Exploring the Traditional Antipsychotic and Glutamatergic Treatment of Schizophrenia: A Comprehensive Literature Review

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Research on the neurobiological basis of schizophrenia has accelerated in the past few decades. The dopamine hypothesis is one of the oldest theories related to schizophrenia. New research indicates the connection between the glutamate system and schizophrenia. It explores abnormal functioning of neurotransmitters such as GABA, NAAG and NMDA, which are all related to the glutamate system. Advanced research related to dopamine and schizophrenia has revealed new abnormalities of dopamine mechanisms involved in schizophrenia. Moreover, advanced technology has also been able to localize various cortical and sub-cortical regions other than the prefrontal cortex associated with schizophrenia. Antipsychotic treatment was the first treatment used to treat schizophrenia, which functions by blocking dopamine receptors. Glutamatergic treatment is a newer treatment recently discovered that is used to treat schizophrenia by targeting the glutamate system. The combined use of glutamatergic and traditional antipsychotic treatments is a very recent approach presented for the treatment of schizophrenia. It involves using antipsychotics on the glutamate system in the brain to lessen the manifestation of symptoms of schizophrenia related to glutamate. The glutamate theory of schizophrenia is relatively new whereas antipsychotic drugs are amongst the most common treatment for schizophrenia. It is difficult to ignore the potential role of race in the effectiveness of these treatments as genetic polymorphisms of drug-metabolizing enzymes affect the metabolization of antipsychotics. Similar polymorphisms are found in members of the same race due to their shared genes, thus, affecting the entire basis of schizophrenic treatment.

Introduction

Race may play a bigger role in the manifestation and treatment of schizophrenia than previously thought. Schizophrenia is a highly treatable psychotic disorder with the key (positive) symptoms being hallucinations, delusions, disorganised thinking and abnormal motor behaviour according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[1]. According to The World Health Organisation (WHO), the lifetime prevalence of schizophrenia is estimated at circa 0.3%-0.7% .

The exact cause of schizophrenia remains imperfectly understood. Competing perspectives emphasise genetic, environmental, or psychological factors that could trigger the onset of the disorder. Importantly, each of these potential causes of schizophrenia affects the effectiveness of its pharmacological treatments, such as traditional antipsychotic and glutamatergic treatments. The frequent use of recreational drugs in large amounts is also known to cause schizophrenia.

Schizophrenia is a chronic and complex disease. As aforementioned, the manifestation of schizophrenia is dependent on genetic, environmental and psychological factors. Being able to understand the neurobiological basis of schizophrenia is imperative to developing more effective treatments. Abnormal cortical development leading to memory and attention deficits along with other abnormalities mainly with the processes involving the prefrontal cortex (PFC) can stand out as causes behind atypical behaviour schizophrenia patients exhibit. Abnormalities in Gama-aminobutyric acid (GABA), dopamine, glutamate and N-methyl-D-aspartate (NMDA) in the PFC, are the key chemical indicators of schizophrenia. The aforementioned approaches allow for an in-depth nuanced exploration of the neurobiological basis of schizophrenia and its treatments through multiple outlooks.

Typical treatments for schizophrenia include glutamatergic and traditional antipsychotic drugs, which target different neurobiological features of schizophrenia. Glutamatergic treatments function by targeting the glutamate system in the brain. Whereas, traditional antipsychotics primarily operate by blocking dopamine receptors. Advancements in the fields suggest that a combination of these treatments may yield better results faster[2]. Unfortunately, this field has largely ignored other factors that may be hindering treatment success.

While present and past research related to glutamatergic and traditional antipsychotic treatments offer promising results and great scope for further development of treatments. It is important to note that the sample for the majority of such studies is made up of caucasian males, they seldom include samples that involve people of colour. Many studies have found that genetic variations can be correlated with the metabolisation of pharmacological drugs. Therefore, the effects of such treatments on

people of colour (POC) are still undetermined[3].

This literature review aims to summarise current views on glutamatergic and antipsychotic treatments. It will explore the effectiveness of glutamatergic and anti-psychotic treatments of schizophrenia in various races and ethnicities. This approach is not extensively researched as caucasian males make up the sample for most studies on schizophrenia. Looking at the effect of these treatments from such a point of view will hopefully allow room for more research on schizophrenia in different ethnicities, races and genders. It will elucidate the effect of the combined use of glutamatergic and antipsychotic treatments pointing out both negative and positive side effects of such an approach. It will provide a nuanced perspective on the effectiveness of glutamatergic and traditional antipsychotic treatments by comparing and contrasting them while pointing out and effectively reviewing the various conditions that could affect their effectiveness.

Neurobiological basis of Schizophrenia

GABA

Neurobiological research related to schizophrenia has skyrocketed in recent times due to advancements in technology and the development of new theories. Regardless, the genetic and neurobiological basis of schizophrenia remains largely unexplored. GABA is the primary inhibitory neurotransmitter for the nervous system with its primary function being inhibiting nerve transmission to reduce neuronal excitability. GABA primarily runs through the PFC[4]. GABA is a precursor of glutamate. GABA receptors activate when GABA is released in the post-synaptic cleft[5].

Before understanding the connection between GABA and schizophrenia it is important to note that most evidence collected on GABAergic abnormalities is based on animal and postmortem studies. The presence of clinical features of schizophrenia is associated with an atypical concentration of cortical GABAergic neurons. GABA has two isotopes GAD65 and GAD67 which support the rapid synthesis and maintenance of basic GABA levels respectively.

Several studies correlated the presence of alterations in the neurotransmission process of GABA in the dorsolateral prefrontal cortex (dlPFC) with the presence of schizophrenia[6,7,8]. In particular, lower expressions of the GAD67 form of GABA are associated with varied activity in the dlPFC which are believed to cause cognitive defects of schizophrenia. Little detail is known about the effect of altered levels of pre-frontal GAD67[9]. A postmortem study investigating the effects of abnormal levels of prefrontal GAD67 using quantitative polymerase chain reaction found that GAD67 mRNA levels and protein levels were significantly lower in schizophrenia subjects by 15% and 10% (in total grey matter) respectively. The study arrived at the conclusion that lower GAD 67 mRNA levels were common in patients with schizophrenia and attributed to dlPFC malfunction and impaired cognition[10]. Many similar studies using different research and experimentation methods have achieved similar conclusions of reduced concentrations of GAD67 mRNA levels and/or reductions in the density of neurons positive for GAD67 mRNA in the dlPFC in subjects with schizophrenia.

GAT1 is a GABA transporter that operates to terminate synaptic activity i.e. synaptic reuptake. Many research studies related to GABA, GAT1 transporter and schizophrenia have discovered that people with schizophrenia appear to have reduced densities of the GAT1 immunoreactive axon cartridges in the dlPFC[11], interestingly the density of GAT1 varicosities remains unchanged in schizophrenia. Moreover, these studies do not reveal whether alterations in GAT1 mRNA can be attributed to reductions in immunoreactive axon cartridges of GAT1 levels. The majority of studies only found changes in layers 1-5 of the PFC[12]. It is unclear if the combination of decreased expressions of GAD67 mRNA and GAT1 mRNA results in an increase or decrease of the inhibitory tone on the pyramidal cells[13].

GAD67 and GAT1 are presynaptic regulators of GABA, and abnormalities in these mechanisms contribute to the manifestation of schizophrenia[8]. Parvalbumin is a calcium-binding protein present in various types of neurons containing GABA. It is also necessary to explore abnormalities in post-synaptic GABAergic mechanisms that may result in and may indicate the presence of schizophrenia. $GABA_A$ is a post-synaptic ionotropic receptor of GABA responsible for mediating the inhibitory effects of GABA by allowing chloride ions to flow into the neuron, which hyperpolarises the cell.

$GABA_A$ has several subunit structures derived from various gene families one of them being $\alpha 1$–6[14]. In patients with schizophrenia, parvalbumin-containing neurons targeting the axon initial segment (AIS) of the pyramidal neurons, exhibit reduced expressions of GAD67 and GAT1 mRNAs. The subunit $\alpha 2$ of $GABA_A$ from the α-type subunit family has been observed to be upregulated in the axon initial segment of pyramidal neurons in patients with schizophrenia. Research has established that this phenomenon may occur in response to lowered extracellular GABA concentrations as a result of reduced synthesis of GABA. The density of $\alpha 2$ pyramidal neurons is inversely correlated with GAT1 immunoreactive axon cartridges to compensate for the diminishing GABA activity[15]. This implies that as GAT1 is downregulated, $GABA_A$ $\alpha 2$ is upregulated in the axon initial segment (AIS) of the pyramidal neurons[16,8]. The downregulations of the subunits of $GABA_A$ are localised in the dlPFC in patients with schizophrenia.

