INTERNATIONAL RESEARCH JOURNAL OF PHARMACY **ISSN 2230 – 8407**
Available online http://www.irjponline.com
Review Article

NOVEL ATYPICAL ANTIPSYCHOTIC AGENTS

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Article Received on: 20/03/2011 Revised on: 25/04/2011 Approved for publication: 04/05/2011

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ABSTRACT
Antipsychotics are a group of drugs commonly but not exclusively used to treat psychosis. Antipsychotic agents are grouped in two categories: Typical and Atypical antipsychotics. The first antipsychotic was chlorpromazine, which was developed as a surgical anesthetic. The first atypical anti-psychotic medication, clozapine, was discovered in the 1950s, and introduced in clinical practice in the 1970s. Both typical and atypical antipsychotics are effective in reducing positive and negative symptoms of schizophrenia. Blockade of D_2 receptor in mesolimbic pathway is responsible for antipsychotic action. Typical antipsychotics are not particularly selective and also block Dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking D_2 receptors in these other pathways is thought to produce some of the unwanted side effects. Atypical antipsychotics differ from typical psychotics in their "limbic-specific" dopamine type 2 (D_2)-receptor binding and high ratio of serotonin type 2 (5-HT_2)-receptor binding to D_2. Atypical antipsychotics are associated with a decreased capacity to cause EPSs, TD, narcoleptic malignant syndrome, and hyperprolactinemia. Atypical antipsychotic agents were developed in response to problems with typical agents, including lack of efficacy in some patients, lack of improvement in negative symptoms, and troublesome adverse effects, especially extrapyramidal symptoms (EPSs) and tardive dyskinesia (TD).
KEY WORDS -Atypical, antipsychotic, schizophrenia, dopamine, D_2 receptor, 5HT2A receptor

INTRODUCTION

Antipsychotics are a group of drugs commonly but not exclusively used to treat psychosis, which is typified by schizophrenia. Schizophrenia is a mental disorder which is characterized by two types of symptoms first one is Positives symptoms: Hallucination, delusion, disorganized thought, restlessness, insomnia, anxiety, fighting and second one is Negative symptoms: apathy, loss of insight, poverty of speech, social withdrawal.

Over time a wide range of antipsychotics have been developed. The first antipsychotic was chlorpromazine, which was developed as a surgical anesthetic. Antipsychotics can be grouped into two groups, Typical Or First-Generation Antipsychotics: chlorpromazine, haloperidol, thiothixene and Atypical Or Second-Generation Antipsychotics: Clozapine, olanzapine, risperidone Typical antipsychotics are also sometimes referred to as major tranquilizers, because some of them can tranquilize and sedate.

The typical and atypical antipsychotics are both effective in reducing the positive symptoms of schizophrenia such as hallucinations, delusions and positive thought disorder. The negative symptoms of schizophrenia include loss of energy and interest inactivities, and poverty of thought. Recently it has been proposed that the negative symptoms are composed of two subgroups of symptoms: primary negative symptoms (being part of the illness process), and secondary negative symptoms (being apparent rather than actual symptoms of the disorder, which are in fact secondary to drug treatment). Claims are made that the atypical may produce no secondary negative symptoms, and go some way in relieving primary negative symptoms.[1] Other symptoms of schizophrenia include cognitive and mood difficulties and reduced quality of life. Evidence indicates that the atypical antipsychotics can be helpful in all of these domains.[2]

The first antipsychotic was chlorpromazine, which was developed as a surgical anesthetic. The first atypical anti-psychotic medication, clozapine was discovered in the 1950s, and introduced in clinical practice in the 1970s.

ATYPICAL ANTIPSYCHOTIC AGENTS

Atypical antipsychotic agents were developed in response to problems with typical agents, including lack of efficacy in some patients, lack of improvement in negative symptoms, and troublesome adverse effects, especially extra pyramidal symptoms (EPSs) and tardive dyskinesia (TD). The extra pyramidal system is composed of two pathways, in one the neurotransmitter is dopamine and in the other, acetylcholine. When the dopamine pathway is blocked by the antipsychotic the balance in the system is disrupted, resulting in spasm.

