***Review Article***

**Beyond the fundamental mechanisms of Anti-Psychotic Drugs: Exploring novel Pharmacological targets for improved outcomes. A Systematic Review.**

**Abstract**

Schizophrenia is a disease with a complex pathological mechanism that is influenced by multiple genes. The study of its pathogenesis is dominated by the dopamine hypothesis, as well as other hypotheses such as the 5-hydroxytryptamine hypothesis, glutamate hypothesis, immune-inflammatory hypothesis, gene expression abnormality hypothesis, and neurodevelopmental abnormality hypothesis. . Multi-target drugs are a promising approach against polygenic diseases with complex pathomechanisms such as schizophrenia. Indeed, second generation or atypical antipsychotics target a number of aminergic G protein-coupled receptors (GPCRs) simultaneously. Novel strategies in drug design and discovery against schizophrenia focus on targets beyond the dopaminergic hypothesis of the disease and even beyond the monoamine GPCRs. The first generation of antipsychotics was developed based on dopaminergic receptor antagonism, which blocks dopamine D2 receptors in the brain to exert antipsychotic effects. The second generation of antipsychotics acts by dual blockade of 5-hydroxytryptamine and dopamine receptors. From the third generation of antipsychotics onwards, the therapeutic targets for antipsychotic schizophrenia expanded beyond D2 receptor blockade to explore D2 receptor partial agonism and the antipsychotic effects of new targets such as D3, 5-HT1A, 5-HT7, and mGlu2/3 receptors. According to recent research, several receptors, including 5-hydroxytryptamine, glutamate, γ-aminobutyric acid, acetylcholine receptors and norepinephrine, play a role in the development of schizophrenia. As a result, the goal of creating novel antipsychotic medicines has switched to agonism or inhibition of these receptors. The development of NMDAR stimulants, GABA receptor agonists, mGlu receptor modulators, cholinergic receptor modulators, nicotinic receptor modulators, muscarinic receptor modulators, and alpha-2 receptor modulators has been the primary focus. This review paper aims to provide a systematic overview of the research on therapeutic targets and medications for schizophrenia, hence offering valuable insights for both treatment and further research in this field.

**Keywords:** schizophrenia, multi target drugs, neurotransmitter, antipsychotic drugs.

1.0 **Background or Introduction**

Schizophrenia is a chronic disorder that results in psychosis and a deterioration in mental function. It is a complex disorder that affects millions of people globally and has significant public health concerns (Luvsannyam *et al*., 2022). Schizophrenia can be caused by genetic, environmental, or neurochemical imbalances, but the complicated pathomechanism of this disease is not well understood (Henriksen *et al*., 2017). The clinical picture of schizophrenia includes three types of symptoms: positive (hallucinations, delusions, and thought disorders), negative (social withdrawal, apathy, and lack of motivation), and cognitive deficits (memory and learning impairments, attention deficiencies). It is generally agreed that the symptoms of schizophrenia come from disruptions in neurotransmission involving a considerable number of receptors and enzymes, primarily within the dopaminergic, glutamatergic, serotoninergic, and adrenergic systems (Nimgampalle *et al.*, 2023; Singh *et al*., 2020).

In this aspect, the dopaminergic hypothesis remains the central notion of the condition, with all marketed antipsychotics targeting the dopamine D2 receptor. However, fresh results in the field of neuroscience link schizophrenia with aspects beyond the dopaminergic theory, highlighting in particular the significance of the glutamatergic system in the development of the disease (Buck *et al*., 2022; Fišar, 2023). To effectively treat complex neuropsychiatric illnesses like schizophrenia, it is vital to move beyond the "magic bullet" idea. This drug development strategy was predicated on the notion that single-target medications are safer since they have fewer adverse effects due to their selectivity. However, it turned out that this is only true for single-gene disorders, and the number of initial single-target medications were performing below expectations (Kondej *et al*., 2018; Stępnicki *et al*., 2021). Thus, the "one-drug, one-target" paradigm has been gradually substituted by the concept of multi-target medicines (MTDs), often known as "magic shotguns." MTDs, as opposed to clean single-target medicines, were historically referred to be dirty or promiscuous medications. Single-targeted treatments have been shown to be mostly ineffective for diseases with complicated pathomechanisms, such as neuropsychiatric diseases or cancer (Kondej *et al.*, 2018). The majority of strong antipsychotics, particularly second-generation or atypical antipsychotics, target multiple aminergic G protein-coupled receptors. Clozapine, which is used to treat drug-resistant schizophrenia, has a nanomolar affinity for numerous aminergic GPCRs. In this scenario, drug design and discovery has moved from the molecular and cellular level to the systems biology-oriented level to reflect minor processes occurring on the biological networks that lead to the disease (Kussmann *et al.*, 2017). MTDs have several advantages than single-target medicines, including increased efficacy due to synergistic or additive effects and enhanced dispersion in the target tissue. However, it is not easy to construct powerful MTDs, and challenges occur starting from a correct target selection through affinity balancing to preventing affinity to related off-targets (Vlocskó *et al.*, 2022; Wang *et a*l., 2022).