There is sufficient evidence localising abnormal GABA processes to brain regions other than the dlPFC. Research has shown that other cortical and sub-cortical areas are also associated with schizophrenia[17]. Affirming, that the PFC is not the only area associated with schizophrenia. However, other brain areas asso-

ciated with schizophrenia are found to include certain GABAergic mechanisms correlated with schizophrenia suggesting that they play a role in the background in the brains of patients with schizophrenia[8]. Through extensive research done on the role of GABA in schizophrenia in recent years, it would not be wrong to conclude that abnormalities in various GABA-related mechanisms localised in the PFC play a key role in the dysfunction of the PFC in schizophrenia.

In schizophrenia, post-synaptic GABAergic disorders include changes to a variety of receptors and signalling pathways. Changes in GABA-A receptor subunit expression, namely decreased $\alpha 5$ subunit levels in the hippocampus and changed receptor sensitivity are important results[8]. Changes in postsynaptic density proteins such as gephyrin and disturbances in chloride homeostasis have been noted. Altered calcium signalling, downstream signalling cascades, and impaired receptor trafficking and localization further exacerbate GABAergic dysfunction[18]. Together, these anomalies, which can differ across different parts of the brain and interact with other neurotransmitter systems, affect inhibitory neurotransmission in schizophrenia, underscoring the disorder's complexity and the difficulties in creating focused solutions[19].

Endophenotypes

Endophenotypes are intermediate phenotypes, they lie between the underlying molecular genetic background and the disease. Hence, by studying endophenotypes one can understand a disease without studying the psychopathology[20]. They are inheritable and, therefore, can be used to study the genetic prevalence of psychological diseases, in this case, schizophrenia. Endophenotypes reflect abnormalities in specific neural pathways and regions triggered by schizophrenia.

P50 and P300 are endophenotypes strongly associated with schizophrenia[21]. To be able to understand the neurobiological basis of schizophrenia through endophenotypes it is imperative to note that abnormalities in the neural pathways and regions appear visibly as symptoms. P300 is an endophenotype of schizophrenia. P300 is a parietal central positivity that occurs when an informative task-relevant stimulus is detected[22]. P300 response generators are scattered throughout the cortex and subcortex therefore making it easier to record the amplitude of P300 waves through electroencephalogram (EEG) recordings. Auditory targeted stimulus P300 responses surface from inferior parietal and supramarginal cortical regions[23].

Abnormalities and hypofunction in response to auditory targeted stimuli and stimuli discriminating tasks are the strongest physiological markers associated with schizophrenia, corroborated by numerous studies achieving increasingly similar results[24]. Although the amplitude of P300 in other studies varies due to differences in experiment designs they too conclude that reductions in P300 waves in response to auditory targeted stimulus are associated with schizophrenia[25,26]. P300 waves in response to stimuli discriminating tasks also reflect the effect on attention and working memory in patients with schizophrenia[21,27].

P300 response has functional significance for cognitive and attentional deficits in schizophrenia. The brain's capacity to devote cognitive resources to important stimuli is linked to the P300 component, which is normally evoked during activities demanding attention and sensory distinction. The P300 amplitude is frequently decreased in schizophrenia, suggesting problems with these functions that show up as deficiencies in working memory, attention, and judgment. It is believed that this deficit is related to underlying dysfunctions in the glutamate and dopamine signalling pathways, that influence the disorder's mental functioning and brain connections. Research indicates that negative symptoms and cognitive deficits in schizophrenia are associated with reduced P300 amplitudes, which can lead to difficulties with everyday tasks and social functioning. The P300 response is therefore helpful in monitoring the development of symptoms and the results of therapy for schizophrenia as it not only provides a quantifiable indicator of psychological impairments. The adverse neurological and cognitive symptoms of schizophrenia are intimately linked to underlying cognitive deficits, such as memory, attention, and executive function issues, which are reflected in P300 deficiency. Abnormalities in the dopamine and glutamate systems, which are essential to the neurobiology of schizophrenia, have been connected to reduced P300 amplitude[28,29,30].

Sensory gating refers to the physiological phenomenon wherein the brain exhibits reduced response to repeated stimuli and is commonly explored through EEG recordings[31]. P50 is a measure of sensory gating believed to be triggering positive symptoms of schizophrenia. Numerous research studies have established that there are deficits in P50 suppression in the presence of auditory stimuli in patients with schizophrenia. These deficits have been said to cause hallucinations from sensory overload as a result of failure to impede unrequired sensory inputs. Recent research also suggests that P50 deficits cause attention deficits in patients with schizophrenia[32,33,24]. P50 suppression impairments draw attention to sensory gating issues, especially when it comes to filtering recurrent stimuli, whereas anomalies in P300 responses reveal information about cognitive deficiencies including attention and working memory. When combined, these endophenotypes provide complementary insights into the cognitive and sensory deficits associated with schizophrenia and highlight the larger brain dysfunctions underlying the disorder.

Schizophrenia is characterised by dysfunction of the PFC. Working memory is a brain function that depends on the dlPFC. Working memory is a brain system that functions to manipulate and temporarily store information required for complex cognitive tasks[34]. Atypical functioning of the dlPFC results in abnormalities and deficits with working memory, making it a

primitive indicator and endophenotype of schizophrenia. We are also able to use working memory deficits to predict the severity of schizophrenia in a patient[6]. Working memory dysfunction can be identified through a variety of tests aimed at examining the performance of one's working memory. Patients with schizophrenia exhibiting good working memory are inefficient in using their pre-frontal networks[21].

Measurements of working memory offer a trustworthy and impartial method for forecasting the severity and course of schizophrenia. Researchers may measure cognitive deficits, link them with clinical symptoms, and utilize the data to predict patient outcomes using activities like the digit span and n-back tests. These discoveries not only broaden our knowledge of the cognitive foundations of schizophrenia but also have applications in prevention and treatment planning. Therefore, including working memory tests into clinical practice is essential to improving the accuracy and efficacy of treatment for schizophrenia[35],[36].

Dopamine

Dopamine was one of the first neurotransmitters to be attributed to schizophrenia. Dopamine is a neurotransmitter that acts like the brain's reward system and modulates cognitive functioning in the PFC[37]. The earliest hypothesis associated with dopamine in regard to schizophrenia was that hyper-activity of dopamine transmission causes positive symptoms associated with schizophrenia. Dopamine has 5 receptor types that are D1, D2, D3, D4, and D5. Early research (through post-mortem studies) was able to extensively deduce the changes in the dopamine receptor D2 present in the brains of patients with schizophrenia.

D1 receptors are mostly located in the PFC and control cognitive processes such as working memory. Cognitive problems, particularly those related to attention and decision-making, are widespread in schizophrenia and might result from malfunctioning in these receptors. Antipsychotic medications primarily target these receptors since they are implicated in psychotic symptoms including delusions and hallucinations[38],[39]. In the striatum, overactivity at D2 receptors is linked to indicators of schizophrenia[40],[41]. D3 receptors are linked to cognitive and mood-related features of schizophrenia and are concentrated in limbic brain areas responsible for emotional regulation. D3 receptor-targeting antipsychotics, which are more recent, have demonstrated potential in treating negative symptoms including motivational decline and social disengagement[42],[43]. D4 receptors, which are mostly located in the PFC, are involved in regulating emotions and cognitive functions. It is believed that dysregulation of these receptors has a role in the cognitive abnormalities that are common in schizophrenia, including working memory and attention problems[44],[45]. Higher-order cognitive processes, such as memory and learning, are influenced by D5 receptors, which are found in the PFC. Although their exact function in schizophrenia is undetermined, D5 receptors may influence how dopamine affects cognition, and abnormalities in their activity may be a factor in patients' cognitive impairment[46].

Advancements in technology and the development of new theories have led to discoveries in the connection between schizophrenia and dopamine mechanisms. New research (brain imaging studies) suggests that alterations in dopamine mechanisms are localised in the PFC and sub-cortical areas. Dopamine dysregulation in schizophrenia is complex and involves both hyperdopaminergic activity in the mesolimbic pathway and hypodopaminergic activity in the prefrontal cortex leading to positive and negative symptoms respectively.

In schizophrenia, aberrant reward processing is largely caused by dopamine impairment in subcortical areas, particularly the ventral striatum and nucleus accumbens. The reward circuit in the brain, which employs dopamine to communicate desire, and pleasure, and reinforce learning, is centred in these areas. Dopamine surplus in schizophrenia may contribute to positive symptoms[47],[48]. At the same time, the release of dopamine for real rewarding events is frequently suppressed, which hinders reinforcement learning and results in anhedonia (decreased desire and pleasure). Individuals find it difficult to predict or learn from good events as a result of this disruption, which impacts reward prediction and anticipation. This leads to social disengagement, a lack of desire (avolition), and cognitive deficiencies in goal-directed conduct. When everything is taken into account, these anomalies emphasize both the positive and negative symptoms of schizophrenia and point to the need for interventions that may more effectively address these fundamental deficiencies in reward processing[49].

