Southeast Asian Journal of Case Report and Review 2022;9(4):77–85

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Southeast Asian Journal of Case Report and Review

Journal homepage: https://www.sajcrr.com/

Review Article

The first generation and second generation antipsychotic drugs and their pharmacology in treatment of schizophrenia

Afroj A. Shaikh[1,*], **Jaydeep B. Pawar**[2], **Sachin J. Anbhule**[3]

[1]*Dept. of Pharmacy, HSBPVT, GOI, Faculty of Pharmacy, Kashti, Shrigonda, Maharashtra, India*
[2]*Dept. of Microbiology, HSBPVT, GOI, Faculty of Pharmacy, Kashti, Shrigonda, Maharashtra, India*
[3]*Dept. of Medicinal Chemistry, HSBPVT, GOI, Faculty of Pharmacy, Kashti, Shrigonda, Maharashtra, India*

ARTICLE INFO

Article history:
Received 15-12-2022
Accepted 29-12-2022
Available online 25-01-2023

Keywords:
Psychosis
Mental disorder
Schizophrenia
Antipsychotics
Brahmyadiyoga
Ayurvedic Treatments

ABSTRACT

In this review report, an attempt made to present an overview of schizophrenia & those drugs which are used in treatment of psychiatric disorders as well as some treatments for psychosis. In 1908, the schizophrenia word was coined by Eugen Bleuler (Swiss psychiatrist). The use antipsychotics as medication began from 1933 in France. Laborit and Huguenard administrated the aliphatic Phenothiazine, Chlorpromazine during surgery due to its potential anesthetic effect, in 1951. Thereafter, Hamon and Delay extended the use of this treatment in psychiatric patients. Due to abnormal brain structure & functioning occurs schizophrenia as well as psychotic disorders. Schizophrenia a condition in people unable to differentiate between real & imaginary world. In this article we all know about Schizophrenia & Antipsychotics drugs. In that include symptoms & their types, cause, risk factor, antipsychotics classification & their pharmacology etc. In that there are three types of symptoms namely positive, Negative, Cognitive. Exact causes of schizophrenia are unknown. In the treatment of Schizophrenia or psychotics disorders the physicians commonly used antipsychotic medicines or drugs to treat their symptoms. Antipsychotic drugs further divided into two major classes namely Typical & Atypical antipsychotics. Chlorpromazine is the first medicine or drug which is used to treat symptoms of schizophrenia and schizoaffective disorders. Clozapine is most effective or potent antipsychotics drug. Which is belongs to the atypical antipsychotics which are reducing the risk of schizoaffective patients. Physicians recommend a combination of antipsychotics along with psychotherapy. In this article we have covered Brahmyadiyoga is an Ayurvedic remedies.

1. Introduction

Schizophrenia is complex, long-term mental illness illustrated by a many symptoms such as delusion, hallucination, speech disorders etc,.[1] "The word "Schizophrenia" comes from Greek word "Schizo" means "Split" & "Phrene" means "Mind". In 1908, the term Schizophrenia was introduced by the Sweden psychiatrist Eugen Bleuler.[2] According to WHO, almost 20 million peoples worldwide suffer from a disease called schizophrenia[3] & WHO has declared schizophrenia to be one of the ten leading causes of developed countries in the world.[4] Antipsychotic means those drugs or medicines used to treat psychiatric disorders like schizophrenia, bipolar disorder, schizoaffective conditions etc. In 1950, some new classes of medications come under the psychiatric practice such as antipsychotics. French pharmaceutical company Rhone-Poulenc synthesized chlorpromazine in 1950s, but not used in treatment of schizophrenia & In the US in 1960, the first clinical trial of chlorpromazine conducted with other antipsychotics. The two psychiatrics namely Jean Delay & Pierre Deniker used chlorpromazine on the

* *Corresponding author*.
E-mail address: afrojs952@gmail.com (A. A. Shaikh).