Understanding the behavioral signs of psychosis has proven difficult due to the diversity of psychotic diseases. Symptoms are subjective and based on the patient's personal views (Beck *et al*., 2012). There is a need to establish the underlying neurobiology so that psychosis may be characterized through neuropathology rather than symptomology, which may vary from individual to individual **(**Kandratavicius *et al.*, 2014)**.** The most prevalent theory of psychosis is that of chemical imbalance in the brain, marked by dysregulation of the mesolimbic pathway as a result of dopaminergic hyperactivity (Rawani *et al*., 2024). Dopamine dysregulation is known to be related with various other psychiatric diseases without the onset of psychosis, hence there is a rising emphasis on researching additional processes of physiological function instead of exclusively focusing on neurotransmitter interactions (Rawani *et al.*, 2024; Rezaei, 2022). Our current understanding of psychosis does not account for many of the emerging mechanisms or describe multiple interactions.

**1.1 Pathophysiology of Psychosis**

Viewing psychosis via a neuroendocrine-immunomodulation lens has shown a multifaceted etiology and this has resolves certain gaps in our understanding. This perspective emphasizes the interactive nature of communication between the neurological, endocrine, and immune systems (Alessi *et al*., 2020; Straub *et al*., 2024). The underlying neurological pathways that lead to psychosis are of great interest and importance. Neurotransmitter dysregulation (dopamine, glutamate, serotonin), neuroinflammation, the hypothalamic-pituitary-adrenal (HPA) axis, the gut-brain axis (GBA), oxidative stress, and mitochondrial dysfunction are all neurobiological pathways that contribute to psychosis.

**1.1.1 Neurotransmitter Dysregulation**

**(i) Dopamine**

Although various hypotheses have been proposed to clarify the neurobiological mechanisms that govern the onset of psychosis, the dopamine hypothesis remains a popular explanation. This concept, based primarily on early pharmacological discoveries with antipsychotics, postulates that psychotic symptoms are linked to the activation of dopaminergic neurons in the mesolimbic pathway (Kendler *et al*., 2011). The mesolimbic route is a dopaminergic system that begins in the ventral tegmental region (VTA) and extends to the nucleus accumbens. The route delivers dopamine signals to various specialized regions, including the amygdala, hippocampus, ventral and associative striatum, thalamus, and prefrontal cortex (PFC) (Hui *et al*., 2022). The underlying function of dopamine in the mesolimbic pathway in psychosis has been proposed as hyperactivity exhibited at D2 dopamine receptors. The initial dopamine theory has recently been broadened to include other symptoms of schizophrenia, such as negative symptoms and cognition that do not appear to be explained by dopamine hyperactivity in the mesolimbic pathway (Yang *et al*., 2017).

The dopamine hypothesis has had a significant impact on pharmacotherapy because many antipsychotics produced and now in use oppose dopamine D2 receptors. However, many of these antipsychotics are ineffective in addressing negative symptoms and cognitive deficits in schizophrenia (Gross *et al*., 2012).

Furthermore, in some psychotic individuals who are treatment-resistant, there is no obvious dopamine dysregulation (Amato *et al.*, 2019). Although the mesolimbic circuitry is closely linked to goal-directed behavior, research has shown that mesolimbic dopamine signaling also integrates homeostatic functions, responding to changes in physiological state via HPA axis regulation. This shows an involvement of other variables in psychosis, in addition to mesolimbic dopamine (Stanton *et al*., 2019). It has been found that when patients have hallucinations, the thalamus, hippocampus, and striatum become more activated. Schizophrenic individuals with delusions have overactivation of the PFC and impaired inactivation of thalamic and striatal networks. Furthermore, isolated brain lesions can cause psychotic symptoms, such as hallucinations, without appearing to impede normal subcortical dopamine function in parts of the mesolimbic circuitry (Rawani *et al.*, 2024).

**(ii) Serotonin**

There is evidence that the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is involved in psychotic pathogenesis. According to the serotonin theory, psychosis is associated with excessive activation of 5-HT2A receptors, particularly those on glutamate neurons in the anterior cingulate cortex and dorsolateral frontal lobe (Burstein, 2021). Upregulation of these 5-HT2A receptors may result in excess glutamate release in the cortex. Therapeutic interventions have indicated that blockade of serotonin 5-HT2A receptors is useful in lowering psychotic symptoms in Parkinson's disease (Kantrowitz, 2020). Several atypical (second-generation) antipsychotics inhibit both dopamine D2 and 5-HT2A receptors; however, they differ significantly in their efficiency in blocking the psychotic effects of methamphetamine.