According to recent studies, dopamine dysregulation in schizophrenia could potentially be a side effect of underlying glutamatergic malfunction, particularly hypofunction of the NMDA receptor. This puts greater emphasis on a more complicated model that incorporates the involvement of glutamate, a neurotransmitter essential to learning, memory, and synaptic plasticity, rather than the conventional dopamine hypothesis, which mainly links schizophrenia to excessive dopamine activity. According to the NMDA receptor hypofunction theory, cortical circuit inhibitory regulation is disrupted when GABAergic interneurons' NMDA receptors exhibit decreased activity. Because of this malfunction, the brain's excitatory and inhibitory signals become unbalanced, which results in reduced dopamine activity in cortical areas like the prefrontal cortex and increased dopamine release in subcortical locations. The hallmark symptoms of schizophrenia are exacerbated by this simultaneous imbalance[50],[51],[52].

A study discovered that substantia nigra (brain area associated with the production of dopamine) had elevated levels of tyrosine hydroxylase (a rate-limiting enzyme involved in the synthesis of dopamine) in patients with schizophrenia as compared to

a healthy sample. Thus, people with schizophrenia have an increased capacity for dopamine production[53]. Changes in the forebrain and atypical behaviour, reminiscent of symptoms of schizophrenia are caused due to the overexpression of dopamine receptor D2[21].

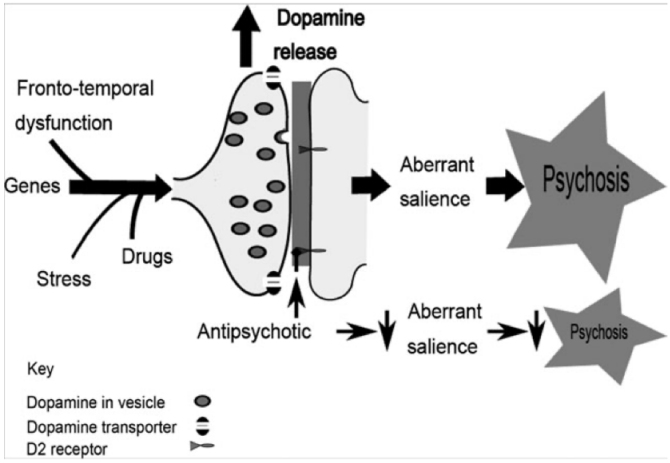

Figure 1: Drug interactions, environmental stress, and genetic factors all contribute to fronto-temporal dysfunction, which in turn causes the mesolimbic pathway to release more dopamine. Delusions and hallucinations, two of the defining symptoms of psychosis, are exacerbated by elevated dopamine activity, which causes the assignment of aberrant salience, in which irrelevant stimuli are mistakenly regarded as significant. By focusing on D2 dopamine receptors, antipsychotic medications seek to lessen this overactivity, reestablishing equilibrium in the dopamine system and lowering symptoms of psychosis. The graphic does, however, also show how other factors—genetic predisposition and environmental triggers—interplay, suggesting that dopamine dysregulation is not the only explanation for schizophrenia. In order to comprehend how dopamine deficiency interacts with other pathways, such the glutamatergic and GABAergic systems, to cause the condition, an integrated approach is necessary[54].

Moreover, observational studies have linked deficits in dopamine receptor D1 localised in the PFC with negative symptoms and cognitive impairments exhibited in schizophrenia. The density of the dopamine receptor D4 was found to increase six-fold in patients with schizophrenia as it binds to clozapine (an antipsychotic drug)[44]. The aforementioned, research can provide convincing evidence that dopamine release and presynaptic dopamine availability are increased in patients with schizophrenia[53],[55].

The dopamine hypothesis implies that sufficiently high doses of certain drugs can stimulate dopamine which causes psychotic schizophrenia-like symptoms to develop in non-schizophrenic persons, these symptoms can be controlled if dopamine receptor blocking drugs are administered[56]. It takes into account the effect of abnormal densities of all dopamine receptors related to psychotic disorders but especially focuses on the dopamine receptor D2.

Presynaptic dopamine mechanisms are strongly associated with schizophrenia, but there are still quite a few uncertainties with post-synaptic dopamine mechanisms being specifically related to schizophrenia. There is no strong evidence that dopamine transporters (DAT) change in the presence of schizophrenia[57]. The D2 receptor is highly focused upon as it is one of the few dopamine receptors to show numerous differences in patients with schizophrenia and its abundant presence in the corticular regions nearest to the scalp thus, making it easy to study as well[58].

NMDA

The NMDA receptors act as the primary excitatory neurotransmitter in the brain. It is key for synaptic plasticity, which forms the basis of memory formation, they are also involved in the process of excitotoxicity. It is a glutamate receptor[59]. The NMDA receptor is an ionotropic glutamate receptor. NMDA receptors are critical post-synaptic mediators of activity-dependent synaptic plasticity and are found to be widely distributed throughout the brain[60].

Schizophrenia is characterised by hypofunction of the NMDA receptor and its subunits. Research has revealed that ketamine and phencyclidine (PCP) function as NMDA receptor channel blockers and cause cognitive deficits and other full-range schizophrenia symptoms in healthy subjects. Patients with schizophrenia have shown sensitivity towards ketamine as compared to healthy subjects. PCP blocks flow through the NMDA glutamate receptor. Ketamine is a structural analogue of PCP that binds itself to the PCP receptor site with one-tenth of PCP potency[61],[62].

Post-mortem studies have found decreased expressions of NMDA receptors in various areas of the brain including the PFC. GluN1, GluN2 and GluN3 are the three sub-units of NMDA receptors. Recent studies have found decreased expression of the GluN1 mRNA and GluN1 protein localised in the PFC in participants with schizophrenia, there were no significant changes in the mRNA and protein of GluN2 and GluN3. The current research presents a considerable decrease in the activity of signalling cascades downstream of the NMDA receptor in schizophrenia in the postsynaptic density fraction despite increased expressions of NMDA receptor density and GluN1. Moreover, people with schizophrenia have lower GluN1 levels in the dentate gyrus of their hippocampal regions[63].

Schizophrenia is a neurobiologically complex disorder involving numerous brain functions and regions many of which have been discovered and many which are yet to be discovered. Given the complexity of the disorder, it is important to understand the biological basis and origins to be able to treat it successfully and

efficiently. To understand schizophrenia, findings related to the neurobiology and genetics of schizophrenia must be correlated with findings related to normal brain functioning. New emerging technologies can help study the sub-cortical basis of schizophrenia better. In conclusion, the atypical functioning of GABAergic mechanisms, dopamine receptors, P50 and P300 endophenotypes and working memory in the PFC are the most prominent and primitive neurobiological indicators of the manifestation and presence of schizophrenia in an individual[64]. Research has indicated potent variations in GABA, dopamine and NMDA.

Antipsychotic treatments

Antipsychotics are drugs used to treat psychotic illnesses one of them being schizophrenia as they can treat acute psychosis originating from any cause. They function by targeting to block dopamine receptor D2 which causes many symptoms of psychotic disorders like schizophrenia[65]. Their basic system of functioning is based on the dopamine hypothesis. They block the D2 receptor to prevent neurotransmission of excess dopamine which causes symptoms similar to schizophrenia.

Classification of antipsychotic drugs

Antipsychotic drugs can be broadly classified between, first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA). FGA also known as typical antipsychotics or neuroleptics, refers to the first 10 antipsychotic drugs that were developed over 70 years ago, they are conventional antipsychotic drugs used. FGAhave a high tendency to cause extrapyramidal symptoms[66]. SGA also known as atypical antipsychotics refers to the antipsychotic drugs developed about 20 years after FGA were developed. SGA have a low tendency to cause extrapyramidal symptoms although they are much less effective (except clozapine) than FGA and cause a host of other serious symptoms[67],[63],[68].

Despite their success in alleviating positive symptoms of schizophrenia, FGA have major drawbacks that go beyond their incapacity to cure negative symptoms. FGA that target D2 receptors frequently result in catastrophic motor undesirable effects, such as tardive dyskinesia (a possibly perpetual condition that involves recurring, unconscious facial and body movements) and extrapyramidal symptoms (EPS), including rigidity, tremors, and uncontrolled movements[40],[41]. The dopamine-blocking activity of FGAs in motor neurons generates these adverse effects, which make long-term usage more difficult and frequently affect patients' commitment to treatments. These restrictions have therefore prompted the creation of SGA, which provide more balanced symptom control while reducing EPS by interacting on a wider variety of receptors, including serotonin receptors[42].

