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**Review**

# Schizophrenia Research: From Epidemiological Trends to Experimental Models, In Vitro Studies, and Emerging Treatments

**Mridhulmohan.P*[1], Diva Suresh.R[1], Fathima Saniya.M[1], Hiba Sherin A.V.[1], Jahana Sherin[1], Dr. E. Tamil Jothi[1]**

*Department of Pharmacology, Devaki Amma Memorial College of Pharmacy, Pulliparamba Post, Chelembra, Malappuram Dt-673634*

*Author for Correspondence: Mridhulmohan. P
Email: mridhulmohan236@gmail.com

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## Abstract

Schizophrenia is a severe mental illness affecting over 21 million individuals worldwide, leading to cognitive, social, and emotional impairments. It is characterized by positive symptoms (hallucinations, delusions), negative symptoms (anhedonia, avolition), and cognitive deficits. While traditionally viewed as a distinct disorder, emerging perspectives suggest schizophrenia exists on a psychosis spectrum. The condition has strong genetic links, with environmental factors such as fetal development issues, urban residence, and cannabis use increasing risk. Neurotransmitter imbalances, particularly in dopamine, serotonin, and glutamate pathways, contribute to its pathophysiology. Treatment strategies primarily rely on antipsychotic medications, but one-third of patients exhibit treatment resistance. Clozapine remains the standard for refractory cases, while psychosocial interventions improve long-term outcomes. Emerging treatments include novel pharmacologic agents like TAAR-1 agonists, transdermal asenapine, and long-acting injectables, targeting cognition, negative symptoms, and adherence issues. Despite advancements, schizophrenia remains a complex and multifaceted disorder, requiring continued research to improve therapeutic outcomes and quality of life for affected individuals.

**Keywords:** Schizophrenia, psychosis, neurotransmitters, antipsychotics, cognitive impairment, treatment-resistant schizophrenia, epidemiology, pathophysiology, behavioral models, emerging therapies.

## INTRODUCTION

Schizophrenia is a severe mental illness (SMI) that affects over 21 million individuals globally, often leading to long-term disability and impairments in cognitive, social, and emotional functioning. It is currently understood to be characterized by positive symptoms (such as delusions and hallucinations), negative symptoms (including anhedonia, alogia, avolition, and social withdrawal), and cognitive deficits (such as impairments in attention, processing speed, verbal learning, visuospatial learning, problem-solving, working memory, and

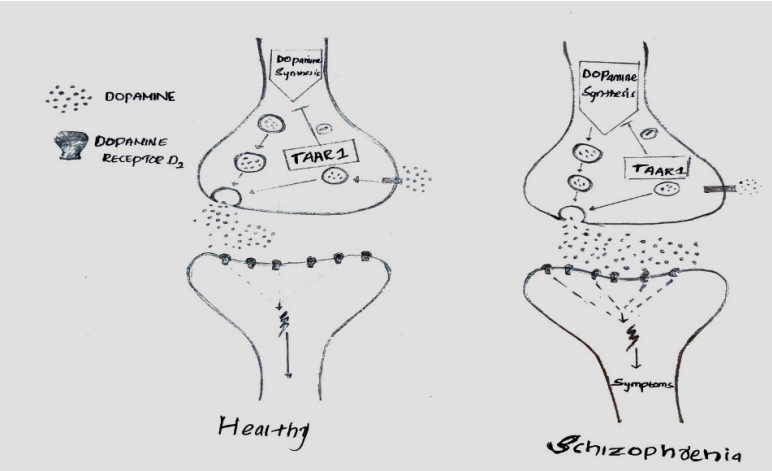
cognitive flexibility). Additionally, deficits in social cognition (such as emotional intelligence, facial emotion recognition, emotion evaluation, and social inference) can significantly hinder functional recovery in schizophrenia, affecting interpersonal relationships, community integration, and vocational abilities. Schizophrenia patients are also more likely to experience co-occurring medical and/or mental health conditions, including substance use disorders (primarily involving alcohol and cannabis), with prevalence rates reaching up to 41%. Factors such as a disordered lifestyle, poor diet, lack of exercise, smoking, side effects of antipsychotic medications, limited healthcare access, and the illness itself increase the likelihood of schizophrenia patients developing metabolic syndrome, cardiovascular diseases, diabetes, endocrinopathies, immune system disorders, and pulmonary conditions, particularly chronic obstructive pulmonary disease. The presence of additional mental health disorders further contributes to higher rates of symptom relapse, hospitalizations, suicidality, and social issues (including incarceration due to mental health relapses, treatment discontinuation, impulsivity, and aggressive behaviors), resulting in an increased risk of adverse outcomes, including higher mortality rates in the short term. A recent meta-analysis revealed that mortality rates were significantly higher among individuals with schizophrenia compared to the general population. The leading causes of death included suicide, injury, poisoning, pulmonary diseases, endocrine disorders, respiratory diseases, urogenital conditions, diabetes, cancer, and cardiovascular events. Interestingly, treatment with antipsychotic medications, particularly second-generation long-acting injectable antipsychotics (SGA-LAIs), appears to offer some protection against all causes of mortality. (1)

