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

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**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. Traditionally, dopamine, serotonin, and adrenaline receptors have been important molecular targets for antipsychotics. GPCRs activation results in slow synaptic transmission through multiple downstream pathways, some of which involve intracellular Ca2+ mobilization. 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 comprehensive and targeted therapies for this complex psychiatric disease.

**KEYWORDS**: Schizophrenia, Neurotransmitters, G protein-coupled receptors, Multi-target, Lumateperone, Synaptic plasticity.

1. **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). Disturbances in neurotransmission involving multiple receptors and enzymes within the dopaminergic, glutamatergic, serotoninergic, and adrenergic systems have been implicated in schizophrenia. The dopaminergic hypothesis has been a major concept in the disease, but novel findings are also linking schizophrenia with the glutamatergic system. The traditional "magic bullet" concept of single-target drugs has shown limitations in the treatment of complex neuropsychiatric diseases like schizophrenia (Stępnicki et al., 2018). Multi-target drugs (MTDs) or "magic shotgun" drugs have gained importance due to their potential to target multiple receptors and pathways, providing improved efficacy and fewer side effects. Drug discovery has shifted from the molecular and cellular level to systems-biology-oriented approaches like network pharmacology. MTDs take into account connectivity, redundancy, and pleiotropy of biological networks, reflecting the complex interactions occurring in the disease. MTDs offer several advantages over single-target drugs, including improved efficacy due to synergistic or additive effects, better distribution in target tissues, faster therapeutic onset, predictable pharmacokinetics, fewer drug interactions, and lower risk of toxicity, improved patient compliance, and reduced risk of drug resistance (Kondej et al., 2018). Designing potent MTDs comes with challenges, including proper target selection, affinity balancing, and avoiding interactions with off-targets. Schizophrenia is a complex neuropsychiatric disorder with a multifaceted pathophysiology involving various neurotransmitter systems. The shift towards multi-target drugs and network pharmacology provides new perspectives in drug discovery for the treatment of schizophrenia and other complex diseases. However, the design and development of effective MTDs remain a challenge in the field of pharmacology (Rossi et al., 2021).

The review aims to present classical and novel drug targets for the treatment of schizophrenia and discuss the advantages and challenges of multi-target drugs (MTDs). The authors conducted a literature search primarily using the PubMed database, focusing on references from the last five years, with specific search 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.

1. **SCHIZOPHRENIA TREATMENT: UNLEASHING THE POTENTIAL OF MULTI-TARGET ANTIPSYCHOTICS**

Antipsychotic agents used to treat schizophrenia are typically categorized into three generations based on their mechanism of action. First-generation antipsychotics have a complex receptor profile and primarily exert their therapeutic effects by blocking dopamine D2 receptors. They can be further divided into several chemical classes, including phenothiazines, butyrophenones, and thioxanthenes. The term "multi-target compounds" refers to second and third-generation antipsychotics, as their efficacy in alleviating schizophrenia symptoms arises not only from their affinity for dopamine receptors but also for serotonin receptors, particularly 5-HT2A and 5-HT1A receptors. Other dopamine receptors, such as D3, are also of interest. When designing novel multi-target antipsychotics, consideration should be given to off-target receptors, such as 5-HT2C, H1, or M1 receptors. First-generation antipsychotics affect a wide spectrum of receptors, leading to numerous adverse effects. Blocking dopamine D2 receptors in the nigrostriatal circuit causes extrapyramidal effects (unwanted movements, dyskinesia, akathisia, dystonias), while antagonism in the tuberoinfundibular circuit results in excessive prolactin release. Antihistaminic effects of first-generation antipsychotics cause sedation, and blocking α1 adrenergic receptors may lead to hypotension (Li et al., 2016).