Mechanism of Action

Receptor binding characteristics are the main chemical difference between FGA and SGA. FGA target D2, making it crucial in regulating symptoms like hallucinations and further increasing the likelihood of EPS including stiffness and tremors. When used over an extended period, these medications' powerful blocking of D2 receptors along with an elevated affinity for them might cause serious motor adverse effects. However, SGAs have a wider mode of action and are less preferential for D2 receptors. Additionally, they work on serotonin receptors, reducing EPS and improving the management of positive as well as negative symptoms. Although SGAs are often less problematic when it comes to motor side effects than FGAs, their increased serotonin receptor affinity adds to a distinct side effect profile, particularly metabolic problems. Clozapine, an SGA that is particularly effective in treatment resistance, although may have serious side effects, such as agranulocytosis, which makes routine blood testing essential. Despite their disadvantages, these modifications have made SGA more desirable in many treatments, particularly for individuals who are more susceptible to motor adverse effects from FGA. They vary in terms of their efficacy and adverse effect profiles in addition to their development schedules[69],[70],[71],[72].

Clozapine is an SGA drug with commendable results in patients with treatment-resistant schizophrenia. Clozapine is one of the most successful SGA drugs. Antipsychotic drugs have shown to have been very efficient in treating symptoms of schizophrenia in trials using SGA specifically clozapine, olanzapine, amisulpride, and risperidone. Conversely, NMDA receptor hypofunction may cause certain symptoms of schizophrenia through one neural network and other symptoms through another; it's also feasible that one or more neural networks—or perhaps a third and distinct network—may cause structural alterations in the brain. In the event that there are several relevant networks and that dopaminergic and NMDA receptor hypofunction mechanisms are present in each, it is plausible that certain dopamine receptor subtypes influence one network while D2 receptors exclusively affect the other (or networks). Then, typical antipsychotic drugs that mainly target D2 receptors would only be able to stop structural brain alterations if the alterations are brought about by the particular network modifications that D2 receptors control[73].

Combination Therapy

New research is being conducted on combination anti-psychotic treatment which involves combining two or more antipsychotic drugs to be able to optimise the treatment of patients with schizophrenia. Some combination approaches are already being used to a limited extent several antipsychotic medications like quetiapine, risperidone, olanzapine and clozapine. Since most SGA constitute inherent combination therapy due to their broad-

spectrum receptor blockade, it can be argued that they are more effective than high-potency conventional antipsychotics because of the antipsychotic called clozapine.

Long-term response to antipsychotic medication is significantly predicted by response during the first 2-4 weeks of treatment. The greatest benefit, however, could not materialize for several months, and each patient's response trajectory is unique. Antipsychotic response differs depending on the stage of the disease. Antipsychotic drugs have a less uniform impact on negative symptoms, and a large portion of their negative symptom reduction may be attributed to a drop in positive symptoms. Antipsychotic medications can exacerbate negative symptoms related to EPS, even while they can lessen negative symptoms associated with positive symptoms. Thus, an antipsychotic's overall impact on negative symptoms is usually measured by how much it lessens negative symptoms linked to positive symptoms and increases negative symptoms connected to EPS.

Antipsychotics are ineffective against the core persistent negative symptoms. On the other hand, antipsychotic drugs have the ability to reduce depressed symptoms while simultaneously improving positive feelings; nevertheless, they can also result in "neuroleptic dysphoria". Antipsychotics can help individuals with schizophrenia improve their attention span, there is conflicting evidence on how well they work on other cognitive problems, and they may even make things worse. The net impact of an antipsychotic is determined by its positive effects on attention, negative effects caused by EPS, and anticholinergic activity, both of which are used to treat EPS. No consistent differences have been found among antipsychotics in their effects on neurocognitive dysfunction[74].

Chlorpromazine

Chlorpromazine was the first antipsychotic drug to be discovered, it spurred research on antipsychotic treatment for schizophrenia. Chlorpromazine to this day remains the most used drug for the treatment of schizophrenia and is a benchmark for the evaluation of other antipsychotic drugs. Recent studies investigating the effectiveness of chlorpromazine compared to other newer and more expensive antipsychotic drugs reached the same conclusion that chlorpromazine still remains extremely effective against symptoms of schizophrenia[75]. No new drug exhibited any significant changes in effectiveness in comparison to chlorpromazine. When exposed to sunlight, chlorpromazine can cause abnormal skin pigmentation (ASP) in areas exposed to sunlight. It can also cause pigmentary deposits in the eye when exposed to sunlight, such as the anterior capsule of the lens in the pupillary gap and the posterior side of the cornea exposed by the lid fissure.

Numerous other neuroleptics have been linked to changes in the skin and eyes. ASP affects one per cent to two per cent of mentally ill people who are institutionalized on a long-term basis. Even after stopping a medication, ASP is thought to be permanent. Thus, it is important to ascertain an alternative antipsychotic medication to chlorpromazine and a medication that is able to reverse ASP caused due to chlorpromazine. Studies show that ASP is reversible after a few years of chlorpromazine withdrawal. Although, only withdrawal from chlorpromazine is not enough schizophrenic patients should also be placed on alternative antipsychotic drugs. Some drugs that were tested and yielded positive results were haloperidol, levomepromazine, trifluoperazine, thioproperazine and phenothiazine, these drugs aid healing from ASP and other side effects caused due to chlorpromazine[76].

Dopamine Pathways and Schizophrenia

Dopamine pathways may cause blockades which leads to side effects in the nigrostriatal pathway, which regulates motor control. Antagonism refers to the way a medication works to prevent or mitigate the impact of a particular molecule or receptor in the body. Antagonists attach to but do not excite the D2 receptor. Rather, it stops other molecules from attaching and activating the receptor itself, especially the natural ligand, which in this case is dopamine. Therefore, schizophrenics on FGA commonly experience EPS like tremors and stiffness. Recognizing the reason why dopamine receptor antagonism is a crucial treatment approach for schizophrenia depends on the dopamine hypothesis. According to this theory, the hallmark symptoms of schizophrenia, are caused in part by excessive dopamine activity, especially in the brain's mesolimbic pathway. Dopamine promotes motivation, reward, and other cognitive processes at normal levels. A hyperactive dopamine system, however, interferes with these functions in schizophrenia, resulting in aberrant thoughts and perceptions. Treatments that strike a compromise between symptom management and limiting side effects are also necessary since D2 antagonism eliminates dopamine overactivity linked to positive feelings, it also interferes with regular motor pathways[77],[78],[79].

The hypothesis that schizophrenia is linked to hyperactivity of subcortical transmission at D2 receptors is supported by findings from modern imaging techniques that measure presynaptic activity in striatal dopamine afferents. The dopamine theory of schizophrenia developed from these observations, the psychotogenic consequences of prolonged stimulation of dopamine function by psychostimulants, and the known mechanism of action of contemporary antipsychotic therapy are all supported by these studies. Furthermore, these findings imply that only a portion of the positive symptoms is explained by the periodic character of the dopamine hyperactivity of subcortical circuits. Alternatively, imaging techniques may indicate a role for hypodopaminergic dysfunction in the dlPFC in the development of cognitive symptoms seen by individuals with schizophrenia[55].

Glutamatergic treatments

Despite improvements in antipsychotic therapies, even with the best treatment plans, a sizable portion of individuals with schizophrenia still experience treatment resistance or inadequate results. FGA and SGA which mainly target the dopamine system, do not provide sufficient symptom relief for about 20–30% of schizophrenic patients[51]. Glutamatergic treatments show potential by activating distinct brain pathways for the treatment of schizophrenic individuals who experience treatment resistance from FGA and SGA.

Glutamate is a non-essential amino acid and the primary excitatory neurotransmitter in the brain. It is also involved in a variety of brain processes including long-term potentiation, synaptic plasticity, and learning and memory. Glutamate and glutamatergic mechanisms form the basis of glutamatergic treatments. Early research links elevated expressions of glutamate to excitotoxicity and death of neuronal cells in the brain. This paved the way for a plethora of studies linking glutamate toxicity to neurodegenerative disorders (NDDs) including but not limited to schizophrenia.

