

THE FIRST GENERATION AND SECOND-GENERATION ANTIPSYCHOTIC DRUGS AND THEIR PHARMACOLOGY IN TREATMENT OF SCHIZOPHRENIA

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Received: June 08, 2022; Revised: July 13, 2023; Accepted: November 06, 2023

Abstract

Schizophrenia is a complex and severe psychiatric disorder that affects millions of people worldwide. Antipsychotic drugs have been widely used for the treatment of schizophrenia for over 60 years. The first-generation antipsychotic drugs (FGAs) were introduced in the 1950s and revolutionized the treatment of schizophrenia. However, their use is associated with a number of adverse effects, including Extrapyramidal Symptoms (EPS) and Tardive Dyskinesia (TD). Second-generation antipsychotic drugs (SGAs), also known as atypical antipsychotics, were developed in the 1990s and have become the preferred treatment for schizophrenia due to their lower incidence of EPS and TD. They also have a broader range of therapeutic effects, such as improving negative symptoms and cognitive impairment associated with schizophrenia. This review article summarizes the pharmacology of both FGAs and SGAs, including their mechanism of action, pharmacokinetics, and adverse effects. The efficacy and safety of these drugs in the treatment of schizophrenia are also discussed. In addition, this review examines the controversy surrounding the use of SGAs and their potential metabolic side effects, such as weight gain, hyperlipidemia, and diabetes. Despite the availability of SGAs, FGAs still have a role in the treatment of schizophrenia, particularly for patients who are unresponsive to SGAs or experience intolerable side effects. Furthermore, research continues to identify new pharmacological targets and treatment strategies for schizophrenia. Understanding the pharmacology and clinical use of antipsychotic drugs is essential for optimizing the treatment of schizophrenia and improving patient outcomes.

Keywords: Antipsychotics; Ayurvedic Treatments; Brahmyadiyoga; Mental Disorder; Psychosis; Schizophrenia

Background

Schizophrenia is a complex, long-term mental illness characterized by a range of symptoms such as delusions, hallucinations, and speech disorders (Patel *et al.*, 2014). The word “schizophrenia” originates from the Greek words “schizo,” meaning “split,” and “phrene,” meaning “mind.” Eugen Bleuler, a Swedish psychiatrist, introduced the term “schizophrenia” in 1908 (Farah *et al.*, 2018). According to the World Health Organization (WHO), almost 20 million people worldwide suffer from schizophrenia, and it is one of the ten leading causes of disability worldwide (Kirkpatrick *et al.*, 2014; Schizophrenia, 2019). Antipsychotics are drugs used to treat psychiatric disorders such as schizophrenia, bipolar disorder, and schizoaffective conditions. In the 1950s, new classes of medications, such as antipsychotics, emerged in Psychiatric practice. Chlorpromazine was synthesized by the French pharmaceutical company Rhone-Poulenc in the 1950s, but it was not used to treat schizophrenia. In the US, the first clinical trial of chlorpromazine and other antipsychotics was conducted in 1960. Two psychiatrists, Jean Delay and Pierre Deniker, used chlorpromazine on patients with psychiatric disorders such as mania and schizophrenia (Haddad *et al.*, 2016).

Schizophrenia is a psychiatric disorder that affects the thinking, behavior, emotions, and other aspects of patients. The symptoms of schizophrenia are usually observed between the ages of 16 and 30 and are divided into three types: positive, negative, and cognitive symptoms (Kaur *et al.*, 2020). Antipsychotic medications are primarily used to treat schizophrenia and other psychotic disorders such as mental illness and bipolar disorder. Antipsychotic medications are classified into two major classes, typical and atypical, also known as first and second-generation drugs (John and Maccabe, 2015). Antipsychotic drugs take around 7–14 days to reach their desired therapeutic effect. Antipsychotics are unable to treat negative symptoms but can treat/cure positive symptoms of schizophrenia. Atypical antipsychotics possess negative symptoms such as an inability to feel pleasure (anhedonia), alogia, flattening, apathy, and avolition (Farah *et al.*, 2018).