https://doi.org/10.18231/j.sajcrr.2022.017

patients who suffering from psychiatric disorder such as mania & schizophrenia.[5]

Schizophrenia is psychiatric disorders that are affect the thinking, behaves, emotions etc, of the patients. The symptoms of schizophrenia are commonly observed at the age of 16-30. The symptoms of schizophrenia are divided into three types: Positive, Negative & Cognitive symptoms.[6] Antipsychotics medications are principally used in treatment of schizophrenia & other psychotic disorders such as mental sickness, Bipolar disorder, etc. Antipsychotic medications are classified into two major classes Typical & Atypical it's also called first & second generation drugs.[7] Antipsychotic drugs are taking around 7-14 days to reach their desire therapeutic effect. Antipsychotics unable to treat negative symptoms & able to treat / cure positive symptoms of schizophrenia. Atypical antipsychotics shows/ possess negative symptoms such as incapable to feel pleasure (Anhedonia), Alogia, Flattening, Apathy, Avolition etc,.[2]

2. Symptoms of Schizophrenia

The psychological symptoms of schizophrenia are divided into three main classes: Positive, Negative & Cognitive Symptoms. While Positive & Cognitive Symptoms are almost omnipresent in schizophrenia, Positive symptoms have unrelated with cognitive symptoms. However, this relationship appeared to be accompanied by negative symptoms.[8]

2.1. Positive symptoms

Positive symptoms are related with the hyperdopaminergic transmission occurring in the mesolimbic region of brain. Dopamine Receptor Antagonist drugs such as Chlorpromazine & Haloperidol are used to reduce the positive symptoms of schizophrenia.[9] It is associated with psychological behavior that is not widespread in an enthusiastic person. Suffering people may lose a touch of truth. Following some symptoms include such as delusions, hallucination, dysfunctional way of intellectual, agitated body movement, thought disorder & lack of speaking etc,.[6,10]

2.2. Negative symptoms

A negative symptom indicates the abnormal normal mental function involving thoughts, behaviors & perceptions.[11] From these interruptions they can vary in general feelings and behaviors. The flat effect that the expression of emotions is reduced by facial expressions or tone of voice. Difficultly in initiating and sustaining activity and mutism (Speak Disorder).[10] In Negative Symptoms you might notice: Anhedonia, Alogia, Flattening, Apathy, Avolition etc.[11]

2.3. Cognitive symptoms

The cognitive symptoms of schizophrenia are belongs to thinking of persons. Although cognitive symptoms aren't used to detect schizophrenia.[12] These symptoms can vary from person to person.[13] Victims may experience normal to serious changes in their intelligence or in any other aspect of thought. Symptoms may include difficulty concentrating; memory problem, lack of execution facilities, i.e. difficulty in understanding information & making decisions.[14] In it seen some symptoms such as Unable to Concentrate, Memory problems, Reduced Executive Function, Lack of Insight etc.[12]

3. Causes

An exact cause of Schizophrenia is unknown. Researchers are continuously trying to find about the etiology of the disease.[15] But abnormal brain structure, enter-changes in neurotransmitter functioning, genetic & environmental factors causes schizophrenia.[16]

4. Risk Factor

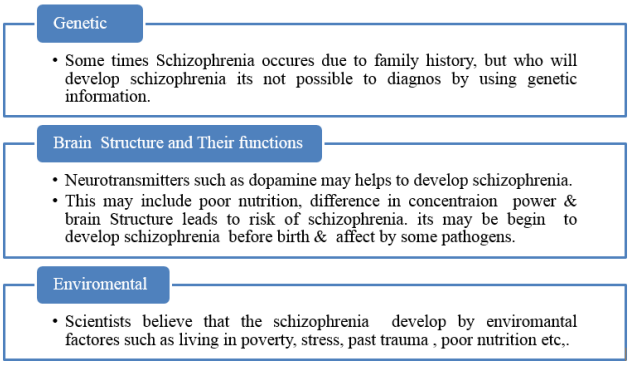

Fig. 1: Risk factors[15]