Acute neurological side-effects occur secondary to D_2 receptor blockade in the extra pyramidal system (and are also called **acute EPS**). They can appear on the first day of treatment and can take various forms of involuntary muscle spasm, particularly involving of the jaw, tongue, neck and eyes.

Medium-term neurological side-effects are also due to D_2 blockade. **Akathisia** usually occurs within the first few day of treatment and involves either a mental and/or motor restlessness). **Parkinsonism** usually occurs some days or weeks after the commencement of treatment. There is a masklike face, rigidity of limbs, bradykinesia, and loss of upper limb-swing while walking. Tremor and festinating gait are less common.

Chronic neurological side-effects (also known as chronic or **late EPS**) usually occur after months or years of continuous D2 blockade. **Tardive dyskinesia (TD)** manifests as continuous choreoathetoid movements of the mouth and tongue, frequently with lip-smacking, and may also involve the head, neck and trunk. Late EPS may continue after cessation of the typical antipsychotic.

Neuroendocrine effects result from blockade of dopamine transmission in the infundibular tract. Prolactin levels rise, producing galactorrhea, amenorrhea and infertility

Neuroleptic malignant syndrome (NMS) is probably due to disruption of dopaminergic function, but the mechanism is not understood. The symptoms include muscle rigidity, hyperthermia, autonomic instability and fluctuating consciousness.

Anticholinergic side-effects include dry mouth, difficulty with micturition, constipation, blurred vision and ejaculatory failure. Anticholinergic effects can contribute to a toxic confusional state. The atypical drugs are far less likely to cause extra-pyrammidal side-effects (EPS), drug induced involuntary movements, than are the older drugs. The atypical antipsychotic drugs may also be effective in some cases that are resistant to older drugs.

Atypical antipsychotics differ from typical psychotics in their "limbic-specific" dopamine type 2 (D_2)-receptor binding and high ratio of serotonin type 2 (5-HT2)-receptor binding to D2. Atypical antipsychotics are associated with a decreased capacity to cause EPSs, TD, neuroleptic malignant syndrome, and hyper prolactinemia.

Atypical antipsychotics are increasingly being used for indications other than schizophrenia, such as the management of aggression, mania, and depression. Atypical antipsychotics are often considered first-line agents for treating schizophrenia and are promising treatment alternatives for other psychiatric and neurologic conditions. Atypical are a heterogeneous group of otherwise unrelated drugs united by the fact that they work differently from typical antipsychotics. Most share a common attribute of working on serotonin receptors as well as dopamine receptors. One drug, amisulpride, does not have serotonergic activity, instead it has some partial dopamine agonism. Another drug, aripiprazole, also displays some partial dopamine agonism, 5-HT_{1A} partial agonism and 5-HT_{2A} antagonism.[3]

CLASSES OF ATYPICAL ANTIPSYCHOTIC AGENTS

The atypical antipsychotic agents, sometimes called the "novel" antipsychotic agents are a group of drugs which are different chemically from the older drugs used to treat psychosis. The "conventional" antipsychotic drugs are classified by their chemical structures as the phenothiazines, thioxanthines (which are chemically very similar to the phenothiazines), butyrophenones, diphenylbutylpiperadines and the indolones. All of the atypical antipsychotic agents are chemically classified as dibenzepines. They are considered atypical or novel because they have different side effects from the conventional antipsychotic agents. Chemically atypical antipsychotic agents are grouped in five classes. Classes are given in Table1.

MECHANISM OF ACTION

All antipsychotic drugs tend to block D_2 receptors in the dopamine pathways of the brain. Typical antipsychotics are not particularly selective and also block Dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking D_2 receptors in these other pathways is thought to produce some of the unwanted side effects.

The dopamine pathways in the brain.

