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Review

An Integrated Review: Symptomology, Diagnostic Frameworks, Neurobiological Pathways and Therapeutic Approaches

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	Abstract
Published on: 20 Nov 2025	<p>Schizophrenia, a severe and long-lasting neuropsychiatric illness. It causes severe social and professional dysfunction and is typified by symptoms like delusions, hallucinations, disordered speech, and cognitive impairment [1][2]. Schizophrenia is still caused by a variety of factors, including environmental factors, neurobiological abnormalities, and genetic predisposition [2][3][4]. Prognosis and quality of life can be improved with early detection and ongoing treatment. The goal of ongoing research is to better manage schizophrenia by comprehending neurochemical mechanisms and creating innovative therapeutic approaches [5][6][7]. Its pathophysiology heavily relies on glutamatergic and dopaminergic dysfunctions [8]. Antipsychotic drugs and psychosocial therapies are used in treatment, with the diagnosis being mainly clinical and based on DSM-5 or ICD-10 criteria [9][10][11][12].</p>
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	<p>Keywords: Dopamine hypothesis, neurotransmitters, schizophrenia, psychosis, antipsychotics, cognitive dysfunction, mental illness, psychosocial therapy.</p>

INTRODUCTION:

Schizophrenia is a mental disorder that affects about 0.75% of people worldwide suffer from schizophrenia, a severe mental illness that costs the US economy over \$150 billion annually (Cloutier et al., 2016) and between 0.02% and 1.65% of GDP globally (Chong et al., 2016).

Despite having a low prevalence, schizophrenia ranked 12th among 310 diseases and injuries worldwide in terms of disability in 2016 (Charlson et al., 2018).

It is a disabling condition because of its early onset and chronic course [13]. Psychotic symptoms are the primary characteristics of schizophrenia and related psychotic disorders, which include delusional disorder, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and schizotypal personality disorder [14]. A complex, long-term mental illness, schizophrenia can be identified by a wide range of symptoms, such as hallucinations, delusions, disordered speech or behaviour, and cognitive impairment. Schizophrenia, which translates to "split mind," was named for the idea that various aspects of a patient's personality, including thought, emotion, and perception, had become divided or fragmented. A certain amount of detachment from reality is implied by the term psychotic [15][16][17][18].

SYMPTOMS:

- **Cognitive symptoms:** Attention, working memory, or executive function impairments.
- **Negative symptoms:** Loss or deficits, frequently lead to disability.
- **Positive symptoms:** suspicion, delusions, and hallucinations can lead to relapse.

Teenage schizophrenia symptoms are similar to those of adult schizophrenia, but it may be more difficult to diagnose. Many teenagers exhibit some of the early symptoms of schizophrenia, which come before hallucinations, delusions, and disorganization [19].

- **Delusions:** These are common in people with schizophrenia. These typically entail hearing or seeing things that others aren't aware of. Schizophrenia patients perceive these things as real [20][21]. Similar symptoms can also be brought on by recreational drug use, including marijuana, stimulants like cocaine and methamphetamines, or hallucinogens [22].
- **Illusions:** This occurs when people hold beliefs that aren't accurate or real. Schizophrenia patients, for instance, may believe they are being harassed or hurt when in fact they are not. They might believe that they are the object of particular gestures or remarks when in fact they are not. They might believe they are extremely talented or well-known when in reality they are not or they might think a big catastrophe is coming, but that isn't the case [23].
- **Unorganized thoughts and speech:** Thinking becomes disorganized when speech is disorganized. For those who have schizophrenia, social interaction can be challenging. It's possible that the responses provided by individuals with schizophrenia have nothing to do with the questions themselves or inquiries might not receive a thorough response. Unrelated words may occasionally be combined in speech in an incomprehensible manner. This could manifest as anything from childish foolishness to unfounded agitation [24].

Early Teenage symptom:

- removing oneself from family and friends
- Changing social circles or friends
- a shift in concentration and focus
- issues with sleeping
- agitation and irritability
- trouble with homework
- or anxiety related to poor academic performance
- hazy suspicion strange concepts feeling unique compared to other people

Teens with schizophrenia may experience hallucinations more frequently than delusions, compared to adults with the disorder. Especially in male gender, a chronic illness with multiple relapses, a family history of suicide, prior suicidal and impulsive behavior, a negative attitude toward treatment, and concurrent substance use are the main risk factors that are implicated[24][25][26].