5. Antipsychotic

Antipsychotic is a drugs which are used to treat symptoms of psychosis. They are also used to treat Schizophrenia, Depression, Bipolar disorder, schizoaffective disorders & Anxiety. Antipsychotics drugs shows adverse effect.[16]

5.1. Classification of antipsychotic drugs

Antipsychotic drugs are classified into two subtypes such as Typical (First generation) & Atypical (Second generation). Typical medications have been used since the 1950s. It's oldest or first type of antipsychotic drugs or medicines. Atypical medications have been used since the 1990s. It's new or second type of antipsychotic class of drugs.[17] The use of antipsychotic drugs has the benefit of reducing the symptoms of psychosis and the risk of numerous side

effects, including a difficult trade-off. Antipsychotic drugs are not therapeutic & do not eliminates long term thought disorders but they often negate the power of illusion, delusions & allow a person with schizophrenia to act in a caring situation.[18]

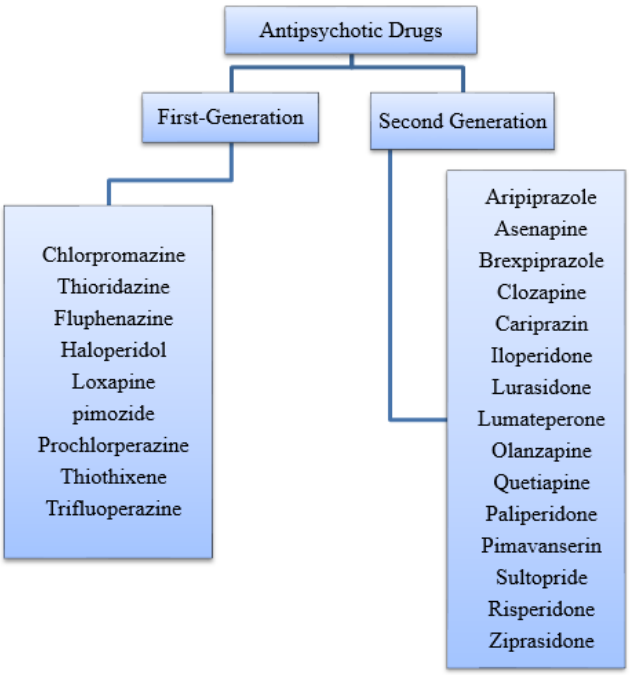

Fig. 2: Classification of antipsychotic drugs

Antipsychotic medicine is a principle psychological strategy for the treatment of schizophrenia. These substances limit the effectiveness of treatment in individual patients & are associated with side effects. Taking antipsychotics is considered. While these drugs have no effect on negative symptoms. All of these drugs stop the action of postsynaptic dopamine D_2 receptors. However, modern medicine has a wide spectrum of targeted Serotonin, nor epinephrine, Acetylcholine, Histamine & Glutamate. Clozapine, considered an Atypical antipsychotic, is associated with a variety of neuro-receptors (Dopamine, 5-HT serotonin & noradrenergic receptor) & and some acts as a multi-neuroreceptor antagonist. Clozapine is the most potent or highly effective antipsychotic drug & it's does also reduce the risk of suicide of schizoaffective patients who tolerate to other antipsychotic drugs.[2]

5.2. Mechanism of Action

There are many drugs used to treat schizophrenia & they have different mechanism of action to create desired therapeutic effects. Mostly antipsychotics drugs help to treat Schizophrenia.[19]