**(iii) Glutamate**

Although the dopamine hypothesis remains an essential theory of psychosis, it has also proven useful in the development of antipsychotic drugs. Other variables are crucial in the etiology of psychosis, including dysregulation of other neurotransmitters in addition to dopamine (Panov *et al*., 2024; Rawani *et al.*, 2024). The glutamate hypothesis suggests that symptoms of schizophrenia and cognitive impairments are caused by hypo function of N-methyl-D-aspartate receptors (NMDARs) on γ-aminobutyric acid (GABA) interneurons in the cerebral cortex. This results in over activation of downstream glutamate signaling to the VTA and, possibly, dopamine release in the mesolimbic system (Adell, 2020; Snyder *et al.*, 2020).

Although there is evidence that the dopamine-glutamate interaction is critical to disturbed synaptic connectivity, there is some disagreement over directionality. Increased synaptic cleft concentrations of dopamine, such as those produced acutely by amphetamines, may result in enhanced glutamate signaling, implying glutamate dysregulation is a downstream consequence that may induce excitotoxicity and subsequent neuronal damage (Shrestha *et al*., 2022). However, it has also been shown that high levels of glutamate release can cause dopamine hyperactivity (McCutcheon *et al*., 2020). NMDAR antagonists, like ketamine, have been clinically shown to cause psychotic symptoms (Lisek *et al.*, 2017).

Normal functional communication in the brain relies on a balance between excitatory and inhibitory networks, which use glutamate and GABA as neurotransmitters, respectively, and a perturbation of the excitatory/inhibitory (E/I) balance contributes to neural network dysfunction and leads to cognitive and behavioral deficits (Kirischuk, 2022). Abnormalities in GABA neurotransmission are also linked to the effects of hypoactive NMDARs on GABA interneurons, resulting in E/I imbalance as a probable cause of increased dopamine activity and, eventually, psychosis (Heckers *et al*., 2015). In addition to the significance of glutamate in psychosis, there has been a lot of research in recent years in the potential relevance of the amino acid D-serine, a powerful co-agonist at the glycine position on the NMDAR. Abnormalities in the levels of D-serine and/or the activity of enzymes involved in its production and catabolism have been hypothesized in schizophrenia. D-serine and inhibition of its catabolism have been claimed to be effective in the treatment of schizophrenia (Nasyrova *et al.*, 2022).

Psychosis could also involve interactions with other physiological systems such as neuroinflammation, oxidative stress, and mitochondrial dysfunction, which are associated to the inhibition of neurogenesis and the initiation of cell death (Gorlova et al., 2023; Rawani *et al.*, 2024), as a result, investigating these aspects in the context of psychosis has been a popular research topic.

**1.1.2 Neuroinflammation**

Because the blood-brain barrier (BBB) protects the brain, the effects of neuro-immune interactions are frequently underestimated. However, extensive experimental and clinical data now points to major neural-immune connections and a bidirectional contact between the neurological and immune systems (Dantzer, 2018). Inflammation is a two-edged sword. While an inflammatory response is a protective mechanism, untreated chronic inflammation can be damaging, making it an underlying mechanism of action for neuropathology (Rousseau *et al*., 2023; Sadrameli et al., 2020). Many mental diseases are associated with an inflammatory response characterized by high pro-inflammatory cytokine concentrations, and the discovery that neuroinflammation tends to precede psychosis symptomology implicates it as part of the psychotic etiology (Bishop *et al*., 2022). Pro-inflammatory cytokines, including IL-6, IL-8, and TNF-α, contribute to the continuous inflammation (Malkov *et al*., 2021). Although low levels of cytokine production are necessary for homeostasis, the severity of clinical symptoms in schizophrenia has been linked to pro-inflammatory cytokine levels. Clinical studies have found higher levels of IL-β, IL-6, and TGF-β in patients with persistent schizophrenia and first-episode psychosis (Reale *et al*., 2021).

Glial cells are known to contribute considerably to inflammation and can also influence other mechanisms that may contribute to psychosis (Dietz *et al*., 2020).