The concept of schizophrenia is increasingly being questioned. Once supported for decades by psychology, it now seems to have been critically undermined by psychiatry, the very field that initially upheld it. Its demise is unlikely to be mourned. Currently, a diagnosis of schizophrenia is linked to a life expectancy reduction of nearly two decades. According to some criteria, only one in seven individuals fully recover. Despite touted advancements in treatment, the recovery rate has not improved over time, highlighting a deeper issue. Part of the challenge lies within the very concept of schizophrenia. Arguments supporting schizophrenia as a distinct illness have been "fatally undermined." Much like how we now understand autism spectrum disorder, psychosis—characterized by troubling hallucinations, delusions, and disorganized thinking—is also considered to exist on a continuum, varying in severity. Schizophrenia represents the extreme end of this spectrum. Jim van Os, a professor of psychiatry at Maastricht University, asserts that transitioning to this new perspective requires a shift in language. He argues that the term schizophrenia should be discarded and replaced with the concept of psychosis spectrum disorder. (2) Abnormalities in neurotransmission have provided the basis for various theories regarding the pathophysiology of schizophrenia. Most of these theories focus on either an excess or deficiency of neurotransmitters, such as dopamine, serotonin, and glutamate. Other theories also suggest that neurochemical imbalances involving aspartate, glycine, and gamma-aminobutyric acid (GABA) may contribute to the development of schizophrenia. (3)

Abnormalities in multiple neurotransmitters, including dopaminergic, serotonergic, and alpha-adrenergic hyperactivity, as well as glutamatergic and GABA hypoactivity, have been implicated in schizophrenia. Genetics also plays a crucial role; for instance, there is a 46% concordance rate in monozygotic twins, and the risk of developing schizophrenia rises to 40% if both parents are affected. The Neuregulin (NGR1) gene, which is involved in glutamate signaling and brain development, has been linked to the disorder, as has Dysbindin (DTNBP1), which aids in glutamate release, and the Catecholamine O-Methyl Transferase (COMT) polymorphism, which regulates dopamine function. As mentioned earlier, several environmental factors are also associated with an increased risk of developing schizophrenia, including:

- Abnormal fetal development and low birth weight
- Gestational diabetes
- Preeclampsia
- Emergency cesarean sections and other birthing complications
- Maternal malnutrition and vitamin D deficiency
- Winter births, which are associated with a 10% higher relative risk
- Urban residence, which increases the risk by 2% to 4%

Additionally, the incidence of schizophrenia is up to ten times higher in children of African and Caribbean migrants compared to white children, according to a study conducted in Britain. The link between cannabis use and psychosis has been widely studied, with recent longitudinal studies indicating a 40% increased risk. These studies also suggest a dose-effect relationship between cannabis use and the likelihood of developing schizophrenia. (2)




Current diagnostic systems for schizophrenia, such as the DSM-5-TR and ICD-11, have limitations due to their failure to fully capture the biological, pathophysiological, and clinical heterogeneity of the disorder. While these systems facilitate communication and research, they don't address the neurodevelopmental aspects, genetic factors, or subthreshold vulnerabilities associated with schizophrenia. The RDoC initiative, introduced by the National Institute of Mental Health, offers a dimensional approach to understanding schizophrenia, focusing on underlying brain circuits and cognitive functions. Other research, like the Hierarchical Taxonomy of Psychopathology (HiTOP), aims to redefine psychiatric disorders by grouping related symptoms along continuous dimensions, reducing diagnostic instability and improving the identification of subthreshold cases. Additionally, biotype-based models, like the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP1), explore biomarkers to distinguish psychosis subtypes, which could lead to more personalized and precise treatment approaches for schizophrenia. (1)

## EPIDEMIOLOGY

Schizophrenia generally emerges in adolescence or early adulthood, with approximately 1% of the global population estimated to be affected (Castle & Morgan, 2008). A review of numerous studies from various geographic regions shows lifetime prevalence rates ranging from 0.2% to nearly 1.5% (Simeone et al., 2015). Men are more likely to develop the disorder than women (Grignon & Trottier, 2005). While it has long been believed that schizophrenia prevalence remains fairly consistent worldwide (Nixon & Doody, 2005), some recent studies challenge this view, showing that factors such as sex, age, ethnicity, and geography influence its incidence (McGrath et al., 2011; McGrath, 2006). Some research indicates a rise in general schizophrenia rates (Boydell et al., 2003; Bray et al., 2006), while other studies have not found such trends (Nixon & Doody, 2005; Suvisaari et al., 1999).

There is ongoing debate about whether schizophrenia is a single disorder or a group of different syndromes. This idea is supported by research showing that distinct biological markers are associated with varying responses to antipsychotic drugs (Garver et al., 2000), suggesting that schizophrenia may involve multiple syndromes rather than a singular disease. Ross (2014; 2006) challenges the widely accepted notion that schizophrenia is primarily an inherited biological disorder treated only with medication. He proposes that the positive symptoms of schizophrenia are more akin to dissociative identity disorder and suggests the existence of a dissociative subtype of schizophrenia. Kroll (2007), after reviewing numerous cross-cultural studies of psychosis, argues that the many shared risk factors for both psychotic and affective disorders question the necessity of a clear distinction between them. (4)

### Life time prevalence

Schizophrenia affects nearly 1% of the population at some point in their lifetime. One of the most thorough studies on this comes from Finland, where Perala et al. estimated the lifetime prevalence of schizophrenia, based on DSM-IV criteria, to be 0.87%, while schizoaffective disorder had a prevalence rate of 0.32%.

### Incidence

For many years, it was widely believed that the incidence of schizophrenia was stable both geographically and over time. However, this view has since been disproven. A systematic review revealed that the incidence of schizophrenia varies significantly, with rates ranging from 7.7 to 43.0 per 100,000, representing a

fivefold difference. Although data on long-term trends is limited, it has been shown that the incidence of schizophrenia in South London, as defined by operational criteria, doubled between 1965 and 1997.