5.3. 1^{ST} Generation

The first generation of antipsychotics follows inhibiting mechanism. They are highly effective when they block 72% of the D_2 dopamine receptors in the brain. They also show antagonism action at the Noradrenergic, Cholinergic & Histaminergic receptors. It's mainly used to treat positive symptoms such as hallucinations & delusions.[19,20] In Typical antipsychotics show some adverse effect such extra-pyramidal side effects & anticholinergic adverse effect such as dry mouth, constipation etc. sedation, abnormal heart rates, sudden death, seizure threshold, hypotension, discoloration of skin, hydration, confusion, fever, acute renal failure etc, as well it's have some contraindications like CNS depressant, cardiac abnormalities, history of allergy & seizure disorders, prostatic hypertrophy, dyskinesia, etc,.[20]

5.4. 2^{ND} Generation

The second generation of antipsychotics follows blocking mechanism. Its block the D2 dopamine receptors as well as serotonin receptors antagonist. 5-HT2A sub-type of the serotonin receptor is most commonly involved, thus may be associated with a reduce the risk of these adverse effect. In 2016, 12 Atypical Antipsychotics are approved by Food & Drug Administration (FDA).[19,20] In Atypical antipsychotics show some side effects such as weight gain, metabolic syndrome development, dizziness, anxiety, sedation, thermo-sensitive, increased appetite, somnolence, hypotension, agitation, headache, restlessness, hyper salivation, etc,. and it have some contraindications like parkinsonism, narcoleptic, tardive dyskinesia, during pregnancy, glaucoma, liver disease, severe neutropenia, deficiency hexosaminidase etc,.[20]

6. Treatment

6.1. Antipsychotic drugs

Physician recommended a combination of psychotic drugs along with the psychotherapy.

6.2. Ayurvedic treatmeant

Brahmyadiyoga is an herbal preparation which is used in the treatment of Schizophrenia. Brahmyadiyoga developed by Central Council for Ayurvedic & Siddha, under Ministry of Health & Family Welfare of India. It includes Brahmi, Jatamansi, Sarpagandha, Vacha, Kusta, Tagar etc. For the treatment of schizophrenia, herbal combination of water-based extract of bramhi & Jatamansi are as effective as modern antipsychotics drugs.[21]

Table 1: First Generation/ Typical Antipsychotics

First-generation/ Typical antipsychotics Drugs	Mechanism	Adverse Effect	Route	Half-Life of Excretion	Brand Name	Metabolism	Ref.
Chlorpromazine	Combined form of Chlorpromazine Antagonized Histamine (H_1), Dopamine (D_2) & Muscarinic (M_1) receptors.	Weight gain, sedation, acute movement disorder, parkinsonism, hypotension, dizziness, Akathisia, tardive dyskinesia etc.	Oral, rectal, IM, IV	30hr	Largactil	Hepatic	22–30
Loxapine	Antagonism of post synaptic Dopamine (D_2) & serotonin (5-HT2) receptors	Taste disorder (Dyspepsia), tardive dyskinesia, malignant syndrome, Depressogenic effect, Akathisia, etc.	Oral, IM, Inhalation	4-12hr	Xylac, Adasuve	Hepatic	
Prochlorperazine	Blocking D_2 receptor in brain, Histaminic, cholinergic & noradrenergic receptors. It's Independent on dopamine antagonism.	Dystonic reactions, neuroleptic malignant syndrome, Akathisia, Anorexia, loss of vision, sexual dysfunction, constipation, cardiac abnormalities, hypotension, dry mucosa, urinary retention, tardive dyskinesia, neuroleptoic malignant syndrome etc,.	Oral, parenteral, IM & Rectal	4-8hr	Compazine, Stemetil	Liver	
Thiothixene	Antagonist of Dopamine (D_1,D_2,D_3,D_4), histamine, serotonin (5-HT1, 5-HT2), Cholinergic (M_1,M_2) & Alpha-Adrenergic receptor	Muscle Stiffness, loss of vision, , Hand tremor, Dry Mouth, Coma, weakness, salivation, hypotension, tremors, neuroleptoic malignant syndrome etc,.	Oral	10-20hr	Navane	Hepatic	
Trifluoperazine	Block dopamine D_2 & D_1 receptor in mesocortical & mesolimbic pathway.	Akathisia, dystonia, parkinsonism, somnolence, xerostomia, neuroleptic malignant syndrome, mydriasis, glaucoma etc.	Oral, IM	10-20hr	Stelazine, Eskazinyl, Eskazine, Jatroneural	Liver	

