Chapter 1: Introduction-Understanding the Psychiatric Disorder
1) Chapter 1: Introduction—Understanding the Psychiatric Disorder

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1. INTRODUCTION

1.1 PSYCHIATRIC DISORDER

Psychiatric disorder occurs due to chemical and neurohumoral imbalance or genetic factor. In current scenario psychiatric occurrence of diseases increased due to change in lifestyle, increase in stress, violence, terrorism, disturbed family and social relations. Psychiatric illness affect nation in form of morbidity, mortality and economics. Diagnosis of psychiatric disorder is based on recognized pattern of symptoms.¹

World Health Organization (WHO) estimated about 450 million people worldwide currently suffer from some form of mental or behavioral disorders.² One in four people might have suffered from mental illness at some time in life, according to a report from the WHO. Cases of disorder were rated as mild (prevalence of 1.8%-9.7%), moderate (prevalence of 0.5%-9.4%) and serious (prevalence of 0.4%-7.7%).³

WHO in “2001”, stated that 33% of the Years Lived with Disability (YLD) are due to neuropsychiatric disorders, unipolar depressive disorder alone lead to 12-13% of YLD and rank as third leading contributor to the global burden of disease. Four of the six leading causes of YLD are due to neuropsychiatry disorder like: depression, alcohol use, schizophrenia and bipolar disorder.⁴

Large scale surveys replicated and updated between 2000 and 2003 indicated prevalence of anxiety disorder (28.8%), mood disorder (20.8%), impulse control disorder (24.8%) or substance use disorder (14.6%).⁵

A 2004 cross-european study found that approximately one in four people reported meeting criteria at some point in their life for one of the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) assessed, which included mood disorders (13.9%), anxiety disorders (13.6%) or alcohol disorder (5.2%). Approximately one in ten met criteria within a 12-month period. Women and younger people of either gender showed more cases of disorder.⁶
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A 2005 review of prior surveys in 46 countries on the prevalence of schizophrenic disorders, including a prior 10-country WHO survey, found an average (median) figure of 0.4% for lifetime prevalence up to the point of assessment and 0.3% in the 12-month period prior to assessment. A related figure not given in other studies (known as lifetime morbid risk), reported to be an accurate statement of how many people would theoretically develop schizophrenia at any point in life regardless of time of assessment, was found to be “about seven to eight individuals per 1000” (0.7/0.8%). The prevalence of schizophrenia was consistently lower in poorer countries than in richer countries (though not the incidence) but the prevalence did not differ between urban/rural areas or men/women.\(^7\)

Mental health might not be on the priority list of public health practitioners in India, but an analysis of government data shows that around 20 per cent of all patients seen by primary healthcare doctors in India have one or more mental disorders. The findings show that one in four families is likely to have at least one member with a behavioural or mental disorder.

These disorders account for 10.5 per cent of the global burden of disease in 1990. This burden increased to 12 per cent in 2000 and an analysis of trends in the World Health Report—2001 indicates this burden will increase to 15 per cent by 2020.

According to the National Family Health survey, in India, at a given point of time, nearly 15 million people suffer from serious psychiatric illness and another 30 million from mild to moderate psychiatric problems.\(^8\)

1.1.1 Common Characteristics:

The major symptom of psychiatric disorder is psychosis, or delusions and hallucinations. Delusions are false beliefs that significantly hinder a person’s ability to function. For example, believing that people are trying to hurt you when there is no evidence of this, or believing that you are somebody else, such as Jesus Christ or Cleopatra. Hallucinations are false perceptions. They can be visual (seeing things that aren’t there), auditory (hearing), olfactory (smelling), tactile (feeling sensations
on your skin that aren't really there, such as the feeling of bugs crawling on you), or
taste.

1.2 PSYCHOSIS

1.2.1 History:

The word psychosis was first used by Ernst von Feuchtersleben in 1845\textsuperscript{110} as an
alternative to insanity and mania and stems from the Greek word (psychosis), "a
giving soul or life to, animating, quickening" and that from psyche, "soul" and the
suffix osis, in this case "abnormal condition".\textsuperscript{111,112} The word was used to distinguish
disorders which were thought to be disorders of the mind, as opposed to "neurosis",
which was thought to stem from a disorder of the nervous system.

The division of the major psychoses into manic depressive illness (now called bipolar
disorder) and dementia praecox (now called schizophrenia) was made by Emil
Kraepelin, who attempted to create various mental disorders identified by 19th
century psychiatrists, by grouping diseases together based on classification of
common symptoms. Kraepelin used the term 'manic depressive insanity' to describe
the whole spectrum of mood disorders, in a far wider sense than it is usually used
today. In Kraepelin's classification this would include 'unipolar' clinical depression, as
well as bipolar disorder and other mood disorders such as cyclothymia. These are
characterized by problems with mood control and the psychotic episodes appear
associated with disturbances in mood, and patients will often have periods of normal
functioning between psychotic episodes even without medication. Schizophrenia is
characterized by psychotic episodes which appear to be unrelated to disturbances in
mood, and most non-medicated patients will show signs of disturbance between
psychotic episodes.

During the 1960s and 1970s, psychosis was of particular interest to counter culture
critics of mainstream psychiatric practice, who argued that it may simply be another
way of constructing reality and is not necessarily a sign of illness. For example, R. D.
Laing argued that psychosis is a symbolic way of expressing concerns in situations
where such views may be unwelcome or uncomfortable to the recipients. He went on
to say that psychosis could be also seen as a transcendental experience with healing and spiritual aspects. Thomas Szasz focused on the social implications of labeling people as psychotic; a label he argues unjustly medicalises different views of reality so such unorthodox people can be controlled by society. Psychoanalysis has a detailed account of psychosis which differs markedly from that of psychiatry. Freud and Lacan outlined their perspective on the structure of psychosis in a number of works.

Since the 1970s, the introduction of a Recovery approach to mental health, which has been driven mainly by people who have experienced psychosis (or whatever name is used to describe their experiences), has led to a greater awareness that mental illness is not a lifelong disability, and that there is an expectation that recovery is possible, and probable with effective support.

1.2.2 Definition

**Psychosis** is a generic psychiatric term for a mental state often described as involving a “loss of contact with reality”. People suffering from this is said to be psychotic.\(^9\) Psychosis is not pathognomic (a sign or symptom specific to a disease or condition) of psychiatric illness. It is a nonspecific cluster of sign and symptom that may occur in a broad array of medical, neurological and surgical disorder or as consequence of pharmacological treatment, substance abuse or the withdrawal of drug and alcohol.\(^10\)

Psychosis appears as a symptom of a number of mental disorders, including mood and personality disorders, schizophrenia, delusional disorder and substance abuse. It is also the defining feature of the psychotic disorders (i.e., brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, and substance-induced psychotic disorder).

Patients suffering from psychosis are unable to distinguish the real from the unreal. They experience hallucinations and/or delusions that they believe are real, and they typically behave in an inappropriate and confused manner\(^11\).
The cause of this disorder is typically an extremely stressful event or trauma. Presence of psychotic symptoms (delusions, hallucinations, disorganized speech, and/or disorganized behavior) which lasts at least one day but not more than one month\textsuperscript{12}.

1.2.3 Type of psychosis\textsuperscript{13}

In medical practice today, a descriptive approach to psychosis (and to all mental illness) is used, based on behavioral and clinical observations. This approach is adopted in the standard guide to psychiatric diagnoses employed in the United States, the Diagnostic and Statistical Manual of Mental Disorders (DSM). Since the DSM provides a widely-used standard of reference.

The DSM-IV-TR lists 9 formal psychotic disorders, but many other disorders may have psychotic symptoms. The formal psychotic disorders are:

I. Schizophrenia

About one percent of the U.S. population has schizophrenia. Schizophrenia is a disease of disorganization of social and psychological function, including social withdrawal and eccentric behavior. The psychosis experienced in schizophrenia can take many forms. Commonly, a person with the disease will hear voices that offer a running commentary of their activities. In more extreme, cases these voices can be damaging and very frightening. People with schizophrenia can also experience extreme paranoia which may cause a person to seclude themselves to avoid others from ‘spying’ on them. The paranoia a person with schizophrenia experiences can also make a person to believe that they have a tracking device within their own body and lead them to try to remove it, often with disastrous medical consequences.

II. Schizoaffective disorder

The term schizoaffective implies a combination of schizophrenia and an affective (or mood) disorder, which is actually quite accurate. The psychotic (or schizophrenic like symptoms) must be present without any disturbance in mood for a minimum of two weeks.
III. Schizophreniform disorder

It is characterized by the presence of symptoms of schizophrenia. These include: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms. The disorder - including its prodromal, active, and residual phases - lasts longer than 1 month but less than 6 months.

IV. Brief psychotic disorder

Brief psychotic disorder is a period of psychosis whose duration is generally shorter, none re-occurring, and not better accounted for by another condition. The disorder is characterized by a sudden onset of psychotic symptoms, which may include delusions, hallucinations, disorganized speech or behavior, or catatonic behavior. The symptoms must not be better accounted for by schizophrenia, schizoaffective disorder, delusional disorder or mania in bipolar disorder. They must also not be caused by a drug (such as LSD) or medical condition (such as a brain tumor).

V. Delusional

A delusion is commonly defined as a fixed false belief and is used in everyday language to describe a belief that is false, fanciful or derived from deception. In psychiatry, the definition is necessarily more precise and implies that the belief is pathological (the result of an illness or illness process). As a pathology it is distinct from a belief based on false or incomplete information or certain effects of perception which would more properly be termed an apperception or illusion.