**Age of onset**

As part of the extensive AESOP (etiology and Ethnicity of Schizophrenia and Other Psychoses) study, Kirkbride et al. examined the incidence of psychosis in three English cities. Figure 1 displays age-specific incidence rates for psychosis overall and for the main diagnostic categories. It can be seen that the peak incidence of schizophrenia in males occurred between ages 20 and 24, while in females, it peaked between ages 29 and 32, with a more gradual curve and more cases emerging later in life. This finding from the AESOP study supports previous evidence of an earlier onset of schizophrenia in males. A detailed study on gender differences, which involved 477 first-contact cases of schizophrenia (including those presenting in later life), found that while the mean age of onset was later, males still exhibited an earlier average onset of the illness (31.2 vs. 41.1 years). Castle et al. also found that, while the incidence of mild schizophrenia was fairly equal between the sexes, narrowing the diagnostic criteria revealed a higher incidence in males. Other studies confirm that narrowly defined schizophrenia is more common in men (with a risk ratio of 1.4:1) and tends to be more severe in them. The earlier onset in males has been attributed to the male brain's increased susceptibility to neurodevelopmental disorders, while the higher incidence in postmenopausal women may be linked to the loss of estrogen's antidopaminergic effects.

**Mortality**

On average, individuals with schizophrenia have a shorter life expectancy compared to the general population. A systematic review of mortality studies by McGrath et al. found that the standardized mortality ratio (SMR) for people with schizophrenia was 2.6, with suicide and cardiovascular disease being the primary contributors. Unfortunately, their findings also showed that the SMR has been increasing in recent decades. (5)

**BEHAVIORAL MODEL STUDIES OF SCHIZOPHRENIA**

Animal models are crucial for studying the neurobiology of psychiatric disorders and testing new therapeutics. However, assessing core symptoms like thoughts and verbal memory is challenging, as they are unique to humans. Behavioral outcomes are indexed rather than directly quantified, requiring inference about the psychiatric state. There is no 'gold standard' medication to treat all symptoms, which limits positive controls in preclinical studies. While drugs like haloperidol and clozapine address positive symptoms, they have limited efficacy for negative and cognitive symptoms and may interfere with interpretation due to side effects. Effective models of schizophrenia should exhibit face validity (symptom homology), construct validity (neurobiological basis), and predictive validity (pharmacological response). A valid model would include abnormalities such as post pubertal onset, hippocampal/cortical dysfunction, dopamine dysregulation, glutamatergic hypofunction, stress vulnerability, reward response abnormalities, social withdrawal, and cognitive impairment. Studies (e.g., Floresco et al., 2005; Millan and Brocco, 2008) have reviewed models to assess their validity for evaluating treatments targeting cognitive and negative symptoms. (6)

**1. Latent inhibition (LI)**

Latent inhibition (LI) refers to the cognitive process in which prior exposure to a conditioned stimulus, without an unconditioned stimulus, hinders the ability of that stimulus to form new associations when later paired with the unconditioned stimulus. In simpler terms, LI involves the delay in a subject's ability to learn or associate a stimulus due to previous non-rewarded experiences. Research has shown that LI is diminished in individuals with schizophrenia, making it an important parameter for evaluating schizophrenia models. Pharmacological interventions can lead to two distinct abnormalities in LI: disrupted LI, which is associated with the positive symptoms of schizophrenia, and abnormally persistent LI, which aligns with the negative symptoms of the disorder.

**2. Object and spatial recognition memory (OSRM)**

Object and spatial recognition memory (OSRM) assesses cognitive abilities by evaluating an animal's inherent capacity to explore new environments and objects. This is typically done through tests such as the novel object recognition test and the object location test. Schizophrenia patients often exhibit impairments in OSRM, with both spatial and object recognition memory showing significant disruptions. In individuals with schizophrenia, these two types of memory are highly correlated, but there is greater variability in performance on spatial recognition tasks compared to object recognition tasks. This indicates that spatial recognition memory may be more susceptible to disruption in schizophrenia than object recognition memory.

**3. Social interaction test (SIT)**

The Social Interaction Test (SIT) was developed to quantitatively assess social behavior in mice when they encounter a standard subject—another mouse of the same species, shape, age, and weight. Social animals, such as rodents, naturally engage in social interactions when placed with others of their kind. During the test, various behavioral actions are observed, including both playful and aggressive behaviors like chasing, crawling over/under, boxing, wrestling, pouncing, biting, sniffing (anogenital), and social grooming. The test is conducted over a 10-minute period, during which multiple behavioral parameters are recorded, such as avoidance, approach behavior, aggression, attacking, locomotor activity, and self-grooming. Key measurements include the total time spent, the number of events, and the percentage of animals displaying specific behaviors. In the context of schizophrenia, reduced social interaction is a negative symptom commonly observed in affected individuals. Therefore, the SIT is a valuable tool for evaluating both negative and cognitive symptoms in schizophrenia models.

