# Original Article: Schizophrenia: Mechanisms and Neurotransmitters

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## ABSTRACT

Schizophrenia has existed throughout history, as ancient Greek physicians have described it with different symptoms. However, it was not seriously studied until the second half of the nineteenth century. During the second half of the nineteenth century, the classifications related to Schizophrenia developed, which of course was very personal. Pick (2019) was the first to use the term dementia praecox to describe the apparently Hebephrenic type of psychiatric disorder. Schizophrenia is a mental disorder characterized by persistent or recurrent forms of psychosis. The main symptoms include hallucinations, delusions, and disordered thinking. Schizophrenia is a chronic and severe brain disease that affects a person's thoughts, feelings, and behaviors, as well as impairing a person's realism. The onset of the disease is between the ages of 16 and 30, but in rare cases it is also seen in childhood. The prevalence is equal in men and women, but the onset age is earlier in men than women. The age of onset in women is two peaks. The age of onset is 10 to 25 years for men and 25 to 35 years for women. The onset of the disease before the age of 10 and after the age of 60 is rare. In cases that start after the age of 45, it is called schizophrenia with a late onset.

## Introduction

A Karplin (2019) was the first to describe the disease in detail in psychiatric textbooks with a different perspective, emphasizing a distinct cognitive process and the early onset of the disorder. Bluler (2016) first used the term schizophrenia. He believed that mental functions undergo a splitting process that forms the basis of the disease [1-3].

He showed that despite the different symptoms, it is a single disease and the etiology and pathophysiology are the same in different patients. Meyer (2016) considered schizophrenia to be a reaction to life stress and called it a schizophrenic reaction [4]. This study investigated schizophrenia mechanisms and

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neurotransmitters. About one percent of the human population has schizophrenia, usually starting at age 25 and lasting for the rest of their lives. This disease is seen in all social classes. Although schizophrenia is described as a single disease, it probably belongs to a group of disorders that have a heterogeneous etiology and includes patients whose clinical manifestations, response, and course of the disease are not the same [5].

In fact, schizophrenia is a clinical syndrome rather than a single disease [6]. There is no test that can completely diagnose the disease. Familiar acquaintances can comment on the disease. To diagnose a person with schizophrenia, doctors confirm that there are symptoms and functional disorders for six months or a month. Many people with schizophrenia also have other mental disorders, the most important of which include substance use disorders, depressive disorders, anxiety, and obsessive-compulsive disorder [7-9].

### *Etiology*

The underlying etiological process of schizophrenia is still unknown. However, numerous biological, psychological and biopsychosocial factors play a role in the development of schizophrenia. Schizophrenia is caused by a genetic interaction with the environment. Before the onset of psychosis, mood, cognitive and primary negative symptoms are seen, which have minor effects on performance and interpersonal relationships [10].

### *Inflammation in schizophrenia*

Inflammation is an essential response to infection, harmful chemicals and tissue damage. In addition to protecting the body, it may have harmful effects, as seen in infectious and autoimmune diseases, such as multiple sclerosis (MS) [11-13]. Contrasting effects of inflammation are also seen in the central nervous system (CNS), where they may be neuroprotective or neurotoxic. Whether the inflammatory response has positive or negative effects depends on the interaction between environmental factors and the various components of the inflammatory response, according to which genetic diversity plays an important role [14-17].

The negative effects of inflammation also depend on whether the inflammatory condition is acute or chronic. Acute encephalitis in the CNS, for example, can be fatal within hours or days, while chronic inflammation in the CNS can have adverse effects for months or years and even a lifetime. Multiple Sclerosis (MS) is another example of an inflammatory disease that can be acute, recurrent with periods of recovery, or chronic and progressive. Both acute and chronic manifestations of MS as a result of inflammation in the CNS are said to mean "burning inflammation" [18-20].

### *Vulnerability model - schizophrenic stress*

Forty years ago, Zubin and Spring (2019) first introduced the schizophrenia vulnerability-stress model. This model suggests that stress, both physical and mental, can trigger a period of psychosis. Today, this model needs to be expanded to become a vulnerability-stress-inflammation model because it is known that inflammation plays a role in schizophrenia and can be caused by stress [21-23].