VI. Shared psychotic disorder

Also referred to as ‘Folle a` Deux,’ the cause is not well understood. Primary symptoms are delusions such as in delusional disorder which are similar in content to those of an individual who already has an established delusion.
VII. **Substance induced psychosis**

Substance abuse is one of the most common causes of psychosis. Combining alcohol and drug such as a barbiturate may fatal. Inappropriate use of medication can cause brain damage so severe that the person is left in permanent “vegetative” coma.

Some of the most frightening and disorienting mental reaction can come from ingestion of hallucinogenic drug: lysergic acid diethylamide (LSD), mescaline, psilocybin or phencyclidine (PCP, called “angle dust”), and occasionally marijuana or hashish. The consequence include panic and anxiety, fear of “losing your mind,” disorientation, delusions, illusion and hallucination.

VIII. **Mania**

Sometime, but not always, alternating with periods of depression, mania includes episode of mood elevation. During a episode, a person will be excessively optimistic, may show increase energy, have excessive drug and alcohol use, have lessened for may be excessively talkative, and show poor judgment or lack of common sense to the point of making dangerous or unusual decision.

IX. **Organic brain disorder**

One of the most common sign of organic brain disorder is delirium. Specifically, delirium involve disturbance of attention, memory and orientation. A demented person is usually disoriented in term of time and space and has incoherent thought and speech.

1.2.4 **Difference between Psychosis and Schizophrenia**

It is valuable to understand the difference between psychosis and schizophrenia. Psychosis is a general term used to describe psychotic symptoms while schizophrenia is a kind of psychosis. Several different brain disorders can lead to psychotic symptoms, including lesions in the brain resulting from head traumas, strokes, tumors, infections or the use of illegal drugs. If a serious depression goes untreated for a long time, psychotic symptoms may develop. These examples
demonstrate that not all psychosis is schizophrenia. If is for this reason that doctors may take quite some time (6 months or more) to diagnose someone, because while the symptoms of schizophrenia are quite obvious - the fact that the symptoms are not being caused by some other brain disorder is frequently not obvious.

Psychosis is merely a symptom of schizophrenia, but it can appear in other conditions such as severe depression or bipolar disorder. People who are otherwise mentally healthy can also experience psychosis due to extreme stress or insomnia. If you are prescribed anti-psychotic medication, it does not mean you have schizophrenia, it doesn't even have to mean you're psychotic!

Schizophrenia is a specific form of psychosis. Psychosis is a general term for a group of psychiatric and medical conditions that involve certain symptoms, usually delusions and hallucinations. Lots of illnesses can involve psychotic symptoms. Not only schizophrenia but severe mood disorders, schizoaffective disorder, delusional disorder, delirium, dementia, substance intoxications and withdrawals, neurological disorders, metabolic disorders and several others. The antipsychotic drugs reduce or eliminate symptoms such as delusions, hallucinations, disorganized thinking, incoherent speech and grossly bizarre behavior that are common in not only schizophrenia but many other psychoses.

1.3 SCHIZOPHRENIA

1.3.1 History

Descriptions of schizophrenia like symptoms date back to circa 2000BC in the book of heart part of the ancient Egyptian Ebers Papyrus. However, study of the ancient Greek and Roman literature shows that although the general population probably had an awareness of psychotic disorders, there was no recorded condition that would meet the modern criteria for schizophrenia. Symptoms resembling schizophrenia were, however, reported in Arabic medical and psychological literature during the middle ages. In the Canon of Medicine, for example, Avicenna described a condition
somewhat resembling schizophrenia which he called (severe madness), which he distinguished from other forms of madness such as mania and manic depressive psychosis.一名

Although a broad concept of madness has existed for thousands of years, however the disease was first identified as a discrete mental illness by Dr. Emile Kraepelin in the 1887 and the illness itself is generally believed to have accompanied mankind through its history. He was the first to make a distinction in the psychotic disorders between what he called dementia praecox (early dementia, a term first used by psychiatrist Benedicts Morel [1809-1873]) and manic depression. Kraepelin believed that dementia praecox was primarily a disease of the brain, and particularly a form of dementia, distinguished from other forms of dementia, such as Alzheimer's disease, which typically occur later in life.

The word schizophrenia; which translates roughly as "splitting of the mind" and comes from the Greek root schiz ein ("to split") and phren - ("mind") - was coined by Eugen Bleuler in 1908 and was intended to describe the separation of function between personality, thinking, memory, and perception. Bleuler described the main symptoms as 4 A's: flattened Affect, Autism, impaired Association of ideas and Ambivalence. Bleuler realized that the illness was not a dementia as some of his patients improved rather than deteriorated and hence proposed the term schizophrenia instead.

The term schizophrenia is commonly misunderstood to mean that affected persons have a "split personality". Although some people diagnosed with schizophrenia may hear voices and may experience the voices as distinct personalities, schizophrenia does not involve a person changing among distinct multiple personalities. The confusion arises in part due to the meaning of Bleuler's term schizophrenia (literally "split" or "shattered mind"). The first known misuse of the term to mean "split personality" was in an article by the poet T. S. Eliot in 1933.

Different countries followed different definitions of schizophrenia, and duration and mode of onset were considered to be better. Diagnostic aids than the symptoms of
acute illness. Now it is almost agreed by various defining institutions that duration of symptoms must be at least for one month.

1.3.2 Definition

Schizophrenia, from the Greek roots schiz ein (“to split”) and phren (“mind”), is a psychiatric diagnosis that describes a mental illness characterized by psychosis (loss of contact with reality), hallucinations (false perceptions), delusions (false beliefs), disorganized speech and behavior, flattened affect (restricted range of emotions), cognitive deficits (impaired reasoning and problem solving), and occupational and social dysfunction. Onset of symptoms typically occurs in young adulthood, with approximately 0.4–0.6% of the population affected. Diagnosis is based on the patient's self-reported experiences and observed behavior. No laboratory test for schizophrenia exists.

1.3.3 Epidemiology of schizophrenia

Schizophrenia occurs equally in males and females although typically appears earlier in men with the peak ages of onset being 20–28 years for males and 26–32 years for females. Much rare are instances of childhood-onset and late (middle age) or very-late-onset (old age) schizophrenia. The lifetime prevalence of schizophrenia, that is, the proportion of individuals expected to experience the disease at any time in their lives, is commonly given at 1%. Systematic review of many studies in 2002, found a lifetime prevalence of 0.55%. Despite the received wisdom that schizophrenia occurs at similar rates throughout the world, its prevalence varies across the world, within countries, and at the local and neighborhood level. One particularly stable and replicable finding has been the association between living in an urban environment and schizophrenia diagnosis, even after factors such as drug use, ethnic group and size of social group have been controlled for. Schizophrenia is known to be a major cause of disability. In a 1999 study of 14 countries, active psychosis was ranked the third-most-disabling condition, after quadriplegia and dementia and before paraplegia and blindness.
The Prevalence Rate for schizophrenia is approximately 1.1% of the population over the age of 18 (source: NIMH) or, in other words, at any one time as many as 51 million people worldwide suffer from schizophrenia, including:

- 6 to 12 million people in China (a rough estimate based on the population)
- 4.3 to 8.7 million people in India (a rough estimate based on the population)
- 2.2 million people in USA
- 285,000 people in Australia
- Over 280,000 people in Canada
- Over 250,000 diagnosed cases in Britain

![Relative Prevalence of Schizophrenia](image)

**Figure 1: Prevalence of schizophrenia compared to other well-known diseases**

[Note: The term 'prevalence' of Schizophrenia usually refers to the estimated population of people who are living with Schizophrenia at any given time. The term 'incidence' of Schizophrenia refers to the annual diagnosis rate, or the number of new cases of Schizophrenia diagnosed each year.]
1.3.4 Types of schizophrenia

Psychiatric disorder today recognizes six subtype of schizophrenia:

(1) Paranoid Schizophrenia

(2) Disorganized Schizophrenia

(3) Catatonic Schizophrenia

(4) Residual Schizophrenia

(5) Schizoaffective Schizophrenia

(6) Undifferentiated Schizophrenia

(1) **Paranoid Schizophrenia**: Paranoid schizophrenia is the most common type of schizophrenia in most parts of the world. The clinical picture is dominated by relatively stable, often paranoid, delusions, usually accompanied by hallucinations, particularly of the auditory variety, and perceptual disturbances. Disturbances of affect, volition, and speech, and catatonic symptoms, are not prominent.

(2) **Disorganized Schizophrenia**: (Hebephrenic Schizophrenia) In this case the person is verbally incoherent and may have moods and emotions that are not appropriate to the situation. Hallucinations are not usually present. People with disorganized schizophrenia display disorganized thinking, grossly disorganized behavior, and absent or inappropriate emotional expression. The disease significantly disrupts a person’s ability to function in regular daily activities and interactions with other people.

(3) **Catatonic Schizophrenia**: In this case, the person is extremely withdrawn, negative and isolated, and has marked psychomotor disturbances. People with catatonic schizophrenia display extreme inactivity or activity that’s disconnected from their environment or encounters with other people (catatonic behavior). These episodes can last for only minutes or up to hours.
(4) **Residual Schizophrenia**: In this case the person is not currently suffering from delusions, hallucinations, or disorganized speech and behavior, but lacks motivation and interest in day-to-day living.

(5) **Schizoaffective Disorder**: These people have symptoms of schizophrenia as well as mood disorder such as major depression, bipolar mania, or mixed mania. There are two types of schizoaffective disorder: the bipolar type and the depressive type. In general, schizoaffective disorder bipolar type has a better prognosis than the depressive type, which can result in a residual defect with the passing of time.

(6) **Undifferentiated Schizophrenia**: Conditions meeting the general diagnostic criteria for schizophrenia but not conforming to any of the above subtypes, or exhibiting the features of more than one of them without a clear predominance of a particular set of diagnostic characteristics.

