

“THE FIRST GENERATION AND SECOND GENERATION ANTISSYCHOTIC DRUGS AND THEIR PHARMACOLOGY IN TREATMENT OF SCHIZOPHRENIA”

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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 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.

Key words: Psychosis, Mental disorder, Schizophrenia, Antipsychotics, Brahmyadiyoga, Ayurvedic Treatments.

BACKGROUND

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 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).

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)

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. 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)

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. (15) In it seen some symptoms such as Unable to Concentrate, Memory problems, Reduced Executive Function, Lack of Insight etc. (12)

CAUSES:

An exact cause of Schizophrenia is unknown. Researchers are continuously trying to find about the etiology of the disease (16). But abnormal brain structure, enter-changes in neurotransmitter functioning, genetic & environmental factors causes schizophrenia.(17)

RISK FACTOR

Genetic

- Some times Schizophrenia occurs due to family history, but who will develop schizophrenia it's not possible to diagnose by using genetic factors.

Brain Structure and Their functions

- Neurotransmitters such as dopamine may help to develop schizophrenia.
- This may include poor nutrition, difference in concentration power &

Environmental

- Scientists believe that schizophrenia develops by environmental factors such as living in poverty, stress, past trauma, poor nutrition etc.

Figure 1: Risk Factors (16)**ANTIPSYCHOTIC:**

Antipsychotic drugs are used to treat symptoms of psychosis. They are also used to treat Schizophrenia, Depression, Bipolar disorder, schizoaffective disorders & Anxiety. Antipsychotic drugs show adverse effects.(17)

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. (18) 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 eliminate long term thought disorders but they often negate the power of illusion, delusions & allow a person with schizophrenia to act in a caring situation.(19)

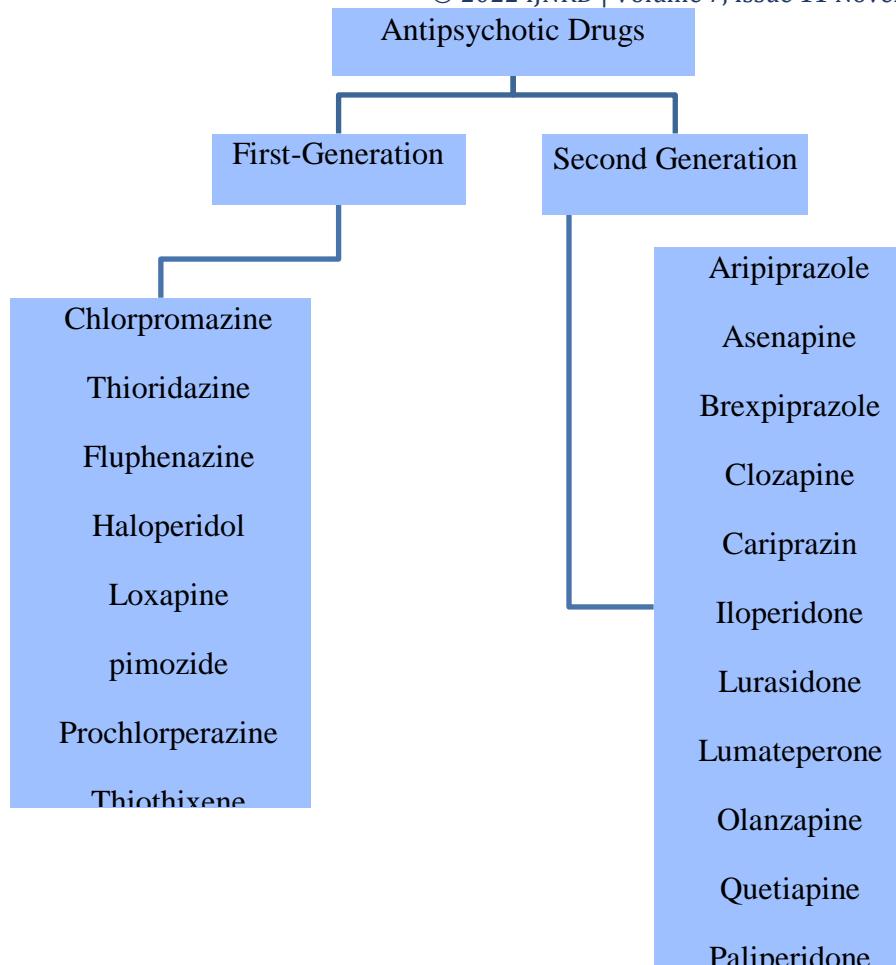


Figure 2: Classification of antipsychotic drugs

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 D₂ 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)

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. (22)

1ST GENERATION

The first generation of antipsychotics follows inhibiting mechanism. They are highly effective when they block 72% of the D₂ 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. (21)(22) 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., (21)

2ND 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).(21)(22) 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., (21)