1) M**esocortical** pathway, extends from the ventral tegmental region of the mid-brain to the cortex. It is possible that under activity of this pathway may be involved in the negative symptoms of schizophrenia. The side-effect of antipsychotics known as the “secondary” negative symptoms may arise in large part through disruption of transmission in this pathway.

2) **Mesolimbic** pathway, extends from the ventral tegmentum to the nucleus accumbens, a limbic system structure. Hyper activity in the mesolimbic pathway which produces the positive symptoms of hallucinations and delusions. In this theory, the antipsychotics are directed at this pathway. As the limbic system is also involved in pleasurable sensations, this pathway may also be involved in negative symptoms.

3) **Nigrostriatal** pathway extends from the substantia nigra of the midbrain to the basal ganglia. Blockage of

this pathway by the antipsychotics is unintended and results in movement side-effects. To rebalance the extrapyramidal system an acetylcholine blocker is administered.

4)**Tuberoinfundibular** pathway extends from the hypothalamus to the portal system which serves the anterior pituitary. Tonic release of dopamine into this system inhibits the release of prolactin. Unintentional disruption of this system releases prolactin and the side-effects of gynecomastia, galactorrhea and sexual dysfunction.

The mechanism of action of these agents is unknown, and differs greatly from drug to drug. modulation of the dopamine neurotransmitter system is the most important mechanism by which anti-psychotics exert their benefits, the role of the serotonergic activity of the atypicals is debated. Some researchers believe that D_2 receptor antagonism, coupled with 5-HT_2A receptor antagonism, is responsible for the "atypicality" of atypical anti-psychotics. Others believe that fast dissociation (a fast Koff) from the D_2 receptor, allowing for better transmission of normal physiological dopamine surges, better explains the pharmacological evidence.

There is extensive evidence that atypical anti-psychotics have less of an affinity for D_2 receptors and more of an affinity for the D_4 receptors This is primarily because atypical anti-psychotics are somewhat less likely to cause tardive dyskinesia The idea is that D_2 receptors are dopaminergically ubiquitous and affect the motor system as much as the motivational aspect of the dopamine system. On the other hand, D_4 is a more accurate dopamine receptor subtype. Atypical anti-psychotics also affect the norepinephrine, acetylcholine, and histamine receptors of various subtypes.[4] However, studies have shown that D_4 selective antagonism has no anti-psychotic effect.

SIDE EFFECTS

Most of the side effects encountered with the typical antipsychotics can be encountered with the atypical agents, however, they are less frequent and generally less severe. Below are listed the most common side effects of the atypicals and side effects are given in Table 2.

Weight gain is problem in schizophrenia and other mental disorders, in part because of poor eating habits and lack of exercise. However, the atypical antipsychotics exacerbate this problem. A meta-analysis[5] estimated that over a 10 week period the mean increase was as given in Table 3.

Metabolic side effects with atypical antipsychotics

Recently, metabolic concerns have been of grave concern to clinicians, patients and the FDA. In 2003, the Food and Drug Administration (FDA) required all manufacturers of atypical antipsychotics to change their labeling to include a warning about the risks of hyperglycemia and diabetes with atypical antipsychotics. It must also be pointed out that although all atypicals must carry the warning on their labeling, some evidence shows that all atypicals are not equal in their effects of weight and insulin sensitivity. The general consensus is that clozapine and olanzapine are associated with the greatest effects on weight gain and decreased insulin sensitivity, followed by risperidone and quetiapine. Ziprasidone and aripiprazole are thought to have the smallest effects on weight and insulin resistance, but clinical experience with these newer agents is not as developed as that with the older agents.

Hyperlipidemia (raised cholesterol and triglycerides) appears to be associated with the dibenzodiazepine-derived antipsychotics (clozapine, olanzapine and quetiapine).

QTc interval prolongation has been a matter of concern. The average QTc interval in healthy adults is about 400 msec, and a QTc interval of 500 msec or more is a risk factor for torsade de pointes (a ventricular arrhythmia which can lead to syncope, ventricular fibrillation and sudden death).

One study found the QTc interval prolongations as given in Table 4.