### 1.3.5 Schneiderian classification

The psychiatrist Kurt Schneider (1887–1967) listed the forms of psychotic symptoms that he thought distinguished schizophrenia from other psychotic disorders. These are called Schneider's first-rank symptoms, and they include delusions of being controlled by an external force; the belief that thoughts are being inserted into or withdrawn from one's conscious mind; the belief that one's thoughts are being broadcast to other people; and hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices. The reliability of first-rank symptoms has been questioned, although they have contributed to the current diagnostic criteria.

- Hallucinations
  - Audible thoughts,
  - Voice heard arguing,
  - Voice commenting on one’s action
- Delusional perception
- Thought alienation phenomena
1. Thought withdrawal
2. Thought insertion
3. Thought diffusion

1.3.6 Stages of Schizophrenia

There are three phases of schizophrenia: prodromal (or beginning), active, and residual. They tend to occur in sequence and appear in cycles throughout the course of the illness.

**Prodromal phase**

When symptoms develop gradually, people may begin to lose interest in their usual pursuits and get withdrawn from friends and family members. They may easily become confused, have trouble concentrating, and feel listless and apathetic, preferring to spend most of their days alone. They may also become intensely preoccupied with religion or philosophy. Family and friends may be upset with this behavior, believing the person is lazy rather than ill. Occasionally, these symptoms reach a plateau and do not develop further but, in most cases, an active phase of the illness follows. The prodromal period can last weeks or months.

Although the symptoms described above are typical of the prodromal phase of schizophrenia, they may also be due to other causes. If these symptoms are present, they should be discussed with a doctor.

**Active phase**

During the active phase of the illness, psychotic symptoms such as delusions, odd behavior and hallucinations are prominent and are often accompanied by strong affect such as distress, anxiety, depression, and fear. If untreated, the active phase may resolve spontaneously or may continue indefinitely. With appropriate treatment (preliminary medication) the active phase is usually able to be brought under control. It is during the active phase that most individuals present for treatment, whether it is their first presentation or an exacerbation of their symptoms.
Residual phase

The active phase of the illness is usually followed by a residual phase. The residual phase is similar to the Prodromal phase although during the residual phase blunted affect and impairment in role functioning are more common. While psychotic symptoms may persist into the residual phase, the psychotic symptoms are less likely to be accompanied by such strong affect as experienced during the active phase. There is great variation in the severity of the residual phase from one person to the next. Some individuals will function extremely well while others may be considerably more impaired.

The most common course of the disorder generally involves numerous active phases of illness with residual phases of impairment between episodes. The extent of residual impairment often increases between episodes during the initial years of the disorder although may possibly become less severe during the later phases of the illness.

1.3.7 Cause of Schizophrenia

Data from a Position Emission Tomography (PET) study suggests that the less the frontal lobes are activated during a working memory task, the greater the increase in abnormal dopamine activity in the striatum, thought to be related to the neurocognitive deficits in schizophrenia.

While the reliability of the diagnosis introduces difficulties in measuring the relative effect of genes and environment (for example, symptoms overlap to some extent with severe bipolar disorder or major depression), evidence suggests that genetic and environmental factors can act in combination to result in schizophrenia. Evidence suggests that the diagnosis of schizophrenia has a significant heritable component but that onset is significantly influenced by environmental factors or stressors. The idea of an inherent vulnerability (or diathesis) in some people, which can be unmasked by biological, psychological or environmental stressors, is known as the stress-diathesis model. The idea that biological, psychological and social factors are all important is known as the "biopsychosocial" model.
Figure 2: The Path to Schizophrenia

[The diagram above shows how biological, genetic and prenatal factors are believed to create a vulnerability to schizophrenia. Additional environmental exposures (for example, frequent or ongoing social stress and/or isolation during childhood, drug abuse, etc.) then further increase the risk or trigger the onset of psychosis and schizophrenia. Early signs of schizophrenia risk include neurocognitive impairments, social anxiety (shyness) and isolation and "odd ideas". (Note: "abuse of DA drugs" refers to dopamine affecting (DA) drugs).]

- Genetic

Estimates of the heritability of schizophrenia tend to vary owing to the difficulty of separating the effects of genetics and the environment although twin studies have suggested a high level of heritability.\textsuperscript{42} It is likely that schizophrenia is a condition of complex inheritance, with several genes possibly interacting to generate risk for schizophrenia or the separate components that can co-occur leading to a diagnosis.\textsuperscript{43} Genetic studies have suggested that genes that raise the risk for developing schizophrenia are non-specific, and may also raise the risk of developing other psychotic disorders such as bipolar disorder.\textsuperscript{44} Recent research has suggested that rare deletions or duplications of tiny DNA sequences within genes (known as copy number variants) are also linked to increased risk for schizophrenia.\textsuperscript{45}
Chapter 1  Introduction-Understanding the Psychiatric Disorder

- **Prenatal**

It is thought that causal factors can initially come together in early neurodevelopment, including during pregnancy, to increase the risk of later developing schizophrenia. One curious finding is that people diagnosed with schizophrenia are more likely to have been born in winter or spring, (at least in the northern hemisphere). There is now evidence that prenatal exposure to infections increases the risk for developing schizophrenia later in life, providing additional evidence for a link between in utero developmental pathology and risk of developing the condition.47

- **Social**

Living in an urban environment has been consistently found to be a risk factor for schizophrenia. Social disadvantage has been found to be a risk factor, including poverty and migration related to social adversity, racial discrimination, family dysfunction, unemployment or poor housing conditions. Childhood experiences of abuse or trauma have also been implicated as risk factors for a diagnosis of schizophrenia later in life. Parenting is not held responsible for schizophrenia but unsupportive dysfunctional relationships may contribute to an increased risk.50

- **Substance use**

The relationship between schizophrenia and drug use is complex, meaning that a clear causal connection between drugs use and schizophrenia has been difficult to distinguish. There is strong evidence that using certain drugs can trigger either the onset or relapse of schizophrenia in some people. It may also be the case, however, that people with schizophrenia use drugs to overcome negative feelings associated with both the commonly prescribed antipsychotic medication and the condition itself, where negative emotion, paranoia and anhedonia are all considered to be core features. Amphetamines trigger the release of dopamine and excessive dopamine function is believed to be responsible for many symptoms of schizophrenia (known as the dopamine hypothesis of schizophrenia), amphetamines may worsen schizophrenia symptoms. Schizophrenia can be triggered by heavy use of hallucinogenic or stimulant drugs. One study suggests that cannabis use can
contribute to psychosis, though the researchers suspected cannabis use was only a small component in a broad range of factors that can cause psychosis.\textsuperscript{54}

- \textbf{Psychological}

A number of psychological mechanisms have been implicated in the development and maintenance of schizophrenia. Cognitive biases that have been identified in those with a diagnosis or those at risk, especially when under stress or in confusing situations, include excessive attention to potential threats, jumping to conclusions, making external attributions, impaired reasoning about social situations and mental states, difficulty distinguishing inner speech from speech from an external source, and difficulties with early visual processing and maintaining concentration. Some cognitive features may reflect global neurocognitive deficits in memory, attention, problem-solving, executive function or social cognition, while others may be related to particular issues and experiences.\textsuperscript{55} Despite a common appearance of "blunted affect", recent findings indicate that many individuals diagnosed with schizophrenia are highly emotionally responsive, particularly to stressful or negative stimuli, and that such sensitivity may cause vulnerability to symptoms or to the disorder. Some evidence suggests that the content of delusional beliefs and psychotic experiences can reflect emotional causes of the disorder, and that how a person interprets such experiences can influence symptomology. Further evidence for the role of psychological mechanisms comes from the effects of therapies on symptoms of schizophrenia.\textsuperscript{56}

- \textbf{Neural}

Functional magnetic resonance imaging (FMRI) and other brain imaging technologies allow for the study of differences in brain activity among people diagnosed with schizophrenia.

Studies using neuropsychological tests and brain imaging technologies such as FMRI and PET to examine functional differences in brain activity have shown that differences seem to commonly occur in the frontal lobes, hippocampus, and temporal lobes.\textsuperscript{57} These differences have been linked to the neurocognitive deficits often
associated with schizophrenia. The role of antipsychotic medication, which nearly all those studied had taken, in causing such abnormalities is also unclear.58

Particular focus has been placed upon the function of dopamine in the mesolimbic pathway of the brain. This focus largely resulted from the accidental finding that a drug group which blocks dopamine function, known as the phenothiazines, could reduce psychotic symptoms. An influential theory, known as the dopamine hypothesis of schizophrenia, proposed that a malfunction involving dopamine pathways was the cause of (the positive symptoms of) schizophrenia. This theory is now thought to be overly simplistic as a complete explanation, partly because newer antipsychotic medication (called atypical antipsychotic medication) can be equally effective as older medication (called typical antipsychotic medication), but also affects serotonin function and may have slightly less of a dopamine blocking effect.59

Interest has also focused on the neurotransmitter glutamate and the reduced function of the N-methyl-D-aspartate (NMDA) glutamate receptor in schizophrenia. This has largely been suggested by abnormally low levels of glutamate receptors found in postmortem brains of people previously diagnosed with schizophrenia60 and the discovery that the glutamate blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition.61 The fact that reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function and that glutamate can affect dopamine function, all of which have been implicated in schizophrenia, have suggested an important mediating (and possibly causal) role of glutamate pathways in schizophrenia.62 Further support of this theory has come from preliminary trials suggesting the efficacy of coagonists at the NMDA receptor complex in reducing some of the positive symptoms of schizophrenia.63

There have also been findings of differences in the size and structure of certain brain areas in schizophrenia, starting with the discovery of ventricular enlargement in those for whom negative symptoms were most prominent.64 However; this has not proven particularly reliable on the level of the individual person, with considerable variation between patients. More recent studies have shown various differences in brain structure between people with and without diagnoses of schizophrenia.65 while brain
structure changes have been found in people diagnosed with schizophrenia who have never been treated with antipsychotic drugs there is evidence that the medication itself might cause additional changes in the brain's structure. However, as with earlier studies, many of these differences are only reliably detected when comparing groups of people, and are unlikely to predict any differences in brain structure of an individual person with schizophrenia.