For example, if an inflammatory response is stimulated in the second trimester or in mothers while the CNS is still growing, children are more vulnerable to schizophrenia. Animal studies have shown that stress leads to increased levels of proinflammatory cytokines. As described in the defense hypothesis of the pathogen host, genetic makeup also contributes to the degree of vulnerability to stress. The markers of inflammation and the effects of inflammation on the neurotransmitter systems in schizophrenia are described in detail below [24-26].

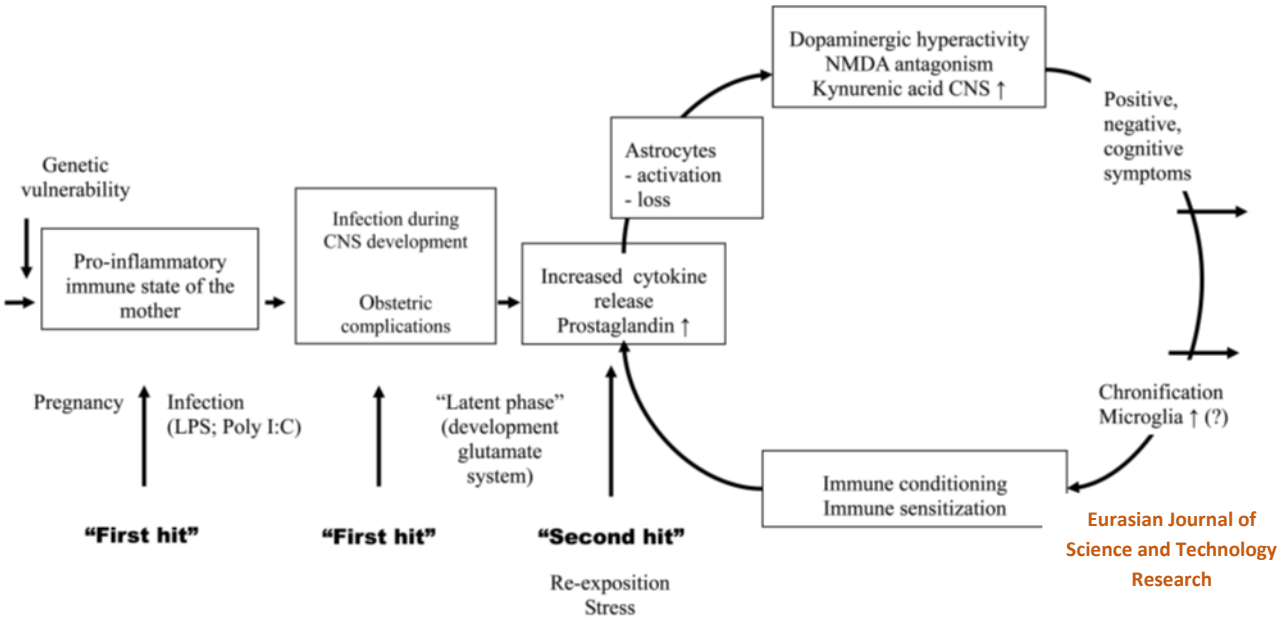


**Figure 1.** Overview of the Vulnerability-Stress-Inflammation Model of Schizophrenia. Taken from LPS: lipopolysaccharide. poly I: C: polyinosinic-polycytidylic acid.

### *Markers of inflammation*

Due to space constraints, only some studies of inflammatory markers can be discussed here. Such studies have found that fibrin degradation products, a protein that increases inflammatory processes, are found in the brains of post-mortem schizophrenics and in the cerebrospinal fluid (CSF) of about 50% of patients with schizophrenia. In addition, several studies have shown an increase in cytokine type 2 in patients with untreated schizophrenia [27-29]. Meta-analysis of cytokines in schizophrenia have shown higher levels of proinflammatory cytokines in peripheral blood in both patients with first-episode schizophrenia and recurrent patients than in healthy individuals, but some anti-inflammatory cytokines were also higher in controls. Meta-analysis of cytokines in CSF have shown similar results, with higher levels of proinflammatory cytokines and lower levels of inflammatory triticokines. However, there are different means of communication between the environmental safety system and the CNS system. An inflammatory process has been suggested that is involved in the pathophysiology of at least one subgroup of patients with schizophrenia [30].

