ABSTRACT

Typical first-generation agents work through potent blockade of the dopamine D2 receptor and act indiscriminately at all the dopaminergic pathways. This uniformity of action results in similarities in clinical responses. With the introduction of clozapine followed by risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, the field was transformed. Each of these second-generation antipsychotic agents has been shown to be effective in the treatment of schizophrenia. However, each of these agents possesses unique receptor-binding properties, resulting in very different side-effect profiles. Understanding the individual receptor activity of each agent can not only aid in our understanding of the differential clinical actions of the various medications but also guide us in the clinical decision-making process.

Although the availability of the many atypical agents has expanded our therapeutic options, the alternatives have made the treatment decision process more complex. Several studies have demonstrated that besides being efficacious in the treatment of schizophrenia, the atypical agents offer some advantages in helping with cognition and alleviating negative symptoms. However, potentially serious side effects, such as weight gain, hyperlipidemia, and glucose dysregulation, are observed with the atypical agents to varying degrees. Therefore, maximizing clinical effectiveness while minimizing the side-effect burden is required to optimize clinical interventions. (Adv Stud Med. 2005;5(7B):S740-S746)

RECEPTOR PROFILES OF THE ATYPICAL AGENTS

The typical agents were all hypothesized to exert clinical effectiveness by acting on the dopaminergic system through antagonism of the D2 receptor subtype. The potency of the agents is proportional to the extent of the blockade. The dopaminergic theory of schizophrenia and psychosis was developed, based in part on the dopamine-blocking action of the first generation of antipsychotic agents. Another line of evidence supporting the role of dopamine in schizophrenia was the ability of dopamine releasers, such as amphetamine, to illicit a paranoid psychosis in humans. The typical agents were effective in ameliorating many of the positive symptoms, such as auditory hallucinations and delusions, as a result of dopamine blockade.

With the introduction of the first atypical agent, clozapine, it became clear that other receptor systems and subtypes may be involved in the relief of psychotic symptoms. Clozapine was unique in its clinical action in that it was effective in treatment-resistant patients not responsive to typical agents. However, clozapine is burdened with many side effects, including potentially fatal agranulocytosis. Neuroscientists have been attempting to unravel the multiple neurotransmitter actions of clozapine and design other less toxic but equally efficacious atypical agents.

UNIQUE RECEPTOR PROFILES—UNIQUE CLINICAL PROFILES

It is clear that all of the atypical agents work well in the alleviation of a wide range of symptoms in schizophrenia. However, each agent possesses a unique receptor profile that helps to explain the clinical differences in side effects and clinical profiles. Some of the many receptors influenced by the atypical agents include the dopamine receptors D1, D3, D4; seroto-
nergic receptors 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>; α<sub>1</sub> and α<sub>2</sub> adrenergic receptors; H<sub>1</sub> histaminergic receptors; and M<sub>1</sub> cholinergic receptors. Clozapine has been shown to have high D<sub>1</sub> receptor activity and a near-equivalent occupancy of the D<sub>1</sub> and D<sub>2</sub> receptors<sup>4</sup> and possess 5-HT<sub>1A</sub> agonist activity. This serotonergic receptor may be involved in improving cognition and relieving negative symptoms through its capacity to increase dopamine release in the prefrontal cortex.<sup>5,6</sup> Aripiprazole also possesses 5-HT<sub>1A</sub> activity.<sup>7,8</sup>

Aripiprazole is the first of the atypical neuroleptics to demonstrate partial agonist/antagonist receptor actions at the D<sub>2</sub> receptor and the 5-HT<sub>1A</sub> receptor.<sup>9</sup> At the 5-HT<sub>2A</sub> receptor, aripiprazole functions as an antagonist. As a partial agonist/antagonist at the D<sub>2</sub> and 5-HT<sub>1A</sub> sites, aripiprazole has the capacity to act as a functional agonist or an antagonist depending on the surrounding neurotransmitter and receptor environment.<sup>10</sup> If a full agonist is not present to compete with the partial agonist, then an agonist response will be produced. Alternatively, if a full agonist is present, then the partial agonist will demonstrate antagonistic properties.

Another possible factor differentiating the atypical antipsychotic agents is the rate of dissociation from the D<sub>2</sub> receptor, which is most rapid in quetiapine and clozapine.<sup>11</sup> It has been posited that this fast dissociation or “hit-and-run” property is central to the clinical efficacy of these agents and may confer some clinical advantages, such as the low rate of extrapyramidal symptoms (EPS).<sup>12,13</sup> Ziprasidone also shows multiple unique receptor actions.<sup>14</sup> The 5-HT<sub>2A</sub>/D<sub>2</sub> receptor-binding ratio is approximately 8:1, the highest of the atypical agents.<sup>15</sup> The high serotonergic function may help to explain the cognitive and affective improvement noted with ziprasidone. Serotonergic action in the dorsolateral prefrontal region may result in positive cognitive effects, and serotonergic activity in the anterior cingulate gyrus, medial prefrontal cortex, and orbitofrontal cortex may improve mood.<sup>16</sup>

The potent 5-HT<sub>1A</sub> antagonism activity may help ziprasidone to reduce motor side effects and alleviate negative symptoms and those of anxiety, depression, and hostility.<sup>17,18</sup> Clozapine also manifests partial agonist properties at this receptor; it has been speculated that this explains, in part, its efficacy in treatment-resistant cases.