1.3.8 Diagnosis of Schizophrenia

Diagnosis is based on the self-reported experiences of the person as well as abnormalities in behavior reported by family members, friends or co-workers, followed by secondary signs observed by a psychiatrist, social worker, clinical psychologist or other clinician in a clinical assessment. There is a list of criteria that must be met for someone to be so diagnosed. These depend on both the presence and duration of certain signs and symptoms.¹⁰

The most widely used criteria for diagnosing schizophrenia are from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) the current version being DSM-IV-TR, and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems currently the ICD-10.

DSM IV-TR Criteria

Psychiatric Diagnoses are categorized by the Diagnostic and Statistical Manual of Mental Disorders, Better known as the DSM-IV, the manual is published by the American Psychiatric Association and covers all mental health disorders for both children and adults. It also lists known causes of these disorders, statistics in terms of gender, age at onset, and prognosis as well as some research concerning the optimal treatment approaches. No single symptom is definitive for diagnosis; rather, the diagnosis encompasses a pattern of signs and symptoms, in conjunction with impaired occupational or social functioning.

To be diagnosed with schizophrenia, a person must display ⁹
(1) **Characteristic symptoms:** Two or more of the following, each present for a significant portion of time during a one-month period (or less, if successfully treated)

- Delusions
- Hallucinations
- Disorganized speech (e.g., frequent derailment or incoherence; speaking in abstracts).
- Grossly disorganized behavior (e.g., dressing inappropriately, crying frequently) or catatonic behavior
- Negative symptoms, i.e., affective flattening (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation).

Only one of these symptoms is required if delusions are bizarre or hallucinations consist of hearing one voice participating in a running commentary of the patient's actions or of hearing two or more voices conversing with each other.

(2) **Social/occupational dysfunction:** For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.

(3) **Duration:** Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if successfully treated). Additional criteria are also given that exclude the diagnosis; thus schizophrenia cannot be diagnosed if symptoms of mood disorder or pervasive developmental disorder are present, or the symptoms are the direct result of a substance (e.g., abuse of a drug/medication) or a general medical condition.

(4) **Schizoaffective and mood disorder exclusion:** Schizoaffective disorder and mood disorder with psychotic feature have been ruled out because either (1) no major depressive, manic or mixed episode have occurred concurrently with the active phase symptom; or (2) if mood episodes have occurred during active phase
symptoms, their total duration has been brief relative to the duration of active residual period.

(5) **Substance and general medical condition exclusion**: The disturbance is not due to the direct physiological effect of substance (e.g., a drug of abuse and medication) or general medical condition.

(6) **Relationship to a pervasive developmental disorder**: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusion or hallucinations are also present.

1.3.9 **Symptom of schizophrenia**

The symptoms of schizophrenia are divided into three broad categories: (1) Positive symptom, (2) Negatives symptoms and (3) Cognitive symptoms.

**1) Positive symptoms**

a. **Delusions** are firmly held erroneous beliefs due to distortion or exaggeration of reasoning and/or misinterpretation of perception or experiences. Delusion of being followed or watched are common, as are beliefs that comments, radio or TV programmes, etc are directing special messages to him/her.

b. **Hallucination** are distortion or exaggerations of perception in array of the senses, although auditory hallucination (‘hearing voices’ within, distinct from one’s own thought) are the most common, followed by visual hallucination.

c. **Disorganized speech/thinking** also described as “thought disorder” or “loosening of association,” is a key aspect of schizophrenia. Disorganized thinking is usually assessed primarily based on the person’s speech. Therefore, tangential, loosely associated, or incoherent speech severe enough to substantially impair effective communication is used as an indicator of thought disorder by the DSM-IV.

d. **Grossly disorganized behavior** include difficulty in goal directed behavior (leading to difficulties in activities in daily living), unpredictable agitation or
silliness or behaviors that bizarre to on lookers. Their purposelessness distinguishes them from unusual behavior prompted by delusional beliefs.

e. **Catatonic behaviors** are characterized by marked decrease in reaction to the immediate surrounding environment, sometime taking the form of motionless and apparent unawareness, rigid or bizarre postures, or aimless excess motor activity.

f. **Other symptom** sometime present in schizophrenia but not often enough to be definitional alone include affect inappropriate to the situation or stimuli, unusual motor behavior (pacing, rocking), depersonalization, derealization and somatic preoccupation.

(2) **Negative symptoms**

   a. **Affective Flattening** is the reduction in the range and intensity of emotional expression, voice tone, eye contact, and body language.

   b. **Alogia**, or poverty of speech, is the lessening of speech fluency and productivity, thought to reflect slowing or blocked thoughts and manifested as short, empty, replies to question.

   c. **Avolitionis** the reduction, difficulty, or inability to initiate and persist in goal directed behavior, it is often mistaken for apparent disinterest (example of avolition include: no longer interested in going out and meeting with friends, no longer interested in activity that the person use to show enthusiasm for, no longer interested in much of anything, sitting in the house for many hours a day doing nothing).

(3) **Cognitive symptoms**

Cognitive symptom are subtle and are often detected only when neuropsychological test are performed. They include the following:

   a. Poor “executive functioning” (the ability to absorb and interpret information and make decision based on the information)

   b. Inability to sustain attention
c. Problem with “working memory” (the ability to keep recently learned information in mind and use it right away)

1.3.10 Pathophysiology of Schizophrenia

For many years, the science of schizophrenia seemed stuck at the level of neurotransmitters and receptors. Decades of research had apparently proven the singular importance of dopamine and dopamine receptors to the understanding of schizophrenia and its treatment.

Unfortunately, this awareness had brought us only so far in understanding the underlying pathophysiology and the ways in which we could improve outcomes in our patients. While the positive symptoms of schizophrenia, including hallucinations, delusions, and disorganized thinking, were often effectively ameliorated with typical antipsychotics -- with a singular mechanism action of D₂ blockade, the negative and cognitive symptoms were left untouched and understudied. While the Pathophysiology of schizophrenia remains unclear, several neurotransmitter systems have been suggested to be implicated, e.g. dopamine, glutamate and Ach. Among these dopamine system has received most attention. ⁶⁶

1.3.10.1 DOPAMINERGIC SYSTEM

Dopamine, a Neurotransmitter in the Central Nervous System

On the basis of their efferent projections, the dopamine neurons are organized into four subsystems: the nigrostriatal, the mesolimbic, the mesocortical and the tuberoinfundibular dopaminergic systems. The nigrostriatal dopaminergic system originates in the Substantia nigra and projects primarily to the striatum. This system is involved in motor control, and degeneration of this system causes the symptoms of Parkinson’s disease. Accordingly, it is involved in EPS that frequently occur during treatment with typical antipsychotic drugs. Both the mesolimbic and the mesocortical systems originate in the Ventral tegmental area. The mesolimbic dopaminergic
system projects to the nucleus accumbens (NAC), the nuclei of the stria terminalis, parts of the amygdale and the hippocampus, the lateral septal nuclei, the cingulate and the entorhinal cortices. This system plays a role in emotional control, motivation and reward. The mesocortical dopaminergic system projects to the neocortex, and most densely to the prefrontal cortex. The prefrontal cortex is generally involved in executive planning; temporal organization of behavior, attention and social behaviors, and the prefrontal dopaminergic system may be importantly involved in the negative symptoms and cognitive deficits in schizophrenia. Finally, the tuberoinfundibular dopaminergic system originates in the arcuate nucleus of the hypothalamus and projects to the pituitary stalk. This system is involved in endocrine control. Many antipsychotic drugs may also modulate this system, causing an increased prolactin secretion, which results in side-effects such as gynaecomastia, galactorrhoea, sexual dysfunction, infertility and amenorrhoea. The midbrain dopamine neurons located in SN and VTA, i.e. the origin of the nigrostriatal, the mesolimbic and the mesocortical systems, receive noradrenergic, serotonergic, cholinergic, glutamatergic and γ-aminobutyric acid (GABA)-ergic inputs.

Figure 3: Dopaminergic pathway in brain
1.3.10.1.1 Synthesis and metabolism of dopamine

Dopamine synthesis in the pigmented cells in the substantia nigra and dopamine synthesized from the amino acid tyrosine involves a number of enzymatic reactions.