### *The effect of inflammation on neurotransmitters*

Disorders of dopaminergic neurotransmission have long been a major focus of research in the neuroscience of schizophrenia, and it is clear that schizophrenia involves dopamine dysfunction. However, the exact relationship between this disorder and the disease has not yet been determined, and the results of studies on anti-dopaminergic drugs are unfavorable [31-33]. At least two interleukins (ILs) appear to play an important role in influencing neurotransmitter systems in schizophrenia: IL-1β, which induces mouse mesenchymal progenitor cells to become a dopaminergic phenotype, and IL-6, which reduces the survival of serotonergic neurons in the fetal brain [34].

Although an increase in proinflammatory cytokines is not specific to schizophrenia and has been described in other psychiatric disorders, the interaction between cytokines and neurotransmitters in specific areas of the brain, especially during brain development, contributes to the pathophysiology of schizophrenia. The researchers have suggested that this may be related to an increase in dopamine in the midbrain, a structure involved in human schizophrenia. Persistent latent infections have been suggested that potentially

cause an imbalance in the immune response. Chronic administration of interferon-α in animals is associated with decreased striatal dopamine secretion and anhedonia. This finding points to the different effects of inflammation on dopaminergic neurotransmission, which may play a role in the development of schizophrenia. It is well known that anhedonia is one of the most prominent negative symptoms in schizophrenia, and negative symptoms are often seen in chronic schizophrenia [35-37].

Glutamate, the most pervasive neurotransmitter in the CNS, is thought to be a major factor in the pathophysiology of schizophrenia due to its involvement in tryptophan/ quinornine metabolism to guide cytokines. Kinorenic acid is the only NMDA receptor antagonist naturally known in human $CNS_{53}$ and is one of three or more active neurotransmitters in the kinornin pathway. In the proposed mechanism of action in schizophrenia, a dominant immune response inhibits indole amine 2,3-dioxygenase (IDO), which leads to increased production of quinornic acid resulting in antagonism of NMDA receptors and lack of glutamate neurotransmission. The finding that NMDA receptor antibodies are present in about 10% of drug-free patients with acute schizophrenia supports the view that NMDA receptor antagonism is involved in the pathology of schizophrenia [38-40].

However, the findings regarding the association of quinornic acid in schizophrenia are contradictory. Some studies have shown increased levels of quinornic acid, mainly in the CSF and brain of patients with schizophrenia and in animal models of schizophrenia while others have shown no increase in the level of quinornic acid in the peripheral blood of patients with schizophrenia first episode or other groups. The important point about many of the studies discussed in this section is that patient specimens are generally not antipsychotic, and antipsychotic drugs can potentially interfere with the levels of biomarkers, including metabolites of kynornic metabolism. In addition, quinornic acid in CSF and blood may show different concentrations in schizophrenia because CSF may show a better pathological process than peripheral blood [41].

### *Biological factors*

The total brain weight in these patients decreases by about 20%, and the younger the onset of the disease, the higher this rate. Although the exact pathology of schizophrenia is not known, many studies have identified a disorder of the brain circuits, and suggested areas as major areas of involvement in patients' brains, including the limbic system, basal ganglia, and frontal lobe.

Of course, the thalamus and the brainstem also play a side role [42]. Wernicke (1956) used Disconnection Syndrome in his studies and found pathology in major neurological circuits during imaging studies. According to these studies, the gray matter areas in the cortex area shrink and enlargement in some areas of subcortex was found. Disruptions were also found in white matter structures, which are mainly present in communication circuits. Further studies with advanced imaging techniques such as DT-MRI (Diffusion Tensor MRI) found anisotropic reduction in parts of the brain of these patients and most areas were associated with Left Frontal Lobe and Left Temporal [43].