Although first-generation antipsychotics are still commonly used and effective in reducing positive symptoms of schizophrenia, they often fail to address negative and cognitive symptoms. Their mechanism of action primarily involves dopamine D2 receptor antagonism, but they have a complex receptor profile leading to various adverse effects, including extrapyramidal side effects (EPS). The introduction of clozapine marked a new era in schizophrenia treatment. Second-generation antipsychotics, including drugs like quetiapine, olanzapine, risperidone, and others, act mainly through antagonism at serotonin 5-HT2A receptors. Their multi-receptor profile contributes to reducing positive, negative, and cognitive symptoms of schizophrenia. They are generally better tolerated than first-generation antipsychotics and have a lower probability of causing EPS. Drugs like aripiprazole, brexpiprazole, and cariprazine belong to the third generation of antipsychotics. They are distinctive because their mechanism of action involves partial agonism at dopamine D2 receptors, making them "dopamine stabilizers." Depending on extracellular dopamine levels, they can act as full or partial agonists or antagonists at the D2 receptor. They also have partial agonism at 5-HT1A receptors and affect other receptors like D3, 5-HT2A, 5-HT2B, and 5-HT7 (Gomes & Grace, 2021).

Third-generation antipsychotics are applicable in other psychiatric conditions besides schizophrenia and have a low probability of causing EPS, except for akathisia, which is more frequent than with low-potency first-generation antipsychotics. Indeed, the introduction of second- and third-generation antipsychotics has brought significant advancements in the management of schizophrenia (Mailman & Murthy, 2010). However, the debate regarding their superiority over older drugs in terms of effectiveness remains ongoing. Multi-target drugs (MTDs) have demonstrated notable clinical benefits in the treatment of schizophrenia due to their ability to target multiple neurotransmitter pathways. By addressing various receptors involved in the pathophysiology of schizophrenia, MTDs have the potential to provide broader therapeutic effects and alleviate a wider spectrum of symptoms, including positive, negative, and cognitive symptoms (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.

1. **TARGETS FOR THE TREATMENT OF SCHIZOPHRENIA**

**3.1 DOPAMINE AND SEROTONIN RECEPTORS**

The foremost hypothesis of schizophrenia revealed that schizophrenia is a result of hyperactivity of dopamine (DA) transmission in the brain, especially in the striatum. In the mammalian brain, there are five dopamine-binding receptors, called D1 to D5. These receptors are divided into two subcategories: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, and D4). The development of novel antipsychotics likely dopaminergic hypothesis of schizophrenia as it was noticed that positive symptoms of the disease can be reduced with dopamine receptor antagonists. Nevertheless, some findings against this hypothesis, e.g., clozapine, which is a very effective antipsychotic in patients with resistant schizophrenia, has a low affinity to dopamine D2 receptors. As dopamine receptors play an important role in movement, memory and perception, emotion and affect, and the regulation of prolactin secretion, blocking D2-like receptors may result in side effects linked with the long-lasting antipsychotics medication (Brisch et al., 2014).

Serotonin (5-hydroxytryptamine, 5-HT) is one of the largely deliberated neurotransmitters, acting through clear G protein-coupled receptors (GPCRs) and ligand-gated ion channels. Serotonin is extended all over the brain. It is required physiologically in sleep, wakefulness, mood, feeding behaviour, and emotional changes. Serotonin receptors are available as 14 different subtypes. The results of different studies illustrated an alliance between serotonin receptor polymorphism and disease sensitivity for schizophrenia. Findings highlight the crucial role of serotonergic neurotransmission in the pathophysiology of schizophrenia. Nevertheless, further studies are needed to improve the efficiency of an antipsychotic drug that regulates the activity of serotonin receptors (McCorvy & Roth, 2015).