The two enzymes monoamine oxidase (MAO) and Catechol O- methyltransferase (COMT) convert DA to the 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 3-methoxytyramine (3-MT), which are the main product of the DA metabolism in brain.\textsuperscript{76}

\begin{itemize}
\item [(1)] Conversion of tyrosine to DOPA by tyrosine hydroxylase.
\item [(2)] Conversion of DOPA to DA by L-aromatic amino acid decarboxylase.
\item [(3)] Pooling of DA in a vesicle.
\item [(4)] Exocytosis of a vesicle and DA-release into the synaptic cleft.
\item [(5)] Activation of postsynaptic DA-receptors.
\item [(6)] Activation of DA-autoreceptors.
\item [(7)] Inhibition of tyrosine hydroxylase.
\item [(8)] Reuptake of DA by the DA-transporter.
\item [(9)] Metabolism of DA: conversion to 3-methoxytyramine by COMT.
\item [(10)] Oxidation of MT to homovanillic acid by MAO.
\item [(11)] Mitochondrion.
\item [(12)] Mitochondrial oxidation of DA to DOPAC (dihydroxyphenylacetic acid) by MAO.
\end{itemize}
1.3.10.1.2 Dopamine receptors classification

The application of biochemical, pharmacological and physiological techniques to the study of dopamine receptors showed clearly that there were multiple receptors for dopamine, and in 1978 it was proposed that there were two subtypes of the dopamine receptor (D₁ and D₂). The application of molecular biological techniques in the late 1980s showed that there were at least five dopamine receptor subtypes (D₁, D₂, D₃, D₄ and D₅). On the basis of structural, pharmacological, functional and distributional similarities, all dopamine receptor subtypes fall into one of the two initially recognized receptor categories, here designated dopamine D₁- or dopamine D₂-like receptors. Dopamine D₅ receptors share extensive similarities with dopamine D₁ receptors, while dopamine D₃ and D₄ receptors more closely conform to the features of dopamine D₂ receptors. The properties of the two subfamilies closely resemble those of the dopamine D₁ and D₂ receptor subtypes as originally defined by Kebabian and Calne.⁷⁶

The classical “dopamine hypothesis of schizophrenia” postulates a hyperactivity of dopaminergic transmission at the dopamine D₂ receptor in the mesencephalic projections to the limbic striatum²⁰,²¹. This hypothesis remains the preeminent neurochemical theory, despite several limitations²². The notion was initially supported by a tight correlation between the therapeutic doses of conventional antipsychotic drugs and their affinities for the D₂ receptor²³,²⁴. In addition, indirect dopamine agonists (e.g., L-dopa ¹, cocaine ², and amphetamines ³) can induce psychosis in healthy subjects and at very low doses, provoke psychotic symptoms in schizophrenics²¹. The dopamine hypothesis has received support from postmortem and positron emission tomography (PET) indications of increased dopamine D₂ receptor levels in the brains of schizophrenic patients (Table 2)²⁵. However, it has been suggested that up regulation of D₂ receptor expression may be the result of adaptation to antipsychotic drug treatment rather than a biochemical abnormality intrinsic to schizophrenia. In fact, some PET studies show no significant difference in D₂ receptors densities between neuroleptic schizophrenics and healthy controls²⁶.
There is emerging evidence for a presynaptic dopaminergic abnormality in schizophrenia, implying dysfunction in presynaptic storage, vesicular transport, release, reuptake, and metabolic mechanisms in mesolimbic dopamine systems. It has been further hypothesized that dysregulation and hyper-responsiveness of presynaptic dopamine neurons could lead to lasting consequences through the induction of sensitization and/or oxidative stress. On the contrary, the functional activity of dopamine may be decreased in the neocortex in schizophrenia, which could be, at least partially, associated with negative symptoms (e.g., emotional or cognitive impairment). Whether a dopamine hyper function or hypo function occurs under minimal stress remains an open question.

Direct evidence for a hyperdopaminergic state in schizophrenia has been complicated to demonstrate, given the difficulty of measuring dopamine transmission in the human brain. However, clinical data have revealed an increased striatal dopamine synthesis as well as increased central dopamine release after amphetamine challenge. These findings suggest that psychotic symptoms may indeed be related to enhanced release of subcortical dopamine. Yet, reduced blood flow in the prefrontal cortex has been shown in some patients with schizophrenia and, specifically, that the blood flow is not enhanced during intellectually challenging tasks. The negative symptoms of schizophrenia have been suggested to be correlated to this hypofrontality. In addition, positive symptoms aggravate following administration of drugs that increase dopaminergic transmission, such as amphetamine, whereas negative symptoms may partly improve. Moreover, drugs that block dopamine D2 receptors or dopamine neuronal storage are able to improve positive symptoms but negative symptoms are less responsive and may even worsen. Based on the above findings, the classical dopamine hypothesis has been modified, and a notion of a regional imbalance of central dopamine systems.
has emerged\textsuperscript{39,40}. A modified dopamine hypothesis suggests that hypo- and hyperdopaminergic states may occur in schizophrenic patients in different regions of the brain\textsuperscript{39}. Thus, whereas a hyperdopaminergic state in subcortical regions may trigger positive symptoms, negative symptoms and cognitive impairment may occur as a result of the hypodopaminergic state in cortical regions.

Table 1: Dopamine receptor subtype\textsuperscript{81}

<table>
<thead>
<tr>
<th>Receptor localization</th>
<th>‘D(_1)-like’</th>
<th>‘D(_2)-like’</th>
</tr>
</thead>
<tbody>
<tr>
<td>D(_1)</td>
<td>D(_5)</td>
<td>D(_2)</td>
</tr>
<tr>
<td>caudate/putamen, nucleus accumbens, olfactory tubercle, hypothalamus, thalamus frontal cortex</td>
<td>hippocampus, thalamus, lateral mammillary nucleus, straitum, cerebral cortex</td>
<td>caudate/putamen, nucleus accumbens, olfactory tubercle, cerebral cortex (low)</td>
</tr>
<tr>
<td>Agonist</td>
<td>Dopamine, Apomorphine, Bromocriptine</td>
<td>Dopamine, Apomorphine, Bromocriptine</td>
</tr>
<tr>
<td>Antagonist</td>
<td>Chlorpromazine, Haloperidole, Clozapine</td>
<td>Chlorpromazine, Haloperidole, Spiperone Sulpride, Clozapine</td>
</tr>
<tr>
<td>Response</td>
<td>Adenylyl Cyclase increase</td>
<td>Adenylyl cyclase decrease</td>
</tr>
<tr>
<td>Effect</td>
<td>Mainly postsynaptic inhibition</td>
<td>Pre and postsynaptic inhibition stimulation or inhibition of hormone release</td>
</tr>
</tbody>
</table>
1.3.10.2 THE SEROTONERGIC HYPOTHESIS:

Figure 5: Serotonergic pathways in the human brain

Recent attention has focused on the involvement of serotonin 4 (5-HT) in the Pathophysiology of schizophrenia. The “serotonin hypothesis of schizophrenia” is developed by several observations:

a) Serotonin receptors are involved in the psychotomimetic and psychotogenic properties of hallucinogens [e.g., lysergic acid diethylamide 5 (LSD)];

![Chemical structures of 5-HT](image)

b) The number of cortical 5-HT$_{2A}$ and 5-HT$_{1A}$ receptors is altered in schizophrenic brains (Table 3);
c) 5-HT\textsubscript{2A} and 5-HT\textsubscript{1A} receptors play role in the therapeutic and/or side-effect profiles of atypical antipsychotics;

d) Certain polymorphisms of the 5-HT\textsubscript{2A} receptor gene are associated with schizophrenia;

e) The trophic role of serotonin in neurodevelopment may be assured in schizophrenia;

f) 5-HT\textsubscript{2A} receptor - mediated activation of the prefrontal cortex may be impaired in some schizophrenics;

g) Serotonergic and dopaminergic systems are interdependent and may be simultaneously affected in schizophrenia\textsuperscript{41,42}.

1.3.10.3 GLUTAMATERGIC HYPOTHESIS:\textsuperscript{82}

The existence of anatomical and functional interrelationships between dopamine and glutamate systems in the central nervous system suggests that inhibition of the NMDA-R would influence dopamine neurotransmission\textsuperscript{24,43,44}.
Phencyclidine 6 (PCP) and ketamine 7, both potent non-competitive antagonists of the NMDA subtype of glutamate receptor (NMDA-R), induce schizophrenia-like symptoms in healthy individuals and worsen some symptoms in schizophrenia\textsuperscript{45-50}. Decreased NMDA-R function may thus be a predisposing or causative factor in schizophrenia\textsuperscript{51-53}. One of the features that distinguish NMDA-R antagonists from other psychotogenic drugs such as amphetamine 3 and LSD 5 is the degree to which they produce frontal cognitive deficits that mimic schizophrenia\textsuperscript{54}. In addition, alterations in expression of mRNA for NMDA receptor subunits in the prefrontal cortex of patients with schizophrenia have been reported\textsuperscript{55}. In humans, PET studies of dopamine receptor occupancy after acute administration of ketamine 7 suggest that the NMDA-R antagonists increase dopamine release in the striatum\textsuperscript{56-58}. In contrast, chronic administration of NMDA-R antagonists elicits decreased dopamine release\textsuperscript{56} or hypoactivity of dopamine in the prefrontal cortex\textsuperscript{53}. Kapur and Seeman\textsuperscript{59} have recently reported that both PCP 6 and ketamine 7 have direct effects on D\textsubscript{2} and 5-HT\textsubscript{2} receptors. Schizophrenia has been suggested to be related to a hypoglutamatergic state of the brain.