Myocarditis and cardiomyopathy are rare (0.015-0.188 %) side effects of clozapine therapy.[6]

Recommendation for the monitoring/management of the side effects for the atypical antipsychotics have been provided, however, further work is required.[7]

When **weight gain** is anticipated (clozapine, olanzapine, quetiapine and risperidone) weight and BMI should be recorded. Nutritional and life style (exercise) advise is recommended. With excessive weight gain a change to another agent may be considered.

When **diabetes** is anticipated (clozapine and olanzapine in particular) the weight is to be monitored and laboratory measures (e.g. fasting blood glucose) may be indicated. When hyperlipidemia is anticipated (clozapine, olanzapine and quetiapine) serum cholesterol and triglycerides may be monitored.

When **QTc prolongation** is anticipated (ziprasidone, particularly), EEG monitoring is recommended in cases of increased cardiac risk (known heart disease, syncope, family history of early sudden death).

Myocarditis has been associated with clozapine and clozapine clinics have specialized screening procedures. The side effects reportedly associated with the various atypical antipsychotics vary and are medication-specific.

USES

Atypical antipsychotic agents are generally used to treat psychotic disorders including schizophrenia, acute manic episodes, and maintenance of bipolar disorder. Uses of individual drug are given in Table 5.

DRUG-DRUG INTERACTIONS

Drug-drug interactions are given for recently developed antipsychotics in Table 6.

DOSES OF ATYPICAL ANTIPSYCHOTICS

Doses of atypical antipsychotic agents are given in Table 7.

CLOZAPINE

Clozapine is an antipsychotic medication used in the treatment of schizophrenia. The first of the atypical antipsychotics to be developed, it was first introduced in Europe in 1971, but was voluntarily withdrawn by the manufacturer in 1975 after it was shown to cause agranulocytosis, a condition involving a dangerous decrease in the number of white blood cells, that led to death in some patients. The FDA requires blood testing for patients taking clozapine. The FDA also requires clozapine to carry five black box warnings for agranulocytosis, seizures, myocarditis, for "other adverse cardiovascular and respiratory effects", and for "increased mortality in elderly patients with dementia-related psychosis."

Clozapine is used principally in treating treatment-resistant schizophrenia[8], a term generally used for the failure of symptoms to respond satisfactorily to at least two different antipsychotics.[9]

The use of clozapine is associated with a fair number of side effects, many minor though some serious and potentially fatal: the more common include constipation, drooling, muscle stiffness, sedation, tremors, orthostasis, hyperglycemia, and weight gain. The risks of extra pyramidal symptoms such as tardive dyskinesia are much less with clozapine when compared to the typical antipsychotics; this may be due to clozapine's anticholinergic effects.

Clozapine is classified as an atypical antipsychotic drug because its profile of binding to serotonergic as well as dopamine receptors[10]; its effects on various dopamine mediated behaviors also differ from those exhibited by more typical antipsychotics. In particular, clozapine interferes to a lower extent with the binding of dopamine at D_1, D_2, D_3 and D_5 receptors, and has a high affinity for the D_4 receptor. This evidence suggests clozapine is preferentially more active at limbic than at striatal dopamine receptors and may explain the relative freedom of clozapine from extra pyramidal side effects together with strong anticholinergic activity.

ARIPIPRAZOLE

Aripiprazole was approved by the Food and Drug Administration (FDA) on November 15, 2002 for the treatment of schizophrenia, the sixth atypical antipsychotic medication of its kind. More recently it received FDA approval for the treatment of acute manic and mixed episodes associated with bipolar disorder, as well as treatment of depression.

ASENAPINE

Asenapine is a new 5-HT_{2A}- and D2-receptor antagonist under development for the treatment of schizophrenia and acute mania associated with bipolar disorder. Preliminary data indicate that it has minimal anticholinergic and cardiovascular side effects, as well as minimal weight gain. Over 3000 patients have participated in clinical trials of asenapine, and the FDA accepted the manufacturer's NDA on November 26, 2007 for standard review.