Symptoms of Schizophrenia

Schizophrenia is a complex mental illness that manifests in a variety of symptoms, which are categorized into three main classes: Positive, Negative, and Cognitive Symptoms, as shown in Figure 1. While Positive and Cognitive Symptoms

are almost always present in schizophrenia, Positive symptoms are unrelated to cognitive symptoms. However, this relationship appears to be accompanied by negative symptoms. (Khan *et al.*, 2013)

Positive Symptom

Positive symptoms are related to hyperdopaminergic transmission occurring in the mesolimbic region of the brain. Dopamine Receptor Antagonist drugs such as Chlorpromazine and Haloperidol are used to reduce the positive symptoms of schizophrenia. (Nerkar and Bhise, 2020) Positive symptoms are associated with psychological behavior that is not widespread in an enthusiastic person. People with schizophrenia may lose touch with reality. Symptoms include delusions, hallucinations, disordered thinking, agitated body movement, thought disorder, and lack of speaking. (Kaur *et al.*, 2020; Nerkar and Bhise, 2020)

Negative Symptoms

Negative symptoms indicate abnormal mental function involving thoughts, behaviors, and perceptions. (Schizophrenia Symptoms: Positive and Negative Symptoms Explained, 2020) These symptoms can vary in general feelings and behaviors. The flat effect is a reduction in the expression of emotions through facial expressions or tone of voice. Difficulty in initiating and sustaining activity and mutism (speech disorder) may also be present. (Nerkar and Bhise, 2019) Negative symptoms may include Anhedonia, Alogia, Flattening, Apathy, Avolition, etc. (Schizophrenia Symptoms: Positive and Negative Symptoms Explained, 2020)

Cognitive Symptoms

The cognitive symptoms of schizophrenia involve the thinking of persons. Although cognitive symptoms are not used to diagnose

SCHIZOPHRENIA SYMPTOMS		
POSITIVE	NEGATIVE	COGNITIVE
HALLUCINATIONS (AUDITORY, VISUAL)	BLUNTED AFFECT	MEMORY IMPAIRMENT
DELUSIONS	ANHEDONIA	ATTENTION DEFICITS
DISORGANISED SPEECH AND THOUGHTS	ALOGIA	EXECUTIVE FUNCTION DEFICITS
	AVOLITION	
	SOCIAL WITHDRAWAL	

Figure 1. Symptoms of Schizophrenia includes Positive, Negative, and Cognitive symptoms

schizophrenia, they can vary from person to person. (Collins, 2019) Victims may experience changes in their intelligence or in any other aspect of thought, ranging from normal to severe. Symptoms may include difficulty concentrating, memory problems, lack of executive functioning (difficulty in understanding information and making decisions), and lack of insight. (Simpson *et al.*, 2010) Some other symptoms include inability to concentrate, memory problems, reduced executive function, lack of insight, etc. (How Schizophrenia is Diagnosed by Observing Symptoms, 2021)

Causes

The exact cause of Schizophrenia is unknown. Researchers are continuously trying to find out the etiology of the disease (Volkan, 2020). However, abnormal brain structure, enter-changes in neurotransmitter functioning, and genetic and environmental factors cause schizophrenia, as shown in Figure 2. (Khan *et al.*, 2013)

Risk Factor

It is critical to understand that not everyone who is at risk of having schizophrenia will develop the disorder. Some people acquire schizophrenia in the absence of any risk factors.

Some factors appear to raise a person's risk of getting schizophrenia.

Genetics:

A person with a family history of schizophrenia is more likely to develop the disorder. A family member with schizophrenia affects approximately 10-14% of people with schizophrenia, according to Trusted Source.

There is also a link between schizophrenia and other mental health issues. People with schizophrenia are more likely to have a family member who suffers from bipolar disorder or another mental illness.

ADHD in childhood:

According to research, children with attention deficit hyperactivity disorder (ADHD) are more likely to develop schizophrenia, while the link is not totally evident. According to one study, children with ADHD were 4.3 times more likely to develop schizophrenia than those without ADHD.

Both disorders include alterations in the brain's dopamine use. This could explain a portion of the connection. There is no relationship between ADHD drug use and the development of schizophrenia.