1. **Microglia**

Microglia are immune cells that reside in the central nervous system (CNS) that, when activated, promote inflammation. In normal physiological conditions, microglia maintain continuous immunological monitoring and are the first line of defense against dangerous cellular debris (Arcuri *et al*., 2017; Borst *et al*., 2021). However, under pathological situations, such as psychosis, microglia become persistently active, enabling an inflammatory state (Beumer *et al*., 2012; Tay *et al*., 2018). Pro-inflammatory cytokines can cause microglia to switch from a resting to an active state, allowing these cells to generate pro-inflammatory cytokines such as IL-6. Microglia-derived cytokines have a reciprocal effect on neuronal function. Furthermore, higher microglial activity and neuroinflammation have been observed to be associated with psychosis, indicating a positive connection with symptom severity (Marques *et al*., 2019). Chronic microglial activation and high pro-inflammatory markers precede the onset of psychosis, suggesting that an inflammatory condition can predict psychotic symptoms (Kogan *et al.*, 2020). Chronic microglial activation has been discovered as a mechanism behind excessive synaptic pruning, loss of brain volume in the cortex, and cellular dysfunction in the PFC, all of which are typical hallmarks of psychosis in schizophrenia (Parellada *et al*., 2021). Activated microglia can affect the blood-brain barrier (BBB) endothelial function by secreting reactive oxygen species (ROS) and pro-inflammatory cytokines (da Fonseca *et al*., 2014).

1. **Astrocytes**

Astrocytes, the most abundant glial cells in the CNS, are multifaceted cells that express a variety of receptors, transporters, enzymes, and ion channels (Won *et al*., 2025). They play an important role in maintaining CNS homeostasis by regulating the following: neuronal nutrition; neurotransmitters (particularly glutamate); ion and water homeostasis; synaptic formation and modulation; cerebral blood flow and metabolism; development, maintenance, and function of the blood-brain barrier (BBB); iron transport; and oxidative stress defense. Astrocytes transport glucose and lactate to neurons, remove neurotransmitters like glutamate from the synaptic cleft, and release modulatory substances (Verkhratsky *et al*., 2015). It has been observed that astrocytes are responsible for recovering roughly 80% of the glutamate from the synaptic cleft using glutamate transporters (Schousboe, 2019). Astrocytes express GABA-A and GABA-B receptors, as well as GAT-1 and GAT-3 transporters, which can release and control GABA concentration. Astrocytes can improve synaptic function by secreting synaptogenic and neurotrophic substances such as thrombospondins, hevin, and TGF-β1. They also mediate neurotransmitter uptake and release (Liu *et al*., 2021). Astrocytes can also remove synapses through several means, including direct phagocytosis, inducing microglia to phagocytose, and activating the intracellular inositol 1,4,5-triphosphate (IP3) pathway, resulting in the release of Ca2+ from the endoplasmic reticulum (Sancho *et al.*, 2021). Astrocytes are also a crucial component of the glutamate–glutamine cycle. In this cycle, glutamate released by neurons is carried into astrocytes, where it is converted to glutamine, which is then returned to neurons, where it is subsequently converted to glutamate. CSF analysis shows higher glutamine-to-glutamate ratios in patients with first-episode psychosis (FEP) and drug-naive schizophrenia (Kahn *et al.*, 2015). In comparison to healthy controls, schizophrenia patients have a lower density of astrocytes expressing the disrupted-in-schizophrenia 1 (DISC1) gene in the dentate gyrus of the hippocampus (Terrillion *et al.*, 2017). This condition will lead to less synthesis of the NMDAR co-agonist D-serine. Astrocytes may also play a significant function in oxidative stress and neuroinflammation.

Under normal conditions, astrocytes can produce antioxidants (e.g., glutathione), remove glutamate, and activate antioxidant systems such as Nrf2, thereby guarding against oxidative stress-related damage. However, in pathological situations, astrocytes can be a source of reactive oxygen species (ROS) or reactive nitrogen species (RNS) as a result of mitochondrial dysfunction, poor metabolism, elevated glutamate, and/or reduced antioxidant production (Rizor *et al*., 2019). These free radicals increase microglial activation and neuroinflammation. In addition, oxidative stress can harm astrocytes. Oxidative stress is known to influence glutamate metabolism and secretion in astrocytes.