Suicide thoughts and behavior:

Schizophrenia places a heavy burden on patients, families, and society due to its debilitating nature and chronic course. Schizophrenia patients may attempt self-harm as a result of catatonic excitement, depressive symptoms, or threatening or commanding hallucinations. These patients have a 4% to 10% lifetime risk of suicide but parasuicides are higher, ranging from 25% to 50%. In young males, early stages of the illness, high premorbid functioning, multiple relapses/drug dropouts, depression, and prior suicide/parasuicide attempts are the most frequently reported risk factors for suicide in this population [27][28]. Although suicide and parasuicide are more common in people with schizophrenia than in the general population. Ten percent of people with schizophrenia are thought to attempt suicide [29][30][31][32][33]. A high-risk period is thought to be the first year of psychotic illness. Suicidal behaviour was found to be seven times more likely to be linked to substance abuse [34][35].



CAUSES:

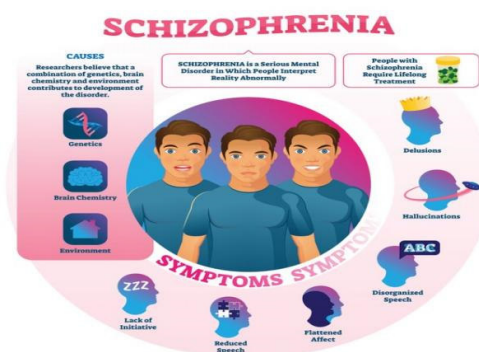
- **Genetics:** According to some research, drug use, especially when a person is a teenager, may raise their Schizophrenia frequently runs in families because of a strong genetic component to the illness. Genes account for about 80% of the risk of developing schizophrenia which is referred as heritability. It implies that you are six times more likely to have schizophrenia yourself if you have a close relative who has it, such as a parent or sibling [36][37][38].
- **Environmental factors:** risk of developing schizophrenia cannot be brought on by drug use alone, nor can drug use during adolescence be held responsible for the illness [39][40].
- **Mental Illness in Identical Twins:** Researchers frequently examine identical twins to ascertain how genetics affects the course of disease because they share 100% of their genes. If one identical twin has schizophrenia, the other twin has a 50% chance of getting the disorder as well. This demonstrates that although there is a significant genetic risk, environmental and epigenetic factors also contribute significantly to the disease's development [40].

RISK FACTORS:

- Prenatal health such as decreased vitamin D levels and uterine viral exposure
- Birth trauma can include premature birth or a lengthy, challenging delivery.
- Brain anatomy, including disparities in the size of brain regions and the connections between them compared to healthy people
- Adolescent substance use, especially cannabis use infections caused by viruses, particularly before birth
- Poor dietary intake
- Autoimmune conditions
- Trauma in childhood
- Poverty

Additionally, researchers think that virus exposure, including during pregnancy, may raise the risk of schizophrenia but they haven't found any particular viruses that cause schizophrenia [41][42][43][44].

- **Epigenetics:** It is a study of how environment and behaviour affect gene function. Strong epigenetic risk factors, according to scientists, influence the onset of schizophrenia. This explains why some individuals with the same genes who are genetically predisposed to the disease experience symptoms, while others do not [45][46][47].



DIAGNOSIS:

A thorough assessment of symptoms, medical history, and ruling out other conditions are all necessary for the diagnosis of schizophrenia, which usually requires the presence of at least two important symptoms over a predetermined period of time [48].

The following criteria must be followed: **Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or International Classification of Diseases, Tenth Revision (ICD-10) Criteria:**

- Presence of symptoms:** At least two of the following symptoms must be present.
 - Delusions: Strongly held false beliefs that are refuted by evidence.
 - Hallucinations: Perceiving unreal sensations, like hearing voices.
 - Incoherent or nonsensical speech patterns: Disorganized speech.
 - Catatonic or disorganized behavior: Inappropriate or erratic behavior.
 - Negative symptoms: Lack of motivation.
- Duration:** At least one month of active symptoms and at least six months of continuous signs of disturbance are required.
- Effect on Functioning:** Social or professional functions must be severely hampered by symptoms [48][49].

Evaluation:

In order to rule out other possible causes, specialized laboratory and radiographic tests are required for schizophrenia, which is essentially a clinical diagnosis. For an initial assessment of a patient with schizophrenia, the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia suggests the following tests [48].

- Hematology:** A complete blood count (CBC) to look for evidence of infection or anemia that could be mistaken for schizophrenia symptoms. If clozapine is being considered or is being used, an absolute neutrophil count (ANC) should be obtained.

