

# UNLOCKING THE THERAPEUTIC MAZE: A MULTIFACETED STRATEGY FOR SCHIZOPHRENIA TREATMENT

## Abstract

Schizophrenia is a complex psychiatric disorder characterized by hallucinations and delusional ideas. While the exact underlying mechanism is not fully understood, current antipsychotics have limitations, and they mainly target positive symptoms, leaving negative and cognitive symptoms untreated. The effectiveness of antipsychotics in treating schizophrenia symptoms is believed to be linked to their interactions with various neurotransmitter receptors. To address the diverse aspects of schizophrenia and improve treatment outcomes, there is a growing need for multi-targeting drugs. The targets for schizophrenia treatment include dopamine and serotonergic receptors, adrenergic and histamine receptors, muscarinic and nicotinic receptors, and metabotropic and ionotropic glutamatergic receptors. First, second, and third-generation antipsychotics are used in treating the condition, each with varying receptor affinities. Innovative drug design approaches involve exploring G protein-coupled receptors (GPCRs) and signaling mechanisms. Historically, receptors for dopamine, serotonin, and adrenaline have held significant importance as molecular targets for antipsychotic medications. Activation of G protein-coupled receptors (GPCRs) leads to gradual synaptic transmission via diverse downstream routes, a subset of which entails the release of intracellular calcium ions ( $Ca^{2+}$ ). In conclusion, developing multi-targeting drugs and exploring novel signaling mechanisms through GPCRs hold promise for enhancing schizophrenia treatment and addressing its various symptoms more effectively. This approach may pave the way for more

## Authors

### **Nirenjen. S**

Department of Pharmacology  
SRM College of Pharmacy  
SRM Institute of Science and Technology  
Potheri, Kattankulathur, Chengalpattu  
Tamil Nadu, India.

### **Tapabrata Khan**

Department of Pharmacology  
SRM College of Pharmacy  
SRM Institute of Science and Technology  
Potheri, Kattankulathur, Chengalpattu.  
Tamil Nadu, India.

### **Vishal Kumar**

Department of Pharmacology  
SRM College of Pharmacy  
SRM Institute of Science and Technology  
Potheri, Kattankulathur, Chengalpattu.  
Tamil Nadu, India.

### **Shreya Dey**

Department of Pharmacology  
SRM College of Pharmacy  
SRM Institute of Science and Technology  
Potheri, Kattankulathur, Chengalpattu.  
Tamil Nadu, India.

### **Rahul Kumar**

Department of Pharmacology  
SRM College of Pharmacy  
SRM Institute of Science and Technology  
Potheri, Kattankulathur, Chengalpattu.  
Tamil Nadu, India.

### **Dr. J. Narayanan**

Assistant Professor  
SRM College of Pharmacy  
SRM Institute of Science and Technology  
Potheri, Kattankulathur, Chengalpattu  
Chennai, Tamil Nadu, India.  
narayanj@srmist.edu.in

comprehensive and targeted therapies for this complex psychiatric disease.