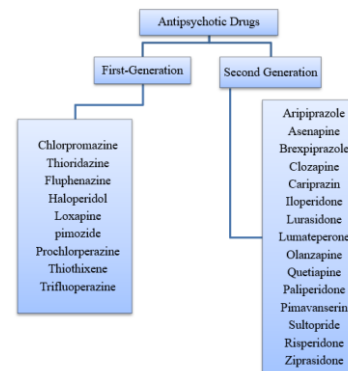


Figure 2. Systematic Classification of Antipsychotic Drugs

Life's stumbling blocks:

Researchers discovered linkages between substantial life stressors and an increased incidence of schizophrenia. People with a family history of schizophrenia are at a higher risk.

Among the stressors are:

Poverty, emotional neglect or isolation, parental violence, and trauma.

According to some studies, kids born prematurely or with a low birth weight are more likely to develop schizophrenia.

Cannabis and smoking:

There are links between schizophrenia and tobacco usage. It is unclear whether cigarette smoking raises the risk of schizophrenia. It is also probable that people with schizophrenia are more likely to smoke as a kind of self-medication.

Cannabis consumption may potentially be linked to schizophrenia. According to research, cannabis may initiate or worsen the symptoms of schizophrenia in certain people.

Psychosis is twice as likely to develop in someone with schizophrenia who also uses cannabis on a regular basis as it is in someone who does not use cannabis.

One in every four patients with schizophrenia also has cannabis use disorder.

Antipsychotic

Antipsychotics are medications used to treat symptoms of psychosis, including those associated with schizophrenia, depression, bipolar disorder, schizoaffective disorders, and anxiety. However, these drugs may also cause adverse effects (List of antipsychotics - generics only, 2021).

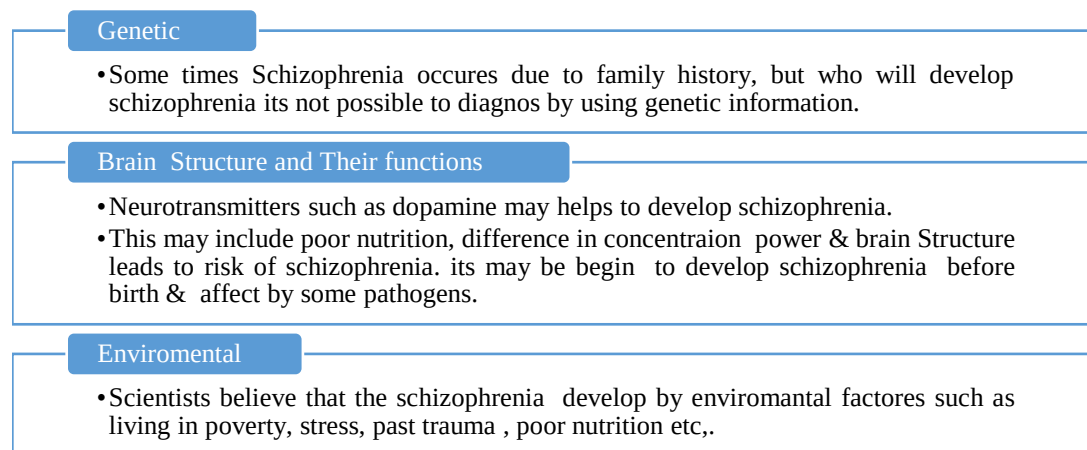


Figure 3. Classification of Antipsychotic Drugs (Schizophrenia, 2020)

Classification of Antipsychotic Drugs

Antipsychotic drugs can be classified into two subtypes: typical (first generation) and atypical (second generation), as shown in Figure 3. Typical medications have been in use since the 1950s and are the oldest type of antipsychotic drugs. Atypical medications, on the other hand, have been in use since the 1990s and are a newer class of antipsychotic drugs. While antipsychotic drugs may reduce the symptoms of psychosis and the risk of numerous side effects, there is a difficult trade-off associated with their use. These drugs do not cure long-term thought disorders but they can reduce the power of illusions and delusions, allowing individuals with schizophrenia to function in a caring situation. (Harvey *et al.*, 2011)