1. **Oligodendrocytes**

Psychosis symptoms have been discovered in clinical disorders characterized by a disturbance of normal myelination, indicating aberrant oligodendrocyte function. In normal physiological settings, oligodendrocytes are the myelinating cells of the CNS, hence they are crucial for the propagation of action potentials and neuronal transmission (Affrald R *et al*., 2024). Post-mortem study of brain tissue from schizophrenia patients found that roughly 14-22% had lower densities of oligodendrocytes (Falkai *et al.*, 2020). Myelin gene knockout mice also exhibit schizophrenia-like behavioral abnormalities, leading to the hypothesis that aberrant oligodendrocyte function contributes to the etiology of psychotic illnesses (Yu *et al.*, 2022). Because patients with myelin-related illnesses have also experienced psychosis, it has been proposed that disruptions in myelination in discrete regions such as the frontotemporal, callosal, and periventricular fiber tracts may be at the root of psychotic behavior. Oligodendrocytes are also vulnerable to the excitotoxic effects of glutamate. These cells are also thought to have immune-inflammatory properties, which can reduce the severity of inflammatory damage. This shows that the loss of oligodendrocytes has a multifaceted effect, leading to poor myelination and allowing the influx of pro-inflammatory cytokines and reactive microglia (Dulamea, 2017). Although oligodendrocytes are the glial cells primarily involved in myelination, it has been reported that microglia and astrocytes, in both their quiescent and activated forms, can modify differentiation of oligodendrocyte progenitor cells into myelinating oligodendrocytes and influence remyelination by oligodendrocytes (Traiffort *et al*., 2020). Microglia and astrocytes interact in a variety of ways, including through direct contact and the production of chemicals that regulate inflammation and exocytosis.

1. **Gut–Brain Axis**

The brain is also in constant communication with the gastrointestinal (GI) system through the GBA, a bidirectional communication network whose effects are exerted through pathways including the neuroendocrine HPA axis, the immune system, and the autonomic nervous system (e.g., the vagus nerve) (Zheng *et al*., 2023). Psychosis is also frequently associated with persistent GI inflammation, suggesting that dysfunction in psychosis may extend to changes in the gut microbiota, which has essential functions in the regulation of host homeostasis. The gut microbiome's activities can directly affect myelination, neurotransmission, BBB organization, the HPA axis, and neural-immune interactions. The gut microbiota can create inflammatory chemicals that cross the BBB. However, inflammatory activities also impact the composition of the gut microbiome (Parker *et al.*, 2020). The gut microbiome also plays a role in regulating the maturation and function of microglia.

The HPA axis and GBA have a bidirectional interaction. Not only does the gut microbiota influence HPA axis activity through mediators that cross the BBB, but exposure to stressors can modify mediators of the HPA axis and eventually affect the GI barrier (Morys *et al*., 2024).

The gut microbiome can also catalyze the production of neurotransmitters like dopamine, noradrenaline, glutamate, GABA, acetylcholine, and serotonin. The gut microorganisms create a lot of tryptophan (the precursor to serotonin) and other tryptophan metabolites such kynurenic acid and quinolinic acid. These metabolites have been postulated to be implicated in the etiology of numerous neuropsychiatric diseases, oxidative stress, and mitochondrial malfunction (Huang *et al*., 2023).

There is additional evidence to show that certain antipsychotics have antimicrobial properties and can influence the composition of the gut microbiota (Caldara *et al*., 2021). Second-generation antipsychotics' metabolic adverse effects have been linked to the gut microbiome (Vasileva *et al.*, 2022). Chronic use of antipsychotics can produce dysbiosis of the gut microbiome, leading to dysregulation of the neurotransmitters dopamine, glutamate, serotonin, and noradrenaline (Rawani *et al.*, 2024).

**1.1.3 Oxidative Stress**

Oxidative stress is commonly defined as an imbalance between the generation of reactive oxygen species, or free radicals, and the body's inability to detoxify these reactive products. Excessive synthesis of these reactive species can cause molecular damage, cellular malfunction, neurotoxicity, and the activation of both the apoptotic and necrotic cell death pathways. The majority of the research on oxidative stress deals with reactive oxygen species (ROS) (e.g., the superoxide free radical and hydrogen peroxide), but there can also be reactive nitrogen species (RNS) such as the nitroxyl anion and different nitrogen oxides (Salvagno *et al.*, 2024). ROS are byproducts of mitochondrial ATP synthesis. Under normal circumstances, the body can maintain a balance of oxidation and reduction in tissues (redox equilibrium). Free radicals can harm substances like lipids, proteins, and nucleic acids under severe stress conditions. To resist excessive accumulation of ROS and RNS, the body possesses a variety of enzymatic (e.g., superoxide dismutase, catalase, and glutathione peroxidase) and non-enzymatic antioxidant defenses (e.g., glutathione, metal binding proteins, and uric acid) (Jomova *et al*., 2024).