**4. Gating deficits**

Studies have shown that the hippocampus (HC) plays a key role in sensory gating. P50 gating, a measure of the startle response in prepulse inhibition (PPI), evaluates the ability to filter out irrelevant stimuli. The "P" refers to a positive peak, while "50" indicates the delay in the onset of the stimulus in milliseconds. Sensory gating deficits are commonly assessed using an auditory paired-click task, which includes components such as P50, N100, and P200 responses. In this task, two successive sounds are presented within 500 milliseconds, and the ratio of these sounds is known as the P50 gating ratio. Each of these gating components serves a specific function: P50 is related to information processing, N100 to the triggering of attention, and P200 to the allocation of attention. P50 gating is particularly useful in studying neurodevelopmental processes and genetic factors during early development, while P300 responses are linked to cognitive processing, and N100 is associated with auditory responses. These measures of sensory gating provide valuable insights into the filtering mechanisms and cognitive functions affected in various neuropsychiatric conditions, including schizophrenia. (7)

**5. Prepulse inhibition (PPI) of startle**

Prepulse inhibition (PPI) of startle is a key measure of sensorimotor gating, which is often impaired in schizophrenia. PPI refers to a neurological process where a low-intensity prepulse (stimulus) reduces the startle response triggered by a subsequent high-intensity pulse (stimulus). This process reflects the brain's ability to filter out irrelevant sensory input. PPI is commonly used in research to understand the brain's inhibitory mechanisms and how their dysfunction contributes to neuropsychiatric disorders such as schizophrenia. A deficiency in PPI is considered an endophenotype of schizophrenia, as it closely mirrors the sensory processing deficits seen in patients with the disorder. Various PPI deficiency models are utilized to study both the positive and negative symptoms of schizophrenia, offering valuable insights into the underlying pathophysiology of the disease.

**6. 5-choice serial reaction time task (5-CSRTT)**

The 5-choice serial reaction time task (5-CSRTT) is a behavioral test used to assess visual attentional processes in rodents, such as rats or mice. In this task, the subject is required to recognize brief flashes of light presented from one of five holes in an operant chamber. The animal must use a nose poke to select the correct hole in response to the light, after which it is rewarded. The test is conducted over 30–40 daily training sessions, during which the subject learns to respond to the light stimulus within a designated time frame. If the subject fails to respond in time, chooses the wrong hole, or fails to react altogether, no reward is given, and a short period of darkness is applied as a form of punishment. This task primarily measures the subject's attention, impulsivity, and vigilance, providing valuable insights into cognitive functions such as sustained attention and response inhibition, which are often impaired in neuropsychiatric disorders like schizophrenia.

**7. Forced swim test (FST)**

The Forced Swim Test (FST) is a behavioral assay where an animal is placed in an inescapable transparent cylinder filled with water to induce feelings of despair and helplessness. The animal's escape-related movements and immobility are observed and measured during the test. The FST is primarily used to evaluate the antidepressant efficacy of new drugs or experimental manipulations aimed at inducing or preventing depressive-like states. Additionally, there have been recommendations for using the FST to assess the antipsychotic efficacy for negative symptoms in schizophrenia. It has been reported that typical antipsychotics can reverse the increase in immobility time induced by blocking NMDA receptors in the FST, suggesting potential utility for evaluating treatments for negative symptoms. However, some studies have shown less promising results, questioning the test's effectiveness in modeling negative symptoms in NMDA receptor antagonist animal models of schizophrenia. Despite these mixed findings, the FST remains a valuable tool for understanding depressive-like behaviors and evaluating potential therapeutic agents.

**8. Sucrose preference test (SPT)**

The Sucrose Preference Test (SPT) is a reward-based behavioral assay where mice are given a choice between two sipper tubes one containing a sucrose solution and the other with plain drinking water. Mice, naturally drawn to sweet tastes, tend to prefer the sucrose solution, but continuous exposure can lead to anhedonia (a reduced ability to experience pleasure). This state of anhedonia, which is commonly associated with depression and schizophrenia, can be reversed by administering antidepressants. The SPT is used to assess negative symptoms like anhedonia, a core feature of both depression and schizophrenia. By measuring the preference for the sucrose solution, the SPT evaluates the hedonic or rewarding effect of sucrose consumption. In schizophrenic or depressive animals, reduced preference for the sucrose solution reflects impaired reward processing, which parallels the anhedonia seen in human patients. This test provides valuable insight into the reward deficits and the potential efficacy of treatments targeting these symptoms.

**9. Open field test**

The Open Field Test is a widely used method to measure voluntary locomotor activity in animals, typically conducted in an open arena over a period ranging from 15 minutes to 2 hours. Various parameters reflecting locomotor function are recorded, including horizontal and vertical activity, movement time, rest time, and total distance traveled. This test is based on the observation that certain drugs, such as amphetamine and phencyclidine (PCP), can induce hyper locomotor activity (an increase in movement), which is a hallmark of psychostimulant drugs. In contrast, antipsychotic drugs tend to produce sedative effects, reducing locomotor activity. The Open Field Test is used to model both positive and negative symptoms of schizophrenia. Amphetamine is commonly used to induce hyperactivity, representing positive symptoms like agitation and disorganized behavior, while phencyclidine (PCP), a NMDA receptor antagonist, is used to model negative symptoms, including social withdrawal and reduced motivation. This test provides valuable insights into the motor and behavioral changes associated with various neuropsychiatric conditions and the effects of potential treatments.

**10. Tail Suspension Test**

Similar to the Forced Swim Test (FST), the Tail Suspension Test (TST) is used to assess depression-like behavior, anhedonia, and avolition—negative symptoms associated with schizophrenia. In this test, mice are suspended by their tails, unable to escape or grab surfaces. Initially, they struggle, but then exhibit periods of immobility, reflecting passive behavior. Increased immobility is commonly seen in animal models of depression and schizophrenia. Recent studies show increased immobility in models such as LPS-treated mice and genetically modified mice (e.g., SREBP1c KO, NCAM-deficient, and COMT-deficient). Pharmacologically, sub chronic ketamine treatment increases immobility, but chronic ketamine or PCP treatment yields inconsistent results. These findings indicate that genetic, pharmacological, and developmental factors contribute to the increased immobility observed in schizophrenia-related models, making the TST valuable for studying negative symptoms.