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## I. INTRODUCTION

Schizophrenia is a severe mental illness affecting approximately 1% of the population. The clinical symptoms of schizophrenia can be categorized into positive (e.g., hallucinations, delusions), negative (e.g., social withdrawal, apathy), and cognitive deficits (e.g., memory and learning impairments, attention deficiencies) (Patel et al., 2014). Schizophrenia has been associated with disruptions in neurotransmission across various receptors and enzymes within the dopaminergic, glutamatergic, serotonergic, and adrenergic systems. While the dopaminergic hypothesis has long been a central idea in understanding the disorder, emerging discoveries are now establishing connections between schizophrenia and the glutamatergic system as well. The conventional "magic bullet" paradigm of single-target drugs has demonstrated limitations in addressing intricate neuropsychiatric conditions like schizophrenia (Stepnicki et al., 2018). Multi-target drugs (MTDs) or "magic shotgun" drugs have garnered attention due to their potential to engage multiple receptors and pathways, offering enhanced efficacy and reduced side effects. The approach to drug discovery has shifted from the molecular and cellular level to systems-biology-oriented strategies like network pharmacology. MTDs consider the interconnectedness, redundancy, and multifunctionality of biological networks, capturing the intricate interactions at play within the disease. MTDs offer several benefits over single-target drugs, including heightened effectiveness from synergistic or additive effects, improved distribution within target tissues, quicker therapeutic onset, and predictable pharmacokinetics, diminished drug interactions, reduced toxicity risk, enhanced patient adherence, and lowered chances of drug resistance (Kondej et al., 2018). Crafting potent MTDs, however, presents challenges such as judicious target selection, managing affinities, and circumventing interactions with unintended targets. Schizophrenia, a multifaceted neuropsychiatric disorder, involves a complex interplay of various neurotransmitter systems. The shift towards multi-target drugs and network pharmacology introduces fresh viewpoints to drug discovery for conditions like schizophrenia and other intricate diseases. Nevertheless, the effective design and development of MTDs remain a formidable task in the realm of pharmacology (Rossi et al., 2021).

The objective of the review is to introduce both traditional and innovative drug targets for addressing schizophrenia, alongside a discussion on the benefits and obstacles associated with multi-target drugs (MTDs). The authors undertook a comprehensive exploration of relevant literature, primarily utilizing the PubMed database. The search predominantly encompassed references from the preceding five years, targeting specific terms related to schizophrenia, drug targets, antipsychotics, multi-target antipsychotics, multi-target ligands, and investigational compounds. The authors may have also discussed existing multi-target antipsychotics available in the market, compounds currently undergoing clinical trials for schizophrenia treatment, and investigational compounds that have shown promise in preclinical studies. The focus on recent references ensures that the review incorporates the latest advancements in the field and provides valuable insights for researchers and clinicians working on schizophrenia treatment.

## II. SCHIZOPHRENIA TREATMENT: UNLEASHING THE POTENTIAL OF MULTI-TARGET ANTIPSYCHOTICS

Antipsychotic medications employed for treating schizophrenia are commonly classified into three generations based on their mechanism of action. First-generation antipsychotics exhibit a complex receptor profile and primarily exert their therapeutic effects by antagonizing dopamine D2 receptors. They can be further categorized into various chemical classes, including phenothiazines, butyrophenones, and thioxanthenes. The term "multi-target compounds" pertains to second and third-generation antipsychotics, as their effectiveness in mitigating symptoms of schizophrenia emerges not solely from their affinity for dopamine receptors but also from their interaction with serotonin receptors, notably 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors. Additional dopamine receptors, such as D<sub>3</sub>, also hold significance. When formulating innovative multi-target antipsychotics, it's crucial to account for off-target receptors, including 5-HT<sub>2C</sub>, H<sub>1</sub>, or M<sub>1</sub> receptors. First-generation antipsychotics exhibit an impact across a broad range of receptors, which consequently gives rise to a multitude of undesirable effects. Their inhibition of dopamine D<sub>2</sub> receptors within the nigrostriatal circuit leads to extrapyramidal effects, characterized by unintended movements, dyskinesia, akathisia, and dystonias. Concurrently, antagonism within the tuberoinfundibular circuit triggers excessive prolactin release. The antihistaminic properties of first-generation antipsychotics induce sedation, while their blockade of  $\alpha$ <sub>1</sub> adrenergic receptors may result in hypotension (Li et al., 2016).