ROS generation is a natural element of aging that is influenced by both environmental and genetic variables. However, under pathological situations such as psychosis, oxidative stress exacerbates and accelerates brain damage via mitochondrial malfunction and pro-apoptotic mechanisms. Oxidative stress communicates with various physiological mechanisms in a bidirectional manner, affecting neurotransmission, neuroinflammation, and homeostatic networks including the HPA axis (Correia *et al*., 2024). Oxidative stress appears to be especially relevant in relation to dopamine. ROS can inhibit the dopamine transporters (DATs) that control dopamine breakdown. Rodent studies indicated that these effects are present in the mesolimbic pathway, as higher dopamine concentrations are detected in the synaptic cleft in the nucleus accumbens following reduced reuptake (Jîtcă *et al.*, 2021). Increased dopamine levels are known to be a significant source of oxidative stress in the brain. Dopamine also reduces the action of antioxidant mechanisms, hence amplifying the effects of oxidative stress. As previously noted, NMDAR dysfunction and excessive glutamate release are hallmarks of psychosis. The resulting glutamate-induced excitotoxicity is linked to the creation of ROS and oxidative stress (Nguyen *et al*., 2011). There is a clear bidirectional link between oxidative stress and NMDA dysfunction. On the one hand, NMDAR hypofunction may cause uncontrolled oxidation and high neurotoxicity in parvalbumin interneurons (PVIs) (Barron *et al.*, 2017). PVIs are inhibitory GABAergic neurons that help maintain an E/I balance (Uliana *et al.*, 2024). These neurons play key roles in neurochemical communication and have a high metabolic demand, making them more vulnerable to oxidative stress and severe harm.

**1.1.4 Mitochondrial Dysfunction**

Mitochondria, which play critical roles in energy metabolism, oxidative stress, and synaptic activity modulation, create nearly all of the cellular ATP in the body through oxidative phosphorylation carried out by the electron transport chain's complexes I through IV. Under normal conditions, mitochondria have an antioxidant defense mechanism. However, changes in that defense system have been found in schizophrenia (Bryll *et al*., 2020; Fizíková *et al*., 2023). Dysfunction of the mitochondrial complex may potentially contribute to oxidative stress in schizophrenia. In terms of inflammation, ROS produced by mitochondria can stimulate the synthesis of pro-inflammatory cytokines (Ranneh *et al*., 2017). In contrast, increasing amounts of pro-inflammatory cytokines in schizophrenia patients may disrupt the mitochondrial anti-oxidative defense system.

**1.3 Novel Antipsychotic Drugs and Targets of Action**

Antipsychotic medications are currently the most essential treatment for schizophrenia, and they are divided into two types: conventional antipsychotic drugs and atypical antipsychotic drugs. Typical antipsychotics are D2 receptor antagonists, which work by blocking the D2 receptor on dopaminergic neurons, reducing the dopamine nervous system's functionality. Blocking D2 receptors lowers limbic dopaminergic overactivity in the midbrain and enables better regulation of positive symptoms; nevertheless, robust D2 receptor blockade is also responsible for side effects such as extrapyramidal diseases and hyperprolactinemia (negative symptoms) (Peng et al., 2024). Some examples of typical or first-generation antipsychotic include haloperidol, fluphenazine and even chlorpromazine.

Positive symptoms have been proven to be the outcome of overactivity in the mesolimbic dopaminergic pathway (the neuronal projection from the ventral tegmental area (VTA) to the nucleus accumbens, amygdala, and hippocampus) activating D2 receptors (Hou *et al.*, 2024). Negative symptoms may occur from a decreased activity in the mesocortical dopaminergic pathway (the projection from the VTA to parts of the prefrontal cortex), where D1 receptors predominate. Other dopaminergic pathways in the central nervous system (such as nigrostriatal and tuberoinfundibular) appear to function correctly in schizophrenia. Thus, in terms of treatment, it would be preferable to suppress dopaminergic transmission in the limbic system while increasing this transmission in the prefrontal cortex.

**1.4 Multi-Target Compounds to Treat Schizophrenia.**

**(i) Second Generation Antipsychotics**

Atypical antipsychotics are those that act on many targets. The second-generation antipsychotics, which are currently the preferred treatment for schizophrenia and bipolar disorder, are essentially multi-target compounds. Second-generation antipsychotics mostly inhibit the D2 and 5-HT2A receptors. Their blockage of D2 receptors is substantially lower than that of normal antipsychotics, reducing the accompanying adverse effects but without weakening the antipsychotic efficacy. Second-generation antipsychotics are thought to work primarily by modulating the serotonin-dopamine relationship (Tollens *et al.,* 2018*)*.

The majority of currently available antipsychotic medicines (excluding third-generation treatments) work by inhibiting dopamine receptors in the central nervous system. Antipsychotic drugs, particularly those classified as second generation, block a variety of receptors, including dopamine D2, D1, D3, D4, serotonin (5-HT2A and 5-HT2C), histamine (H1), and α1-adrenergic receptors. Interaction of antipsychotics with those receptors is associated mainly with occurrence of side effects, such as sedation and drowsiness (H1 receptors), weight gain (H1 and 5-HT2C), sexual dysfunction (5-HT2), or orthostatic hypotension (α1-adrenergic receptors) (Peng et al., 2024). On the other hand, there are suggestions that antagonism of the serotonin 5-HT2A receptor may have a positive influence on the occurrence of extrapyramidal side effects, as well as the reduction of negative and cognitive symptoms in schizophrenia.