OLANZAPINE

Olanzapine is an atypical antipsychotic, approved by the FDA for the treatment of: schizophrenia on 1996-09-30; depressive episodes associated with bipolar disorder. Olanzapine is structurally similar to clozapine, and is classified as a thienobenzodiazepine. Olanzapine has a higher affinity for 5-HT_2 serotonin receptors than D_2 dopamine receptors. Like most atypical antipsychotics, compared to the older typical ones, Olanzapine has a role as a mood stabilizer.[11]

ILOPERIDONE

Iloperidone is an investigational atypical antipsychotic. It is being investigated mainly for the treatment of schizophrenia symptoms. On November 27, 2007, Vanda Pharmaceuticals announced that the US FDA had accepted their NDA for iloperidone, confirming the application is ready for FDA review and approval. Clinical studies have shown that some patients treated with iloperidone show reduced extrapyramidal symptoms and weight gain. Phase II testing has shown that effectiveness in humans is possible with as low as 8 mg per day, and is tolerable up to 32 mg per day. As of the year 2000, Phase III trials are currently in progress, involving 3300 patients.[12]

PALIPERIDONE

Chemically, paliperidone is primary active metabolite of the older antipsychotic risperidone (paliperidone is 9-hydroxyrisperidone, i.e. risperidone with an extra hydroxyl group). It is indicated in the treatment of schizophrenia, as well as manic and mixed episodes occurring in conjunction with Bipolar I Disorder, and depression.

Paliperidone was approved by the FDA for the treatment

of schizophrenia on December 20, 2006. This agent will initially be marketed for the treatment of schizophrenia and then for bipolar mania. Clinical trials of paliperidone for the treatment of schizoaffective disorder are also planned. It may also be used off-label for other conditions. The drug significantly reduces side-effects present in other anti-psychotic drugs formerly used to treat both schizophrenia as well as bipolar disorder. Like risperidone, its possible use in autism and Asperger's syndrome may be studied.

RISPERIDONE

Risperidone was approved by the United States Food and Drug Administration (FDA) in 1993 for the treatment of schizophrenia. On Wednesday, August 22, 2007, Risperdal was approved as the only drug agent available for treatment of schizophrenia in children ages 13–18; it was also approved that same day for treatment of bipolar disorder in youths ages 10–18, joining lithium. Risperidone contains the functional groups of benzisoxazole and piperidine as part of its molecular structure. In 2003 the FDA approved risperidone for the short-term treatment of the mixed and manic states associated with bipolar disorder. In 2006 the FDA approved risperidone for the treatment of irritability in children and adolescents with autism. The use of oral risperidone appeared to be associated with within-group improvements on the cognitive domains of processing speed, attention/vigilance, verbal and visual learning and memory, and reasoning and problem solving in patients with schizophrenia or schizoaffective disorder.[13]

ZIPRASIDONE

Ziprasidone was the fifth atypical antipsychotic to gain FDA approval (February 2001). In the United States, Ziprasidone is Food and Drug Administration (FDA) approved for the treatment of schizophrenia, and the intramuscular injection form of ziprasidone is approved for acute agitation in schizophrenic patients. Ziprasidone has also received approval for acute treatment of mania and mixed states associated with bipolar disorder. Ziprasidone has a high affinity for dopamine, serotonin, and alpha-adrenergic receptors and a medium affinity for histaminic receptors. Ziprasidone also displays some inhibition of synaptic reuptake of serotonin and norepinephrine, although the clinical significance of this is unknown.