**Unique Receptor Profiles—Unique Side Effects**

The unique clinical profiles of these agents also help to explain their unique side effects. For example, risperidone is the atypical agent most prone to EPS<sup>19</sup> and prolactin release,<sup>20,21</sup> an effect related to its tighter D<sub>2</sub> binding. Symptoms of hyperprolactinemia, including galactorrhea, gynecomastia, sexual dysfunction, infertility, oligomenorrhea, and amenorrhea, may be present in a proportion of risperidone-treated individuals. These side effects tend to occur at higher doses of risperidone therapy; however, they have been observed also on relatively low doses. Weight gain, which is most pronounced with clozapine and olanzapine and least with aripiprazole and ziprasidone, has been associated most frequently with histamine H<sub>1</sub> receptor blockade.<sup>22</sup>

**Clinical Aspects of Schizophrenia**

Understanding the basic scientific aspects of the atypical agents is helping us to target clinical interventions more precisely. However, because schizophrenia is a complex disorder with varied presentations among individuals, the decision-making process is complex. The schizophrenic syndrome affects multiple realms of functioning, including those involving perception (eg, hallucinations), thought processes and beliefs (eg, loosening of associations and delusions), affect and mood (ranging from anger and rage to blunted and flat), and cognitive in addition to behavioral functions. These symptoms appear to varying extents in each individual and often fluctuate over time. To incorporate those syndromes that share some of the symptoms,<sup>23</sup> the broader concept of schizophrenia spectrum disorder was developed.

The patient with schizophrenia may present with a varying extent of positive symptoms (eg, hallucinations) or negative symptoms (eg, social withdrawal or blunted affect). Impaired cognitive function is associated frequently with functional deficits. Cognitive abnormalities include deficits in attention, memory, reasoning, language, and executive function. In a study of 171 outpatients with schizophrenia, 73% were noted to have neuropsychological deficits.<sup>24</sup>

**Atypical Agents: Fulfilling the Promise?**

**Amelioration of Cognitive Symptoms**

A study of older outpatients with schizophrenia or schizoaffective disorder has assessed neuropsychologi-
cal performance and ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs). IADLs are defined as activities related to independent living, such as preparing meals, managing money, maintaining a household, or using a telephone. Neuropsychological performance was associated with decreased capacity to carry out all ADLs and IADLs except for basic tasks and functions, such as simple eating, time orientation, and grooming. Negative symptoms also correlated with decrements in functional capacity, whereas positive symptoms and depressed mood did not show this association. Often present early in the course, these deficits have been noted in first-episode patients who are neuroleptic naïve. Cognitive deficits have been shown also to be present in individuals at high genetic risk for schizophrenia, suggesting that dysfunction may exist even before the first onset of symptoms. The course of cognitive deficits is variable, with some patients deteriorating over time, whereas other patients remain stable or even show some improvements.

Abnormalities in the prefrontal cortex and the hippocampus have been associated with intellectual deficits. Functional abnormalities in these areas shown in positron emission tomography scans and magnetic resonance images have been supported by neuropathological findings, such as decreased cell number. Varying receptor abnormalities have been noted also, and targeting of specific receptors and neurotransmitters may help in the amelioration of these deficits. For example, cognitive deficits have been related to the number of D1 receptors and norepinephrine levels in the prefrontal cortex, in addition to the level of cortical choline acetyltransferase activity. Serotonergic dysfunction, as evidenced by deficits in 5-HT2A receptor functioning, has also been associated with cognitive difficulties. Targeting these specific abnormalities offers a means for optimizing treatment to ameliorate these particular symptoms.

A significant advantage of the atypical agents compared to the typical agents is the apparent improvement in cognitive functioning. Many but not all studies have shown some advantages in this area. Bilder et al compared clozapine, olanzapine, risperidone, and haloperidol on 16 measures of neurocognition in 101 patients with schizophrenia or schizoaffective disorder. The greatest improvement was noted with olanzapine and risperidone. Weiser et al also noted that olanzapine and risperidone were superior to haloperidol on cognitive measures. The mean dose of risperidone was 4.35 ± 1.7 mg/day, haloperidol was 10.01 ± 6.1 mg/day, and olanzapine was 10.56 ± 4.9 mg/day.