Despite the continued prevalent usage and efficacy of first-generation antipsychotics in diminishing positive symptoms of schizophrenia, they frequently fall short in addressing negative and cognitive symptoms. Their predominant mechanism of action centres on antagonizing dopamine D<sub>2</sub> receptors, although they exhibit an intricate receptor profile that results in diverse adverse effects, encompassing extrapyramidal side effects (EPS). The advent of clozapine marked a new era in the treatment of schizophrenia. Second-generation antipsychotics, which include medications like quetiapine, olanzapine, risperidone, and others, primarily exert their effects through antagonism of serotonin 5-HT<sub>2A</sub> receptors. Their multi-receptor profile contributes to the alleviation of positive, negative, and cognitive symptoms associated with schizophrenia. These second-generation antipsychotics are generally better tolerated than their first-generation counterparts and carry a reduced likelihood of inducing extrapyramidal side effects (EPS). A third generation of antipsychotics, encompassing drugs such as aripiprazole, brexpiprazole, and cariprazine, has emerged. These medications stand out due to their distinctive mechanism of action involving partial agonism at dopamine D<sub>2</sub> receptors, rendering them as "dopamine stabilizers." Depending on the levels of extracellular dopamine, they can function as full or partial agonists or antagonists at the D<sub>2</sub> receptor. Additionally, they exhibit partial agonism at 5-HT<sub>1A</sub> receptors and impact other receptors, including D<sub>3</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>7</sub> (Gomes & Grace, 2021).

Third-generation antipsychotics find applications beyond schizophrenia and are generally associated with a low likelihood of inducing extrapyramidal side effects (EPS), with the exception of akathisia, which is more prevalent compared to low-potency first-generation antipsychotics. The introduction of second- and third-generation antipsychotics has indeed marked significant progress in the management of schizophrenia (Mailman & Murthy, 2010). However, the debate regarding their superiority over older drugs in terms of

effectiveness continues. Multi-target drugs (MTDs) have exhibited considerable clinical advantages in schizophrenia treatment due to their capability to impact multiple neurotransmitter pathways. By engaging various receptors implicated in the pathophysiology of schizophrenia, MTDs hold the potential to offer broader therapeutic effects, effectively addressing a wider range of symptoms encompassing positive, negative, and cognitive aspects (Löscher, 2021).. The rationale for further investigation of multi-target compounds stems from the complexity of schizophrenia's pathophysiology, which involves disturbances in multiple neurotransmitter systems, including dopamine, serotonin, glutamate, and others. Single-target drugs, especially those primarily targeting dopamine D2 receptors, may not adequately address the full range of symptomatology associated with schizophrenia. Further research and clinical trials are crucial to better understand the benefits and limitations of multi-target compounds and to identify the most effective combinations of receptor targets for optimal schizophrenia treatment.

### III. TARGETS FOR THE TREATMENT OF SCHIZOPHRENIA

**1. Dopamine and Serotonin Receptors:** The leading theory regarding schizophrenia suggests that it arises from heightened dopamine (DA) transmission in the brain, particularly in the striatum. In the mammalian brain, there exist five types of dopamine-binding receptors known as D1 to D5. These receptors can be grouped into two categories: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, and D4). The advancement of new antipsychotic medications has largely supported the dopaminergic hypothesis of schizophrenia, as observed by the reduction of positive symptoms through the use of dopamine receptor antagonists. Nonetheless, there are findings that challenge this hypothesis. For example, clozapine, an especially effective antipsychotic for individuals with resistant schizophrenia, exhibits minimal affinity for dopamine D2 receptors. Because dopamine receptors play crucial roles in functions such as movement, memory, perception, emotions, affect, and the regulation of prolactin secretion, the inhibition of D2-like receptors could lead to side effects linked to prolonged antipsychotic treatment (Brisch et al., 2014).

Serotonin (5-hydroxytryptamine, 5-HT) stands as a prominently discussed neurotransmitter, exerting its effects through distinct G protein-coupled receptors (GPCRs) and ligand-gated ion channels. Serotonin is widely distributed throughout the brain and plays essential roles in physiological processes like sleep, wakefulness, mood regulation, feeding behaviour, and emotional responses. There exist 14 different subtypes of serotonin receptors. Various research endeavours have indicated a correlation between serotonin receptor polymorphisms and susceptibility to schizophrenia. These findings underscore the significant involvement of serotonergic neurotransmission in the underlying mechanisms of schizophrenia. However, further investigations are required to enhance the effectiveness of antipsychotic medications that modulate the activity of serotonin receptors (McCorvy & Roth, 2015).