**11. Three Chamber Sociability Test**

Reduced social interaction, a diminished desire for social communication, and impairments in socio-cognitive functions are key negative symptoms of schizophrenia, often referred to as asociality. While social behavior in humans involves a range of cognitive and emotional structures (agonistic, romantic, affiliative), in rodents, social interactions are primarily driven by sensory modalities, including visual, olfactory, and auditory cues. The three-chamber sociability test is commonly used to assess social behavior in neuropsychiatric and neurological animal models, including those of schizophrenia. The apparatus consists of three connected chambers, where one chamber contains a stranger mouse or novel object, and the other contains a familiar or unfamiliar mouse. The social interaction is quantified by the time spent and the number of interactions with the stranger mouse or object, as well as entries into the chambers, which also serves as a locomotor control. In schizophrenia animal models, a decrease in social interaction is consistently observed. Genetically modified models, including CRMP2 KO, Pcm1 +/−, and SREBP-1c KO mice, as well as pharmacologically induced models using ketamine or PCP, show reduced social interaction. Conversely, certain models, such as the NRG1 +/− mice, demonstrate increased social behavior. However, no change in social interaction was observed in models with heterozygous NRG1 mutations or selective PLC-β1 knockdown in the prefrontal cortex. Recent studies consistently show a decrease in sociability in rodent models of schizophrenia, with impairments linked to deletions of schizophrenia risk genes, alterations in dopaminergic and serotonergic systems, cannabinoid receptor mutations, stress, and dysfunctions in brain regions such as the amygdala. New assays have also been proposed to better measure sociability in a more ethologically valid manner. These findings highlight the complexity of social deficits in schizophrenia, with genetic, pharmacological, and environmental factors all contributing to the observed impairments in social behavior.

**12. Elevated Plus Maze**

Modeling blunted affect, a negative symptom of schizophrenia, is difficult in rodents. However, anti-anxiety behavior in tasks like the Elevated Plus Maze (EPM) is often used as a measure. The EPM leverages rodents' natural aversion to open, high spaces and their exploratory tendencies. It consists of open and closed arms crossing at a central area, with time and frequency spent in each arm reflecting anxiety. Increased time in closed arms suggests anxiety, while more time in open arms indicates less anxiety.

Studies show anxiety-like behavior in genetic models of schizophrenia, including Nlgn2 R215H KI mice, ankyrin G-deficient mice, and kynurenine 3-monooxygenase-deficient mice. Conversely, anxiolytic behavior was observed in free fatty acid receptor 1−/− female mice and CRMP2-deficient mice. These findings highlight the role of genetic factors in modulating anxiety-like behaviors in schizophrenia models. (8)

**INVITRO EXPERIMENTAL STUDIES**

**1. Mitochondrial Dysfunction**

Mitochondria are critical for neuronal function, including synaptic activity, Ca2+ signaling, action potential generation, ion homeostasis, and ATP synthesis. Neurons derived from schizophrenia (SZ) patients showed a two-fold increase in extramitochondrial oxygen consumption and elevated ROS, which were reduced by the mood stabilizer valproic acid (VPA).Cultures of dopaminergic and glutamatergic neurons from SZ patients exhibited impaired differentiation and maturation, with disrupted dopamine and glutamate metabolism, and mitochondrial dysfunction. Notably, SZ patient-derived neurons with 22q11.2DS showed reduced ATP levels and decreased activity in oxidative phosphorylation complexes I and IV, alongside downregulation of mitochondrial-encoded genes. The mitochondrial ribosomal protein L40 (MRPL40) gene, deleted in 22q11.2DS, was reduced in these neurons and linked to altered mitochondrial function and psychosis-related cognitive deficits in mice. In patient-derived NSCs, metabolic analysis revealed altered oxygen consumption, increased basal respiration, and elevated glycolytic proteins linked to axonal guidance and ROS. Mitochondrial impairments such as reduced ATP production and mitochondrial responses to stimulation were observed in brain organoids from other SZ patient hiPSCs. Furthermore, reduced mitochondrial numbers and altered morphology were found in NPCs and hippocampal cells from a SZ patient with de novo mutations. A study of SZ patient-derived cortical inhibitory neurons (cINs) showed compromised Ox Phos function and oxidative stress, which was reversed by Alpha Lipoic Acid/Acetyl-L-Carnitine (ALA/ALC) treatment. In 22q11DS patients, neurons from affected carriers showed reduced ATP and Ox Phos activity, while neurons from unaffected carriers displayed upregulated Ox Phos subunits and mitochondrial biogenesis-related genes.

**2. Developmental Impairments Mediated by miRNA**

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by inhibiting translation or degrading RNA. miR-137, in particular, has been implicated in schizophrenia (SZ), and the DGCR8 gene, involved in miRNA biogenesis, is located within the SZ-associated 22q11.2 region. miR-19 regulates adult-born neuron migration and maturation by targeting Rapgef2. Downregulation of miR-19 in SZ patient-derived NPCs caused abnormal migration, correlating with altered Rapgef2 expression, suggesting miR-19 dysregulation may contribute to SZ.In childhood-onset SZ, miR-9 is downregulated in NPCs from individuals with CNVs (e.g., 22q11.2, 1p33). This inhibits NPC proliferation by suppressing TLX. Overexpression of miR-9 restored migration in SZ-derived NPCs, while miR-9 knockdown induced migration defects in controls, indicating that reduced miR-9 activity increases SZ risk. miR-219, upregulated in SZ brain regions, promotes oligodendrocyte differentiation in OPCs by repressing negative regulators. In DISC1-mutant NPCs, miR-219 upregulation impaired proliferation, which was rescued by restoring TLX or downregulating miR-219, highlighting its role in reducing NSC proliferation in SZ.