- **Blood chemistry:** Electrolyte, kidney, liver, and thyroid-stimulating hormone (TSH) tests are all part of the blood chemistry panel. Psychiatric conditions including sadness and cognitive decline might be mistaken for hypothyroidism.
- **Pregnancy test:** For women of childbearing age, a pregnancy test is advised.
- **Electroencephalogram:** To rule out a seizure disorder, it may be recommended based on the neurological examination.
- **Imaging:** Depending on the neurological examination or history, brain imaging—either CT or MRI, with MRI being preferred—may be recommended.
- **Genetic testing:** Chromosomal testing is recommended.
- **Drug toxicology screen:** To identify substance use that may result in psychotic symptoms, this screen may be clinically recommended.

Further examination:

- **Rapid Plasma Reagin (RPR) Test:** It is used to check for syphilis, which can result in mental symptoms.
- **HIV testing:** HIV infection can mimic mental illnesses.
- **ECG:** It is recommended for patients with cardiac risk factors, elevated baseline QTC intervals, or when adding other medications that can increase QTC intervals [48][49][50].
- **Dyskinesia Identification System or Abnormal Involuntary Movement Scale (AIMS):** Every six to twelve months after starting antipsychotic medication, the Condensed Use Scale (DISCUS) is used to evaluate baseline abnormal movements.

A quantitative assessment should be part of the initial evaluation of a patient suspected of having a psychotic disorder, according to the American Psychiatric Association (APA) [50][51].

PATHO-PHYSIOLOGY:

An imbalance in neurotransmitter systems—specifically, dopamine, glutamate, and GABA—affects brain pathways [52][68]. The illness is also exacerbated by immune system dysregulation, abnormalities in the structure and function of the brain, and problems with synaptic connectivity [53][54].

Dysregulation of neurotransmitters:

1. **Dopamine:** It works by dysregulation of dopamine. While decreased dopamine activity in the mesocortical pathway may be responsible for negative symptoms and cognitive deficits, excessive dopamine in the mesolimbic pathway is thought to contribute to positive symptoms [55][56].
2. **Glutamate:** The primary excitatory neurotransmitter in the brain, glutamate, is also disrupted [57].
3. **GABA:** Changes in the primary inhibitory neurotransmitter in the brain, gamma-aminobutyric acid (GABA), also have an impact.

Functional changes:

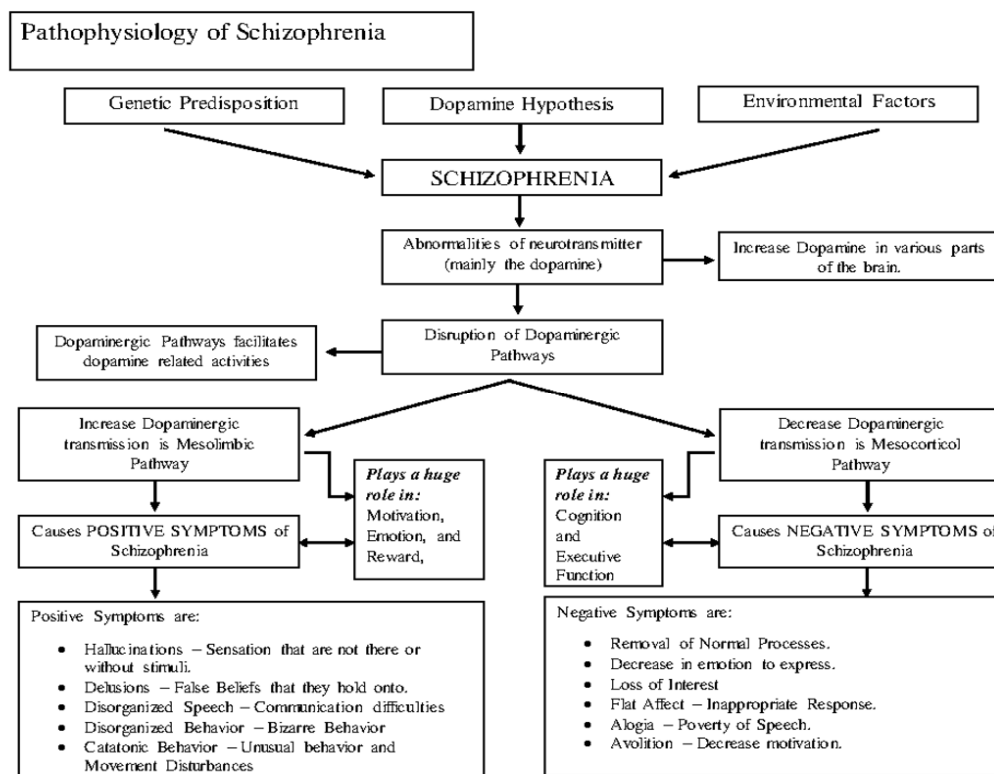
By influencing neurotransmitters and receptors, these can change the structure and function of the brain [58][59]. Neuroimaging methods such as fMRI can identify widespread functional deficits in the brains of individuals with schizophrenia [60]. Schizophrenia is a complicated disorder that results in a disruption in neurodevelopment and function due to a combination of environmental and genetic factors [61][62][63][64]. The immune system inflammatory cytokines causes immune system dysfunction, which may be due to stress or prenatal infections [65][66][67].