Positive symptoms of schizophrenia are believed to stem from excessive activity in the mesolimbic dopaminergic pathway, which triggers D2 receptors in regions like the nucleus accumbens, amygdala, and hippocampus. Conversely, negative symptoms might arise from reduced activity in the mesocortical dopaminergic pathway, where D1 receptors predominate. Many antipsychotic drugs, including second-generation or

atypical ones, not only block dopamine D2 receptors but also engage with an array of other receptors, including different dopamine receptors (D1, D3, or D4), serotonin receptors (especially 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub>), histamine (H<sub>1</sub>), and  $\alpha$ <sub>1</sub>-adrenergic receptors (Collo et al., 2020). These interactions underlie various side effects associated with antipsychotic medications. The serotonin hypothesis of schizophrenia is founded on observations of interactions between hallucinogenic substances like LSD and serotonin. Antipsychotic drugs that antagonize serotonin 5-HT<sub>2A</sub> receptors, such as clozapine and risperidone, have displayed positive effects in treating schizophrenia. Serotonin receptors, particularly 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors, play a pivotal role in modulating dopaminergic transmission within the brain. Blocking 5-HT<sub>2A</sub> receptors may contribute to ameliorating both positive and negative symptoms of schizophrenia while diminishing extrapyramidal side effects (Kim, 2021). Activating 5-HT<sub>1A</sub> receptors could also offer cognitive benefits and reduce extrapyramidal side effects induced by antipsychotics. In the pursuit of novel medications targeting dopamine and serotonin receptors, diverse signaling mechanisms inherent to G protein-coupled receptors (GPCRs) can be exploited. These encompass allosteric modulators, biased ligands, compounds influencing receptor dimers, oligomers, and mosaics, as well as intentionally versatile multi-target ligands (Ohno, 2011).

- 2. Adrenergic and Histaminergic Receptors:** Noradrenaline has been implicated in the underlying mechanism of schizophrenia, although the precise role of  $\alpha$ -adrenergic receptors remains somewhat elusive. Atypical antipsychotics, recognized for their diverse pharmacological effects, are thought to interact with  $\alpha$ -adrenergic receptors, contributing to their distinct properties. Antagonism of  $\alpha$ <sub>1</sub> adrenergic receptors is believed to be advantageous in alleviating positive symptoms, especially during acute phases of schizophrenia (Maletic et al., 2017). Conversely, antagonism of  $\alpha$ <sub>2</sub> adrenergic receptors, as seen in medications like clozapine and, to some extent, risperidone, may hold significance in mitigating negative symptoms and cognitive deficits. Blocking  $\alpha$ -adrenergic receptors could help stabilize dopaminergic neurotransmission in schizophrenia. However, it's worth noting that there are also reports suggesting that activating  $\alpha$ <sub>2A</sub> adrenergic receptors in the prefrontal cortex could enhance cognitive functions. Moreover, supplemental antagonism of  $\alpha$ <sub>2</sub> adrenergic receptors has been demonstrated to enhance the antipsychotic effects of risperidone and promote cortical dopaminergic and glutamatergic neurotransmission (de Bartolomeis et al., 2023).

Histamine H<sub>1</sub> receptor blockade is a commonly observed off-target effect of antipsychotic drugs and is linked to sedation and weight gain. While weight gain and metabolic issues might also be attributed to the blockade of adrenergic or cholinergic receptors, histamine H<sub>1</sub> receptor antagonism is deemed pivotal in the development of obesity stemming from second-generation antipsychotics. The histamine H<sub>3</sub> receptor is gaining attention as a target for novel antipsychotic treatments (Kroeze et al., 2003). Selective antagonists or inverse agonists targeting this receptor subtype have displayed efficacy in addressing cognitive deficits associated with schizophrenia.

In essence, the involvement of noradrenaline and its interaction with  $\alpha$ -adrenergic receptors, along with the signaling of histamine receptors, are crucial considerations in comprehending schizophrenia's mechanisms and the impacts of antipsychotic medications. Nevertheless, it remains crucial to recognize that schizophrenia is intricate

and multifaceted, necessitating further research to fully fathom the distinct roles played by various neurotransmitter systems in its pathophysiology and treatment (Sullivan et al., 2015).