**3. Implications of glial cells in schizophrenia**

Recent evidence suggests glial cells contribute to schizophrenia (SZ) pathogenesis. Excessive microglial activation, combined with genetic predisposition, may drive SZ. Microglia perform synaptic pruning, and excessive pruning correlates with reduced synapse density in SZ. C4 gene variants in the MHC locus, associated with SZ, influence synaptic pruning, with SZ patient-derived microglia showing excessive pruning. Minocycline reduced synapse uptake in vitro and alleviated psychosis, indicating excessive pruning as a potential treatment target. Cortical inhibitory neurons (cINs), particularly PV and SST-expressing cells, are impacted in SZ. SZ patient-derived cINs, co-cultured with activated microglia, showed metabolic, mitochondrial, and synaptic dysfunction, which was reversed by Alpha Lipoic Acid/Acetyl-L-Carnitine. Astrocytes in SZ show impaired function, and glial-mouse chimeras with SZ patient glial cells exhibited abnormal migration, morphology, and behavior, including anxiety and sleep issues. In monozygotic twins discordant for SZ, astrocytes from SZ patients showed sex-specific gene expression changes, including altered glutamate receptor signaling and neuronal survival genes like GRIK2 and CHL1. Astrocyte transplantation into mice caused behavioral changes and altered gene expression linked to inflammation and synaptic dysfunction. These findings emphasize the role of astrocytes,

including sex-specific factors, in SZ. Additionally, SZ-derived oligodendrocyte precursor cells (OPCs) displayed impaired differentiation, reduced white matter integrity, and abnormal morphology, pointing to oligodendrocyte dysfunction as a significant contributor to SZ. (9)

## COGNITIVE ASSESSMENTS IN SCHIZOPHRENIA

### 1. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a cognitive screening tool that provides a total score and five cognitive ability index scores. This study evaluated the test-retest stability of the RBANS in patients with schizophrenia compared to a healthy control group. The RBANS appears to be a valuable tool for assessing cognitive function and may serve as a prognostic indicator in schizophrenia.However, there are important considerations when evaluating its effectiveness in measuring individual changes. Most psychometric instruments report only reliability coefficients, and inappropriate measures like Pearson's correlation are sometimes used to assess reliability. Pearson's correlation may not accurately reflect agreement between ratings, especially when time-2 measures are consistently larger than time-1 measures. The intraclass correlation coefficient (ICC) is a better measure for assessing true agreement, as it evaluates the variation between time-1 and time-2 scores. High agreement results in a high ICC, while large differences yield a low ICC, making the ICC the preferred method over Pearson's correlation for evaluating reliability. (10)

### 2. The Brief Assessment of Cognition in Schizophrenia (BACS)

The Brief Assessment of Cognition in Schizophrenia (BACS) evaluates five cognitive domains through six tests and takes approximately 30-35 minutes to complete in schizophrenia patients. While its reliability and sensitivity to schizophrenia-related deficits have been established, its relationship to functional outcomes remains unclear. Future trials for cognitive-enhancing treatments may assess both cognitive performance and real-world functional outcomes. This study aimed to explore the relationship between the BACS and a potential co-primary measure for cognition treatment studies, and to assess whether this measure explains additional variance in functioning beyond cognitive performance. (11)

Following is a description of the six subtests of the BACS:

1. **List Learning (Verbal Memory)**: Subjects are read 15 words and recall as many as possible over five trials. Eight alternate forms reduce practice effects. Measures: number of words recalled per trial. Time: 7 min.
2. **Digit Sequencing Task (Working Memory)**: Subjects reorder clusters of numbers from lowest to highest. Measures: number of trials with all items in correct order. Time: 5 min.
3. **Token Motor Task (Motor Speed)**: Subjects pick up 100 plastic tokens as quickly as possible for 60 seconds. Measures: number of tokens placed in a container. Time: 3 min.
4. **Verbal Fluency (Processing Speed)**: Category Instances (Semantic Fluency): Subjects generate as many animal names as possible in 60 seconds. Controlled Oral Word Association (Letter Fluency): Subjects generate words starting with F and S in separate 60-second trials. Measures: number of words per trial. Time: 5 min.
5. **Tower Test (Executive Functions/Reasoning and Problem Solving)**: Subjects determine how many moves are required to rearrange balls on pegs to match a given picture. Measures: number of trials with correct moves. Time: 7 min.
6. **Symbol Coding (Attention and Processing Speed)**: Subjects match numerals 1-9 to symbols within 90 seconds. Measures: number of correct items. Time: 3 min. (12)

## CURRENT TRATMENT AND MANAGEMENT STRATEGIES FOR SCHIZOPHRENIA

### 1. Pharmacological Treatment

Antipsychotic medications are the primary treatment for schizophrenia, targeting dopamine, serotonin, and acetylcholine receptors. New drugs like xanomeline and trospium chloride focus on acetylcholine receptors.Treatment aims to manage symptoms with the lowest effective dose, often requiring adjustments. Additional medications, such as antidepressants or mood stabilizers, may also be prescribed. It can take weeks to evaluate effectiveness.Side effects may discourage medication adherence. Psychiatrists monitor and adjust treatment to minimize these. Discuss the risks and benefits of prescribed medications with your provider. Second-generation antipsychotics generally have fewer movement-related side effects, such as tardive dyskinesia, which can be permanent.