Quetiapine has been shown to be more efficacious compared to haloperidol in improving cognition in outpatients with schizophrenia. At a dose of 600 mg, quetiapine manifested a significantly greater amelioration on measures of overall cognition, executive function, and attention and verbal memory. The treatment differences were not related to benztpine usage, side effects from the medications, or symptom improvement. A dose of 600 mg of quetiapine was more effective than 300 mg, confirming the need for higher dosing of this agent to optimize clinical effects. This clinical advantage in quetiapine compared to haloperidol was confirmed in another study. Patients treated with haloperidol (mean dose = 10.01 ± 6.1 mg/day) or risperidone (mean dose = 4.35 ± 1.7 mg/day) manifested more EPS compared to those patients treated with olanzapine (mean dose = 10.56 ± 4.9 mg/day). However, patients treated with risperidone, but not patients treated with haloperidol, manifested improvements in cognitive measures.

Based on the receptor profile of ziprasidone, there are several reasons to expect cognitive improvement with this agent. These reasons include the high 5-HT2A/D2 receptor-binding ratio, 5-HT2C activity, and 5-HT1A antagonism, in addition to reuptake inhibition of serotonin, norepinephrine, and dopamine. Some studies show that switching to ziprasidone from typical agents or other atypical medications resulted in improved cognition. Harvey et al studied cognitive changes in outpatients with schizophrenia switched from typical neuroleptics, olanzapine, or risperidone to treatment with ziprasidone.

**NEGATIVE SYMPTOM IMPROVEMENT**

Another area in which the atypical agents may have some advantage over the typical agents is in improving negative symptoms, such as apathy, social withdrawal, blunted affect, anhedonia, poverty of speech, and inattention. However, the data have not been entirely consistent. Volavka et al conducted a 14-week trial in 157 inpatients with chronic schizophrenia or schizoaffective disorder comparing clozapine (200–800 mg/day), risperidone (4–16 mg/day), olanzapine (10–40 mg/day), and haloperidol (10–30 mg/day). The 3 atypical drugs demonstrated significant improvement...
compared to baseline total scores on the Positive and Negative Symptom Scale (PANSS), whereas haloperidol did not manifest this difference. Negative symptom scores were significantly better in patients treated with olanzapine and clozapine compared to haloperidol. Although significant, the differences were small. However, risperidone did not show this negative symptom advantage over haloperidol. In a 10-week study comparing clozapine to haloperidol in 75 outpatients with schizophrenia, patients completing the clozapine study manifested more improvements in positive but not negative symptoms.

In a comparison study of ziprasidone, patients treated with conventional antipsychotics, risperidone, or olanzapine were switched to that agent. Ziprasidone was superior to each of the other agents on 3 clusters from the PANSS, including cognitive functioning, prosocial functioning, and depression-anxiety that had been derived from factor analysis of this instrument. The improvement in prosocial functioning appeared to be related to the improvement in cognitive functioning.

**Atypical Agents: A Safer Alternative?**

The atypical agents are all superior to the typical agents with regard to acute EPS, such as dystonic reactions and parkinsonian symptoms (with the possible exception of risperidone at higher doses). All of the atypical agents appear to have a decreased incidence of tardive dyskinesia with long-term use. The more favorable EPS side-effect profile resulted in enthusiastic endorsement of the atypicals as a class. However, it is clear that some of atypical agents have significant side-effect burdens of their own that require caution in administration. In addition to the sometimes fatal propensity to induce agranulocytosis, clozapine may induce seizures, weight gain, glucose dysregulation, and lipid abnormalities, among many other side effects. Clozapine was approved only because of its documented superior clinical efficacy in chronically ill treatment-resistant patients with schizophrenia. Other atypical agents also possess some of these negative properties.

**Morbidity and Mortality Associated with Schizophrenia**

Patients with schizophrenia are at higher baseline risk for illnesses compared to the general population. Some of the factors related to the increased health risk include poor self-care, avoidance of medical practitioners, poor diet, increased smoking, obesity, and substance abuse. Neglect by a healthcare system ill equipped to handle the multiple behavioral and social difficulties of the chronically mentally ill compound this problem. Therefore, the clinician must be all the more cautious in using agents that can increase the disease burden further.

**Obesity**

The rate of obesity (defined as a body mass index [BMI] ≥30 kg/m²) in the United States in 1991 was noted to be 12.1%. Only 8 years later the rate had increased to 17.9%. In another study, the prevalence of overweight individuals (BMI ≥25 kg/m²) in 1999 to 2000 was noted to be 64.5%, and the rate of obesity was 30.5%. Obesity is associated with an increase in the incidence of several diseases, including diabetes, gallstones, hypertension, cardiovascular disease, cancer, and stroke (Table 1).