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Table 1 continued

Thioridazine	Block postsynaptic mesolimbic dopaminergic receptors in the brain.	Shortness of breathing, tremor, swallowing trouble, hypotension, neuroleptic malignant syndrome, dizziness, restlessness, confusion, fever, sore throat, drowsiness, dry mouth & skin, nausea, vomiting, constipation, diarrhea etc.,	oral	21-24hr	Mellaril	Hepatic
Fluphenazine	Antagonism of postsynaptic D_2 receptors in mesolimbic, nigrostriatal & tuberoinfundibular neural pathway.	Othrostatsis, Opisthotonos, dizziness, weight gain, tardive dyskinesia, Akathisia, Neuroleptic malignant syndrome, parkinsonian, hypotension, sedation, dry mouth & eyes, constipation, restlessness, Prolongation of QT, Sexual dysfunction, Galactorrhea, etc,.	Oral, IM	14-16hr	Prolixin, Moditen	Liver
Haloperidol	Block the dopaminergic receptors as well as noradrenergic, cholinergic & histaminergic blocking action.	Breathing problems, headache, insomnia, anxious, irregular menstrual cycle, fever, dry skin & mouth, Acute Dystonia, Parkisonism, prolongation in QT, Hyperthermia, tardive dyskinesia etc.	Oral, IM	14.5-36.7hr	Haldol	Liver
Pimozide	Antagonism dopamine (D2) receptors.	Akathisia, hyperhidrosis, nocturia, somnolence, speech disorder, sedation, dizziness, constipation etc.	oral	55hr	Orap	Hepatic

Table 2: Second generation/ Atypical antispychotic

Second-generation/ Atypical antipsychotics							
Drugs	**Mechanism**	**Adverse Effect**	**Route**	**Half Life of Excretion**	**Brand Name**	**Metabolism**	**Ref.**
Aripiprazole	Partial antagonist at D_2 & 5HT1Areceptor & Antagonist at 5-HT2A receptor	Akathisia, parkinsonian, acute Dystonic reactions, tardive dyskinesia, nausea, Weight gain, jaundice, etc.	Oral, IM	-	Ability	Liver	
Paliperidone	Act Antagonist at dopamine, 5-HT2A , adrenergic, histaminic receptors	Sedation, metabolic syndrome, weight gain, insomnia, somnolence, Akathisia, etc.	Oral, IM	42-77 days	Xeolion, Invega	Liver	31–40
Risperidone	Blocked D2 dopamine & (5-HT2A) serotonin receptors	Sedation, metabolic syndrome, dystonia, Akathisia, parkinsonian, tremor, Gynecomastia, galactorrhea, hypertension, diabetes, tachypnea, tachycardia, dementia, etc.	Oral	20hr	Risperdal	liver	
Olanzapine	May act by combination of dopamine & serotonin (5-HT2A) Antagonism	Weight gain, decrease insulin sensitivity, metabolic dysfunction, Akathisia, neutropenia, thrombocytopenia, tardive dyskinesia, neuroleptic malignant syndrome, extra pyramidal symptoms, glucosehomosasis, etc.	Oral, IM	21-54hr	Zyprexa	liver	
Clozapine	Block dopamine & serotonin receptors	Hyper salivation, myocarditis, agranulocytosis, constipation, dystonisa, neuroleptic malignant syndrome, seizures, etc.	oral	12hr	Clozaril	hepatic	
Asenapine	Mechanism of action is unknown. It has been suggested that the combination of antagonist activity at D_2 & 5-HT2A receptors	Weight gain, Akathisia, parkinsonism, hypotension, dizziness, hypersensitivity, anaphylaxis, angioedema, wheezing, rashes, somnolence, oral hypothesis, cardiovascular diseases,	Sublingual	24hr	Saphris	hepatic	
Quetiapine	Blocked Dopamine, histamine, Adrenergic, & serotonin nurotransmitters	Sleepiness, constipation, weight gain, hypotension, seizures, prolonged erection, diabetes, tardive dyskinesia, neuroleptic malignant syndrome, etc.	oral	6hr	Seroquel	liver	