TREATMENT

ANTIPSYCHOTIC DRUGS

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

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	(25)(26)(27)(28)(29)(30)(31)
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	4-12 hr	Xylac, Adasuve	Hepatic	(32)(33)
Prochlorperazine	Blocking D ₂ receptor in brain, Histaminic, cholinergic & noradrenergic receptors. It's Independent on	Dystonic reactions, neuroleptic malignant syndrome, Akathisia, Anorexia, loss of vision, sexual dysfunction, constipation, cardiac	Oral, parenteral, IM & Rectal	4-8 hr	Compazine, Stemetil	Liver	

	dopamine antagonism.	abnormalities, hypotension, dry mucosa, urinary retention, tardive dyskinesia, neuroleptic malignant syndrome etc.,				
Thiothixene	Antagonist of Dopamine (D ₁ ,D ₂ ,D ₃ ,D ₄), histamine, serotonin (5-HT ₁ , 5-HT ₂), Cholinergic (M ₁ ,M ₂) & Alpha-Adrenergic receptor	Muscle Stiffness, loss of vision, , Hand tremor, Dry Mouth, Coma, weakness, salivation, hypotension, tremors, neuroleptic malignant syndrome etc.,	Oral	10-20 hr	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	10-20 hr	Stelazine, Eskazinyl , Eskazine, Jatroneur al	Liver
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	21-24 hr	Mellaril	Hepatic
Fluphenazine	Antagonism of postsynaptic D ₂ receptors in mesolimbic, nigrostriatal & tuberoinfundibular neural pathway.	Othostasis, Opisthotonus, 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	14-16 hr	Prolixin, Moditen	Liver
Haloperidol	Block the dopaminergic receptors as well as noradrenergic, cholinergic &	Breathing problems, headache, insomnia, anxious, irregular menstrual cycle, fever, dry skin & mouth, Acute	Oral, IM	14.5- 36.7 hr	Haldol	Liver

	histaminergic blocking action.	Dystonia, Parkisonism, prolongation in QT, Hyperthermia, tardive dyskinesia etc.					
Pimozide	Antagonism dopamine (D2) receptors.	Akathisia, hyperhidrosis, nocturia, somnolence, speech disorder, sedation, dizziness, constipation etc.	oral	55 hr	Orap	Hepatic	

Table 2: Second Generation/ Atypical Antipsychotic

SECOND-GENERATION/ ATYPICAL ANTIPSYCHOTICS							
Drugs	Mechanism	Adverse Effect	Route	Half Life of Excretion	Brand Name	Metabolism	Ref.
Aripiprazole	Partial antagonist at D ₂ & 5HT1A receptor & Antagonist at 5-HT2A receptor	Akathisia, parkinsonian, acute Dystonic reactions, tardive dyskinesia, nausea, Weight gain, jaundice, etc.	Oral, IM	-	Ability	Liver	(34) (35) (36) (37) (38) (39)
Paliperidone	Act Antagonist at dopamine, 5-HT2A , adrenergic, histaminic receptors	Sedation, metabolic syndrome, weight gain, insomnia, somnolence, Akathisia, etc.	Oral, IM	42-77 days	Xeolian, Invega	Liver	(40) (41) (42) (43) (44) (43)
Risperidone	Blocked D2 dopamine & (5-HT2A) serotonin receptors	Sedation, metabolic syndrome, dystonia, Akathisia, parkinsonian, tremor, Gynecomastia, galactorrhea, hypertension, diabetes, tachypnea, tachycardia, dementia, etc.	Oral	20 hr	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	21-54 hr	Zyprexa	liver	
Clozapine	Block dopamine & serotonin receptors	Hyper salivation, myocarditis, agranulocytosis, constipation, dystonisa, neuroleptic malignant	oral	12hr	Clozaril	hepati	

		syndrome, seizures, etc.				
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	24 hr	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	6 hr	Seroquel	liver
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, Extrapiramidal symptoms, QTc prolongation, Orthostatic hypotension, prolactin elevation, Fatigue, nasal congestion, somnolence, tachycardia, dizziness, Tardive Dyskinesia, etc.	Oral	13 -18 hr	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	18 hr	Latuda	liver
Ziprasidone	Antagonized dopamine (D ₂) & serotonin in mesolimbic pathway & serotonin (5-HT2A) receptors in mesocortical pathway to reduce positive &	Heart Palpitation, weight gain, depression, headache, anxiety, restlessness, Insomnia, drowsiness, Asthenia, Abdomen pain, hypertension, Rectal hemorrhage, dizziness, nausea, constipation,	Oral, IM,	7 - 10 hr	Geodon	liver

	negative symptoms respectively.	tremor, Rashes, Muscles pain, Stuffy nose, etc.,					
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AYURVEDIC TREATMENT:

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.(44)

Table 3: Herbal Plant and Their Major Phytoconstituents

Sr.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

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.

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