Although several of the atypical agents have been found to increase weight, there is a clear differentiation among the medications with regard to this tendency. Clozapine and olanzapine have consistently been noted to lead to the greatest weight increases. Quetiapine and risperidone are intermediate in weight increases, whereas aripiprazole and ziprasidone demonstrate the lowest levels of weight gain. In a survey of 81 studies, the average weight gain after 10 weeks of treatment was 4.45 kg on clozapine, 4.15 kg on olanzapine, 2.10 kg on risperidone, and 0.04 kg on ziprasidone.

**Table 1. Mt. Sinai Guidelines: Recommendations on Weight Gain**

- Consider relative risk of weight gain for the different antipsychotic medications in drug selection for patients with BMI ≥25
- A weight gain of 1 BMI unit indicates a need for an intervention (unless patient is underweight)
- Initiate intervention if patient’s waist circumference is ≥35 inches (woman); ≥40 inches (man)
- Interventions may include:
  - Closer monitoring of weight
  - Engagement in a weight management program
  - Use of an adjunctive treatment to reduce weight
  - Changes in a patient’s antipsychotic medication

HYPERLIPIDEMIA

With several of the atypical agents, increased lipids have been observed. This health risk may be missed in that many clinicians do not routinely monitor lipid levels. However, the long-term health risk of chronically increased lipids, especially in high-risk individuals with comorbid conditions such as obesity, is significant. Similarly, with respect to weight gain, olanzapine and clozapine appear to be the agents most frequently associated with this problem. In a comparison of several atypical agents in patients with schizophrenia, clozapine and olanzapine resulted in the greatest increases in serum triglycerides, weight, and serum leptin levels. Quetiapine increases in these parameters were modest, whereas there were only minimal increases in patients treated with risperidone.

GLUCOSE DYSREGULATION

Perhaps the most serious side effect of some of the atypical agents is the dysregulation of glucose metabolism. Diabetes is already a serious public health problem in the United States, and the atypical agents have been found to increase glucose levels and induce not only diabetes in previous healthy individuals but also the acute onset of the potentially fatal condition of diabetic ketoacidosis. In the United States, the Food and Drug Administration has required all atypical antipsychotic agents to carry the same warning that they may increase the risk of diabetes (Table 2).

PROLACTIN ELEVATION

Elevations in prolactin are often seen in patients treated with typical agents and with risperidone. Increased prolactin is associated with a variety of side effects, including menstrual irregularities, sexual dysfunction, bone demineralization, and gynecomastia, in addition to galactorrhea.

In a study of risperidone in autistic children, the agent was noted to be clinically efficacious in several patients. However, serum prolactin levels increased dramatically from 166 ± 88 UI/mL at baseline to 504 ± 207 UI/mL (P < .0001) at week 12. In a study of male patients with schizophrenia, the prolactin increase in patients treated with risperidone 6 mg/day was equivalent to that observed with haloperidol 20 mg/day. When patients on risperidone were switched to olanzapine, prolactin levels decreased, as did the extent of amenorrhea, cycle irregularities, and sexual dysfunction. Studies comparing ziprasidone to risperidone have demonstrated prolactin elevations on risperidone but not ziprasidone.

CONCLUSIONS

The atypical agents possess varying receptor profiles. Understanding the basic mechanisms underlying these varying profiles helps us to understand the clinical differences between the agents with regard to clinical effectiveness and side-effect burden.

The atypical agents clearly have many advantages compared to the typical agents. All of the agents have been documented to be effective in schizophrenia, and several studies have shown some advantages in helping with cognition and alleviating negative symptoms. However, it has become clear that side effects, such as weight gain, hyperlipidemia, glucose dysregulation, and prolactin elevations, occur to varying degrees with the atypical agents. Therefore, the clinician should balance the clinical advantages of the agents against the negative side-effect profiles to maximize the treatment interventions. It is also important to keep in mind a goal of individualizing treatment to find the right intervention for a specific individual. The future holds interesting possibilities in this pursuit. Clinical tools are being developed that can guide the clinician toward greater specificity in treatment. Genetic profiling, plasma levels, neuroimaging, and pharmacokinetic targeting offer the hope of improving assessment and treatment acutely and in the long term.

Table 2. ADA/APA Consensus Statement

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening Lipid Profile</th>
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<tbody>
<tr>
<td>Olanzapine</td>
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<tr>
<td>Clozapine</td>
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<td>Risperidone</td>
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<tr>
<td>Aripiprazole*</td>
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<tr>
<td>Ziprasidone*</td>
<td>±</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Newer drugs with limited long-term data.
REFERENCES


34. Weiser M, Shneider-Beeri M, Nakash N, et al. Improvement in cognition associated with novel antipsychotic-
ic drugs: a direct drug effect or reduction of EPS?