Clozapine is a classic example of a "dirty" medicine that is nonetheless considered a "gold standard" atypical antipsychotic due to its lack of extrapyramidal syndrome (EPS), superiority in the treatment of drug-resistant schizophrenia, and ability to reduce suicidality. Clozapine has serious adverse effects, including possibly fatal agranulocytosis, weight gain, hyperglycemia, and seizures. Clozapine's complicated pharmacological profile, which includes high affinity for multiple serotonin, dopamine, muscarinic, adrenergic, and other aminergic receptors, contributes to both its effectiveness and side effects (Kondej *et al.*, 2018). Some clozapine adverse effects were alleviated with the introduction of olanzapine, a second-generation antipsychotic. Olanzapine does not produce agranulocytosis, but it still has metabolic side effects that can include weight gain, which can be related with histamine H1 receptor activation (Lett *et al*., 2012). Importantly, the side-effect profile of olanzapine can be deemed positive, with a low frequency of EPS and modest increase in prolactin during acute-phase trials. Olanzapine has a nanomolar affinity for many receptors, including dopaminergic, serotonergic, α1 adrenergic, and muscarinic (Kondej *et al.*, 2018).

Noradrenaline has an important part in the pathogenesis of schizophrenia, however the specific involvement of adrenergic receptors is not well understood. Research suggests that atypical antipsychotics' interactions with α1-adrenergic receptors contribute to their typicality (Maletic *et al*., 2017). Antagonism at α1 adrenergic receptors is beneficial for treating positive symptoms, especially in acute schizophrenia. However, antagonism at α2 adrenergic receptors, such as clozapine and risperidone, may be important for relieving negative symptoms and cognitive impairments (Stępnicki *et al.*, 2021). Blockade of adrenergic receptors may stabilize dopaminergic neurotransmission in schizophrenia. Activating α2A adrenergic receptors in the prefrontal cortex may increase cognitive skills (Perez, 2020). Moreover, supplementary α2 adrenergic receptor antagonism improves the antipsychotic action of risperidone and promotes cortical dopaminergic and glutamatergic neurotransmission via NMDA receptors. Blocking α2C adrenergic receptors, either alone or in combination with dopamine D2 receptor blockage, may be useful for schizophrenia (Uys *et al*., 2017). The histamine H1 receptor is a typical off-target for antipsychotics since blocking it causes drowsiness and may contribute to weight gain. Weight gain and metabolic abnormalities can also be related to inhibition of adrenergic or cholinergic receptors, while antagonism of histamine H1 receptors is regarded as a primary explanation for second generation antipsychotics-induced obesity. In contrast, the histamine H3 receptor is an emerging target for novel antipsychotics since selective antagonists or inverse agonists of this histamine receptor subtype are effective in treating cognitive deficits in schizophrenia (Sadek *et al.*, 2016).

**(ii) Third-Generation Antipsychotics**

Aripiprazole, a third-generation antipsychotic, partially agonizes D2 and 5-HT1A receptors. It improves negative, positive, cognitive, and depressed symptoms. Aripiprazole, brexpiprazole, and cariprazine are all third-generation antipsychotics. The mechanism of action of these medications is still primarily related to dopaminergic neurotransmission, but not to dopamine receptor antagonism, but to partial or biased agonism (functional selectivity) (Ricci *et al*., 2024). Because of its partial agonism attributes, aripiprazole is known as a "dopamine stabilizer". Aripiprazole was one of the first functionally selective D2 receptor ligands discovered, which may stabilize dopaminergic transmission via the D2 receptor. Although aripiprazole was initially classified as a partial D2 receptor agonist, it was later discovered that it might act as a full agonist, partial agonist, or antagonist at the D2 receptor depending on the signaling readout and cell type tested. Aripiprazole is a partial agonist that inhibits cAMP buildup via the D2 receptor. However, it has also been observed that aripiprazole is an antagonist in GTPS binding experiments with the D2 receptor.

The US Food and Drug Administration (FDA) has authorized Cariprazine, a novel atypical antipsychotic. It is a partial agonist of dopamine D3 and 5-HT1A receptors that works well for schizophrenia and bipolar illness. Additionally, its negative effects on the metabolic and cardiovascular systems are low, making it a feasible therapy alternative (Barman et al., 2021). Third-generation antipsychotics, which are now being promoted, target a broader spectrum of receptors and function as partial agonists on the dopamine D2 receptor. They offer a broader therapeutic range than second-generation antipsychotics and have better safety, particularly in terms of metabolic and cardiovascular side effects. They can be used in individuals with schizophrenia who are ineffective or have significant adverse effects of typical antipsychotic medicines, or as adjuvant drugs of classic antipsychotic drugs, providing more options for therapeutic usage of drugs for schizophrenia.