Antipsychotic medication is a primary psychological approach for treating schizophrenia. However, these drugs can reduce treatment effectiveness in some patients and are associated with side effects. While antipsychotics have no effect on negative symptoms, they do block the action of postsynaptic dopamine D2 receptors. Modern medicine has a broad range of targeted neurotransmitters, including Serotonin, nor-epinephrine, Acetylcholine, Histamine, and Glutamate. Clozapine, as an Atypical antipsychotic, acts on a variety of neuro-receptors (Dopamine, 5-HT serotonin, and noradrenergic receptors) and acts as a multi-neuroreceptor antagonist. Clozapine is the most potent antipsychotic drug and has also been shown to reduce the risk of suicide in schizoaffective patients who do not tolerate other antipsychotic drugs. (Farah, 2018)

Mechanism of Action

There are many drugs used to treat schizophrenia, and they have different mechanisms of action to create desired therapeutic effects.

Mostly, antipsychotic drugs help to treat Schizophrenia. (Rasool *et al.*, 2018; First versus second generation, 2021)

1st Generation

The mechanism of action of first-generation antipsychotics involves their ability to block specific receptors in the brain. These drugs primarily exert their effects by blocking about 72% of dopamine D2 receptors in the brain (Chokhawala and Stevens, 2021). In addition, first-generation antipsychotics also exhibit antagonism at other receptors, including noradrenergic, cholinergic, and histaminergic receptors (Chokhawala and Stevens, 2021; First versus second generation, 2021). Extrapyramidal symptoms (EPS) are a common group of side effects caused by the blockade of dopamine receptors in the basal ganglia. Anti-cholinergic effects are another notable side effect of these drugs, leading to dry mouth, constipation, blurred vision, and urinary retention (Chokhawala and Stevens, 2021). Sedation is commonly reported with first-generation antipsychotics, which may contribute to somnolence, lethargy, and decreased alertness (Leucht, 2009). They can cause abnormal heart rhythms, including prolongation of the QT interval and in rare cases can lead to sudden cardiac death (Ozeki, 2010). A lower seizure threshold is another potential risk associated with these drugs (Chokhawala and Stevens, 2021). Concomitant use of the central nervous system (CNS) depressants, such as alcohol or sedatives, should be avoided because of their increased sedation and increased risk of respiratory depression (Chokhawala and Stevens, 2021). People with heart abnormalities, including a history of arrhythmias or recent myocardial infarction, may be at increased risk of cardiovascular complications when taking these drugs (Gardner, 2005). Patients with known

allergies or seizure disorders should be closely monitored because of possible worsening of symptoms (Chokhawala and Stevens, 2021). In addition, first-generation antipsychotics should be used with caution in individuals with an enlarged

prostate as they may worsen urinary symptoms and in patients with dyskinesia, because these drugs can worsen abnormal movements (Leucht, 2009). This all data are summarized in Table 1.