### *Limbic device*

The limbic system is one of the most important areas in the regulation and processing of emotions, which is one of the key symptoms of patients with psychotic disorder. Impairment in emotion processing causes pessimism, delirium, and damage, followed by aggression and reduced social functioning. Disruption of this system also causes disharmony in other related areas such as the amygdala, anterior cingulate, insula, and orbital-frontal cortex. The gray matter of the limbic system is reduced in patients with schizophrenia compared to non-schizophrenics [44].

### *Rule Nodes*

Previously, the function of these nuclei was known in terms of motor function, but more recently, they have been considered to be involved in cognitive and behavioral functions. In patients with schizophrenia, disturbances in these nuclei occur during rest and cognitive activity. Most studies have shown an increase in the volume, normality, and decrease in volume of these nuclei, but there is strong evidence that an increase in volume is associated with the use of typical and atypical antipsychotic drugs. In addition to changes in volume, changes in the shape of these nuclei have been reported in relation to disease [45].

The results of studies have shown a disorder of the dopaminergic system in these nuclei in patients with schizophrenia and indicate an increase in the number of $D_2$ receptors in the striatum area and their association with the onset of positive symptoms in these patients. In FMRI studies, during treatment with antipsychotic drugs, improvement in function was observed in the orbits of the nucleus accumbens and various areas of the prefrontal cortex, such as the anterior cingulate, orbitofrontal, which was associated with improved positive symptoms in patients [46].

### *Forehead Cortex*

The frontal lobes in humans, unlike primates, are larger and are made up of different areas. One of the most important areas is the prefrontal area, which has a lot of connections with other areas of the brain, and its damage causes symptoms including decreased motivation, attention to executive functions, which is very similar to the negative symptoms of schizophrenia patients. Several symptoms of schizophrenia are similar to those seen in prefrontal lobeotomy and include decreased motivation, attention, and recurrence. This decrease in activity is associated with disease duration, disease duration, and negative symptoms [46].

### *Thalamus*

The medial posterior nucleus of the thalamus (mediodorsl), which interacts with the frontal cortex of the forehead, has fewer neurons in patients with schizophrenia. The total number of neurons, oligodendrocytes, and astrocytes decreases by about 30-45%.

### *Genetic Hypotheses*

Genetic factors are involved in some and perhaps all types of schizophrenia. The rate of schizophrenia and schizophrenia-like manifestations is higher among the biological relatives of patients with schizophrenia. The concordance rate for schizophrenia in monozygotic twins is 40 to 50 percent. This is 4 to 5 times the rate of synchronization for bipolar twins and the prevalence of schizophrenia in the biological relatives of adopted children with schizophrenia compared with non-biological relatives, which confirms a significant genetic contribution to the etiology of schizophrenia. However, in general, it can be said that the method of genetic transmission in schizophrenia is unclear [47].

### *Hypotheses about pregnancy and birth complications*

Children born with a history of complications during pregnancy or childbirth are at increased risk for schizophrenia in adulthood. The cause is unknown, but the possible causes are:

a) Abnormal growth during pregnancy, such as low weight and small head circumference;

b) complications of pregnancy such as diabetes, bleeding and preeclampsia; and

c) birth complications such as uterine atony, emergency cesarean section that can cause hypoxic injuries. One of the areas of the brain most involved in schizophrenia is the hippocampus, which is most susceptible to hypoxia [48].

### *Neural Circuits*

Despite decades of understanding the disease, modern science has not been able to find a precise place in the brain for the disease. But the

important point is that this disease is most associated with disruption of neuronal circuits in the brain. Some studies have suggested that the thalamic nuclei are the underlying cause. The thalamus is considered the central nexus point

GABA, and glutamate neurotransmitters in the sensory and cognitive modalities that characterize schizophrenia [49].

*Important Biochemical Assumptions (neurotransmitters)*

Various studies have suggested the involvement of neurotransmitters alone or in balance with each other in schizophrenia. Neurotransmitters such as dopamine, glutamate, GABA and acetylcholine have been mentioned in the occurrence of this disorder. Here, considering the importance of dopamine neurotransmitter, we first discussed the hypotheses related to the role of this neurotransmitter.

