

Review Article

Second Generation Antipsychotics: Pharmacodynamics, Therapeutic Effects Indications and Associated Metabolic Side Effects: Review of Articles

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Introduction

The Second-Generation Antipsychotics (SGAs) are a group of antipsychotic agents that were introduced into clinical psychiatry during the early [1] 1990s. Named Serotonin-Dopamine Antagonists (SDAs) based on the belief that they could be differentiated from the dopamine receptor antagonists based on their high affinity for serotonin 2A (5-HT_{2A}) as well as Dopamine (D₂) receptors [2]. The Second-Generation Antipsychotics (SGAs) are also called Serotonin Dopamine Antagonists (SDAs), newer antipsychotics or atypical antipsychotics [3-5].

History of Atypical Antipsychotics

The first agent in this group was clozapine (Clozaril), an antipsychotic that was introduced in the United States in 1990, although it had been available in some countries in Europe since the early 1970s. Clozapine was considered an “atypical” antipsychotic because it was an effective agent at doses that caused negligible Extrapyramidal Symptoms (EPSs). Moreover, it had broad effectiveness for a range of mood and anxiety symptoms that were common in schizophrenia. The enthusiasm for its effectiveness was balanced by a number of side effects (described later in this section). Attempts to duplicate clozapine’s effectiveness in agents with milder side effects led to the development of a group of agents that included risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), and aripiprazole (Abilify). Unfortunately, none of these drugs duplicated clozapine’s effectiveness in patients who are partially responsive to First-Generation Antipsychotic (FGAs). On the other hand, these drugs are associated with antipsychotic effects at doses less likely to cause EPS. The term atypical is probably outdated since these agents are currently the most prescribed group of antipsychotics. Newer, so-called atypical, antipsychotics such as olanzapine, risperidone, sertindole and clozapine (an old drug which was re-introduced in 1990) are claimed to address these limitations of first generation antipsychotics particularly Extrapyramidal Symptoms (EPS). Atypical agents are, at a minimum, at least as effective as conventional drugs such as haloperidol. They also cause substantially fewer extrapyramidal symptoms [1-11].

The first SDAs 1950’s Clozapine developed. 1970’s Clozapine introduced into general practice. In 1994 Risperidone (Risperdal) introduced. 1996-1997 Olanzapine (Zyprexa) and Quetiapine (Seroquel) introduced. 2001-2002 Ziprasadone (Geodon) and Aripiprazole (Abilify) introduced. Clozapine was briefly marketed and quickly withdrawn for two reasons [4,12-14].

- 1) The embarrassment of not having any EPS, and
- 2) Agranulocytosis

New group of antipsychotics (second generation or atypical) emerged in the 1980s. The second generation antipsychotics showed similar effectiveness but fewer extrapyramidal effects. Clozapine, the first atypical antipsychotic, was introduced in Europe in 1971. It was withdrawn by the manufacturer in 1975 because it could cause agranulocytosis. Its use with the appropriate monitoring was approved in 1989 after having been shown to be effective in treatment-resistant schizophrenia and in reducing suicide rate in patients with schizophrenia [4,14].

The atypical antipsychotics, which differ from typical antipsychotics because of a decrease in associated Extrapyramidal Symptoms (EPS), have now become the standard treatment for youth with early-onset schizophrenia spectrum disorders. For years now, these medications have been given to younger people without specific FDA approval for pediatric populations, and clinicians have provided off-label prescriptions drawing from clinical experience using these medications successfully in adults. However, recently completed double-blind, randomized controlled clinical trials reporting the use of risperidone, olanzapine, and aripiprazole for early-onset schizophrenia spectrum disorders in teenagers have demonstrated effectiveness relative to placebo. As a result of these studies, risperidone and aripiprazole now have a formal indication for the treatment of psychotic symptoms in adolescents with schizophrenia. Several important adverse effects are common with the use of atypical antipsychotics including sedation, metabolic abnormalities, elevated prolactin levels, and movement disorder [4,5].

Types of common second generation antipsychotics [3,4].