Glutamate Receptors and Excitotoxicity

Glutamate receptors are divided into two broad categories; ionotropic and metabotropic[80]. Ionotropic receptors are ion channels that allow ions to pass in response to a neurotransmitter and are typically ligand-gated whereas metabotropic receptors implicitly modulate ionic activity in neurons, they require G proteins and secondary messengers to function[81]. Research has established that overstimulation of glutamate through the ionotropic receptors contributes to NDDs. Excitotoxicity plays a major role in the manifestation of NDDs[2]. Excitotoxicity is caused due to prolonged stimulation of ionotropic receptors and other post synaptic signalling components[80]. Glutamatergic treatment functions by targeting the glutamate system. It functions by manipulating atypically functioning glutamatergic mechanisms and aims to regulate them to prevent the manifestation and worsening of symptoms of schizophrenia. The glutamatergic hypothesis of schizophrenia is a relatively new concept formed through observation of the NMDA receptor agonists ketamine and PCP produces symptoms associated with schizophrenia. mGlu5 is a metabotropic glutamate receptor that controls excitatory neurotransmission. When glutamate binds to mGlu5, it activates intracellular signalling pathways, which is how it functions indirectly in contrast to ionotropic glutamate receptors, which activate ion channels explicitly. mGlu5 receptors have a role in memory, learning, and plasticity of synapses. They are expressed in important brain areas that are essential for cognitive function, such as the PFC.

Interconnected Systems: Glutamate, GABA, NAAG, and Glycine

The onset and longevity of schizophrenia are significantly influenced by the dysregulation of the NAAG, GABA, glutamate, glycine, and mGlu5 receptors, which are intimately related. Excessive glutamate activity associated with schizophrenia can cause excitotoxicity, which impedes cognitive function. By lowering glutamate release, which obliquely promotes GABAergic transmission, NAAG helps offset this. The brain encounters heightened excitatory transmission when GABA levels are low, which can cause cognitive disturbances and contribute to hallucinations. Cognitive ability and synaptic remodelling depend on the mGlu5 receptor. Its malfunction in schizophrenia exacerbates cognitive deficiencies by interfering with brain circuit connection. Glycine also increases the activation of NMDA receptors, which is necessary for appropriate glutamatergic signalling. However, NMDA receptor activity is decreased by glycine pathway abnormalities, which are frequently seen in schizophrenia and further impair cognitive functions. These systems work together to provide finely balanced stimulation and inhibition. Symptoms, such as delusions, and cognitive deficiencies, are caused by the disruption of this equilibrium in schizophrenia, which is characterized by hyperactive glutamate, underactive GABA, and decreased NMDA receptor activity. Beyond dopamine-focused therapies, addressing these connections provides a more thorough strategy for treating schizophrenia.

The N-acetyl aspartyl glutamate (NAAG) modulates the neurotransmission of glutamate and is released alongside glutamate. Glutamine is responsible for the synthesis of glutamate at the glutamatergic terminal. GABA and glutamate are contrasting chemicals in the brain therefore malfunctioning of the glutamatergic system also affects the GABAergic system. Studies confirm that decreased GABAergic function (especially in the hippocampal region) may be the result of NMDA receptor hypofunction. Moreover, GABAergic neurons in certain areas of the hippocampus were found to be more sensitive to the inhibitory effects of NAAG.

Targeting the Glutamate System in Treatment

It has been proposed that there are several possible targets to correct the alleged aberration of glutamatergic transmission in schizophrenia. One of the most obvious targets to correct the glutamate system is increasing synaptic glycine levels, acting directly at the glycine site, or agonism of the mGlu5 receptor to enhance the function of NMDA receptors expressed on GABAergic interneurons[82]. Increasing glycine is generally not optimised as active drugs of the central nervous system suffer from many limitations, including but not limited to meagre pharmacokinetic profile and reduced brain exposure that compromises clinical findings. Nevertheless, this can be overcome by using serine or another amino acid in place of glycine, the

substitution of glycine would propose some change in the outcome[83]. Although this is a highly experimental approach due to differences in metabolic pathways, blood-brain barrier and receptor affinity[84]. Moreover, clinical trials have shown mixed results for both glycine and D-serine in treating schizophrenia symptoms. While some studies report improvements, others do not. Schizophrenia patients often show altered levels of amino acids like glycine and serine[85,83]. For instance, D-serine levels are typically lower in patients, which might affect its therapeutic potential. The enzyme serine racemase converts L-serine to D-serine, and any deficiency or overactivity can impact the treatment outcome The effectiveness of serine may also depend on the type of antipsychotic medication used concurrently. Some studies suggest that certain antipsychotics, like clozapine, may affect the efficacy of NMDA receptor coagonists differently[85,86].

Regretfully, it has proven incredibly challenging to create mGlu5 selective agonists with appropriate qualities for usage as medicinal drugs. The eight mGlu subtypes share a highly conserved glutamate binding site, which makes the development of selective glutamate-site ligands challenging.

Nonetheless, significant advances have been made in creating highly specific mGlu5 activators that function as positive allosteric modulators (PAMs) of mGlu5 rather than at the conserved glutamate binding site. By binding at an antagonistic location, these classic mGlu5 PAMs enhance responses to glutamate without actually activating the receptor[87]. Another target would be the agonism of Trk1 receptors, alpha-7 nicotinic receptors, or M1 receptors to enhance the function of GABAergic inter-neuron. Using drugs with preferential effects at alpha-2 containing GABA receptors to enhance the GABA tone on glutamatergic projection neurons can also help treat schizophrenia glutamatergically[82].

Challenges and Innovations in Drug Development

Apart from mGlu5, significant endeavours have been directed towards the selective activation of two more mGlu subtypes, namely mGlu2 and mGlu3, as an innovative method for treating schizophrenia. Together, the mGlu2 and mGlu3 receptor subtypes are known as the group II mGlu receptors because of their similar pharmacological profile, principal sequence, and activation. These group II mGlu agonists are quite selective for the group II mGlus in comparison to the other mGlu subtypes, yet they exhibit comparable agonist action at mGlu2 and mGlu3. In the majority of neuronal populations, mGlu2/3 agonists do not directly increase NMDA receptor currents, in contrast to mGlu5 PAMs and GlyT1 inhibitors. Rather than acting through NMDA receptor antagonists, these medicines are anticipated to work at the circuitry level, restoring the signalling equilibrium of transmission across forebrain circuits that are known to be disturbed in patients with schizophrenia.

New clinical research concentrates on new PAMs that are highly specific for mGlu2 and do not function at mGlu3, rather than mGlu2/3 agonists. Numerous mGlu2 PAMs have been discovered, and these substances influence excitatory transmission in the PFC in a manner akin to mGlu2/3 agonists. Although the potential benefits of mGlu2 PAMs over mGlu2/3 agonists are unknown, it is possible that mGlu2-specific targeting will result in more consistent effectiveness. Furthermore, it's feasible that long-term use of conventional agonists causes receptor desensitization, which might lessen the agonists' therapeutic effect. Therefore, in addition to mGlu2/3 agonists, specific mGlu2 PAMs may offer a different strategy that may be more advantageous[82,87].

NMDA Receptors

Research indicates, a strong correlation between NMDA receptors and negative symptoms, considering this link to be causative might oversimplify the receptor's function. Schizophrenia is a highly complex disorder where factors like synaptic plasticity processes and intricate connections with other neurotransmitter systems, such as dopamine and GABA highly influence NMDA receptor activity. Thereby, changes in NMDA receptor levels may not always indicate a clear cause-and-effect link, even if they may correspond with the intensity of symptoms[52,53]. This notion coincides with more extensive studies that emphasize how several neurochemical pathways interact in schizophrenia. The complicated role that NMDA receptors play in schizophrenia may be oversimplified by the association between a decrease in negative symptoms and an increase in NMDA receptor levels. Therefore, the link between NMDA receptor levels and schizophrenia should be seen as one part of a larger, interconnected system[60,50].

Drugs used in glutamatergic treatment primarily function to block the neurotoxic effects of NMDA receptor hypofunction. Some drugs that are used In glutamatergic treatment are muscarinic receptor antagonists, GABA receptor facilitators such as Benzodiazepine and barbiturates, sigma receptor ligands, non-NMDA glutamate receptor antagonists and adrenergic receptor agonists[73]. The Glycine modulatory site (GMS) of the NMDAR is not saturated in vivo, making it a viable target for treatment. This finding lends credence to the theory that administering GMS agonists might help patients by improving NMDA receptor activity. The availability or concentration of GMS co-agonists and antagonists can be changed in a number of ways to improve NMDA receptor activity[8].

Combined use of glutamatergic treatments and traditional antipsychotics

The combined use of glutamatergic and traditional antipsychotic treatments could involve using antipsychotics to target the gluta-

mate system and/or glutamatergic drugs to block the dopamine receptor D2, with the former being the more explored treatment avenue.