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Table 2 continued

Cariprazine	Mechanism of action is unknown, but the action is mediated by combination of cariprazine of partial agonist at Dopamine (D_2) & Serotonin (5-HT1A) as well as act as antagonist at serotonin (5-HT2A) receptors.	Extra-pyramidal symptoms, weight gain, prolactin elevation, QTc prolongation, sedation, metabolic syndrome, cardiovascular disease, Anxiety, Insomnia, Akathisia, headache, Dyspepsia, vomiting, Somnolence, restlessness, etc.	oral	1 week	Vraylar	liver
Iloperidone	Dopamine D2 & 5-HT2A receptor antagonist & act as Neuroleptic Agent.	Weight gain, Extrapyramidal symptoms, QTc prolongation, Orthostatic hypotension, prolactin elevation, Fatigue, nasal congestion, somnolence, tachycardia, dizziness, Tardive Dyskinesia, etc.	Oral	13 -18hr	Fanapt	liver
Lurasidone	Its show antagonistic activity by combination of dopamine (D_2) & serotonin (5-HT2A).	Akathisia, Somnolence, Parkinsonism, Dystonia, Nausea, Agitation, Anxiety, weight gain, etc.	Oral	18hr	Latuda	liver
Ziprasidone	Antagonized dopamine (D_2) & serotonin in mesolimbic pathway & serotonin (5-HT2A) receptors in mesocortical pathway to reduce positive & negative symptoms respectively.	Heart Palpitation, weight gain, depression, headache, anxiety, restlessness, Insomnia, drowsiness, Asthenia, Abdomen pain, hypertension, Rectal hemorrhage, dizziness, nausea, constipation, tremor, Rashes, Muscles pain, Stuffy nose, etc,.	Oral, IM,	7 - 10hr	Geodon	liver

Table 3: Herbal Plant and Their Major Phytoconstituents

S.No.	Herbal Plant	Major Phytoconstituents
1.	Brahmi	Asiaticoside & Bacoside
2.	Jatamansi	Virolin & Jatamnsone
3.	Sarpagandha	Reserpine & Ajmaline
4.	Vacha	Asarone
5.	Kusta	Costunolide & Palmitic acid
6.	Tagar	Betulinic acid

7. Conclusion

We concluded from this review article, schizophrenia is a complex psychiatric disorder that is belong to the disordering of brain improvement caused by environmental as well as some genetic factors. Most schizophrenia as well as psychotic disorders occurs due to abnormal brain structure & functioning. In this article we discuss about pharmacology of antipsychotics & Ayurvedic Treatment of psychosis. In that we observe delusion, hallucination, speech & behavior disorder like symptoms. In this we know about pharmacology of antipsychotics drugs but their exact causes of schizophrenia are unknown, I hope in future our researches are find exact causes of schizophrenia.

8. Conflict of Interest

None.

9. Source of Funding

None.

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Author biography

Afroj A. Shaikh, Student https://orcid.org/0000-0001-9189-9848

Jaydeep B. Pawar, Professor

Sachin J. Anbhule, Professor

Cite this article: Shaikh AA, Pawar JB, Anbhule SJ. The first generation and second generation antipsychotic drugs and their pharmacology in treatment of schizophrenia. *Southeast Asian J Case Rep Rev* 2022;9(4):77-85.