1. Dibenzazepines: Clozapine (Clozaril)
2. Benzisoxazole: Risperidone (Risperdal)
3. Thienobenzodiazepines: Olanzapine (Zyprexa)

Pharmacological profiles of some atypical antipsychotics (pharmacodynamics)

The atypical antipsychotics are divided into two major pharmacological groups, namely the multiple receptor antagonists,

such as clozapine, olanzapine and quetiapine, and the more selective 5-HT₂/D₂ antagonists as exemplified by risperidone, sertindole, ziprasidone and zotepine. The benzamide antipsychotic amisulpride is the most selective antagonist for the D₂/D₃ receptors which presumably gives it the mesocortical selectivity of action with a minimal effect on the dopamine receptors in the basal ganglia [4].

Clozapine

Clozapine was the first of the SGAs. It was discovered in 1958 in Bern, Switzerland, and was first studied in animal experiments in 1960. Soon after clinical trials with clozapine began, the drug appeared to be an effective antipsychotic agent that did not cause extrapyramidal side effects. In 1975, clozapine was introduced in Finland, where 16 of 1,600 treated patients developed granulocytopenia (1,600 cells or less per mm³). Eight of the 13 patients in whom granulocytopenia progressed to agranulocytosis died of infectious diseases. After 50 patients around the world had died, clozapine was withdrawn from most European markets, and research with this drug came to a virtual halt [4,13,14].

Clozapine is preferred drug for Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia and reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.

Clozapine (Clozaril®, Sandoz) is a dibenzodiazepine and has dopamine, 5-HT, histamine and adrenergic receptor antagonist properties. Clozapine causes agranulocytosis in between 0.05% and 2% of patients, substantially higher than with standard antipsychotics and because of this increased risk it was withdrawn from use soon after its introduction in the 1970s. In 1989 a relaunch was approved but supply of the drug was conditional upon a stringent programme of white cell count monitoring being carried out (Clozaril Patient Monitoring Scheme). Due to risks of agranulocytosis, Clozaril is available only through a distribution system that ensures WBC and ANC [1,4,7,8,14]. Pharmacological profiles of clozapine (pharmacodynamics).

Clozapine binds with a high affinity (in the nanomolar range) to D₄ and D₂ receptors and with lower affinity for the D₁, D₃ and D₅ receptors. The finding that clozapine had a high affinity for the D₄ receptors was particularly exciting when it was discovered that an elevated expression of D₄ receptors occurred in the brains of schizophrenic patients. However, more recent studies have shown that clozapine also binds with a high affinity to the short form of the D₂ receptor. Further evidence for the relative lack of specificity of clozapine, not only for different types of dopamine receptors but also for 5-HT, muscarinic, adrenergic and histaminergic receptors, suggests that it is a neuroleptic with a very broad basis of action. However, the beneficial effects of clozapine (and other atypical neuroleptics such as risperidone, seroquel and sertindole) may be due to its selective effects on mesolimbic and mesocortical dopaminergic neurons. Clinical and experimental studies suggest that such atypical neuroleptics decrease the negative symptoms of schizophrenia by enhancing prefrontal dopaminergic activity while decreasing the activity of this transmitter in the mesolimbic system, thereby attenuating the psychotic symptoms of schizophrenia [1,4,7,8,14].

Experimental studies also show that clozapine, and other novel atypical neuroleptics, have little effect on the activity of the nigrostriatal dopaminergic system which probably accounts for the low incidence of extrapyramidal side effects seen with these drugs. Clozapine and several other atypical neuroleptics are also potent inhibitors of 5-HT₂ type receptors, particularly the 5-HT_{2A} and 5-HT_{2C} subtypes and it has been postulated that their antipsychotic action combined with a low propensity to cause extrapyramidal side effects may be attributable to the antagonism of 5-HT_{2A} receptors combined with an inhibition of mesocortical D₂ receptors. The experimental evidence to support this view arises from findings that stimulation of 5-HT_{2A} receptors enhances the synthesis and release of dopamine in the rat brain. Conversely 5-HT_{2A} receptor antagonists reduce the stimulant effects of amphetamine, a drug that in high doses can produce symptoms not unlike paranoid schizophrenia, possibly due to its ability to release dopamine in the mesocortical and mesolimbic regions of the brain [1,4].

Contraindications to the use of clozapine

Contraindications to the use of clozapine use are (4):

- 1) WBC count below 3,500 cells per mm³,
- 2) A previous bone marrow disorder,
- 3) History of agranulocytosis during clozapine treatment,
- 4) Concomitant use of another bone marrow suppressant drug such as carbamazepine (Tigerton).