Neurodevelopmental disruption:

The illness is considered a neurodevelopmental disorder that arises during adolescence or fetal development may result in decreased synaptic connectivity and other brain abnormalities [68][69][70].

Structural abnormalities:

Research has revealed variations in the anterior cingulate cortex, and a thinning of some cortical areas. The hippocampus, which is essential for learning and memory, may also exhibit aberrant activity [71][72].



PHARMACOTHERAPY:

Treatment for schizophrenia aims to improve the patient's overall functioning in society, prevent relapse, and target symptoms. Even though medication is a useful cornerstone for managing a disease, residual symptoms may still exist.

Care should also include interventions like psychotherapy determining the best care environment, such as a partial hospital, intensive outpatient, psychosocial rehabilitation, clubhouse models, coordinated specialty care, etc., should also be part of treatment plans. Since acute psychotic exacerbations are linked to emotional distress, life disruption, and a significant risk of dangerous behaviors toward oneself, others, or property, pharmacologic treatment with an FDA-approved antipsychotic medication should be started as soon as schizophrenia is diagnosed [73].

Types of psychotherapy:

Individual Psychotherapy

The patient can learn coping mechanisms for their thoughts and actions from a therapist or psychiatrist during sessions. They Can also gain more knowledge about their condition, its consequences, and how to distinguish between the real and the fake [74].

Cognitive behavioural Therapy

Patient can alter thoughts and actions with the aid of cognitive behavioral therapy (CBT). Patient gains the ability to identify the thought patterns that underlie the negative feelings or actions and learn how to swap them out for constructive ones. The average duration of CBT sessions is one hour. Most people receive CBT for a few months.

Cognitive enhancement Therapy (CET)

Another name for this kind of treatment is cognitive remediation. It improves the patient's ability to identify social cues, also known as triggers. Additionally, it enhances your memory, focus, and cognitive organization. It blends group sessions with computer-based brain training [75][76].

Classification of Antipsychotic Drugs

A. Typical (First-Generation) Antipsychotics (FGAs)

Low potency: Chlorpromazine, Thioridazine

High potency: Haloperidol, Fluphenazine, Trifluoperazine

B. Atypical (Second-Generation) Antipsychotics (SGAs)

Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole

Ziprasidone, Paliperidone, Lurasidone, Asenapine, Cariprazin

Mechanism of Action:

Typical Antipsychotics:

Potent antagonists that block dopamine D2 receptors in mesolimbic pathways reduce positive symptoms. However, extrapyramidal symptoms (EPS) and hyperprolactinemia are brought on by blockade in the tuberoinfundibular and nigrostriatal pathways.

Atypical Antipsychotics:

Dual antagonism at D2 and 5-HT_{2A} receptors → reduces the risk of EPS while improving both positive and negative symptoms.

Clozapine is effective in treating treatment-resistant schizophrenia because of its weak D2 antagonism, strong 5-HT_{2A}, D₄, α -adrenergic, and muscarinic receptor blockade.

Dopamine activity is stabilized by partial D2 agonists like aripiprazole and cariprazine [76].