Table 1. Overview Of First-Generation/ Atypical Antipsychotics

Drugs	Mechanism	Adverse Effect	Route	Half-Life of Excretion	Brand Name	Metabolism
Chlorpromazine	Combined form of Chlorpromazine Antagonized Histamine (H1), Dopamine (D2) & Muscarinic (M1) receptors.	Weight gain, sedation, acute movement disorder, parkinsonism, hypotension, dizziness, Akathisia, tardive dyskinesia etc.	Oral, rectal, IM, IV	30hr	Largactil	Hepatic
Loxapine	Antagonism of post synaptic Dopamine (D2) & serotonin (5-HT2) receptors	Taste disorder (Dysgeusia), tardive dyskinesia, malignant syndrome, Depressogenic effect, Akathisia, etc.	Oral, IM, Inhalation	4-12 hr	Xylac, Adasuve	Hepatic
Prochlorperazine	Blocking D2 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, neuroleptic malignant syndrome etc.,	Oral, parenteral, IM & Rectal	4-8 hr	Compazine, Stemetil	Liver
Thiothixene	Antagonist of Dopamine (D1,D2,D3,D4), histamine, serotonin (5-HT1, 5-HT2), Cholinergic (M1,M2) & 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 D2 & D1 receptors in mesocortical and mesolimbic pathways.	Akathisia, dystonia, parkinsonism, somnolence, xerostomia, neuroleptic malignant syndrome, mydriasis, glaucoma etc.	Oral, IM	10-20 hr	Stelazine, Eskazinyl, Eskazine, Jatroneural	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 D2 receptors in mesolimbic, nigrostriatal, and tuberoinfundibular neural pathways.	Othrostatis, Opisthotonos, dizziness, weight gain, tardive dyskinesia, Akathisia, Neuroleptic malignant syndrome, parkinsonian, hypotension, sedation, dry mouth and 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, and histaminergic blocking action.	Breathing problems, headache, insomnia, anxiety, irregular menstrual cycle, fever, dry skin and mouth, Acute Dystonia, Parkinsonism, prolongation in QT, Hyperthermia, tardive dyskinesia, etc.	Oral, IM	14.5-36.7 hr	Haldol	Liver
Pimozide	Antagonism dopamine (D2) receptors.	Alkathisia, hyperhidrosis, nocturia, somnolence, speech disorder, sedation, dizziness, constipation etc.	oral	55 hr	Orap	Hepatic

(Popovic *et al.*, 2015; Zhang *et al.*, 2016; Cardoso *et al.*, 2017; Din and Preuss, 2021; Gettu and Saadabadi, 2021; Mann and Marwaha, 2021; Pimozide, 2021; Rahman and Marwaha, 2021; Siragusa *et al.*, 2021; NCATS Inxight Drugs - THIORIDAZINE. National Center for Advancing Translational Sciences., 2023; Trifluoperazine, 2023)

2nd Generation

Second-generation antipsychotics, also called atypical antipsychotics, exert their mechanism of action via a complex neurotransmitter modulation interaction that mainly involves the blockade of dopamine and serotonin receptors (Chokhawala and Stevens, 2021). These drugs have a higher affinity for specific receptor subtypes and a more diverse receptor profile than first-generation antipsychotics.

The primary target of second-generation antipsychotics is the dopamine D2 receptor, which plays a key role in regulating dopamine signaling pathways involved in the pathophysiology of psychosis (Meltzer *et al.*, 2013). By blocking the D2 receptors in the mesolimbic areas of the brain, these drugs help reduce positive symptoms such as hallucinations and delusions.

Atypical antipsychotics not only block the D2 receptor but also modulate the serotonin system by targeting different subtypes of serotonin receptors, with the 5-HT2A receptor being of particular

importance (Chokhawala and Stevens, 2021). 5-HT2A receptor antagonism is associated with multiple therapeutic benefits, including improvement in negative symptoms, cognition, and mood stabilization (Meltzer *et al.*, 2013). Furthermore, this selective antagonism of 5-HT2A receptors by second-generation antipsychotics may contribute to fewer extrapyramidal side effects compared to first-generation antipsychotics.

The complex pharmacological profile of second-generation antipsychotics also include interactions with other receptor systems. For example, these drugs may antagonize alpha-1 adrenergic receptors, histamine H1 receptors, and muscarinic receptors to varying degrees (Meltzer *et al.*, 2013). These interactions may contribute to the side effect profile commonly associated with atypical antipsychotics, such as B. Sedation, weight gain, and metabolic effects. This all data are summarized in Table 2.

Table 2. Overview of Second-Generation/ Atypical Antipsychotics

Drugs	Mechanism	Adverse Effect	Route	Half-Life of Excretion	Brand Name	Metabolism
Aripiprazole	Partial antagonist at D2 & 5HT1A receptor & Antagonist at 5-HT2A receptor	Akathisia, parkinsonian, acute dystonic reactions, tardive dyskinesia, nausea, Weight gain, jaundice, etc.	Oral, IM	-	Abilify	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
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, glucosehomosis, etc.	Oral, IM	21-54 hr	Zyprexa	liver
Clozapine	Block dopamine & serotonin receptors	Hypersalivation, myocarditis, agranulocytosis, constipation, dystonia, 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 D2 & 5-HT2A receptors	Weight gain, Akathisia, parkinsonism, hypotension, dizziness, hypersensitivity, anaphylaxis, angioedema, wheezing, rashes, somnolence, oral hypothesia, cardiovascular diseases,	Sublingual	24 hr	Saphris	hepatic
Quetiapine	Blocked Dopamine, histamine, Adrenergic, & serotonin neurotransmitters	Sleepiness, constipation, weight gain, hypotension, seizures, prolonged erection, diabetes, tardive dyskinesia, neuroleptic malignant syndrome, etc.	oral	6 hr	Seroquel	liver