Common side effects of clozapine

Agranulocytosis: Agranulocytosis (absolute neutrophil count less than 500 cells per mm³ or WBC less than 1,000 cells per mm³) The risk for clozapine-induced agranulocytosis is 0.73 percent during the first year of treatment and 0.07 percent in the second year (over all 0.05-2%). Agranulocytosis due to clozapine is a potentially fatal condition that requires immediate medical attention. The risk of agranulocytosis increases with age and is higher in women. Therefore, before treating patients with clozapine, clinicians must register patients with a clozapine monitoring system [4,14].

Clozaril patient monitoring scheme

1. Before initiating therapy, WBC $\geq 3,500/\text{mm}^3$ and ANC $\geq 2,000/\text{mm}^3$
2. First 6 months, weekly monitoring, if WBC $\geq 3,500/\text{mm}^3$ and ANC $\geq 2,000/\text{mm}^3$ then go to every 2 weeks.
3. Six to 12 months, every 2 week monitoring, if WBC $\geq 3,500/\text{mm}^3$ and ANC $\geq 2,000/\text{mm}^3$ then every 4 weeks.

If the patient has a WBC count below 2,000 cells per mm³ or a granulocyte count below 1,000 cells per mm³, clozapine must be discontinued.

Other Adverse Events

- Myocarditis
- Seizures
- Sialorrhea (Hypersalivation)
- Weight Gain

- Diabetes Mellitus
- Metabolic syndromes
- Although the mechanism of action is unknown, there is a slight risk of respiratory depression or collapse if treatment is initiated while patients are taking benzodiazepines

Indications

- 1) Treatment-resistant schizophrenia
- 2) Reduction in risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder
- 3) Treatment-resistant bipolar disorder
- 4) Violent aggressive patients with psychosis and other brain disorders not responsive to other treatments

Risperidone

Risperidone (Risperdal®, Janssen): is a benzisoxazole derivative which combines potent 5-HT₂ and dopamine receptor antagonism. It is licensed for the treatment of acute and chronic schizophrenia. Risperidone was the first SGA medication to be approved following clozapine whereas clozapine was reserved for patients with illnesses that were poorly responsive to available antipsychotic drugs; risperidone was a first-line antipsychotic that could be administered to nearly every patient with a psychotic illness. Following its introduction it was hoped that risperidone would share clozapine's efficacy for a broad range of psychopathology in schizophrenia and that it would be more effective than the FGAs [4,15].

Although this promise has not been met, risperidone has been widely accepted and is among the most prescribed antipsychotics worldwide. Risperidone was the first atypical antipsychotic to be released as a first-line agent in the United States and will soon be available in generic form.

The most frequently prescribed antipsychotic agent for children and adolescents, risperidone has now been approved by the FDA for the treatment of schizophrenia in adolescents as well as for autistic spectrum disorders in children [4,5,15]. After it was introduced in the United States in 1993, early studies using this medication in children and adolescents with early-onset schizophrenia spectrum disorders suggested that risperidone is effective in reducing psychotic symptoms in this group but that it is associated with adverse effects including moderate weight gain, mild sedation, and dose-related EPS [4,15,16].

Risperidone is especially atypical at lower doses but can become more "conventional" at high doses in that EPS can occur if the dose is too high. Risperidone thus has favored uses, not only in schizophrenia at moderate doses but also for conditions in which low doses of conventional antipsychotics have been used in the past, for example, for elderly patients with psychosis, agitation, and behavioral disturbances associated with dementia and for children and adolescents with psychotic disorders. Although risperidone is an SDA, for reasons that are not clear it elevates prolactin to the same degree as conventional antipsychotics, even at low doses [4, 6,7,15].

Many studies show that risperidone is a highly effective agent for positive symptoms of schizophrenia and also improves

negative symptoms of schizophrenia better than do conventional antipsychotics. Early studies show a very low incidence of tardive dyskinesia with long-term use and also show that some patients improve on risperidone when conventional antipsychotics fail, although probably not as well as they would on clozapine. Ongoing studies suggest that risperidone may improve cognitive functioning not only in schizophrenia, but also in dementias, such as Alzheimer's disease. Risperidone may also improve mood in schizophrenia and in both the manic and depressed phases of bipolar disorder. There is less weight gain with risperidone than with some other atypical antipsychotic agents, perhaps because risperidone does not block histamine 1 receptors, but weight gain is still a problem for some patients [3,4,7,8,15]. Pharmacological profiles of risperidone (pharmacodynamics).