TYPE OF DRUG	DOSAGE OF DRUGS		ROA	MOA	ADR's	USES
	INITIAL DOSE	MAINTENANCE DOSE				
1]Typical antipsychotics						
Haloperidol	0.5-2 mg/BID	5-20 mg/day	Oral/IM	D2 blockage	Dry mouth, dyskinesia, dizziness	To treat Schizophrenia Tourette Syndrome To treat schizophrenia, bipolar disorder, severe nausea & vomiting.
Chlorpromazine	25-50 mg/TID	300-800 mg/day	Oral/IM	D2 blockage	Drowsiness, dry mouth dyskinesia.	
2] Atypical antipsychotics						
Risperidone	1 mg/day	2-6 mg/day	Oral/IM	D2 + 5HT2A block	Insomnia, increased appetite, weight gain	Schizophrenia, bipolar disorder
Olanzapine	5-10 mg/day	10-20 mg/day	Oral/IM Depot	D2 + 5HT2A block	Weight gain sleepiness	Schizophrenia,
Quetiapine	25-50 mg/day	300-600 mg/day	Oral	Weak D2, strong 5HT2A	Orthostatic hypotension	Schizophrenia, depression
Clozapine	12.5 mg/day	300-450 mg/day	Oral	D4 + 5HT2A + muscarinic block	Sialorrhea, tachycardia fever	Schizophrenia parkinsonism depression
Aripiprazole	10-15 mg/day	10-30 mg/day	Oral/IM	Partial D2 agonist	Blurred vision tremors	Schizophrenia Tourette disorder depression
Ziprasidone	40 mg Bd	80-160 mg/day	oral	D2 +	Akathisia,	Schizophrenia

Paliperidone	3-6 mg/day	6-12 mg/Day	Oral/IM Depot	5HT2A block D2 5HT2A block	+	vision problems Injection site reactions, sedation	bipolar disorder Schizophrenia effective disorder in adults
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Treatment-Resistant Schizophrenia (TRS)

First recommendation:

Clozapine:

Patients with TRS should be offered clozapine. [SIGN (Grade A)]

Between 25% and 30% of people with schizophrenia are thought to fit the TRS criteria.^{66,67} RCTs have shown that clozapine has response rates in this population ranging from 30% to 60%.⁶⁸ According to established guidelines, clozapine is the only recommended treatment for TRS.⁶⁹ On the other hand, there is inconsistent evidence to support the use of high doses, switching, and combined antipsychotics.^{70–72} Research shows that clozapine is frequently postponed or not taken when prescribed. The strength of clozapine's seemingly unique role in TRS is still being investigated by research and meta-analyses, though there may be some limitations.

Second recommendation:

Patients whose schizophrenia has not improved after two antipsychotics should be evaluated for clozapine.

[From SIGN (Grade B) modified]

Treatment resistance is defined differently in different studies, particularly when it comes to the degree of improvement permitted on a non-clozapine treatment. A relative change in the representative scales (usually $\geq 20\%$ decrease in the Positive and Negative Syndrome Scale) has been used to define a maximum permissible treatment response. Clinically speaking, patients who experience only a 20% decrease in positive symptoms following two or more appropriate courses of non-clozapine antipsychotic medication remain a challenge. Clozapine was found to have the most consistent results in a systematic review of 26 RCTs, some of which had a broader definition than the 20% improvement [76][77].

MONITORING PARAMETERS:

Parameter	Frequency	Rationale
Blood glucose, hba1c, lipid profile baseline	3 months	Annually detects metabolic adverse effects.
Blood pressure	Baseline, each visit	Detect orthostatic hypotension
Body weight, BMI, waist circumference	Baseline, 4 weeks, quarterly	Monitor for metabolic syndrome
CBC (WBC count)	Weekly for first 6 months (Clozapine), then monthly	Detect agranulocytosis
ECG	Baseline and as indicated	QT prolongation risk
Prolactin levels	If symptomatic	Hyperprolactinemia monitoring
EPS/AIMS scale	Periodically	Detect tardive dyskinesia/EPS
Liver function tests (LFTs)	Periodically	Detect hepatotoxicity

Precautions and Preventive Measures:

1. To reduce orthostatic hypotension and sedation, gradually increase the dosage.
2. Steer clear of sudden withdrawal to avoid relapse.
3. Changing one's diet and exercise habits can help avoid weight gain and metabolic syndrome.
4. Keep an eye out for suicidal thoughts, particularly in the early stages of treatment.
5. Steer clear of CNS depressants and alcohol. routine clozapine blood count monitoring.
6. Patient education regarding early relapse symptoms and adherence.
7. Patients at cardiac risk should not take QT-prolonging medications
8. Poor adherence maybe treated depot formation.

Counselling and psychotherapy:

A nonjudgmental, insight-oriented approach with a strong emphasis on the therapeutic alliance [77] and dynamic relational processes with therapists or group members is shared by all psychotherapy interventions that address issues at the individual, family, and community levels. It is believed that using these techniques to work through relationships from the past and present, losses, and disturbances will address underlying psychological processes related to traumatization and facilitate long-term change. Many of the studies we found only gave very general descriptions of these talking-based therapies (like "psychotherapy" or "counselling"), frequently with little to no information on the underlying theory of the methodology [78].

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