**Second Generation Anti-psychotics:** Aripiprazole, Asenapine, Clozapine, Olanzapine
**First Generation Anti-psychotics:** Chlorpromazine, Fluphenazine, Haloperidol, Perphenazine
**Long Acting Injectables:** Aripiprazole, Fluphenazine decanoate, Haloperidol decanoate

### 2. Management of Treatment-Resistant Schizophrenia

About one-third of schizophrenia patients have treatment-resistant schizophrenia, where symptoms persist despite two or more adequate trials of antipsychotics. Clozapine is the recommended treatment for these

cases, with a 40% response rate. It's also recommended for patients at high risk of suicide or aggression. Clozapine requires gradual dose increases to avoid side effects like seizures and sedation. Effective doses are 300–450 mg daily, with a target blood level between 350 ng/mL and 600 ng/mL. ANC monitoring is essential to prevent agranulocytosis, with regular checks through the Clozapine REMS program. Side effects include sialorrhea (excessive salivation), which is managed with nonpharmacologic methods or topical treatments like ipratropium or atropine. Clozapine may also cause gastrointestinal issues, seizures, and myocarditis.For treatment-resistant cases, electroconvulsive therapy (ECT) can be considered, with efficacy rates of 40% to 70%. The APA recommends continuing the same antipsychotic medication for effective symptom management.

**3. Psychosocial Interventions**

After symptom improvement, continuing medication is crucial. Additionally, participating in psychological and psychosocial treatments is vital, including:

- **Individual Therapy**: Talk therapy (psychotherapy) helps improve thought patterns, cope with stress, and identify early warning signs of symptom relapse.
- **Social Skills Training**: This helps enhance communication and social interactions, enabling better participation in daily activities.
- **Family Therapy**: Families learn how to manage and cope with schizophrenia, offering support to the patient.
- **Vocational Rehabilitation and Supported Employment**: This counseling helps individuals with schizophrenia prepare for, find, and maintain jobs.

Most individuals with schizophrenia need daily life support. Many communities offer programs for jobs, housing, self-help groups, and crisis situations. A case manager or treatment team member can assist in finding these resources. With appropriate treatment, many can successfully manage the condition.

**4. Hospital Stay**

During crisis periods or when symptoms are severe, individuals may need hospitalization for their safety. Hospital stays ensure they receive proper nutrition, adequate sleep, and regular hygiene

.

**5. Electroconvulsive Therapy**

For adults with schizophrenia who do not respond to medication, healthcare professionals may consider electroconvulsive therapy (ECT). This procedure is performed under general anesthesia, which means the patient is asleep during the process. Small electric currents are passed through the brain, inducing a therapeutic seizure that lasts 1 to 2 minutes. ECT is also used to treat severe depression when other treatments fail. (13)

**EMERGING AGENTS FOR THE MANAGEMENT OF SCHIZOPHRENIA**

Approximately 30% of individuals with schizophrenia are treatment-resistant to current drug therapies. Additionally, 80%-90% will experience relapse, often due to nonadherence to maintenance therapy. Research has identified gaps in treatment, such as the need for agents that improve cognition, address negative symptoms, manage treatment-resistant cases, have better adverse effect (AE) profiles, and improve adherence. Novel therapies aiming to address these gaps have either recently been approved or are in research stages.

**Novel Treatment Strategies and Emerging Agents for Schizophrenia**

Approximately 30% of individuals with schizophrenia are resistant to current drug therapies, and 80%-90% will experience a relapse, often due to nonadherence to maintenance therapy. Research has identified gaps in pharmacologic therapy, including the need for agents that improve cognition, treat negative symptoms, address treatment-resistant schizophrenia, have better side effect profiles, and enhance adherence. Recent novel therapies are being developed or researched to address these gaps.

**New Formulation Approved: Asenapine Transdermal System**

The Asenapine transdermal system, approved in October 2019, is the only transdermal treatment for schizophrenia. A 6-week study with 616 adults showed that both 3.8 mg/24 hours and 7.6 mg/24 hours doses significantly improved PANSS scores compared to placebo ($P < .01$). CGI-S also showed improvement. Common side effects included EPS, application-site reactions, and weight gain. Transdermal delivery offers benefits like improved adherence and avoidance of side effects seen with sublingual forms. Release date is pending.

**New Agent Approved: Lumateperone Tosylate (ITI-007)**

Lumateperone, approved in December 2019 for schizophrenia, targets dopamine D1/D2 receptors, NMDA receptor GLuN2B, and AMPA currents via the mTOR pathway.

In two Phase 3 trials:

1. ITI-007-301 (450 participants) showed 60 mg/day Lumateperone significantly improved PANSS total score (P = 0.022) versus placebo. Common side effects: somnolence, sedation, fatigue. No significant changes in EPS, weight, lipids, glucose, or prolactin.
2. ITI-007-302 (696 participants) did not show significant separation from placebo, while risperidone did. A larger placebo effect in this trial affected reliability.

**Agents Under Development**

*Olanzapine/Samidorphan*

This combination therapy combines samidorphan (μ-opioid receptor antagonist) with olanzapine to mitigate olanzapine's weight gain and metabolic side effects while maintaining its therapeutic effect.

- ENLIGHTEN-1 (403 patients): Olanzapine/samidorphan showed significant PANSS improvement (P < .001) and CGI-S improvement (P = .002) compared to placebo.
- ENLIGHTEN-2 (561 patients): Olanzapine/samidorphan resulted in less weight gain compared to olanzapine (4.21% vs 6.59%, P = .003).
  The drug was approved in 2020.