Positive symptoms of schizophrenia are thought to result from over activity in the mesolimbic dopaminergic pathway, which activates D2 receptors in areas like the nucleus accumbens, amygdala, and hippocampus. Negative symptoms may arise from lowered activity in the mesocortical dopaminergic pathway, where D1 receptors predominate. Most antipsychotic drugs, including second-generation or atypical antipsychotics, not only block dopamine D2 receptors but also interact with a wide range of other receptors, such as other dopamine receptors (D1, D3, or D4), serotonin receptors (especially 5-HT2A and 5-HT2C), histamine (H1), and α1-adrenergic receptors (Collo et al., 2020). These interactions are associated with various side effects of antipsychotic medications. The serotonin hypothesis of schizophrenia is based on the observation of interactions between hallucinogenic drugs like LSD and serotonin. Antipsychotic drugs that block serotonin 5-HT2A receptors, such as clozapine and risperidone, have been shown to have beneficial effects on the treatment of schizophrenia. Serotonin receptors, particularly 5-HT2A and 5-HT1A receptors, play a significant role in modulating dopaminergic transmission in the brain. Antagonism of 5-HT2A receptors may contribute to the improvement of both positive and negative symptoms of schizophrenia and reduce extrapyramidal side effects (Kim, 2021). Activation of 5-HT1A receptors may also have beneficial effects on cognition and reduce extrapyramidal side effects induced by antipsychotics. Novel drugs acting on dopamine and serotonin receptors can be developed based on different signalling mechanisms typical for G protein-coupled receptors (GPCRs). These include allosteric modulators, biased ligands, compounds acting on receptor dimers, oligomers, and mosaics, as well as intentionally promiscuous multi-target ligands (Ohno, 2011).

**3.2 ADRENERGIC AND HISTAMINERGIC RECEPTORS**

Noradrenaline has been implicated in the pathophysiological mechanism of schizophrenia, but the specific role of α-adrenergic receptors is not yet fully understood. Atypical antipsychotics, which are known for their diverse pharmacological effects, are thought to interact with α-adrenergic receptors, contributing to their atypical properties. Antagonism at α1 adrenergic receptors is believed to be beneficial in treating positive symptoms, especially in acute schizophrenia (Maletic et al., 2017). On the other hand, antagonism at α2 adrenergic receptors, particularly seen in drugs like clozapine and to some extent risperidone, may be important for relieving negative symptoms and cognitive impairments. Blockade of α-adrenergic receptors may stabilize dopaminergic neurotransmission in schizophrenia. However, it's worth noting that there are also reports suggesting that activation of α2A adrenergic receptors in the prefrontal cortex could improve cognitive functions. Additionally, adjunctive α2 adrenergic receptor antagonism has been shown to enhance the antipsychotic activity of risperidone and promote cortical dopaminergic and glutamatergic neurotransmission (de Bartolomeis et al., 2023). Histamine H1 receptor blockade is a common off-target effect of antipsychotic drugs and is associated with sedation and weight gain. While weight gain and metabolic issues may also be attributed to blockade of adrenergic or cholinergic receptors, histamine H1 receptor antagonism is considered a key factor in the development of obesity induced by second-generation antipsychotics. The histamine H3 receptor is emerging as a target for novel antipsychotic medications (Kroeze et al., 2003). Selective antagonists or inverse agonists of this receptor subtype have shown efficacy in treating cognitive deficits associated with schizophrenia. In summary, noradrenaline and its interaction with α-adrenergic receptors, as well as histamine receptor signalling, are important factors to consider in understanding the mechanisms of schizophrenia and the effects of antipsychotic medications. However, it's essential to keep in mind that schizophrenia is a complex and multifaceted disorder, and more research is needed to fully comprehend the specific roles of various neurotransmitter systems in its pathophysiology and treatment (Sullivan et al., 2015).