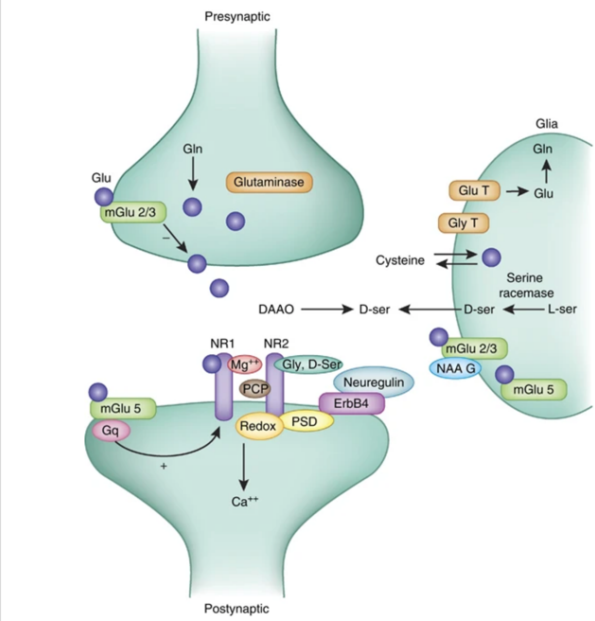

Figure 2: A simple glutamate (Glu) synaptic model showing various possible locations for NMDA receptor function manipulation. The receptor's two main subunits, NR1 and NR2, are shown. Metabotropic group 2 receptors on the presynaptic side can decrease glutamate release. The activity of the synthetic enzyme glutaminase, which changes glutamine (Gln) into Glu, can likewise change the levels of vesicular glutamate. The receptor's function is controlled by a number of regulatory sites on the NMDA channel itself on the postsynaptic site, including the D-serine and glycine (Gly) site, the redox (glutathione), and the magnesium and PCP-binding sites. Furthermore, by engaging through postsynaptic density (PSD) or signal transduction pathways, other membrane-spanning receptors, such the ErbB4 receptor or the metabotropic group 5 (mGlu5) receptor, indirectly affect how NMDAR functions. Numerous proteins found in the glia affect this synapse's presynaptic and postsynaptic function. These include the D-serine-synthesizing enzyme serine racemase, D-serine transporter, cystine–Glu transporter, and transporters for both Glu and Gly. Furthermore, glia express several metabotropic Glu receptors, including as mGluR3 and mGluR5[88].

When exploring the use of antipsychotics to target glutamatergic mechanisms we must take into account the positive and negative effects of each treatment and how it would affect treatment. Limited research has been done in the area of combination therapy for schizophrenia as it is a newly developed avenue. Research regarding this topic is still in its primitive stages with the majority of studies using animal models to test out theories. Very few researchers have moved to using human samples due to the contemporary nature of the topic and the sheer unfamiliarity of the effects associated with combining two treatments targeting two completely different systems. When trying to combine antipsychotic drugs with glutamatergic treatments we must first understand the relationship between them.

This relationship can be expressed through the association of NMDA receptors and dopamine. As one of the functions of dopamine receptors is to block glutamate release, dopamine system deficiency leading to dopamine hyperactivity may induce excessive suppression of glutamate release at the MDA receptors, which in turn may cause the NMDA receptor system to function hypo-functionally, which might be the origin of schizophrenia symptoms. One possible explanation for how dopamine receptor blockers improve schizophrenia symptoms is that they disinhibit glutamate release, which corrects glutamate hypofunction. Several antipsychotic drugs can be used to block the neurotoxic effects of NMDA receptors such as clozapine, fluperlapine and olanzapine .

NMDA Receptor Hypofunction

Here, "neurodegeneration" alludes to the gradual loss of neuronal structure and functioning. Frequently, observed in brain areas such as the hippocampus and PFC, involved in the control of emotion and cognition. Impaired synaptic transmission and greater vulnerability to excitotoxic damage are linked to NMDA receptor hypofunction, which may worsen neurodegenerative processes in these regions[52,60]. By interfering with the brain networks that govern these processes, such degeneration is believed to exacerbate the negative symptoms of schizophrenia[53].

Studies show schizophrenic patients treated with first generation antipsychotic drugs, NMDA receptor levels bound in the left hippocampus are inversely correlated with negative symptoms. This would mean an increase in NMDA receptor levels would result in a decrease in negative symptoms and a decrease in NMDA receptor levels would result in an increase of negative symptoms[89]. There is cause for concern that typical antipsychotic medications may not help lower the risk of NMDA receptor hypofunction-induced neurodegeneration, given that negative symptoms may correlate with structural brain changes and cognitive decline and that typical antipsychotic drugs are only equivocally effective in treating negative symptoms. While thioridazine and haloperidol, two common antipsychotics, prevent NMDA receptor hypofunction-linked neurodegeneration. Clozapine is able to treat both negative and positive symptoms of schizophrenia, including treating treatment-resistant schizophrenia which is non-responsive to typical antipsychotics. This suggests that clozapine-sensitive networks may exist in the NMDA receptor hypofunction[73].

Despite the idea that thioridazine and haloperidol prevent NMDA receptor hypofunction defies the conventional under-

standing of antipsychotic action. New research suggests that antipsychotics may indirectly affect the glutamatergic system through associations with GABAergic and serotonergic pathways. Furthermore, clozapine's manipulation of NMDA receptor-linked neurocircuits suggests an additional process that goes beyond simple D2 receptor blocking and offers more comprehensive therapy for the variety of symptoms associated with schizophrenia. This more comprehensive viewpoint is consistent with current studies looking for non-dopaminergic targets for treatment. New research on schizophrenia offers fresh perspectives on how medications that target glutamate, such as NMDA receptor modulators, are changing our knowledge of the condition. Dopamine pathways, particularly D2 receptor antagonists like clozapine and haloperidol, have historically been a major focus of schizophrenia therapy[90].

Studies reveal that clozapine has shown favourable results in patients who are resistant to haloperidol, indicating that clozapine's special capacity to affect NMDA receptor systems fills a gap left by dopamine-focused therapies. This emphasizes that there are clozapine-sensitive pathways that are different from the mechanisms that other antipsychotics target. Clozapine's ability to modulate both dopaminergic and glutamatergic systems demonstrates its adaptability and lends credence to the idea that NMDA receptor-targeted medicines might be crucial for treating severe negative symptoms and cognitive impairment, two conditions that conventional antipsychotics are not very good at treating. This implies that although common antipsychotics aid in the reduction of symptoms, their limited ability to interact with glutamatergic circuits may account for their incapacity to treat more complicated symptoms of schizophrenia[91,50,92,93].

GABA

P50 gating was seen to be improved in schizophrenia patients by clozapine, which is due to $GABA_B$ receptor stimulation. Additionally, it has been demonstrated that atypical antipsychotics like clozapine and olanzapine have an impact on P50 even if they may not have an effect on drugs that solely target dopaminergic neurotransmission. Studies have also shown that P50 gating ratios vary according to the frequency, severity, and intensity of hallucinations[33]. This is a perfect conceptual example of the combined use of glutamatergic and antipsychotic treatments, to correct P50 gating the antipsychotic medications targeting the $GABA_B$ receptor which is a part of the glutamatergic system.

An additional investigation revealed no alterations in the cingulate cortex after switching to olanzapine from conventional neuroleptics. Consequently, it is challenging to determine the precise impact of neuroleptics on GABA concentrations. The GABA concentration may be lowered by all antipsychotic drugs, including both FGA and SGA. It would be plausible to speculate that unmedicated patients could have a greater GABA concentration[94]. After receiving antipsychotic therapy, studies reported lower glutamate levels. However, some also said they saw no discernible improvements. Following therapy, several studies have shown a drop in glutamate levels in regions such as the anterior cingulate cortex[95,96]. This shows that antipsychotics may have more complicated and regionally particular impacts on brain glutamate than previously believed.

Furthermore, a review indicated that glutamate levels may be influenced by the type and length of antipsychotic medication, albeit no firm conclusions could be made. Overall, the data highlights the necessity of more studies using standardized approaches to learn more about the connection between brain glutamate levels in schizophrenia and antipsychotic therapy. Variations in study methods, patient groups, and the particular brain areas investigated are probably the cause of the inconsistent results[97]. According to research, when schizophrenia patients switched from FGA to olanzapine, their blood glutamate levels increased dramatically, but their brain glutamate levels remained unchanged overall. However, brain glutamate levels also improved in those who showed reductions in negative symptoms. This implies that the effect of olanzapine on glutamatergic transmission may be related to how successful it is[98].