- 3. Muscarinic and Nicotinic Receptors:** Muscarinic receptors play a crucial role in modulating synaptic plasticity within the prefrontal cortex, where their activation induces long-term depression at the hippocampo-prefrontal cortex synapse. Disruptions in cholinergic neurotransmission have been implicated in the context of schizophrenia. Post-mortem examinations have revealed a diminished count of cholinergic interneurons in the ventral striatum of individuals with schizophrenia. Neuroimaging studies have further suggested reduced availability of muscarinic receptors in these patients, and there exists a negative correlation between the availability of muscarinic receptors and the occurrence of positive symptoms in schizophrenia (Scarr, 2012). In the spectrum of schizophrenia-related hypotheses, the muscarinic hypothesis has emerged. It posits that muscarinic receptor antagonists exacerbate cognitive and negative symptoms in patients, whereas muscarinic receptor agonists, such as xanomeline, have demonstrated the ability to ameliorate all symptoms in both human subjects with schizophrenia and relevant animal models. Beyond the muscarinic receptors, nicotinic cholinergic receptors are also implicated in the pathophysiology of schizophrenia. The observation that individuals with schizophrenia are often heavy smokers is thought to be connected to the involvement of nicotinic receptors in the disorder (Foster et al., 2021). Smoking might provide relief from negative symptoms of schizophrenia. The activation of  $\alpha 7$  nicotinic receptors through agonists or positive allosteric modulators has been explored as a promising avenue for treating schizophrenia. However, while accumulating evidence suggests the involvement of cholinergic neurotransmission and cholinergic receptors in schizophrenia, the exact mechanisms and implications for treatment remain subjects of ongoing research. The cholinergic system's intricacies, including its interactions with other neurotransmitter systems in the brain, remain not fully comprehended. As a result, further research is necessary to fully elucidate the precise roles of cholinergic receptors in schizophrenia and to develop effective, targeted treatments for this complex disorder (Olinic & Freedman, 2012).
- 4. Metabotropic and Ionotropic Glutamatergic Receptors:** Glutamate serves as a primary excitatory neurotransmitter in the central nervous system, and the glutamatergic pathways interconnecting brain regions like the cortex, limbic system, and thalamus play a pivotal role in the context of schizophrenia. Irregularities in glutamatergic neurotransmission can impact synaptic plasticity and cortical micro circuitry, particularly the functioning of NMDA receptors (Zhou & Danbolt, 2014). NMDA receptors, acting as ligand-gated ion channels, hold significance for excitatory neurotransmission, plasticity, and excitotoxicity. The glutamatergic hypothesis of schizophrenia draws from the observation that NMDA receptor antagonists, such as phencyclidine or ketamine, induce schizophrenia-like symptoms in animal models and healthy individuals. This hypothesis proposes a hypofunction of NMDA receptors in schizophrenia, although other ionotropic glutamate receptors (AMPA and kainite receptors) and metabotropic glutamate receptors are also implicated. Therapeutic endeavours have demonstrated that compounds augmenting NMDA receptor signaling can alleviate specific symptoms in individuals with schizophrenia (Nakazawa & Sapkota, 2020). Post-mortem investigations have revealed anomalies in glutamatergic receptor density and subunit composition within