 **3.3 MUSCARNIC AND NICOTINIC RECEPTORS**

 Muscarinic receptors play a pivotal role in modulating synaptic plasticity in the prefrontal cortex. Stimulation of these receptors leads to long-term depression at the hippocampo-prefrontal cortex synapse. Disturbances in cholinergic neurotransmission have been implicated in schizophrenia. Post-mortem studies have shown a reduced number of cholinergic interneurons in the ventral striatum in schizophrenia patients. Neuroimaging studies have also indicated lower availability of muscarinic receptors in schizophrenia patients, and positive symptoms of schizophrenia are negatively correlated with muscarinic receptor availability (Scarr, 2012). Muscarinic receptor antagonists worsen cognitive and negative symptoms in schizophrenia patients, while muscarinic receptor agonists like xanomeline have been shown to ameliorate all symptoms in both schizophrenia patients and corresponding animal models. Based on these findings, the muscarinic hypothesis of schizophrenia has been proposed.Nicotinic cholinergic receptors are also involved in the pathophysiological mechanism of schizophrenia. It has been observed that schizophrenia patients are often heavy smokers, which is thought to be related to the involvement of nicotinic receptors in the disease (Foster et al., 2021). Smoking may relieve negative symptoms of schizophrenia. Activation of α7 nicotinic receptors by agonists or positive allosteric modulators has been considered a promising strategy for the treatment of schizophrenia.It is important to note that while there is accumulating evidence of the involvement of cholinergic neurotransmission and cholinergic receptors in schizophrenia, the exact mechanisms and implications for treatment are still subjects of ongoing research. The cholinergic system is complex, and its interactions with other neurotransmitter systems in the brain are not fully understood. Therefore, further research is needed to fully elucidate the role of cholinergic receptors in schizophrenia and to develop effective and targeted treatments for the disorder (Olincy & Freedman, 2012).

 **3.4 METABOTROPIC AND IONOTROPIC GLUTAMATERGIC RECEPTORS**

 Glutamate and Glutamatergic Pathways: Glutamate is a major excitatory neurotransmitter in the central nervous system. Glutamatergic pathways linking various brain regions, including the cortex, limbic system, and thalamus, are crucial in schizophrenia. Abnormalities in glutamatergic neurotransmission may influence synaptic plasticity and cortical micro circuitry, particularly NMDA receptor functioning (Zhou & Danbolt, 2014). NMDA receptors are ligand-gated ion channels and are pivotal for excitatory neurotransmission, excitotoxicity, and plasticity. The glutamatergic hypothesis of schizophrenia is based on observations that NMDA receptor antagonists, such as phencyclidine or ketamine, produce schizophrenia-like symptoms in animal models and healthy individuals. The hypothesis suggests that there is hypo function of NMDA receptors in schizophrenia, although other ionotropic glutamate receptors (AMPA and kainite receptors) and metabotropic glutamate receptors are also involved. Therapeutic trials have shown that compounds promoting NMDA receptor signalling can relieve certain symptoms in patients with schizophrenia (Nakazawa & Sapkota, 2020). Post mortem studies have reported abnormalities in glutamatergic receptor density and subunit composition in specific brain regions, such as the prefrontal cortex, thalamus, and temporal lobe, which are associated with altered stimulation during cognitive actions in schizophrenia patients. NMDA receptor hypo function may lead to morphological and structural brain changes associated with psychosis. Antipsychotic medications may interfere with glutamatergic neurotransmission by influencing the release of glutamate, modulating glutamatergic receptors, or changing the density or subunit composition of glutamatergic receptors. Some second-generation antipsychotics have been found to act on NMDA receptors in a distinct way compared to first-generation antipsychotics (Coyle et al., 2012). Abnormalities in glutamatergic neurotransmission have been considered a potential drug target for schizophrenia, especially for the treatment of cognitive impairment and negative symptoms. Ligands stimulating NMDA receptors in a controlled manner, particularly targeting the glycine modulatory binding pocket on NMDA receptors, may be attractive drug targets to avoid excitotoxicity. Positive allosteric modulators of AMPA receptors and modulators of metabotropic glutamatergic receptors, such as mGluR2/3 receptor ligands, are also being explored as potential medications for schizophrenia based on the glutamatergic hypothesis. The glutamatergic hypothesis of schizophrenia has shed light on the involvement of glutamatergic neurotransmission, particularly NMDA receptors, in the pathophysiology of the disorder. This has opened up new avenues for potential treatments targeting glutamatergic receptors to address cognitive impairment and negative symptoms in schizophrenia. However, further research and clinical trials are needed to fully explore the safety and efficacy of these potential treatments (Rubio et al., 2012).