Table 2. Overview of Second-Generation/ Atypical Antipsychotics

Drugs	Mechanism	Adverse Effect	Route	Half-Life of Excretion	Brand Name	Metabolism
Cariprazine	Mechanism of action is unknown, but the action is mediated by combination of cariprazine of partial agonist at Dopamine (D2) & 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 and 5-HT2A receptor antagonists act as Neuroleptic Agents.	Weight gain, Extrapyramidal symptoms, QTc prolongation, Orthostatic hypotension, prolactin elevation, Fatigue, nasal congestion, somnolence, tachycardia, dizziness, Tardive Dyskinesia, etc.	Oral	13 -18 hr	Fanapt	liver
Lurasidone	It shows antagonistic activity by a combination of dopamine (D2) and serotonin (5-HT2A).	Akathisia, Somnolence, Parkinsonism, Dystonia, Nausea, Agitation, Anxiety, weight gain, etc.	Oral	18 hr	Latuda	liver
Ziprasidone	Antagonized dopamine (D2) and serotonin in the mesolimbic pathway and serotonin (5-HT2A) receptors in the mesocortical pathway to reduce positive and 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, Stuffiness, etc.,	Oral, IM,	7 - 10 hr	Geodon	liver

(Citrome, 2011; Kane, 2011; Steven and Potkin, 2011; Atypical Antipsychotics, 2018; Physiopedia, 2020; Bouchette *et al.*, 2021; Laszlovszky *et al.*, 2021; McNeil *et al.*, 2021; Thomas and Saadabadi, 2021; Maan *et al.*, 2023)

Table 3. Medicinal Plant with Their Major Phytoconstituents

Sr. No.	Herbal Plant	Major Phytoconstituents
1.	Brahmi	Asiaticoside & Bacoside
2.	Jatamansi	Violin & Jatamnsone
3.	Sarpagandha	Reserpine & Ajmaline
4.	Vacha	Asarone
5.	Kusta	Costunolide & Palmitic acid

TREATMENT

Antipsychotic Drugs

The physician recommended a combination of psychotic drugs along with psychotherapy.

Ayurvedic Treatment

Brahmyadiyoga is an herbal preparation used in the treatment of schizophrenia. It was developed by the Central Council for Ayurveda and Siddha under the Ministry of Health and Family Welfare of India. The preparation includes Brahmi, Jatamansi, Sarpagandha, Vacha, Kusta, Tagar, and other herbs. Medicinal Plant with Their Major Phytoconstituents are shown in the Table 3.

Studies have shown that the combination of water-based extracts of Brahmi and Jatamansi in Brahmyadiyoga is as effective as modern antipsychotic drugs for the treatment of schizophrenia. (Chauhan *et al.*, 2013)

Conclusion

From this comprehensive review article, we can conclude that schizophrenia is a complex psychiatric disorder influenced by a combination of environmental and genetic factors. These factors contribute to disorders in brain development and function and result in the characteristic symptoms seen in schizophrenia and other psychotic disorders. The article provides insights into the pharmacology of antipsychotics and also discusses the Ayurvedic treatment of psychosis, shedding light on the symptom manifestations such as delusions, hallucinations, and speech and behavioral disorders.

Although antipsychotic medications are commonly used to control symptoms, the exact causes of schizophrenia remain unknown. Nonetheless, the article underscores the optimistic perspective that future research efforts will continue to elucidate the exact causes of this complicated

condition. Through this ongoing scientific research, we hope to improve our understanding, which will lead to better approaches to diagnosing and treating schizophrenia.

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