at clinically relevant doses.<sup>4</sup> A low ability to block H<sub>1</sub> receptors may account for the weight-neutral profile of ziprasidone, as binding studies suggest that weight gain in human beings is directly proportional to blockade at this site.<sup>26</sup>

**FROM RECEPTORS TO REAL-WORLD PRACTICE**

Ziprasidone's efficacy and tolerability in clinical trials show consistency with its receptor profile. Improvement in positive and negative symptoms,<sup>27-31</sup> cognitive domains,<sup>32</sup> acute mania,<sup>33</sup> and the affective symptoms of schizophrenia or schizoaffective disorder<sup>28,30</sup> has been described in both short- and long-term controlled clinical trials or in switch studies involving ziprasidone. Interrelated improvements in cognitive and affective symptoms have been correlated with enhanced social engagement in patients switched to ziprasidone from other antipsychotic agents (both conventional and atypical) because of intolerable side effects or inadequate response.<sup>32</sup> As for tolerability, clinical trial data indicate that ziprasidone has a lower liability for EPS than haloperidol,<sup>34</sup> a lower overall movement disorder burden and incidence of prolactin elevation than risperidone,<sup>35</sup> significantly less weight gain associated with it than does olanzapine,<sup>27</sup> and more benign effects on lipid profile and glucose metabolism than olanzapine.<sup>27,36,37</sup>

The psychiatrist's task is to make sense of these data in the cold, hard light of clinical practice. Statistically significant differences between 2 drugs in a clinical trial of

Figure 4. Selecting an Atypical Antipsychotic in Clinical Practice



patients with schizophrenia may not translate into meaningful, clinically relevant differences when the same 2 agents are given to schizophrenic patients in office settings. That being the case, how does one determine which atypical antipsychotic to prescribe for a given patient?

Figure 4 proposes a conceptual approach to this dilemma and suggests that clinicians take several factors into account before selecting an antipsychotic: (1) the patient's core and secondary symptoms; (2) the drug-class effects across the core psychotic symptoms, as well as any special effects on secondary symptoms an individual patient may have; and (3) the patient's current health status and comorbidities in light of the tolerability profile of the drugs under consideration.

This schema acknowledges that although all available antipsychotics improve positive symptoms, attention must also be paid to the other symptoms manifested, be they predominantly negative, affective, cognitive, or some mixture thereof. Schizophrenia is most likely a collection of distinct pathophysiologies that arise more or less sequentially and to a greater or lesser degree in different individuals.

## DISCUSSION

The highly complex, heterogeneous disorder that is schizophrenia is characterized by a diversity of symptoms, psychotic and nonpsychotic, that cannot be attributed to a single neuroanatomical or neurochemical derangement. Similarly, no single mechanism of drug action is likely to

produce therapeutic benefits without triggering unsettling side effects. Judging by its receptor profile, ziprasidone offers a spectrum of activities predictive of efficacy and tolerability. Compared with other first-line atypical antipsychotics, ziprasidone has more diverse serotonergic effects and a much lighter burden of  $\alpha_1$ -adrenergic,  $H_1$ , and  $M_1$  antagonist activities. The clinical benefits predicted by this receptor-binding profile—good control of positive and negative symptoms, improvement in cognitive and affective symptoms, low incidence of EPS, weight gain, and postural hypotension—have been observed in randomized clinical trials.

As we better grasp the pathophysiology of the nonpsychotic aspects of schizophrenia, treatment paradigms will undoubtedly shift. Determination of whether drugs like ziprasidone, each with a unique multireceptor profile, can adequately address the range of symptoms characteristic of schizophrenia, and thereby help patients re-engage in meaningful social life, will require the scrutiny of controlled trials and the accumulated experience of individual clinicians.

*Drug names:* amitriptyline (Elavil and others), aripiprazole (Abilify), buspirone (BuSpar and others), clozapine (Clozaril and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil, Surmontil, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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