distinct brain regions, including the prefrontal cortex, thalamus, and temporal lobe, regions associated with altered stimulation during cognitive tasks in schizophrenia patients. The hypo activity of NMDA receptors might contribute to morphological and structural brain changes linked to psychosis. Antipsychotic medications could potentially influence glutamatergic neurotransmission by affecting glutamate release, modulating glutamatergic receptors, or altering receptor density and subunit composition. Certain second-generation antipsychotics have exhibited distinct interactions with NMDA receptors compared to their first-generation counterparts (Coyle et al., 2012). As a prospective target for treating schizophrenia, abnormalities in glutamatergic neurotransmission, especially within NMDA receptors, have sparked interest. Controlled ligands stimulating NMDA receptors, particularly targeting the glycine modulatory binding site, are being explored to prevent excitotoxicity. Positive allosteric modulators of AMPA receptors and modulators of metabotropic glutamate receptors, such as mGluR2/3 receptor ligands, are also under investigation as potential interventions for schizophrenia based on the glutamatergic hypothesis. The glutamatergic hypothesis has illuminated the involvement of glutamatergic neurotransmission, particularly NMDA receptors, in schizophrenia's pathophysiology. This insight has ushered in novel prospects for treatments targeting glutamatergic receptors, particularly addressing cognitive deficits and negative symptoms in schizophrenia. Nonetheless, further research and clinical trials are essential to thoroughly assess the safety and effectiveness of these potential treatments (Rubio et al., 2012).

## 5. Multi-Target Compounds to Treat Schizophrenia

Drug Class	Drug	Dose	Side Effects
First-generation antipsychotics	Chlorpromazine	200mg/ day	Blank facial expression, Shuffling walk
Second generation anti-psychotics	Clozapine	300-600mg/ day	Tremor, Weight gain, Spinning sensation.
Second generation anti-psychotics	Risperidone	6 – 16mg/ day	Anxiety, Depressed mood, Tremor.
Second generation anti-psychotics	Olanzapine	10- 20mg/ day	Depression, Restlessness, Dizziness.
Second generation anti-psychotics	Quetiapine	300-450mg/ day	Dizziness, Feeling unsteady, Having trouble keeping balance.
Third generation anti-psychotics	Aripiprazole	10-15mg/ day	Nausea, Dyspepsia, Light-headedness



Third generation anti-psychotics	Brexpiprazole	1-4mg/ day	Weight gain, Restlessness, Lightheadedness
Third generation anti-psychotics	Cariprazine	1.5 – 3mg/ day	Blurred vision, Dizziness, Inability to move eyes

#### IV. NEWER DRUG DEVELOPMENT FOR SCHIZOPHRENIA

##### 1. **Unlocking Hope: Lumateperone's Promising Role in Schizophrenia Treatment:**

Lumateperone, known as Caplyta, is an innovative antipsychotic medicine designed for adults with schizophrenia. The U.S. FDA granted approval in December 2019. What sets lumateperone apart is its unique mechanism of action. It functions as a potent antagonist of serotonin 5-HT<sub>2A</sub> receptors and a partial agonist of serotonin 5-HT<sub>1A</sub> receptors (Edinoff et al., 2020). Additionally, it antagonizes dopamine D<sub>2</sub> receptors and exhibits moderate affinity for serotonin 5-HT<sub>2C</sub> and histamine H<sub>1</sub> receptors. This blend allows lumateperone to influence vital neurotransmitter systems associated with schizophrenia's underlying processes. By targeting various receptors, lumateperone achieves a more comprehensive impact on neurotransmitter signaling. Its efficacy in schizophrenia treatment stems from addressing both positive and negative symptoms. Excessive dopamine activity, particularly in the mesolimbic pathway, contributes to positive symptoms like hallucinations and delusions (Orzelska-Górka et al., 2022). Lumateperone's D<sub>2</sub> receptor blockade helps mitigate these symptoms. Moreover, its partial agonism of serotonin 5-HT<sub>1A</sub> receptors may alleviate negative symptoms tied to impaired prefrontal cortex function. These symptoms involve social withdrawal and diminished emotional expression. Activation of these receptors has been linked to better cognitive function and mood regulation. Lumateperone offers an advantage in terms of side effects compared to older antipsychotics. Traditional drugs often lead to extrapyramidal side effects (EPS) due to their strong D<sub>2</sub> receptor antagonism, resulting in issues like Parkinsonism and tardive dyskinesia. Lumateperone's milder D<sub>2</sub> receptor antagonism minimizes the risk of EPS, making it potentially safer (Maini et al., 2021). Clinical trials affirm lumateperone's efficacy. A key study found it significantly improved both positive and negative symptoms compared to a placebo. Additionally, it was well-tolerated, with low EPS incidence. Lumateperone diversifies schizophrenia treatment options. Its multi-pronged approach and balanced receptor modulation offer potential for symptom control and better tolerability. Yet, individual suitability varies, and careful monitoring and communication between patients and healthcare providers remain pivotal (Correll et al., 2020).