1.3.10.4 THE GAMMA (γ)-AMINO BUTYRIC ACID (GABA) HYPOTHESIS:

GABA, the major inhibitory transmitter in the CNS, has many effects that are opposite to those of glutamate, some involving direct GABAergic inhibition of glutamate function. Role of GABA in the etiology of schizophrenia was first proposed in the early 1970s based on the GABAergic regulation of DA neuronal function, specifically in the context of the role of GABA in working memory\textsuperscript{60, 61}. Furthermore, GABA
uptake sites were found to be decreased in the hippocampus, amygdala, and left temporal cortex in schizophrenics with evidence of GABA-A receptor up-regulation and decreases in GABA interneuron. Clinical trials with benzodiazepines, GABA-A agonists, the GABA-B agonist 8 (baclofen), and the anticonvulsant (valproic acid 9, the last used as a putative GABAergic agent) used alone and in combination with antipsychotics have led to mixed outcomes. However, a prototypic GABA uptake inhibitor 10 (CI-966) produced psychotic episodes in a small phase I trial producing symptoms similar to that of psychotomimetics. More recently, genetic evidence has implicated alterations in GABAergic function in the etiology of schizophrenia.
### Table 2: Summary of neurochemical findings in schizophrenia

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine</strong></td>
<td></td>
</tr>
<tr>
<td>Striatal D&lt;sub&gt;2&lt;/sub&gt; receptors ↑</td>
<td>++++</td>
</tr>
<tr>
<td>Dopamine content or metabolism ↑</td>
<td>+++</td>
</tr>
<tr>
<td>Amphetamine-stimulated dopamine transmission↑</td>
<td>+++</td>
</tr>
<tr>
<td>Cortical D&lt;sub&gt;1&lt;/sub&gt; receptors ↓</td>
<td>+</td>
</tr>
<tr>
<td>Cortical D&lt;sub&gt;2&lt;/sub&gt; receptors ↑</td>
<td>+</td>
</tr>
<tr>
<td>D&lt;sub&gt;4&lt;/sub&gt; receptors↑</td>
<td>+/-</td>
</tr>
<tr>
<td>Abnormal configuration of D&lt;sub&gt;2&lt;/sub&gt; receptors</td>
<td>+/-</td>
</tr>
<tr>
<td>Altered dopamine receptor–G protein coupling</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Serotonin</strong></td>
<td></td>
</tr>
<tr>
<td>Cortical 5-HT&lt;sub&gt;2A&lt;/sub&gt; receptors ↓</td>
<td>+++</td>
</tr>
<tr>
<td>Cortical 5-HT&lt;sub&gt;1A&lt;/sub&gt; receptors↑</td>
<td>++</td>
</tr>
<tr>
<td>CSF 5-HIAA concentrations related to negative symptoms</td>
<td>+</td>
</tr>
<tr>
<td><strong>Glutamate</strong></td>
<td></td>
</tr>
<tr>
<td>Expression of non-NMDA receptors in the temporal cortex and hippocampus ↓</td>
<td>++</td>
</tr>
<tr>
<td>Cortical expression of some NMDA receptor subunits ↑</td>
<td>++</td>
</tr>
<tr>
<td>Glutamate reuptake in frontal cortex ↑</td>
<td>+</td>
</tr>
<tr>
<td>Cortical glutamate release ↓</td>
<td>+</td>
</tr>
<tr>
<td>Altered concentrations of glutamate and metabolites</td>
<td>+/-</td>
</tr>
</tbody>
</table>

[+/- = weak; + = moderate; ++ = good; +++ = strong; ++++ = very strong shown by metanalysis. ↑ = increase; ↓ = decrease. ° Though much of the increase is due to antipsychotic medication.]
1.3.11 GENETIC ASSOCIATION WITH SCHIZOPHRENIA:

Genome scans, linkage disequilibrium and association studies in brain tissues from schizophrenic populations, have resulted in the identification of a number of vulnerable genes associated with schizophrenia\(^{63-67, 69, 70, 71-73}\). These associations encompass many neurotransmitter systems in the brain including the enzymes involved in their synthesis and degradation, their receptors and uptake transporters, and a number of novel targets.

There has, however, been considerable debate for viability/relevance of many of these genes, the design methodologies used to identify them, and their replication\(^{74}\), with frequent “failures to replicate” the initial finding occurring in subsequent studies. Additionally, considerable caution is required in ensuring that “schizophrenia-associated” gene associations are not the result of clinical misdiagnosis (one key patient cohort reportedly included brain tissue from a 3-year old “schizophrenic”), the effects of the drugs used to treat the condition on gene function, or the potential identification of putative targets involved in the side effects of the drug class. Additionally, some of the putative genetic associations with schizophrenia, such as the allelic variations in the enzyme catechol-\(O\)-methyl transferase (COMT)\(^{75}\), have been implicated in a broad range of other disease states. These include gender-related pain sensitivity\(^{76}\), obsessive-compulsive disorder\(^{77}\), myofacial pain syndrome\(^{78}\), breast cancer\(^{79}\), blood pressure dysfunction\(^{80}\), anorexia nervosa\(^{81}\), anxiety\(^{82}\), panic disorder\(^{83}\), depression, and Alzheimer’s disease associated psychosis\(^{84}\).

1.3.12 TREATEMENT FOR SCHIZOPHRENIA:

Drug therapy has been the main treatment modality for schizophrenia. Chlorpromazine \(^{11}\), the first modern antipsychotic drug, was introduced into psychiatry in 1952. It was followed by a number of other antipsychotics (e.g. haloperidol \(^{12}\) and thioridazine \(^{13}\)), also called neuroleptics because of their neurological side effects, such as Parkinsonian syndrome and tardive dyskinesia. The antipsychotic properties of these drugs were inseparable from extra pyramidal
effects. Clozapine 14 was introduced into psychiatry in Europe in the 1970s and in the US in the 1990s. The frequency of the extra pyramidal neurological side effects of clozapine 14 is comparable with placebo. Clozapine 14 was followed by the introduction of other antipsychotics (e.g. risperidone 15 and olanzapine 16) with low frequency of neurological adverse events. As the term ‘neuroleptic’ was no longer appropriate for these new drugs, the term ‘atypical neuroleptics’ and later ‘second-generation antipsychotics’ was introduced. Dopamine, especially D2, and later serotonin and other neurotransmitter receptors were identified as targets for antipsychotic drugs. Numerous double-blind studies have compared second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs), with most finding better efficacy and tolerability for SGAs. However, these ‘efficacy trials’ were generally short term and included only highly selected patients. Mostly because of weight gain and other metabolic effects of the SGAs, as well as their high acquisition price, the debate on the (cost) effectiveness of the SGAs led to two pragmatic clinical trials with no sponsorship by industry. Both trials had broad inclusion criteria and long follow-up, and tried to mimic clinical routine: CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and CUTLASS (Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study). CATIE and CUTLASS suggest that SGAs do not live up to all the previous expectations. However, even if most of these advantages are debatable, the lower risk of tardive dyskinesia and the better subjective effects should be strong enough reasons to favour these drugs. There is no single antipsychotic that is best for every schizophrenia patient, as individual responses differ markedly. For successfully individualized treatment, a multitude of antipsychotic options are needed.
Phase 1: Discovery (antihistamines, chlorpromazine)

The discovery in 1947 of phenothiazine antihistamines such as promethazine 17 occurred as a by-product of research into tropical infections. Almost all modern antidepressants and antipsychotics are derived from these antihistamines, and the later differentiation of H<sub>1</sub> and H<sub>2</sub> receptors led to the synthesis of H<sub>2</sub> antagonist. A chlorinated antihistamine, chlorpromazine 11, was discovered in 1952 and was found to exhibit anticholinergic and antiemetic effects. It was for the latter indication that the drug was first licensed – even though psychotropic effects were soon observed as there was no antipsychotic market at that time. The dramatic effects of chlorpromazine 11 on psychotic patients in asylums worldwide and the demonstration of its ability to reverse lysergic acid diethylamide 5 (LSD) induced psychosis, heralded a new era of psychiatric practice. At around the same time, some of the researchers rediscovered the antipsychotic effects of the rauwolfia herb (*Rauwolfia serpentina*), which had been used in India since ancient times. Rauwolfia, and its active ingredient reserpine 18, were introduced as antihypertensive agents and were significantly less expensive than chlorpromazine 11. There was initially little
understanding of the neurochemical basis of chlorpromazine action, although it has been proved that chlorpromazine blocks H₁ histamine, α₁-adrenergic, muscarinic and dopamine receptors. In contrast, the gradual revelation of reserpine’s action as a monoamine-depleting agent was pivotal to the growing science of psychopharmacology and to the development of both the monoamine hypothesis of depressive illness and the dopamine hypothesis of schizophrenia.

Phase 2: Refinement (D₂ antagonists, haloperidol)

In 1958, Janssen produced a new butyrophenone compound, haloperidol, in the process of trying to refine the analgesic effect of pethidine. This was soon found to have a potent antipsychotic effect as well as efficacy in patients with Tourette’s syndrome, in doses far lower than were needed for chlorpromazine. This high-potency neuroleptic was also observed to be more likely to cause extra pyramidal side effects (EPS), but less likely to cause anticholinergic effects than chlorpromazine. Other drugs followed; these first antipsychotics were referred to as major tranquillizers (due to their significant sedative actions) and neuroleptics (due to their potential to cause EPS).

These typical, or ‘classical’, or First generation antipsychotics (FGAs) have class-specific side effects, including:
• Acute and chronic movement disorders (acute and chronic akathisia, acute and tardive dystonia, tardive dyskinesia, drug-induced Parkinsonism)
• Hyperprolactinaemia
• Neuroleptic malignant syndrome

Drug-specific side effects include:

• Anticholinergic symptoms (dry mouth, constipation, blurred vision, confusion)
• Weight gain
• Sedation
• Postural hypotension
• Reduced seizure threshold

In 1963, Carlson and Lindqvist proposed that dopamine antagonism explained the antipsychotic effects of chlorpromazine \textit{11}, haloperidol \textit{12} and reserpine \textit{18}. Antagonism of dopamine D$_2$ receptors became a defining feature of the antipsychotic class. Affinity for dopamine receptors and clinical potency of classical antipsychotics are very highly correlated. Thus, it has been suggested that the key deficit in schizophrenia is increased dopaminergic activity, with over-stimulation in limbic areas responsible for positive symptoms, and decreased dopaminergic activity in the prefrontal cortex, inducing negative symptoms. The dopamine theory of schizophrenia also posits that blockade of mesolimbic dopamine receptors mediates antipsychotic efficacy, with blockade in the tuberoinfundibular, nigrostriatal and mesocortical pathways mediating the side effects of hyperprolactinaemia, EPS and worsening of negative symptoms respectively\textsuperscript{88}.