MELPERONE

Melperone, a butyrophenone, has been shown to possess atypical antipsychotic properties, i.e. ability to produce an antipsychotic effect in man at doses that cause minimal extrapyramidal side effects.[14] In addition, melperone shares the following with other atypical antipsychotic drugs: (1) effectiveness for ameliorating negative symptoms; (2) no prolactin elevation; and (3) effectiveness in the treatment of some patients with neuroleptic-resistant schizophrenia. Melperone has been reported to improve cognitive function.[15]

BLONANSERIN

Blonanserin is a relatively new atypical antipsychotic commercialized by Dainippon Sumitomo Pharma in Japan and Korea for the treatment of schizophrenia.[16,17,18] Relative to many other antipsychotics, blonanserin has an improved tolerability profile, lacking side effects such as extra pyramidal symptoms and excessive sedation and hypotension.[18]

Blonanserin acts as a mixed 5-HT_2 (K_i = 3.98 nM) and D_2 receptor (K_i = 14.8 nM) antagonist.[19] It also exerts some blockade of α_1-adrenergic receptors (K_i = 56.3 nM) and has low affinity for the sigma receptor (IC_{50} = 286 nM)[24]. Blonanserin lacks significant affinity for numerous other sites including 5-HT_1, 5-HT_3, D_1, α_2-adrenergic, β-adrenergic, H_1, mACh, and the monoamine transporters.[19]

MOSAPRAMINE

Mosapramine is an atypical antipsychotic used in Japan.[20] It is a potent dopamine antagonist with high affinity to the D_2, D_3, and D_4 receptors[21]. and with moderate affinity for the 5-HT_2 receptors.[22]

PEROSPIRONE

Perospirone is an atypical antipsychotic of the azapirone chemical class.[23] It was introduced in Japan in 2001 by Dainippon Sumitomo Pharma for the treatment of schizophrenia and acute bipolar mania.[24] Perospirone acts as a 5-HT_{1A} receptor partial agonist, 5-HT_{2A} receptor inverse agonist, and D_2, D_4, and α_1-adrenergic receptor antagonist.[25,26,27,28]

REMOXIPRIDE

Remoxipride is an atypical antipsychotic which was previously used in Europe for the treatment of schizophrenia but was withdrawn due to toxicity concerns (incidence of aplastic anemia in 1/10,000 patients). It was initially launched by Astra Zeneca in 1990 and suspension of its use began in 1993. Remoxipride acts as a selective D_2 and D_3 receptor antagonist and also has high affinity for the sigma receptor, possibly playing a role in its atypical neuroleptic action.[29]

ATYPICAL UNDER DEVELOPMENT

Bifeprunox (**DU-127,090**) is a novel atypical antipsychotic agent which, along with SLV313, aripiprazole, and SSR-181507 combines minimal D_2 receptor agonism with 5-HT receptor agonism.[30]

Bifeprunox has a novel mechanism of action. Conventional antipsychotics are classed into typical and atypical. The typical antipsychotics, such as

chlorpromazine and haloperidol are potent D_2 receptor antagonists. The atypical antipsychotics started with clozapine, these are classified as multi receptor interacting compounds, acting as an agonist towards 5-HT_{1A} and an antagonist towards D_2 receptors among other 5-HT and DA receptors. Bifeprunox and other novel atypical antipsychotics will instead of antagonizing D_2 receptors, will act as partial agonists, as well as agonists towards 5-HT_{1A} receptors.[31]

An NDA for Bifeprunox was filed with the U.S. Food and Drug Administration in January 2007. The FDA rejected the application in August 2007. In the EU, Bifeprunox is still in Phase III clinical trials.

Lurasidone (**SM-13,496**) is an atypical antipsychotic developed by Dainippon Sumitomo Pharma which is currently pending approval for the treatment of schizophrenia and bipolar disorder in the United States.[32] It has completed Phase III clinical trials and an NDA was recently (as of December 30, 2009) submitted to the FDA.

Lurasidone acts as a D_2 (K_i = 1.68 nM), 5-HT_{2A} (K_i = 2.03 nM), 5-HT_7 (K_i = 0.495 nM), and α_{2C}-adrenergic (K_i = 10.8 nM) receptor antagonist, and 5-HT_{1A} (K_i = 6.75 nM) receptor agonist.[33] It has only weak or negligible actions at the 5-HT_{2C}, α_1-adrenergic, H_1, and mACh receptors.[33]

In clinical studies, lurasidone alleviates both positive (e.g., hallucinations, delusions) and negative (e.g., apathy, emotional withdrawal) symptoms of schizophrenia without inducing extra pyramidal side effects, despite its potent D_2 antagonistic actions.[33,34] It has a relatively well-tolerated side effect profile, with low propensity for extrapyramidal symptoms, QTc interval changes, and weight-, lipid-, and glucose-related adverse effects. Side effects reported in at least 5% of subjects and at least twice the frequency of placebo include akathisia (17.6% vs 3.1% placebo), somnolence (11.7% vs. 5.5%), parkinsonism (6.8% vs 0%), and weight gain (5.1% vs. 2.4%).