##### 2. **G-Protein Coupled Glutamate Receptors and Novel Signalling:** G-protein coupled glutamate receptors (mGluRs) and innovative signaling pathways have garnered significant interest in the realm of schizophrenia research due to their involvement in regulating glutamatergic neurotransmission. Glutamate, the primary excitatory neurotransmitter in the brain, plays a vital role in synaptic plasticity, learning, memory, and cognition. The disruption of glutamatergic neurotransmission has been linked to the pathophysiology of schizophrenia. Historically, the N-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis has been pivotal in comprehending glutamate's role in

schizophrenia. This notion posits that decreased activity of NMDA receptors, a type of ionotropic glutamate receptor, leads to compromised synaptic plasticity and cognitive deficits seen in the disorder. Nevertheless, contemporary research is progressively unveiling the contribution of metabotropic glutamate receptors, particularly G-protein coupled glutamate receptors, to the ailment (Kryszkowski & Boczek, 2021).

G-protein coupled receptors (GPCRs) constitute an expansive family of cell surface receptors engaged in signal transduction. They activate intracellular signaling pathways via interactions with G-proteins, triggering diverse cellular responses. In the context of glutamate, mGluRs are GPCRs that react to glutamate, modulating neuronal activity. These mGluRs encompass multiple subtypes divided into three groups based on sequence homology, signaling mechanisms, and ligand specificity: Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3), and Group III (mGluR4, mGluR6, mGluR7, and mGluR8). Each group exerts distinct effects on glutamatergic neurotransmission and neuronal excitability. In the context of schizophrenia, deviations in mGluR expression and function have been observed, particularly in the prefrontal cortex and hippocampus—regions pivotal for cognition and emotional processing. These altered expressions and signaling patterns of mGluRs are believed to contribute to the cognitive deficits and negative symptoms characteristic of the disorder. Novel signaling pathways linked to mGluRs involve their interactions with intracellular proteins like Homer proteins and the post-synaptic density (PSD) signaling complex. These interactions regulate intracellular calcium levels, thereby influencing synaptic plasticity and neurotransmitter release. Investigating mGluRs and their novel signaling pathways in schizophrenia has prompted the exploration of fresh treatment approaches. Targeting these receptors with selective agonists or positive allosteric modulators is being examined as a potential therapeutic avenue to mitigate cognitive deficits and negative symptoms associated with schizophrenia. The aim is to restore proper glutamatergic neurotransmission and synaptic plasticity, thereby alleviating the core symptoms of the disorder. It's crucial to acknowledge that while the research on mGluRs and novel signaling pathways in schizophrenia holds promise, it's still in its infancy, necessitating further studies to fully grasp the underlying mechanisms and develop effective and safe therapeutic interventions. As with any emerging research, prudence is advised in extrapolating findings to clinical applications until robust evidence is established. Nevertheless, these advancements offer a glimmer of hope for enhancing treatment possibilities for individuals grappling with schizophrenia (Tuteja, 2009).

- 3. Synaptic Plasticity as a Therapeutic Frontier in Schizophrenia:** Focusing on synaptic plasticity as a target for improved treatments in the complex landscape of schizophrenia has gained considerable attention. Synaptic plasticity refers to the capacity of synapses, which are connections between neurons, to adjust their strength in response to activity and experience. This fundamental process underpins learning, memory, and adaptive brain function. Within the context of schizophrenia, disruptions in synaptic plasticity have been implicated as a potential foundational mechanism for the cognitive impairments and other symptomatic manifestations associated with the disorder. Multiple lines of evidence suggest that irregularities in synaptic plasticity might contribute to the malfunctioning of neural circuits observed in schizophrenia. At the forefront of neurotransmitter systems crucial to synaptic plasticity lies the glutamatergic system, particularly the N-methyl-D-aspartate (NMDA) receptors. These receptors play a pivotal role in long-term potentiation