**3.5 MULTI-TARGET COMPOUNDS TO TREAT SCHIZOPHRENIA**

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| --- | --- | --- | --- |
| **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 |

1. **NEWER DRUG DEVELOPMENT FOR SCHIZOPHRENIA**

**4.1 UNLOCKING HOPE: LUMATEPERONE'S PROMISING ROLE IN SCHIZOPHRENIA TREATMENT**

Lumateperone, also known by its brand name Caplyta, is a novel antipsychotic medication that has been developed for the treatment of schizophrenia in adults. It was approved by the U.S. Food and Drug Administration (FDA) in December 2019. Lumateperone's mechanism of action sets it apart from traditional antipsychotic drugs. It primarily works as a potent serotonin 5-HT2A receptor antagonist and a partial agonist at serotonin 5-HT1A receptors (Edinoff et al., 2020). Additionally, it acts as an antagonist at dopamine D2 receptors and shows moderate affinity for serotonin 5-HT2C and histamine H1 receptors. The combination of these actions allows lumateperone to modulate the activity of key neurotransmitter systems implicated in the pathophysiology of schizophrenia. By targeting multiple receptor types, lumateperone can exert a more balanced and broad effect on the brain's neurotransmitter signaling. Lumateperone's effectiveness in treating schizophrenia is attributed to its impact on both positive and negative symptoms of the disorder. Positive symptoms, such as hallucinations, delusions, and disorganized thinking, are believed to arise from excessive dopamine activity in certain brain regions, particularly the mesolimbic pathway (Orzelska-Górka et al., 2022). By blocking dopamine D2 receptors, lumateperone helps to reduce these symptoms. Moreover, lumateperone's partial agonist activity at serotonin 5-HT1A receptors may contribute to its effect on negative symptoms. Negative symptoms, like social withdrawal, lack of motivation, and reduced emotional expression, are associated with impaired function of the prefrontal cortex and other brain regions. Activation of serotonin 5-HT1A receptors in these regions has been linked to improved cognitive functions and mood regulation. Another significant advantage of lumateperone is its favorable side effect profile compared to older antipsychotic medications. Extrapyramidal side effects (EPS), such as Parkinsonism, dystonia, and tardive dyskinesia, are common with traditional antipsychotics due to their strong dopamine D2 receptor antagonism. However, lumateperone's relatively weaker D2 receptor antagonism reduces the risk of EPS, making it a potentially safer option for patients (Maini et al., 2021). Clinical trials have demonstrated the efficacy of lumateperone in treating schizophrenia. In one pivotal study, lumateperone was found to significantly improve both positive and negative symptoms compared to a placebo. Additionally, lumateperone was generally well-tolerated, with a low incidence of EPS. Lumateperone represents a valuable addition to the treatment armamentarium for schizophrenia. Its multi-target approach and balanced receptor modulation offer the potential for improved symptom control and enhanced tolerability. However, like all medications, it may not be suitable for everyone, and individual responses to the drug can vary. As with any antipsychotic treatment, close monitoring and communication between patients and healthcare providers are essential to optimize outcomes and manage potential side effects effectively (Correll et al., 2020).

**4.2 G-PROTEIN COUPLED GLUTAMATE RECEPTORS AND NOVEL SIGNALLING**

G-protein coupled glutamate receptors (mGluRs) and novel signaling pathways have emerged as areas of interest in the study of schizophrenia due to their involvement in the regulation of glutamatergic neurotransmission. Glutamate is the main excitatory neurotransmitter in the brain and plays a crucial role in synaptic plasticity, learning, memory, and cognition. Dysregulation of glutamatergic neurotransmission has been implicated in the pathophysiology of schizophrenia. Conventionally, the N-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis has been the primary focus in understanding the role of glutamate in schizophrenia. This hypothesis suggests that reduced activity of NMDA receptors, which are ionotropic glutamate receptors, leads to impaired synaptic plasticity and cognitive deficits observed in schizophrenia. However, recent research has also started to shed light on the role of metabotropic glutamate receptors, specifically G-protein coupled glutamate receptors, in the disease (Kryszkowski & Boczek, 2021).