Phase 3: Atypical agents (clozapine-like drugs)

Clozapine \textit{14}, the most successful of the tricyclic antipsychotics, was originally synthesized in 1958 but withdrawn from most markets because of the risk of lethal agranulocytosis. It took the pivotal results of a seminal study of clozapine \textit{14} in treatment-resistant schizophrenia 30 years later for it to gain approval from the US Food and Drug Administration (FDA) and subsequent wide use. Clozapine \textit{14} has an
extremely complex binding profile, including \( D_1, D_4 > D_{2,3} \) antagonism, 5-HT\(_{2A/2C,3,6,7}\) antagonism, potent muscarinic (M\(_4\)) agonism, as well as \( H_1 \) histaminergic and \( \alpha_{1,2} \) binding actions. This abundance of psychopharmacological actions has complicated the search for clozapine-like antipsychotics, which became known as second-generation or atypical antipsychotics (SGAs). There is no uniform definition of atypicality, but the cardinal feature is a similar psychopharmacological profile to clozapine. This is variously interpreted, and a host of clinical features and associated pharmacological criteria have been proposed to account for the atypical action of these drugs. Most authors suggest that atypicals have three essential features:

- Efficacy in treating positive symptoms
- Low incidence of EPS
- 5-HT\(_2\) as well as \( D_2 \) antagonism

The revelation that clozapine has a higher affinity for 5-HT\(_{2A}\) receptors than for \( D_2 \) receptors prompted a wider investigation of the role of 5-HT in the mechanism of action of antipsychotic drugs. Observations that several 5-HT\(_{2A}\) receptor agonists such as LSD 5 and mescaline 20 produce hallucinations in humans, and post-mortem evidence of high cortical density of 5-HT\(_2\)-like receptors in schizophrenic patients, support a serotonin hypothesis of schizophrenia. Co-administration of the 5-HT\(_{2A}\) antagonist ritanserin 21 with the typical antipsychotic haloperidol resulted in improvement of negative symptoms and diminished EPS. Additionally, 5-HT\(_{2A}\) receptors are highly localized to cortical layer V pyramidal neurons, making them well positioned to mediate the cognitive and perceptual integrative functions of antipsychotic drugs. In spite of these promising findings, drugs such as cyproheptadine 22 have 5-HT\(_2\) antagonist properties but negligible antipsychotic effect, and agents such as chlorpromazine 11 and thioproperazine 23 also have high 5-HT\(_2\) affinity but are not considered atypical in their action. The serotonin hypothesis thus proposes that both serotonin and dopamine antagonism together (especially high 5-HT\(_2\):\( D_2 \) ratios) are needed for atypical antipsychotic action. An exception to this is the benzamide antipsychotic amisulpride 24, which has antagonistic effects at dopamine \( D_2 \) and \( D_3 \) receptors, negligible 5-HT\(_2\) antagonism and yet has effective antipsychotic effects with low extra pyramidal side effects. This observation is applicable by a proposal that the defining feature of atypicality is not simply due to...
dual 5-HT₂:D₂ receptor antagonism but by a drug having a low affinity for the D₂ receptor, which is ultimately determined by a fast dissociation from the D₂ receptor. Clozapine 14, the atypical antipsychotic, demonstrates a far shorter occupancy rate of striatal D₂ receptors than that of haloperidol. Amisulpride 24 and quetiapine 25 both exhibit fast dissociation property.

![Chemical structures](image)

**Phase 4: Beyond D₂ antagonism (partial D₂ agonism, aripiprazole)**

Current research has began to challenge the axiom that D₂ antagonism is essential for antipsychotic effect. Aripiprazole 26, now licensed in Australia, the UK, the USA and other countries, is the first antipsychotic that is not a D₂ antagonist. It is a quinolinone derivative with a unique mechanism of action: it exhibits partial agonist activity at D₂ and 5-HT₁A receptors and antagonist activity at 5-HT₂A receptors.

Preclinical and early clinical data support functional antagonism in dopaminergic hyperactivity states as well as functional agonism in states of dopaminergic hypoactivity without concomitant significant undesirable extra pyramidal side effects. This effect is sometimes referred to as 'dopamine stabilization'. Thus, aripiprazole 26 is a potentially effective treatment of both positive and negative symptoms of schizophrenia. Early clinical data confirm that it is more efficacious than haloperidol with respect to negative symptoms, and is comparable to haloperidol 12 and
risperidone 15 in the treatment of positive symptoms. It appears to be very well tolerated, with minimal evidence of significant EPS, hyperprolactinaemia, weight gain, metabolic disturbance or QTc prolongation, although it can cause nausea, proving a degree of dopamine agonism. Compound 27 was, however, not approved by the FDA in August 2007 because of a lack of demonstrated efficacy. Compounds 28 (SSR-181507), 29 (RGH-188), and 30 (F-15603) are other D2 receptor partial agonists. It remains to be demonstrated in a large clinical study that partial DA receptor agonism alone is sufficient to reliably elicit antipsychotic efficacy because it is unclear as to what degree of partial D2 agonism is required for efficacy.

1.3.13 OTHER NOVEL INVESTIGATIONAL APPROACHES: 152-215

1.3.13.1 Modulation of NMDA receptor neurotransmission

One of the most frequently studied approaches to improve cognitive function and reducing negative symptoms of schizophrenic patients is enhancing NMDA receptor function by acting on the glycine modulatory site (GMS). A recent review of a series of relatively small placebo-controlled studies have suggested that either high-dose glycine 31, D-serine 32, or the partial agonist D-cycloserine 33 improve negative symptoms, cognitive dysfunction, and depression when added to antipsychotic drugs other than clozapine [93]. In contrast, either symptom exacerbation or lack of symptomatic improvement has been observed with agonists or partial agonists when the GMS are added to ongoing treatment with clozapine.
recent meta-analysis of glutamatergic drugs (e.g., glycine 31, D-serine 32, D-cycloserine 33, and the AMPAkine CX516 34) added to antipsychotic drug treatment found a moderate effect size for glycine or D-serine 32 added to antipsychotics with respect to negative symptoms94. Only a trend was present for cognitive dysfunction. Little evidence for a beneficial effect was found with D-cycloserine 33 augmentation. D-Amino acid oxidase (DAAO) catalyzes the oxidation of d-amino acids including d-serine, a full agonist at the glycine 31 site of the NMDA receptor. A series of benzo[d]isoxazol-3-ol derivatives (CBIO) 35 and AS057278 36 were synthesized and evaluated as DAAO inhibitors95, 96.

\[ \text{HO} \quad \text{OH} \]
\[ \text{O} \quad \text{NH} \]
\[ \text{O} \quad \text{NH}_2 \]
\[ \text{N} \quad \text{O} \quad \text{HO} \]
\[ \text{Cl} \]

1.3.13.2 Serotonin 5-HT2A antagonists

One example of an extensively explored approach for selectively targeting a single receptor thought to play a key role in pathophysiology of schizophrenia is the investigation of selective 5-HT2A receptor antagonists as putative antipsychotic drugs. The development of the highly selective 5-HT2A receptor antagonist, M100907 3597, was discontinued after two phase 3 studies in the U.S. found M100907 37, although superior to placebo, to be inferior to haloperidol and a European phase 3 study in schizophrenic patients with predominant negative symptoms failed to observe separation of the M100907 37 from placebo98. The termination decision was derived in large part from objective receptor occupancy studies in healthy humans that confirmed that M100907 37 was tested at doses that saturate prefrontal cortical 5-HT2A receptors99. Furthermore, a phase 2 study of SR46349B (eplivanserin) 38, another 5-HT2 receptor antagonist with approximately 20-fold selectivity for 5-HT2A over 5-HT2C receptors, also showed antipsychotic efficacy intermediate between that
of placebo and haloperidol. An unresolved challenge is how a modestly effective therapeutic with a presumed superior side effect profile can be used in the clinic either as a monotherapy or in combination with other agents during different stages of the schizophrenia syndrome.

1.3.13.3 Neurokinin-3 (NK₃) receptor antagonists

Another mechanism of action that may be associated with a relatively modest degree of efficacy is blockade of neurokinin-3 (NK₃) receptors. The same meta-trial that found modest efficacy for the Sanofi-Aventis (Paris France) 5-HT₂ receptor antagonist also reported antipsychotic efficacy for the NK₃ receptor antagonist, SR142801 (osanetant) 39, that was intermediate between placebo and haloperidol. This NK₃ receptor antagonist is in a phase 2b trial. GlaxoSmithKline (UK, USA) also working on a NK₃ receptor antagonist, talnetant (SB-223412) 40, that undergoing phase 2b testing) involving both a placebo and an active comparator (risperidone) 15.
1.3.13.4 Dopamine D₄ receptor antagonists

Dopamine D₄ antagonists appear to lack appreciable efficacy in the treatment of acute schizophrenia. A relatively small phase 2 study reported a slight worsening of patients relative to the placebo group following treatment with L-745,870 41 and NRA0160 42. These results were confirmed in a recent, large multicenter, placebo-and active comparator (olanzapine)-controlled, Study involving a 40-fold dose range for a Pfizer (USA) dopamine D₄ receptor antagonist (sonepiprazole) 43. Given these results, it is not surprising that a dopamine D₄/5-HT₂A/α₁ adrenergic receptor antagonist also did not exhibit antipsychotic efficacy in a relatively small (97) patients with approximately 2:1 active: placebo randomization) phase 2 study in the treatment of schizophrenia patients 44.