Treatment outcomes for schizophrenia vary greatly based on a number of underlying variables, such as environmental, neurochemical, and genetic effects. Individuals' responses to both FGA and glutamatergic treatments are significantly influenced by genetic differences, namely polymorphisms in drug-metabolizing enzymes and neurotransmitter receptors. In particular, racial and ethnic variations in drug-metabolizing enzymes can change how antipsychotic medications are metabolized and how efficient they are, which can affect both the risk of side effects and the success of treatment. Furthermore, the symptoms of schizophrenia are mostly caused by neurochemical imbalances, such as dysregulation in the dopamine and glutamate pathways, which also affect how patients react to particular treatment options.

Therefore, combined treatment should focus on taking advantage of the relationship between glutamate and dopamine to control symptoms of schizophrenia. It would be more viable to use SGA as they have produced positive results in blocking NMDA receptor hypofunction and producing changes in GABAergic systems. The side effects of such combined treatment to be considered essentially should be that of antipsychotic drugs. SGA produce many more adverse side effects than typical antipsychotics, when using them to target a completely different system these pre-existing side effects should be kept in mind.

Potential role of race in the effectiveness of treatment

It is a well-known fact that most psychological research studies involving the use of human samples show sampling bias towards caucasian males. Therefore, the effect of treatment on POC with schizophrenia can vary to a great extent. Research shows that genetic differences can interfere with drug metabolisation and cause it to function differently. However, we must also look at the fact that many POC are disproportionately diagnosed, thus subjecting them to treatment when they do not have the disorder in the first place.

A study highlights how POC are diagnosed with schizophrenia spectrum disorders and other psychotic disorders at a disproportionate rate[99]. This has serious negative effects, such as incarceration, and fewer opportunities. According to the research, racial prejudices in the medical and mental health industries are mostly to blame for these gaps rather than biology. Due to systematic racism, POC usually face greater levels of stress, which can worsen mental health difficulties.

Physicians error is made worse by a lack of culturally sensitive care, where a lack of empathy and insufficient treatment are caused by unconscious prejudices directed at POC. The study also touches on the historical background of psychosis in psychology, emphasizing the ways in which racial misconceptions have shaped POC diagnosis and care in the past. Additionally, research also delves into the perilous function of law enforcement, since racial prejudices along with psychotic symptoms heighten the likelihood of police brutality and early death among POC patients. To correct this gap, systemic improvements in mental health treatment, are required highlighting the need for racially sensitive education and training to enhance the lives of POC with serious mental illnesses. The need of the hour is the deployment of initiatives that address these ingrained racial prejudices and an update on the mental health treatments that are offered to coloured communities[99].

Polymorphisms and Drug Metabolism in POC

Drug metabolising enzymes are enzymes that biotransform drugs to generate metabolites to improve solubility for elimination processes or inactivation of drug action[100]. Studies confirm the presence of mutated drug metabolising enzymes in POC[3],[101],[102]. Polymorphisms are natural variants present in the structural makeup of products and the genes they encode. Drug metabolising enzymes, receptor proteins, and other proteins involved in drug response or disease development are significant gene products in this context. All human genes have polymorphisms, but only a small percentage of these affect how the gene product functions and even fewer of them have a markedly varied frequency in different population groups. Drug metabolism enzyme polymorphisms have been the subject of much research due to their widespread effects on a wide range of medications. The metabolism of antiarrhythmics, antidepressants, beta-blockers, neuroleptics, opioids, barbiturates, and benzodiazepines is impacted by the two most significant polymorphisms for this subject. Caffeine and isoniazid metabolism are impacted by a third polymorphism.

The efficacy of drugs can be significantly influenced by polymorphisms in proteins involved in the course of illness and in drug targets. Variations in the serotonin receptor gene impact how the body reacts to clozapine and antipsychotics. By changing a medicine's pharmacokinetic (absorption, distribution, metabolism, excretion) or pharmacodynamic (impact on the body) attributes, polymorphisms affect how a drug acts. Clinically, the anticipated length and strength of the pharmacological action may change, and people from diverse groups may require considerable dose modifications. Additionally, medications within a class may vary in their sensitivity to genetic variations in metabolism, as different compounds within the same class are eliminated by distinct metabolic routes. The pathophysiology of illness may vary between ethnic groups, and certain medications will work vary in efficacy than in a given racial group[103]. The breakdown of antipsychotic medications like clozapine and haloperidol is impacted by CYP2D6 polymorphisms. Polymorphisms of the NMDA receptors and other neurotransmitters involved in schizophrenia also play a role in the overall manifestation of schizophrenia and the effect of treatment on the disease.

Cultural Barriers and Treatment Gaps Across Minority Groups

Studies have shown that Asians react to lower doses of antipsychotic medications and experience toxic side effects at lower dosages than caucasian people[104],[105]. In these investigations, compared to Caucasians, Chinese and other Asian populations received a lower clinically adjusted dosage of haloperidol. In a similar vein, Korean Americans received a lower clinically adjusted dosage of clozapine than Caucasian people. There was no difference in the pharmacokinetic characteristics between African-American and Caucasian patients in research including trifluoperazine and fluphenazine. Due in part to the perception that African-Americans are harder to control and less obedient, as well as possible diagnoses of more serious diseases, African-Americans have historically received far larger dosages of antipsychotics.

Thorough research is required to identify the biological and cultural pathways that may underlie these therapeutic approaches as well as to describe the pharmacokinetics and pharmacodynamics of these strong, possibly harmful drugs in African-American communities. Antipsychotic medications may also have varied impacts on other ethnic groups, such as Ashkenazi Jews, particularly in terms of adverse effects. Accord-

ing to research, clozapine, has been linked to the development of agranulocytosis in Jewish patients. However, in the overall population, this adverse response occurs in around 1% of chronic schizophrenia patients. Every afflicted Ashkenazi Jewish patient had a haplotype that was shared by 83% of those with agranulocytosis. Typically, this haplotype is present in less than 1% of American Caucasian people, although it is present in 10%–12% of Jewish people in both Israel and the US. Given the high frequency of this haplotype in this ethnic group, Ashkenazi Jews in this research may be more susceptible to the development of clozapine-induced agranulocytosis.

Care for Latino people with schizophrenia is greatly impacted by cultural stigma and linguistic obstacles. According to research, Latinos who are born in the US have a greater prevalence of psychiatric problems than Latino immigrants, indicating that acculturation and mental health have intricate relationships. Furthermore, Latinos are less likely to obtain care for schizophrenia that is consistent with guidelines, frequently because they have less access to culturally appropriate therapies and Spanish-speaking mental health specialists [106, 107].

Due to restricted access to specialist treatments, Native Americans confront particular difficulties when it comes to the treatment of schizophrenia. This highlights the necessity of culturally grounded approaches that honour conventional healing methods while incorporating evidence-based treatments. Given the risk of misdiagnosis and cultural variations in symptom manifestation, the prevalence of schizophrenia in these groups is frequently underreported [108]. Asians may exhibit more physical signs of psychological discomfort and have a tendency to underuse mental health treatments. Clinicians may fail to identify culturally unique symptoms of schizophrenia, which might result in misdiagnosis or delayed treatment [109].

The Importance of Individualized Treatment in Schizophrenia

These differences highlight the need to provide culturally sensitive care while treating schizophrenia. Making the case for the creation of culturally sensitive therapies and the significance of comprehending cultural perspectives on mental illness in diverse communities. Regardless of a person's race or ethnicity, this method is crucial for enhancing diagnostic precision, treatment compliance, and overall results for all people with schizophrenia [110].

Clinicians in practice who treat individual patients as well as institutional policy makers should be conscious of the consequences of racial and ethnic variations in medication management. This is especially crucial. Policies with restrictions may put patients from diverse racial and ethnic origins at higher risk. The latest research in this area makes it abundantly evident that judgments about prescription and regimen selection must take individual racial and ethnic characteristics into account. If not, institutional pharmaceutical policies that limit customized medication therapy may disfavour certain populations [103]. The perspective that all drugs metabolise and all illnesses affect all humans the same, is an extremely outdated approach. It is extremely important, to understand the varied effects of drugs and illnesses in various races and ethnic groups to be able to treat patients in the most efficient and just manner. Polymorphism is one of many views on how variations in genetic makeup affect silently healthcare.

Discussion and Conclusion

Other than race, generally diagnosing schizophrenia poses be difficult as its symptoms and key markers may appear similar to other disorders. When discussing about schizophrenia it is important that we are able to differentiate it from other disorders that may present seemingly similar symptoms to be able to administer the most suitable treatment. Paranoid personality disorder is one such disorder that presents symptoms that appear to be very similar to schizophrenia. The major difference between the two is that a patient with paranoid personality disorder would not experience hallucinations. Such patients would experience delusions and paranoia. Whereas, a schizophrenic patient could experience hallucinations that may cause paranoia. If their hallucinations lead to paranoia their disorder would be classified under paranoid schizophrenia. Although, it is not necessary that one may experience hallucinations during the manifestation of schizophrenia. This makes schizophrenia difficult to diagnose as symptoms may seem similar to other disorders.