Pimavanserin (**ACP-103**) is a drug developed by Acadia Pharmaceuticals which acts as an inverse agonist on the serotonin receptor subtype 5-HT_{2A}, with 10x selectivity over 5-HT_{2C}, and no significant affinity or activity at 5-HT_{2B} or dopamine receptors.[35] As of September 3 2009, pimavanserin has not met expectations for Phase III clinical trials for the treatment of Parkinson's disease psychosis, and is in Phase II trials for adjunctive treatment of schizophrenia alongside an antipsychotic medication. It is expected to improve the effectiveness and side effect profile of antipsychotics.[36,37,38]

Vabicaserin (**SCA-136**) is a novel antipsychotic and anorectic under development by Wyeth. As of 2010 it is in phase II clinical trials for the treatment of psychosis and is in preclinical evaluation for obesity. It was also under investigation as an antidepressant but this indication appears to have been dropped.

Vabicaserin acts as a selective 5-HT_{2C} receptor full agonist (K_i = 3 nM; EC_{50} = 8 nM; IA = 100% (relative to 5-HT)) and 5-HT_{2B} receptor antagonist (IC_{50} = 29 nM).[39] It is also a very weak antagonist at the 5-HT_{2A} receptor (IC_{50} = 1,650 nM), though this action is not clinically significant. By activating 5-HT_{2C} receptors, vabicaserin inhibits dopamine release in the mesolimbic pathway, likely underlying its efficacy in alleviating positive symptoms of schizophrenia, and increases acetylcholine and glutamate levels in the prefrontal cortex, suggesting benefits against cognitive symptoms as well.

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TABLE1: CLASSES OF ATYPICAL ANTI-PSYCHOTICS

Class	Drugs
Dibenzazepines	Clozapine, Quetiapine, Clotiapine
Thienobenzodiazepine	Olanzapine
Benzisoheterazoles	Risperidone
Quinolinone	Aripiprazole
Benzamide	Amisulpride, Sulpiride
Azapirone	Perospirone

TABLE 2: SIDE EFFECTS OF ATYPICAL ANTI-PSYCHOTICS

Drug	Side effects
Clozapine	Constipation, drooling, muscle stiffness, sedation, tremors, orthostasis, hyperglycemia, and weight gain.
Risperidone	Akathisia, anxiety, insomnia, low blood pressure, muscle stiffness, muscle pain, sedation, tremors, increased salivation, and stuffy nose, with minimal to moderate weight gain, breast tenderness and eventually lactation in both genders, increaseprolactin, tardive dyskinesia (TD), extrapyramidal symptoms (EPS), and neuroleptic malignant syndrome (NMS).
Olanzapine	Appetite increase, weight gain, and altered glucose metabolism leading to an increased risk of diabetes mellitus
Quetiapine	Common side effects include sedation, headache, and orthostatic hypotension
Ziprasidone	Rash, hypertension, and (rarely) nondose-dependent QT-interval prolongation.
Aripiprazole	Akathisia, headache, unusual tiredness or weakness, Uncontrollable twitching or jerking movements, tremors and seizure, muscle stiffness, faster breathing, sweating, reduced consciousness,
Asenapine	Preliminary data indicate that it has minimal anticholinergic and cardiovascular side effects, as well as minimal weight gain.
Iloperidone	The drug was fairly well tolerated, although hypotension, dizziness, and somnolence were very common side effects ranging from mild to moderate in severity.