G-protein coupled receptors (GPCRs) are a large family of cell surface receptors that are involved in signal transduction. They activate intracellular signaling pathways through interactions with G-proteins, leading to various cellular responses. In the case of glutamate, mGluRs are GPCRs that are sensitive to glutamate and modulate the activity of neurons. There are several subtypes of mGluRs, categorized into three groups based on their sequence homology, signaling mechanisms, and ligand selectivity: Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3), and Group III (mGluR4, mGluR6, mGluR7, and mGluR8). Each group has distinct effects on glutamatergic neurotransmission and neuronal excitability. In schizophrenia, abnormalities in the expression and function of mGluRs have been observed, particularly in the prefrontal cortex and hippocampus, brain regions crucial for cognition and emotional processing. Altered expression and signalling of mGluRs are thought to contribute to cognitive deficits and negative symptoms seen in the disorder. The novel signaling pathways associated with mGluRs involve their interactions with intracellular proteins, such as Homer proteins and the signaling complex called the post-synaptic density (PSD). These interactions regulate intracellular calcium levels and influence synaptic plasticity and neurotransmitter release. Research on mGluRs and novel signaling pathways in schizophrenia has led to the exploration of new treatment strategies. Targeting these receptors with selective agonists or positive allosteric modulators is being investigated as a potential therapeutic approach for managing cognitive deficits and negative symptoms associated with schizophrenia. The aim is to restore proper glutamatergic neurotransmission and synaptic plasticity to alleviate the core symptoms of the disorder. It is important to note that while the research on mGluRs and novel signaling pathways in schizophrenia is promising, it is still in its early stages, and further studies are needed to fully understand the underlying mechanisms and to develop effective and safe therapeutic interventions. As with any emerging research, caution should be exercised in extrapolating findings to clinical applications until robust evidence is available. Nonetheless, these developments offer hope for the advancement of treatment options for individuals living with schizophrenia (Tuteja, 2009).

**4.3 SYNAPTIC PLASTICITY AS A THERAPEUTIC FRONTIER IN SCHIZOPHRENIA**

Targeting synaptic plasticity in schizophrenia has become an area of interest in the search for more effective treatments for this complex mental illness. Synaptic plasticity refers to the ability of synapses (connections between neurons) to change their strength in response to activity and experience. It is a fundamental process in learning, memory, and adaptive brain function. In schizophrenia, disruptions in synaptic plasticity have been implicated as a potential underlying mechanism for the cognitive impairments and other symptoms seen in the disorder. Several lines of evidence suggest that aberrant synaptic plasticity may contribute to the neural circuitry dysfunction observed in schizophrenia. One of the primary neurotransmitter systems involved in synaptic plasticity is the glutamatergic system, particularly the N-methyl-D-aspartate (NMDA) receptors. NMDA receptors play a critical role in long-term potentiation (LTP) and long-term depression (LTD), which are cellular mechanisms of synaptic plasticity associated with learning and memory. Studies have shown that NMDA receptor hypo function is linked to schizophrenia, as drugs that block NMDA receptors, such as phencyclidine (PCP) or ketamine, can induce schizophrenia-like symptoms in 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.

**5. CONCLUSION AND FUTURE PERSPECTIVES:**

In today's rapidly evolving world, various factors contribute to the prevalence of mental disorders, including schizophrenia. While treatments for positive symptoms of schizophrenia have shown some effectiveness, there remains a significant challenge in addressing negative and cognitive symptoms, as well as drug-resistant cases.

The multi-target approach in medicinal chemistry has gained significant attention, especially for complex diseases like schizophrenia. It stands out as a promising strategy for managing the condition, offering potential benefits that single-target treatments cannot provide. Incorporating nicotinic and glutamatergic targets in modern multi-target drugs may prove advantageous for tackling negative symptoms and cognitive impairments. Additionally, exploring novel signalling mechanisms, particularly those related to GPCRs such as allosteric modulation, biased signalling, and receptor oligomerization, holds promise. The success of this approach may be enhanced by targeting multiple receptors simultaneously.

In conclusion, while current multi-target antipsychotics primarily focus on orthosteric ligands of aminergic GPCRs with SSRI or SERT inhibitory activity in some cases, there remains a vast unexplored territory to include other receptors and enzymes as potential drug targets. Embracing a broader spectrum of signalling mechanisms beyond the conventional ternary complex model of GPCRs could lead to exciting advancements in schizophrenia treatment.

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