Moreover, it is also important to note that most studies related to schizophrenia take place in Western countries, where POC usually form minority populations, making it harder to obtain a POC-rich sample. It should also be noted that people from Eastern countries heavily rely on Eastern medicine (deeply rooted in culture, tradition and nature), and they may receive different care for schizophrenia or schizophrenia-like illnesses. According to WHO, the vast majority of people with schizophrenia do not receive adequate care [111]. It is important to treat persons with schizophrenia as they present a higher risk of suicide than the general population.

Difficulty in the diagnosis of schizophrenia eventually leads to difficulty in providing adequate treatment thereby unknowingly allowing the patient's condition to worsen. As aforementioned, schizophrenia-related studies samples for the majority of such studies are made up of caucasian males, they seldom include samples with POC. The lack of research on schizophrenia in POC also makes it difficult for doctors to recognise symptoms of schizophrenia in people of colour. Certain atypical symptoms of schizophrenia may manifest in people of colour, and licensed healthcare providers may ignore them as they are more likely to consider disorderly behaviour caused by schizophrenia as normal in certain ethnicities and races.

Over the past 35 years, research has revealed notable variations in drug metabolism rates, clinical responses to medications, and adverse effects amongst racial and ethnic groups. Individual genetic variations do not divide people into distinct groupings that are consistent with the popular conception of race; rather, their prevalence varies gradually across continents. Race serves as a crude proxy for these genetic variations. Race and ethnicity should be taken into account when it comes to certain medicines, in addition to other variables like age, gender, nutrition, smoking status, and other variables that frequently but not always alter the risk of illness or drug reaction [103].

Future work should focus on better sampling techniques to be able to include a diverse population. Better sampling will allow researchers to better understand the side effects of treatment on the general populous as a whole and will allow research to take into account varied genetic factors from the start. Moreover, current treatment for treatment-resistant schizophrenia only involves using the antipsychotic clozapine. It is imperative to do a comprehensive study on the genetic and epigenetic variables linked to schizophrenia. Studying how environmental variables affect the expression of genes while discovering certain genetic differences may help develop more specialized approaches and individualized treatment plans.

Researchers and clinicians might strive toward more fair and efficient schizophrenia care by addressing these particular problems that various racial and ethnic groups confront. To close the present gaps in our knowledge and treatment of schizophrenia across all populations, future research should focus on various patient samples and look into culturally unique risk factors, treatment responses, and intervention tactics [110].

Early identification and intervention options have the potential to halt the progression of schizophrenia or reduce its severity, hence they should be given priority in research. This entails researching groups that are at risk and creating trustworthy biomarkers for early detection. Long-term studies that monitor participants over an extended period are necessary to comprehend how schizophrenia develops, the value of early therapies, and the long-term consequences of therapy. These studies can guide best practices for long-term care and assist in identifying crucial times for intervention.

There are currently few alternatives for treatment-resistant schizophrenia. The only antipsychotic medication licensed expressly for treatment-resistant schizophrenia is clozapine; nevertheless, it comes with substantial side effects, such as agranulocytosis, that require frequent blood testing. To give patients better care, it is necessary to find innovative, efficient therapies with fewer side effects. A large amount of the financial strain linked to schizophrenia is attributable to treatment-resistant schizophrenia because of the need for long-term care, frequent hospitalizations, and higher healthcare expenses. Reducing these expenses and easing the burden on healthcare systems may be achieved by developing more potent treatment-resistant schizophrenia.

The enduring symptoms of treatment-resistant schizophrenia can cause significant impairment in social and vocational functioning, as well as an elevated risk of homelessness, drug misuse, and suicide. To improve long-term results, improve quality of life, and lower death rates among these patients, research in this field must be advanced. Studying treatment-resistant schizophrenia may help provide more light on the genetic and molecular causes of schizophrenia. Gaining insight into the reasons behind certain patients' non-response to normal therapies may open up new avenues and targets for drug development, which might result in advances in the treatment of schizophrenia in general as well as treatment-resistant schizophrenia. It is also important to research sub-cortical areas of the brain that are speculated to be associated with schizophrenia, in order to develop novel treatments that are able to affect schizophrenia vehemently. Therefore, future research should aim to explore concepts in a holistic manner. There is a lot of scope in schizophrenic research as current evidence has only scratched the surface of the disorder, the development of new technology is helping researchers understand and explore the disease better and develop new theories about the treatment and origins of schizophrenia.

This comprehensive literature review aimed to explore the effectiveness between glutamatergic and traditional antipsychotic treatments for schizophrenia and the circumstances that would affect their efficacy. It has explored through a compare and contrast of both treatment types and exploring the neurobiological basis of schizophrenia, anti-psychotic treatments and glutamatergic treatments. It also explored the potential role of race in the effectiveness of these treatment types as medications are known to work differently with people of colour.

Antipsychotic treatment of schizophrenia has been used and researched for much longer than glutamatergic treatment. They both target important neurotransmitter systems that are primitive indicators of schizophrenia, dopamine and glutamate respectively. This paper has gone into detail about the various glutamatergic and dopamine mechanisms in the brain associated with schizophrenia. Although antipsychotic treatments are well known they are associated with many adverse and serious side effects and most can only block D2 receptors. Antipsychotic drugs are old and were developed on the basis of primitive knowledge about schizophrenia. As new knowledge surfaces antipsychotic drugs are also being re-evaluated.

Glutamatergic treatment functions by manipulating atypically functioning glutamatergic mechanisms and aims to regulate them to prevent the manifestation and worsening of symptoms of schizophrenia. Although glutamatergic systems are new they offer promising results and hope for better treatment of schizophrenia with minimal side effects. The combined use of glutamatergic and antipsychotic treatments is a very recent avenue researchers have begun exploring. This idea is still in its primitive stage with limited human sample studies.

When exploring the use of antipsychotics to target glutamater-

gic mechanisms we must take into account the positive and negative effects of each treatment and how it would affect treatment. Current research involves using antipsychotic medication to treat glutamate systems. This approach of combination treatment works based on the connection between glutamate and dopamine and how they affect each other. the goal of combination treatment should be to manage symptoms of schizophrenia by leveraging the glutamate-dopamine interaction.

Research suggests that using SGA would be more practical because of their shown ability to modify GABAergic systems and inhibit NMDA receptor hypofunction. The negative effects of antipsychotic medications should largely be taken into consideration while evaluating the combination therapy. It is important to consider the pre-existing side effects of SGA when utilizing them to target a different system, as they create a greater number of unpleasant side effects than normal antipsychotics. Although FGA are beneficial for symptoms related to dopamine dysregulation because they mainly target dopamine receptors, individuals who have both dopamine and glutamate abnormalities may benefit better from combination treatments that also target the glutamate system. The effectiveness of therapies that target only one route is frequently reduced by environmental conditions, such as substance misuse or chronic stress, which can exacerbate neurochemical imbalances and further confound therapy responses. Knowing each of these possible reasons enables more individualized and successful treatment plans, emphasizing the promise of customized medicine and combination treatments in the management of symptoms of schizophrenia.

Race also plays a major role in the treatment of schizophrenia due to the presence of polymorphisms due to genetic variations that affect drug-metabolising enzymes interfering with the metabolising ability of medications and making them function differently. Although race should not be the only lens one should view difficulty in the treatment of schizophrenia, the similarity of symptoms with other mental disorders is also a factor worth considering as it often leads to misdiagnosis. Polymorphisms develop according to genetic variations, not race factors, similar polymorphisms can develop in the same ethnic group due to their shared history but it is not confined to it therefore, race and ethnicity cannot be the deciding factors regarding treatment variation. More research consisting of ethnically diverse samples must be conducted to study variations caused due to genetic differences in illnesses and drugs from the foundation of the theory development. It is also important to use new technology to study sub-cortical areas associated with schizophrenia, possibly allowing for the development of better treatment of schizophrenia. The cases made and evidence presented here in this review have important ramifications for clinical practice. For example, early detection and intervention tactics can be improved by incorporating working memory tests, like the digit span and n-back tests, into standard diagnostic evaluations. Additionally, understanding how pharmacological reactions and genetic predispositions interact can help inform individualized treatment regimens, which may enhance long-term results and adherence.

Schizophrenia is an extremely serious illness causing social and personal problems for people with schizophrenia and must be dealt with utmost sensitivity. It is a complex disease, and current evidence only provides for a surface-level analysis of the biological and genetic origins of the disease.

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