![Chemical structures](image1)

1.3.13.5 Neurotensin NTS₁ antagonist

The placebo-controlled meta-trial using haloperidol as a positive comparator that demonstrated moderate efficacy for the Sanofi-Aventis NK₃ receptor antagonist and 5-HT₂ receptor antagonist failed to see any efficacy for a neurotensin NTS₁ antagonist (SR48692 44).
1.3.13.6 Cannabinoid CB₁ receptor antagonist

An emerging literature has suggested that endocannabinoids including 45 (anandamide) may be involved in aspects of the pathophysiology of schizophrenia with conflicting reports of changes in cannabinoid (CB) receptors in schizophrenics. Individuals with Δ-9-tetrahydrocannabinol intoxication have a perceptual dysfunction similar to that seen in schizophrenics. Compound 46 (rimonabant/SR141716), a selective CB1 receptor antagonist, can reduce stimulant-induced hyperactivity. CB ligands including 46, 47 (AVE-1625), and 48 (SLV-319) are under investigation for the treatment of schizophrenia.
1.3.13.7 Muscarinic Cholinergic Agonists

The cholinergic deficits that occur in patients with dementia with Lewy bodies (DLB)\textsuperscript{110} lead to visual hallucinations, delusions, apathy, agitation, dementia, and mild-Parkinsonism, all aspects of the schizophrenia phenotype\textsuperscript{111}. Treatment of DLB patients with cholinesterase inhibitors such as 49 (rivastigmine) and 50 (donepezil) can diminish these symptoms, thus leading to antipsychotic-like activity\textsuperscript{112,113}. However, the peripheral cholinergic side effects of these drugs preclude their broader use outside of DLB and Alzheimer’s disease (AD). Compound 51 (xanomeline) and other selective muscarinic agonists (e.g., 52 NGX267) have an antipsychotic-like profile in animal models of psychosis similar to that seen with D\textsubscript{2} antagonists with the exception that muscarinic agonists do not elicit catalepsy\textsuperscript{114}. 

![Chemical structures](image-url)
1.3.13.8 Histamine H₃ Receptor Antagonists

Examination of the therapeutic utility of histamine for the treatment of schizophrenia dates back to the 1930s with inconclusive results. With the discovery of the histamine H₃ receptor and the development of selective drug like antagonists for this GPCR, it has been well established in animal models that NCEs like (JNJ-10181457), (GSK189254) and (BF2.649) and analogues of like (A-688057) may have potential in the treatment of the cognitive dysfunction associated with schizophrenia. There has been no proof of concept in clinical trials for this approach to date.

1.3.13.9 N-Acetyl-L-aspartyl-L-glutamate (NAAG)

N-Acetyl-L-aspartyl-L-glutamate (NAGG) is a peptide with putative neurotransmitter function that acts as an endogenous agonist at group II mGluR receptors. It is catabolized to N-acetylaspartate and glutamate by the NAAG peptidases, glutamate carboxypeptidase II and III present on the cell surface of astrocytes. Therefore, NAAG peptidase inhibitors, by increasing NAAG levels, could provide antipsychotic
efficacy via activation of group II mGluRs. Compounds \textbf{58} (2-PMPA), \textbf{59} (GPI5693), and \textbf{60} (ZJ38) represent first generation NAAG peptidase inhibitors\textsuperscript{127}.

1.3.13.10 Dopamine Receptor Modulators

Dopamine D\textsubscript{1} receptor agonists such as \textbf{61} (dihydrexidine) and \textbf{62} (SKF-81297) have precognitive effects in animal models\textsuperscript{128}. The D\textsubscript{1}/D\textsubscript{5} agonist \textbf{63} (adrogolide, ABT-431, DAS-431) had cognition enhancing activity in a rat model of antipsychotic-induced working memory deficit\textsuperscript{129} that was not replicated in more traditional animal models of cognitive performance, e.g., Morris water maze. D\textsubscript{1}/D\textsubscript{5} agonists also have limited potential as drugs because of the inherent tolerance of their mechanism. Nonetheless, there still appears to be to continuing interest in D\textsubscript{1}/D\textsubscript{5} agonists for the treatment of cognitive deficits\textsuperscript{130}. There is also an ongoing effort to identify improved D\textsubscript{2} receptor antagonists with the current focus being on selective D\textsubscript{3} receptor antagonists. These are anticipated to have reduced EPS liability compared to D\textsubscript{2} receptor antagonists\textsuperscript{131}. Recent examples include the tetrahydrobenzazepine, \textbf{64} (SB-414796), \textbf{65} ST-280, the benzazepinone, \textbf{66} (A-706149), \textbf{67} (S-33138)\textsuperscript{132} and \textbf{68} (PNU-177864). Past interest in selective D\textsubscript{4} receptor antagonists as antipsychotics was driven by the higher affinity of clozapine for the dopamine D\textsubscript{4} receptor relative to the D\textsubscript{2} receptor\textsuperscript{133}. D\textsubscript{4} receptors appear to be involved in working memory\textsuperscript{134} and can prevent stress-induced cognitive deficits in monkeys\textsuperscript{135}. A number of selective D\textsubscript{4} antagonists have been identified including \textbf{69} (L-745,870), \textbf{70} (fananserin, RP62203), \textbf{71} (NGD 94-1), \textbf{72} (PNU-101,387), \textbf{73} (CP-293019), and \textbf{74} (PD-172938)\textsuperscript{136-137}. In both preclinical\textsuperscript{136} and clinical studies\textsuperscript{137}, \textbf{69} failed to show an antipsychotic profile, a result that may reflect partial D\textsubscript{4} agonist activity similar to that reported for \textbf{71}\textsuperscript{138}. 

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1.3.13.11 5-HT Receptor Ligands

Research has also continued on the 5HT receptor axis of schizophrenia. Newer targets/Ligands include the 5-HT$_{2A}$ receptor inverse agonist 75 (ACP-103)$^{139}$ and the 5-HT$_{2C}$ receptor agonists 76 (WAY-163909), 77 (VER-2692), and 78 (Ro 60-0175). Activation of the 5-HT$_{2C}$ receptor reduces mesolimbic DA neurotransmission$^{140}$. Interest in 5-HT$_6$ receptor antagonists, like that for D$_4$ receptor antagonists, was driven by the high-affinity binding of 14 to this receptor$^{141}$ and also the ability of 14 to
down-regulate the 5-HT$_6$ receptor$^{142}$. This has resulted in considerable patent activity in the area of 5-HT$_6$ antagonists$^{143}$. While these antagonists have been implicated in enhancing cognition with potential utility in Alzheimer’s disease and schizophrenia$^{142}$, NCEs including 79 (SB-271046) and 80 (Ro 04-6790) have been reported to have cognition enhancing activity, an effect sensitive to NMDA receptor antagonists$^{144}$. The utility of 5-HT$_6$ antagonists as cognition enhancers, however, has been questioned$^{145,146}$. Newer compounds active at this 5-HT receptor include 81 (SGS-518), 82 (ALX-0440), 83 (BGC-20-761), 84 (E-6801), 85 (PRX-07034), and 86 (WAY181187).
1.3.13.12 MAO - B inhibitors

It has been suggested that negative symptoms of schizophrenia may be manifestations of regionally deficient dopaminergic activity in the brain, thus augmentation of dopaminergic neurotransmission could be a beneficial treatment strategy. Selegiline 87 (deprenyl) is a monoamine oxidase (MAO-B) inhibitor that selectively enhances dopaminergic activity. Selectivity for inhibition of MAO-B without inhibition of MAO-A is clinically important, since MAO-A inhibition is responsible for most of the side effects of MAO inhibitors. Although several case series reported the beneficial effects of selegiline (87) on negative symptoms of schizophrenia147-149, one double-blind, controlled study of the agent as adjunct to antipsychotic treatment failed to offer therapeutic benefit150. The selective irreversible MAO-B inhibitors, selegiline 87 and rasagiline 88, have been shown to possess neuroprotective activities in cell culture and in vivo models of parkinson’s disease [151]. For example, these agents can prevent experimentally induced apoptotic DNA damage, and induce pro-survival genes152. Thus, the MAO-B inhibitors may rescue degenerating dopamine neurons through inhibiting death signal transduction, but clinical trials failed to confirm it151. So far, no solid conclusions could be drawn from the data regarding the effects of the MAO-B inhibitors on schizophrenia.

1.3.13.13 PDE10 inhibitors

PDE10A is a recently identified cyclic nucleotide phosphodiesterase expressed at high levels in the brain and more specifically in the medium spiny neurons of the striatum and associated nucleus accumbens and olfactory tubercle153. Papaverine 89, a potent and selective PDE10A inhibitor, can dose-dependently attenuate
hyperactivity induced by both amphetamine and PCP in rats. The agent does not affect extracellular dopamine in the striatum nor alter PCP-induced dopamine release in the nucleus accumbens. Papaverine can also produce a dose-dependent reduction in conditioned avoidance responding in rodents. These data suggest the possibility that selective inhibitors of PDE10 may provide a target for the development of a new class of antipsychotic drugs.
Table 3: Marketed drug

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<th>Key marketed brands</th>
<th>Generic name</th>
<th>Company name</th>
<th>Launch Year</th>
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</thead>
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<tr>
<td>Haldol</td>
<td>Haloperidol</td>
<td>Johnson &amp; Johnson</td>
<td>1959</td>
</tr>
<tr>
<td>Dogmatil</td>
<td>Sulpiride</td>
<td>Sanofi-Synthelabo</td>
<td>1969</td>
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<td>Clozapine</td>
<td>Novartis</td>
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<td>Dogmaty</td>
<td>Sulpiride</td>
<td>Fujisawa</td>
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<td>Solian</td>
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<td>Risperidone</td>
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<td>asenapine</td>
<td>Asenapine</td>
<td>Akzo Nobel</td>
<td>2005</td>
</tr>
</tbody>
</table>

Some of the drug which are approved recently or not approved by FDA.

- Piperidone (Invega) (FDA approval: 2006).
- Sertindol (Serlect) (Not approved by the FDA for use in the USA).
- Zotepine (Not approved by the FDA for use in the USA).
- Amisulpride (Not approved by the FDA for use in the USA).
- Bifeprunox (Not approved by the FDA for use in the USA).
- Melperone Approved in Europe. Currently in clinical trial in USA.