(LTP) and long-term depression (LTD)—cellular mechanisms of synaptic plasticity intricately tied to learning and memory. Research has unveiled a link between NMDA receptor hypo function and schizophrenia. This connection is evidenced by drugs that block NMDA receptors, like phencyclidine (PCP) or ketamine, which can induce symptoms akin to those of schizophrenia in otherwise healthy individuals (Obi-Nagata et al., 2019). Given the significance of NMDA receptors in synaptic plasticity and their potential role in schizophrenia, there has been growing interest in developing treatments that can modulate NMDA receptor activity to restore proper synaptic plasticity and neural circuitry function. Some potential strategies include:

- **NMDA Receptor Enhancers:** Compounds that enhance NMDA receptor function or increase its availability in the brain may improve synaptic plasticity and cognitive function. These enhancers are being investigated as potential adjunct therapies for schizophrenia.
- **Glycine Site Agonists:** The glycine site on the NMDA receptor is involved in its regulation. Agonists that bind to this site and facilitate NMDA receptor activity are being studied for their potential therapeutic effects in schizophrenia.
- **Glutamate Release Enhancers:** Drugs that increase the release of glutamate, the main excitatory neurotransmitter, may enhance synaptic plasticity and cognitive function in schizophrenia.
- **Positive Allosteric Modulators:** These compounds bind to a different site on the NMDA receptor and can enhance its activity without directly activating the receptor. Positive allosteric modulators are being explored as a potential means to enhance NMDA receptor function selectively.
- **Other Glutamatergic Targets:** In addition to NMDA receptors, other glutamatergic targets, such as metabotropic glutamate receptors (mGluRs), are also being investigated for their role in synaptic plasticity and as potential therapeutic targets for schizophrenia.

It is important to note that the development of drugs targeting synaptic plasticity in schizophrenia is still in its early stages, and much research is needed to fully understand the complexities of synaptic dysfunction in the disorder. Additionally, while targeting synaptic plasticity holds promise as a potential treatment approach, it is unlikely to be a standalone therapy, and a comprehensive understanding of the neurobiology of schizophrenia is necessary for the successful development of effective treatments. Nevertheless, the exploration of synaptic plasticity as a therapeutic target represents a promising avenue for advancing our understanding of schizophrenia and developing novel treatment strategies to improve the lives of individuals affected by this challenging condition.

## V. CONCLUSION AND FUTURE PERSPECTIVES

In our rapidly evolving world, an array of factors contributes to the prevalence of mental disorders, including schizophrenia. Although treatments have demonstrated efficacy against positive symptoms, addressing negative symptoms, cognitive deficits, and drug-resistant cases presents an ongoing challenge.

Within this context, the multi-target approach in medicinal chemistry has garnered considerable attention, particularly for intricate conditions like schizophrenia. This approach shines as a promising strategy for managing the disorder, offering advantages that single-target treatments may lack. Incorporating nicotinic and glutamatergic targets into contemporary multi-target drugs could prove beneficial in combatting negative symptoms and cognitive impairments. Furthermore, delving into novel signaling mechanisms, especially those tied to G-protein coupled receptors (GPCRs) like allosteric modulation, biased signaling, and receptor oligomerization, holds potential.

The success of this approach might be augmented by simultaneously targeting multiple receptors. To sum up, while current multi-target antipsychotics mainly focus on orthosteric ligands of aminergic GPCRs with selective serotonin reuptake inhibitor (SSRI) or serotonin transporter (SERT) inhibitory activity in some instances, a vast realm of unexplored possibilities exists, encompassing other receptors and enzymes as potential drug targets. Expanding the horizon to encompass a broader spectrum of signaling mechanisms beyond the conventional ternary complex model of GPCRs could pave the way for remarkable advancements in the treatment of schizophrenia.

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