*Dopamine*

Chlorpermazine was first used in 1952 to reduce psychotic symptoms, and after a while the role of dopamine in the development of schizophrenia symptoms was considered [5]. Here is some evidence to support the involvement of dopamine in schizophrenia.

*Clinical Effects of Dopaminergic Drugs*

The fact that dopamine receptor antagonists improve psychotic symptoms may indicate that the dopamine system is overactive in schizophrenia. But this conclusion is questionable because, first, dopamine receptor antagonists are used to treat various types of psychosis and are not specific to schizophrenia. Second, blockage of D2 receptors occurs within the first few hours, but the clinical effects appear a few days to a few weeks later. Third, these drugs are mainly effective in the positive symptoms of schizophrenia and have no significant effect on the negative and cognitive symptoms [18, 19].

*Development of psychosis by dopamine agonists*

in the nervous system, and it acts in connection with other parts of the brain through circuits. In patients with chronic schizophrenia, the most important circuit is the cortico-thalamic-striatal circuit. This circuit works through dopamine,

Long-term use of dopamine agonists such as amphetamines can cause a type of paranoid psychosis, and the question arises as to why, although amphetamines release dopamine shortly after use, psychotic symptoms often occur after being seen from long-term use with high doses.

Hyperdopaminergic in the subcortex, specifically in the mesolimbic (striatum, which contains the nuclei of quidite and putamen), causes positive symptoms of the disease, as well as a decrease in dopamine levels in the dorsolateral prefrontal cortex and its association with negative symptoms. Tyrosine is converted to L-dopa by the enzyme tyrosine hydroxylase, which is also converted to dopamine by the enzyme dopacarboxylase. Cell bodies of dopaminergic neurons are mainly found in the following areas, especially the areas of the substantia nigra and the abdominal segmental region of the midbrain nuclei: Black body (pars compacta), ventral tegmental area, the hypothalamus and the gray matter around the aqueduct; dopamine is found in the peripheral tissues of the kidneys, dilating the arteries of the kidneys and excreting urine and sodium.

*The four main dopamine pathways in the central nervous system are:*

a) Negro-striatal pathway, which is from the substantia nigra to the striatum;

b) the mesocortical pathway, which begins at the VTA and ends at the frontal cortex, regulates attention and memory. Decreased activity of this pathway causes negative symptoms;

c) meso-limbic pathway, from the V.T.A to the limbic system and the nucleus accumbens and temporal lobes, and antipsychotic drugs appear to affect this pathway and reduce positive symptoms;

d) tuberculinfendibular pathway.

There are at least 5 types of dopamine receptors. In terms of functional mechanism, D3 and D4 receptors are similar and D2 and D5 are similar to D1 [16].

### *Glutamate*

There is evidence of glutamate dysregulation in the mesolimbic and its association with dopaminergic system dysregulation. Injection of ketamine, which is a glutamate receptor antagonist, in normal individuals causes symptoms similar to those of schizophrenia patients, and injection in patients with schizophrenia exacerbates both positive and negative symptoms by affecting the prefrontal cortex and thalamus. Glutamate is the brain's main excitatory neurotransmitter. Glutamanergic neurons connect the cortex, limbic system, and thalamus (pathways in schizophrenia). Glutamate has two types of ionotropic and metabotropic receptors that bind to both. Ionotropic receptors include NMDA and AMPA. By further identifying the role of the NMDA receptor in regulating cognition and behavior and discovering the interaction of the glutamatergic system with dopaminergic, gabanergic and cholinergic, attention was drawn to glutamate as an effective factor in the pathophysiology of schizophrenia. Blockade of this receptor in healthy people with anesthetics such as phencyclidine and ketamine causes schizophrenia-like symptoms, including negative and cognitive symptoms, and increases the release of dopamine in the dopaminergic system. Substances that indirectly increase the activity of NMDA receptors reduce negative symptoms and improve cognitive function in these patients.