Risperidone has been developed as a combined D₂/5-HT_{2A} receptor antagonist. In addition, it has a high affinity for 5-HT_{1A} and 5-HT₇ receptors. Whether such an effect has any relevance to its beneficial effects on the negative symptoms of schizophrenia, and lack of extrapyramidal side effects at moderate therapeutic doses, is unknown. An important advantage of risperidone over clozapine lies in its lack of antagonism of muscarinic receptors [3,4,15].

Risperidone has high affinity for dopamine D₂ receptors and for serotonin 5-HT_{2A} receptors. Risperidone's presumed mechanism of action is associated with its potent central antagonism of both 5-HT_{2A} and D₂ receptors. Risperidone also demonstrates high affinity for adrenergic α₁- and α₂-receptors and histaminergic H₁ receptors. It has moderate affinity for serotonin 5-HT_{1C}, 5-HT_{1D}, and 5-HT_{2A} receptors, and weak affinity for dopamine D₁ receptors. Risperidone has no affinity for cholinergic muscarinic receptors or adrenergic β₁ and β₂ receptors. Although risperidone has high affinity for D₂ receptors, it does not have the rates of EPS that the high-potency FGA medications have. This is most likely due to the dopamine-promoting effects of 5-HT_{2A} antagonism. Risperidone blocks 65 percent of D₂ receptors (the lowest threshold percentage for antipsychotic efficacy) at an average dose of 2 mg per day. At an average of 6 mg per day, 80 percent of D₂ receptors are blocked, and EPS may occur. At the 2 mg dose 5-HT_{2A} effects may not be optimal [3,4,7,8,15].

Indications

1. Schizophrenia and Psychosis: Acute Treatment
2. Schizophrenia and Psychosis: Maintenance Treatment
3. Schizophrenia and Psychosis: Adolescents
4. Bipolar Mania: Adults
5. Bipolar Mania: Children and Adolescents
6. Irritability Associated with Autism: Children and Adolescents

Olanzapine

Olanzapine (Zyprexa®, Lilly) is a thienobenzodiazepine, and is a potent 5-HT₂ and dopamine antagonist, with anticholinergic activity, an activity profile very similar to that of clozapine atypical antipsychotic introduced in the United States following risperidone was olanzapine [3,4,17]. Pharmacological profiles of Olanzapine (pharmacodynamics) Olanzapine, like clozapine, has a broad

spectrum of action on dopamine, 5-HT, adrenergic, histaminel and muscarinic receptors. While the precise significance is presently unclear, it is of interest that whereas clozapine binds with a high affinity to 5-HT₆ and 5-HT₇ receptors, olanzapine only shows a high affinity for 5-HT₆ receptors [3,4,17]. Clinical studies have demonstrated that olanzapine has a similar profile to clozapine without causing agranulocytosis; preliminary studies also show that it does not cause extrapyramidal side effects or increase prolactin release. Olanzapine has recently been introduced for the treatment of mania. Olanzapine is a high affinity antagonist at 5-HT_{2A} / 2C, 5-HT₆, D₁ - 4, H₁, and adrenergic α ₁- receptors and a moderate affinity antagonist at M₁-5 and 5-HT₃ receptors. It resembles most of the SGAs by having a combination of high 5-HT₂ and D₂ activity. PET studies indicate that typical doses of olanzapine such as 10 to 20 mg result in 68 to 84 percent D₂ occupancy. Its 5-HT₂ activity is approximately eight times as strong as its dopamine receptor blockade. Compared with risperidone, quetiapine, and ziprasidone, olanzapine has greater M and H receptor antagonism. This histamine activity may explain its tendency to cause weight gain [3,4,17-20].