TABLE 3: WEIGHT GAIN MEAN INCREASE

Drug	Mean increase
Clozapine	4.45 kg
Olanzapine	4.15 kg
Risperidone	2.1 kg (Quetiapine probably similar)
Ziprasidone	0.04 kg (Aripiprazole probably similar).

TABLE 4: QT INTERVAL PROLONGATION

Drug	Prolongation
Ziprasidone	20.3 ms
Quetiapine	14.5 ms
Risperidone	11.6 ms
Olanzapine	6.8 ms
Haloperidol	4.7 ms

TABLE 5: USES OF ATYPICAL ANTI-PSYCHOTICS

Drug	Uses
Clozapine	Clozapine is used principally in treating treatment-resistant schizophrenia.
Risperidone	Schizophrenia, schizophrenia in children ages 13–18, bipolar disorder in youths ages 10–18, the mixed and manic states associated with bipolar disorder
Olanzapine	Used to treat psychotic disorders including schizophrenia, acute manic episodes, and maintenance of bipolar disorder.
Quetiapine	Used primarily to treat bipolar disorder and schizophrenia, and "off-label" to treat chronic insomnia and restless legs syndrome, treatment of psychosis in elderly patients with Alzheimer's disease and Parkinson's disease,
Ziprasidone	Schizophrenia, acute treatment of mania and mixed states associated with bipolar disorder.
Aripiprazole	Schizophrenia, acute manic and mixed episodes associated with bipolar disorder, as well as treatment of depression.
Paliperidone	Schizophrenia, as well as manic and mixed episodes occurring in conjunction with Bipolar I Disorder, and depression.
Asenapine	Schizophrenia and acute mania associated with bipolar disorder.
Iloperidone	Schizophrenia symptoms

TABLE 6: DRUG-DRUG INTERACTION

Drug-Drug interaction	Effects
Clozapine and Carbamazepine	Concurrent administration of clozapine and carbamazepine results in considerable reductions in plasma clozapine concentrations. It appears that carbamazepine reduces plasma clozapine concentrations by an average of 50%. Carbamazepine is a potent inducer of hepatic metabolic enzymes involved in the cytochrome P450 enzyme system. Concurrent treatment with clozapine and carbamazepine is not recommended
Olanzapine and Carbamazepine	hinistered concomitantly with olanzapine, carbamazepine therapy (200 mg twice daily) may significantly increase olanzapine clearance. Carbamazepine is a potent inducer of cytochrome P450 1A2 enzyme activity; olanzepine clearance may be increased approximately 50% due to this inducing effect on the cytochrome P450 enzyme system
Quetiapine and Phenytoin	Adjuvant administration of quetiapine and phenytoin may increase mean oral quetiapine clearance by as much as five-fold. While the mechanism associated with this interaction has not been determined, it is speculated that phenytoin, a known hepatic enzyme inducer, induces quetiapine metabolism. Increased quetiapine doses may be necessary to maintain antipsychotic effects when quetiapine and phenytoin are administered concurrently
Ziprasidone and Carbamazepine	Ziprasidone is extensively metabolized after oral administration primarily by CYP3A4. Likewise, carbamazepine is a potent inducer of CYP3A4. Concurrent administration of ziprasidone and carbamazepine has resulted in marked decreases in the area under the curve (AUC) for ziprasidone. Patients prescribed ziprasidone and carbamazepine concomitantly may require higher ziprasidone dosages to maintain the desired ziprasidone therapeutic effect.

TABLE 7: DOSES OF ATYPICAL ANTIPSYCHOTICS

Drug	Dose
Clozapine	Dosing 0.25 to 6 mg per day
Risperidone	Dosing 0.25 to 6 mg per day
Olanzapine	Dosing 2.5 to 20 mg per day
Quetiapine	Dosing starts at 25 mg and continues up to 800 mg maximum per day
Ziprasidone	Dosing 20 mg twice daily initially up to 80 mg twice daily
Aripiprazole	Dosing 1 mg up to maximum of 30 mg has been used