Therefore, decreased function of NMDA receptors in the corticolimbic pathway may play a role in the pathophysiology of the underlying symptoms of schizophrenia, including negative symptoms, and predict the therapeutic effect of activating the NMDA receptor complex. This strategy is difficult to perform because glutamatergic activity is neurotoxic. However, the activity of the NMDA receptor complex through the glycine site has been confirmed by glycine and D-cycloserine or D-serine to reduce the negative symptoms of schizophrenia [19].

### *Acetylcholine*

Acetylcholine affects the muscarinic and nicotine receptors that spread throughout the brain. Decreased levels of nicotine and muscarinic receptors in the frontal, hippocampus, thalamus, and striatum are seen in patients with schizophrenia. In postmortem studies in schizophrenic patients, muscarinic receptors in the hippocampus, coccyx, putamen, and certain areas of the prefrontal cortex have been reduced. Cholinergic mechanisms are involved in the regulation of attention, memory, and sensory gating. In addition, nicotinic alpha 7 receptors play an important role in sensory gating and are problematic in schizophrenics [19].

### *Cursed light*

Norepinephrine is a biogenic amine produced by the enzyme dopamine hydroxylase on dopamine. Noradrenergic neuron cell bodies are located primarily in the locus ceruleus in the fourth ventricular floor. Defects in the noradrenergic reward system or selective degeneration of noradrenergic neurons lead to nausea or lack of purposeful spontaneous behavior, which some consider to be a central symptom of schizophrenia. Elevated norepinephrine levels are associated with general symptoms of schizophrenia, especially positive symptoms and paranoia.

In the acute phase of the disease, the amount of norepinephrine in plasma and cerebrospinal fluid increases and decreases with the onset of the acute phase. Treatment with neuroleptic drugs reduces the amount of this neurotransmitter and as a result reduces the patient's psychotic symptoms [20].

### *Serotonin*

Serotonin is also an amiobiogenic made from tryptophan. The cell bodies of serotonergic neurons are located mainly in the brainstem in

the dorsal raphe nuclei. Chronic stress stimulates the serotonergic pathway, especially in the areas of the anterior cortex cingulate (ACC) and external posterior frontal lobe (DLFL), which is one of the main causes of schizophrenia [21].

5HTA1 is the most important receptor in the cortex that binds to phospholipase A2 and by autopsy of patients and are related to the prognosis of the disease [21, 22].

### *Psychosocial factors*

### *Psychodynamic theories*

Freud (2013) hypothesized that schizophrenia arises from the stabilization of growth at earlier stages than the emergence. He also considered the ego defect, which leads to the symptoms of schizophrenia, to be important. Thus, psychosocial conflict due to premature fixation and ego defect, which may have resulted from primary object relationships, causes psychotic symptoms [23].

Solivan (2019) considered schizophrenia to be a disorder of interpersonal relationships. Severe anxiety in these patients creates a feeling of disconnection that turns into a state based on the feeling of stinging and injury called pararataxic distortion [23, 24].

According to Mahler (2005), a person with schizophrenia never achieves constancy object, which is a sense of personal identity and arises from close attachment to the mother during infancy [24].

### *Theories about the family*

A specific family pattern does not play a causal role in the development of schizophrenia. Understanding morbid familial behavior is clinically important because such a behavior can significantly increase the emotional stress that a patient with vulnerable schizophrenia has to deal with. Some theories about the family are as follows.

### *Double dependence*

stimulating this receptor with serotonin, it is removed from the phospholipid of the cell membrane and in the peripheral system of these patients causes hemolytic anemia and coagulation disorders (coagulopathy). The central brain system causes atrophy. These findings have been confirmed by MRI & PET and

In this hypothetical family, the child receives conflicting messages about behavior, attitudes, and feelings from his or her parents. In this hypothesis, the child takes refuge in a psychotic state to escape from a confusing and unsolvable situation [23, 24].

### *Disruption and one-sided family*

There is a significant rift between the parents, so that one of them is getting too close to a child of the opposite sex, or a one-way relationship with one of the parents, a parent-child conflict, and domination.

### *Excitement expressed*

Parents or other caregivers treat schizophrenia with criticism, hostility, and over-intervention, and the recurrence of schizophrenia is high in families with high levels of emotion.