Indications

- 1) It is FDA approved antipsychotics for maintenance treatment of mania
- 2) Treatment of schizophrenia in adults
- 3) Acute manic or mixed episodes of bipolar (alone or with lithium/valproate)
- 4) Acute agitation associated with bipolar or schizophrenia
- 5) Depressive associated with bipolar disease
- 6) Treatment of refractory depression

Quetiapine (Seroquel®, Zeneca) was launched in the UK in October 1997 and is licensed for the treatment of schizophrenia. Three placebo-controlled trials have been published confirming its efficacy. Quetiapine has also been compared in patients with acute exacerbations of schizophrenia with both chlorpromazine and haloperidol in studies lasting 6 weeks. No significant differences in efficacy between quetiapine and the conventional drugs were found but there were significantly fewer, or less deterioration in, extrapyramidal symptoms in the quetiapine groups [4,21].

The efficacy of quetiapine is superior to placebo and generally equivalent to other antipsychotic medications. Quetiapine can be distinguished by a lower incidence of extrapyramidal side effects than any of the other SGAs, with the possible exception of clozapine. Other side effects include drowsiness, orthostatic hypotension, increased

heart rate, dry mouth, constipation, weight gain, hyperlipidemia, and hyperglycemia. No blood dyscrasias or effects on prolactin concentrations have been observed in long-term trials. In addition to its indication for treatment of schizophrenia, recently quetiapine received FDA approval for the treatment of depressive episodes in bipolar I and II and manic episodes in bipolar I. A new formulation, quetiapine extended release, has recently been made available. This formulation allows once-daily dosing rather than the recommended twice-daily dosing for the original formulation [4,7, 21,22].

Sertindole

Sertindole (Serdolect®, Lundbeck) is a selective antagonist of dopamine and 5-HT₂ receptors. It is licensed for the treatment of schizophrenia. Sertindole was no more effective than haloperidol for all measurements of psychosis. There were significantly fewer extrapyramidal events with any dose of sertindole compared with haloperidol. Adverse effects includes nasal congestion and reduced ejaculatory volume (in men) were significantly more common with sertindole compared with placebo [23,24].

Ziprasidone

Ziprasidone was the fifth SGA approved in the United States. It was synthesized in 1987 by Harry Howard of Pfizer Pharmaceuticals. Tom Seeger screened the compound and identified the activity at D₂ and 5-HT₂ receptors. Early on it was noted that ziprasidone differed from the other agents in this class by not being associated with weight gain and having relatively little sedative side effect. Its approval in the United States was delayed due to concerns regarding its tendency to prolong the QT interval on the ECG. The Recent concerns about weight gain, diabetes, and lipid elevations have led to an increase in the use of ziprasidone. For example, in the NIMH CATIE trial, patients randomized to ziprasidone showed negligible changes in weight, glucose, or lipids. Moreover, patients who gained weight on other antipsychotics were likely to show substantial weight loss when they were switched to ziprasidone [4,8].

Amisulpride

Amisulpride (Solian®, Lorex Synthelabo) has also been launched in the UK (November 1997), and is licensed for acute or chronic schizophrenia where positive and/or negative symptoms are prominent [25].

Side effects of SGAs: Metabolic problems and the metabolic Syndrome Metabolic problems of greatest concern pertain to the body's ability to properly manage (1) glucose and (2) lipids (their storage, consumption, and conversion to metabolically useful chemicals). Glucose dysregulation includes high blood sugar that can progress to

Table 1: Shows metabolic risks associated with second generation antipsychotics.

Medications	Weight gain	Glucose metabolism abnormalities	Dyslipidemia	Metabolic syndromes
Clozapine	High	High	High	High
Risperidone	Medium	Medium to low	Medium	low
Olanzapine	High	High	High	High
Quetiapine	Medium	Medium to low	High	High
Ziprasidone	Low	Low	Low	Low
Amisulpride	Low	Low	Low	-

diabetes. Dysregulation of lipid (fat) metabolism, commonly referred to as “high cholesterol,” may be called dyslipidemia. Although most people who experience metabolic disturbances also experience being overweight or obese, metabolic dysregulation can occasionally occur without weight gain. Excess weight/obesity, hyperglycemia/diabetes, dyslipidemia, cigarette smoking, and lack of physical activity are well-established risk factors for the development of CAD. When symptoms develop in CAD, the condition is called CHD [4,7,8]. Clozapine and Olanzapine associated with greatest risk of causing metabolic side effects followed by quetiapine. Aripiprazole and Ziprasidone are among atypical antipsychotics lowest risks of metabolic symptoms and syndromes (Table 1) [3,4].

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