***Paliperidone***

Paliperidone long-acting injectable (LAI) formulations (monthly/trimonthly) are used to improve adherence. A phase 3 trial for a 6-month formulation is ongoing, with completion expected in 2020.

***Pimavanserin***

Approved for Parkinson's psychosis, pimavanserin is under Phase 3 investigation for residual positive symptoms in schizophrenia. Although the primary endpoint was not significant (P = .094), secondary negative symptom improvements were noted.

***Risperidone ISM***

This formulation of risperidone is designed to improve adherence by eliminating the need for initial oral antipsychotics. Phase 3 PRISMA-3 results show significant improvements in PANSS and CGI with 75 mg and 100 mg doses (P < .0001).

***Roluperidone***

Roluperidone targets negative symptoms and cognitive dysfunction in schizophrenia. Phase 3 trials (501 patients) aim to assess PANSS Marder negative symptoms score changes. Top-line results are expected in mid-2020.

***TAAR-1 Agonists***

SEP-363856, a TAAR-1 agonist, showed significant PANSS improvement (P = .001) in a Phase 2 study and has received FDA breakthrough designation. A Phase 3 trial, DIAMOND, is ongoing with over 1000 participants, targeting completion in 2022. (14)

## CONCLUSION

Schizophrenia is a complex and multifaceted disorder, characterized by profound impacts on an individual's behavior, cognition, and overall quality of life. With an estimated global prevalence of 1%, schizophrenia continues to pose significant challenges for both patients and healthcare providers. Its early onset, typically in late adolescence or early adulthood, necessitates prompt intervention to mitigate its long-term effects. Behavioral and cognitive assessments remain vital in the accurate diagnosis and ongoing management of the disease, with tools like the PANSS and cognitive assessments providing essential insight into symptom severity and progression. Recent advances in in vitro studies have enhanced our understanding of the underlying pathophysiology of schizophrenia, particularly the roles of neurotransmitters like dopamine, serotonin, and glutamate in its onset and persistence. These insights are driving the development of emerging agents that target new molecular pathways to address the limitations of current therapies. As treatment-resistant schizophrenia remains a major challenge, novel agents such as lumateperone, olanzapine/samidorphan, and TAAR-1 agonists show promise in improving therapeutic outcomes, particularly in reducing side effects like weight gain and metabolic disturbances. Though the pharmacologic landscape is evolving, the need for better adherence, improved cognitive outcomes, and more targeted treatments remains. Long-acting injectable formulations, novel mechanisms of action, and combination therapies represent the future of schizophrenia management, offering hope for more personalized and effective treatments. Despite the progress, continued research is crucial to address the unmet needs of schizophrenia patients, particularly in improving cognitive function and reducing the burden of treatment-resistant cases.

## REFERENCES

1. 1.Orsolini L, Pompili S, Volpe U. Schizophrenia: A Narrative Review of Etiopathogenetic, Diagnostic and Treatment Aspects. Clin Med. 2022;11(17):5040.

2. Saparia P, Patel A, Shah H, Solanki K, Patel A, Sahayata M. Schizophrenia: A Systematic Review. Clin Exp Psychol. 2022;8(7):65-70.
3. Chaudhary S, Chaudhary S, Tyagi V. A Review on Schizophrenia: Outline and Treatment. Int J Pharm Sci Rev Res. 2022;73(2):35-46.
4. Volkan K. Schizophrenia: Epidemiology, Causes, Neurobiology, Pathophysiology, and Treatment. J Health Med Sci. 2020;3(4):487-521.
5. Stilo SA, Murray RM. The Epidemiology of Schizophrenia: Replacing Dogma with Knowledge. Dialogues Clin Neurosci. 2022;12(3):305-315
6. Jones CA, Watson DJG, Fone KCF. Animal models of schizophrenia. *J Psychopharmacol*. 2011;25(5):1-13.
7. 7.Malik JA, Yaseen Z, Thotapalli L, Ahmed S, Shaikh MF, Anwar S. Understanding translational research in schizophrenia: A novel insight into animal models. *[Journal Name]*. 2023 Jan 24.
8. Ang MJ, Lee S, Kim JC, Kim SH, Moon C. Behavioral tasks evaluating schizophrenia-like symptoms in animal models: A recent update. *Curr Neuropharmacol*. 2021 Apr 29;19(5):641–664.
9. Dubonyte U, Asenjo-Martinez A, Werge T, Lage K, Kirkeby A. Current advancements of modelling schizophrenia using patient-derived induced pluripotent stem cells. Acta Neuropathol Commun. 2022;10(1):125
10. Wilk CM, Gold JM, Bartko JJ, Dickerson F, Fenton WS, Knable M, Randolph C, Buchanan RW. Test-retest stability of the Repeatable Battery for the Assessment of Neuropsychological Status in schizophrenia. Am J Psychiatry. 2002;159(5):838-844.
11. Keefe RSE, Poe M, Walker TM, Harvey PD. The relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to functional capacity and real-world functional outcome. Schizophr Res. 2006;28(2):260-269.
12. Keefe RSE, Harvey PD, Goldberg TE, Gold JM, Walker TM, Kennel C, Hawkins K. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr Res. 2008;102(1-3):108-115.
13. Hany M, Rehman B, Rizvi A, Chapman J. Schizophrenia. [Updated 2024 Feb 23]. In: StatPearls . Treasure Island (FL): StatPearls Publishing; 2025 Jan-.
14. Maroney M. A Managed Care Review of Schizophrenia: Evaluating Unmet Medical Needs, New Treatments, and Health Economics. Managed Care. 2020;26(3):42-48.