### *Clinical protests*

Often, before the onset of psychotic symptoms, there is a period of mild but progressive behavioral symptoms that we usually notice when we retrospectively evaluate the patient. This prodromal stage can last from a few weeks to several years. Symptoms seen at this stage include physical symptoms such as headache, back pain, and weakness. Gastrointestinal problems, change or decrease in occupational and social performance, new interest in philosophical issues, abstract beliefs, occult and religious subjects, strange behaviors, abnormal emotions, and strange perceptual experiences [23, 24].

In general, the symptoms of these patients are divided into positive and negative symptoms.

### *Positive symptoms*

Positive symptoms can entail illusions, delusions, abnormal behaviors, disturbances in the form of thinking such as frequent derailment, tangential thinking, marginalization, and loosening of associations.

### *Negative symptoms*

It refers to the patient's very gradual manifestations, which often emerge before the onset of positive symptoms. The question that arises about negative symptoms is whether the negative symptoms are transmitted independently. Karplin and Blueler (2008) based their work on negative signs. Due to his knowledge and lack of treatment for negative symptoms, Schneider (2008) expressed his diagnostic criteria based on positive symptoms, but after a while, it was seen that despite the treatment of positive symptoms and their elimination, the negative symptoms remained; as a result, the focus was on examining these symptoms. Studies have shown that about 28-36% of patients suffer from negative symptoms [24].

Negative symptoms of schizophrenia have been attributed to impaired lobe frontal function, but its mechanism is unclear. It may be due to impaired dopamine transport in the frontal cortex in the chronic phase of the disease because frontal lobe function is lowest in patients with high HVA levels in the CSF. Imaging studies suggest that there is a close association between negative symptoms and increased ventricular size in chronic patients and mental disorders. Negative symptoms are classified into different forms. One type of division is based on the primary and secondary nature of the symptoms [25]. Considering early negative symptoms, the core of the symptoms is schizophrenia and they exist from the beginning; and secondary negative symptoms are due to the following causes:

a) Improper control of positive symptoms such as withdrawal due to pessimism;

b) extra-pyramidal effects of antipsychotic drugs, including Akinesian psychomotor condensation; c) depression due to depression after psychosis or drug causes; and

d) accommodation in maintenance centers.

Some of these negative symptoms include superficiality of emotion, decreased spontaneous movements, disproportionate emotion, poverty of speech and its content, impotence, indifference during psychological examinations, apathy, lack of motivation, lack of interest and decreased interactions, socially and interpersonally [23, 24].

From the disintegration of speech, the loosening of associations and block of thought is considered by some as a positive sign and some as a negative sign [14]. Using PET, Liddle et al., showed that severe psychomotor deficiency was associated with decreased cerebral blood flow in the prefrontal cortex and deficits in performing performance tests [15]. Other symptoms seen in these patients include the following instances:

### *Mood symptoms*

The most common manifestation is depressed mood, which is difficult to distinguish from negative symptoms. On the other hand, it is difficult to differentiate between depressed mood and dysphoria caused by a severe and debilitating disease such as schizophrenia. Mood symptoms are sometimes part of the prodermal phase of the disease [23, 24].

### *Cognitive symptoms*

These symptoms are seen in people who are also in the first episode of the disease and are predictors of future performance [22].

### *Behavioral disorders*

It includes mannerism, echo-praxia, and stercotyped behavior.

### *Curse and prognosis*

Preliminary symptoms usually appear during adolescence or youth within a few days to a few months. The initial symptoms may last for a year or more before the psychotic symptoms become apparent. After the first period of psychosis, there is a period of gradual recovery and a period of relatively normal functioning may

occur. The general pattern of the disease in the first five years after diagnosis usually predicts its subsequent course. Recurrence of psychosis is associated with further destruction of the underlying function of the disease. Positive symptoms diminish over time, but socially debilitating negative symptoms may intensify. 20 to 30% of patients can lead a normal life. About 20 to 30 percent will still have moderate symptoms, and 40 to 60 percent will have a life of aimlessness, inactivity, frequent hospitalizations, poverty, and homelessness. Some factors such as male gender, onset of the disease at a young age, the presence of negative symptoms, being single, and the long duration of the disease cause the prognosis to worsen [22].

### *Treatment*

Schizophrenia is a complex and multifactorial disorder. Therefore, a single treatment is not enough for this disorder. Although antipsychotic drugs are essential tools in the treatment of schizophrenia, psychosocial interventions enhance clinical recovery. Most patients with schizophrenia receive positive results from combination therapies with antipsychotic drugs and psychosocial methods [26].

### *Psychosocial therapies*

These types of treatment can consist of the following cases: a) developing social skills; b) family-oriented therapies; c) group therapy; d) cognitive behavioral therapy; e) individual psychotherapy; f) residential treatments and housing programs; and g) occupational therapy.

### *Biologic therapies*

In his work, Carplin (2012) paid special attention to the negative symptoms of the disease and considered it morphologically different from other symptoms. Considering that the elimination of negative symptoms causes a return to individual function led to the beginning of NIMH studies in this field and a multifaceted approach to the treatment of the disease. Drugs originally used to treat the disease generally had a positive effect on the disease, and the negative symptoms remained untreated.

In 1950, chlorpromarin was the first drug to be introduced as an antipsychotic drug, and other drugs were introduced as standard or first-generation drugs. All of these drugs had a positive effect on the symptoms of the disease and in turn they caused negative symptoms. With the exception of clozapine, which in addition to positive symptoms also had negative effects and is also effective in Refractory Schizophrenia and the treatment of Tardive Dyskinesia [26]. With the discovery of chlorpromazine, dopamine receptor antagonists entered the field of treatment as the most effective drug treatment for schizophrenia. It acted on various cholinergic, aminergic, and histaminergic receptors, causing many side effects. In addition, due to the fact that their antipsychotic effects seemed to be due to the D2 receptor effect, this group of drugs also increased the incidence of extra-pyramidal effects. Complications include Parkinsonism, dystonia, acacia, and late dyskinesia [26].

The effect of dopamine antagonist drugs on psychotic symptoms strengthened the hypothesis of dopamine system hyperactivity in the pathophysiology of schizophrenia. Although the improvement in the positive symptoms of schizophrenia with these drugs is significant, they have not been very successful in improving the negative symptoms and cognitive deficits. These points led to the production of judges with more (efficacy), especially on negative symptoms, cognitive defects and fewer complications. Based on this and according to the serotonin hypothesis of schizophrenia in the nineties, serotonergic-dopaminergic antagonists were launched [27].

Imaging studies have shown that these drugs are involved in rapid structural changes, neuroplasticity, and remodeling, and are effective in the prognosis of the disease, and in fact cause dynamic changes in the brain. It was observed that at the onset of schizophrenia, the rate of reduction of brain tissue averages 0.5% / years compared with 0.2% in normal population, and this decreased brain rate is proportional to the prognosis of the disease.

Some studies have also shown the superiority of the effect on brain structure in the group of atypical antipsychotic drugs over the typical type [27].

## Conclusion

Schizophrenia is a serious disorder of the brain that affects a person's way of thinking, acting, expressing emotions, and understanding a person's reality. Schizophrenia has complex manifestations with several causes. Despite advances in neuroscience, it has identified patterns for key circuits, particularly the frontal, temporal, and mesothelial brain regions, in the development of positive, negative, and cognitive symptoms. Current drug therapies work by the same mechanism as blocking dopamine D2 receptors, which contribute to their harmful effects.

The Vulnerability-Stress-Inflammation model may help explain the role of inflammation in schizophrenia because stress can increase proinflammatory cytokines and may even contribute to a chronic proinflammatory condition. Common dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission changes described in schizophrenia have also been found in low-grade neuritis and may therefore be a major contributor to schizophrenia symptoms. Further support for the association of a low-level neurological inflammatory process in schizophrenia with decreased central nervous system volume and microglia activation has been shown in neuroimaging studies. Many bio-genetic studies emphasize the role of signaling pathways in neuronal growth and development as well as in mental illness.

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