Since the third generation of antipsychotics, the benefits of D2 receptor partial agonists' antipsychotic effects have been recognized. D2 receptor partial agonists (DRPAs) have significant D2 receptor occupancy, however DRPAs have intrinsic D2 receptor activity lower than that of dopamine, and so may lessen the likelihood of EPS while retaining clinical efficacy, which can be very useful in decreasing antipsychotic side effects (Mohr *et al*., 2021). Simultaneously, research on D3, 5-HT1A, 5-HT7, TAAR1, and mGlu2/3 receptor-related agonists or antagonists is progressing.

**1.5 Potential Therapeutic Targets for Antipsychotics**

The research into therapeutic targets for antipsychotic medicines is based on the notion of neurotransmitter abnormalities in schizophrenia, with the process involving blocking or activating the action of particular receptors to create antipsychotic effects. Previous research on antipsychotic medicines has mostly focused on dopamine; however, certain patients treated with dopamine antagonists may acquire dopamine super sensitivity, thereby reducing therapeutic effectiveness. Blocking dopamine receptors can produce extra-vertebral systemic responses, metabolic challenges, and hyperprolactinemia (Diamanti-Kandarakis *et al.,* 2019). Researchers have concentrated on investigating new antipsychotic medication targets that are not dopamine D2 receptors. Several studies have been undertaken to confirm the usefulness of these alternative neurotransmitter receptors for antipsychotic treatment (Gomes *et al*., 2021). These investigations have yielded promising findings, demonstrating that these targets are feasible for antipsychotic effects.

1. **Muscarinic and Nicotinic Receptors**

Muscarinic receptors play an important role in modulating synaptic plasticity in the prefrontal cortex, and stimulating these receptors causes long-term depression at the hippocampo-prefrontal cortex synapse (Ruggiero *et al.*, 2021). A growing body of research suggests that abnormalities in cholinergic neurotransmission play a fundamental role in schizophrenia. Postmortem studies show that schizophrenia patients have a lower number of cholinergic interneurons in the ventral striatum (Holt *et al*., 2005). Furthermore, neuroimaging investigations revealed that muscarinic receptor availability was much lower in schizophrenia patients, and positive symptoms of schizophrenia are inversely connected with muscarinic receptor availability (Carruthers *et al*., 2015). It should be noted that muscarinic receptor antagonists exacerbate cognitive and negative symptoms in schizophrenia patients, whereas xanomeline, a muscarinic receptor agonist, improves all symptoms in schizophrenia patients and animal models. Based on these and other observations, the muscarinic theory of schizophrenia has been proposed. The involvement of nicotinic cholinergic receptors in schizophrenia pathogenesis may explain why people with schizophrenia are often habitual smokers. It is hypothesized that smoking reduces particularly negative symptoms of schizophrenia. (Lucatch *et al*., 2018).

1. **Metabotropic and Ionotropic Glutamatergic Receptors**

Glutamate is a major excitatory neurotransmitter in the mammalian central nervous system. Glutamatergic networks connecting the brain, limbic system, and thalamus regions are critical in schizophrenia (Cronenwett *et al*., 2010). Abnormalities in glutamatergic neurotransmission may impair synaptic plasticity and cortical microcircuitry, specifically NMDA receptor function (McGrath *et al*., 2022). NMDA receptors are ligand-gated ion channels that regulate excitatory neurotransmission, excitotoxicity, and plasticity. The glutamatergic hypothesis of schizophrenia is based on the discovery that antagonists of N-methyl-D-aspartate (NMDA) receptors, such as phencyclidine or ketamine, cause schizophrenia-like positive, negative, and cognitive symptoms in animal models and healthy persons (Kruse *et al.*, 2022). The glutamatergic hypothesis of schizophrenia focuses on the hypofunction of NMDA receptors, but other ionotropic glutamate receptors (α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid, AMPA, and kainate receptors) and metabotropic glutamate receptors also play a role. In therapeutic studies, drugs that increase NMDA receptor signaling were discovered to improve specific symptoms in people with schizophrenia (Zhang *et al.*, 2024). Furthermore, postmortem investigations have found alterations in glutamatergic receptor density and subunit composition in the prefrontal cortex, thalamus, and temporal lobe, which are brain areas with altered activation during cognitive processes done by schizophrenia patients (Yonezawa *et al.*, 2022). NMDA receptor hypofunction may cause morphological and structural alterations in the brain, leading to the development of psychosis.

Antipsychotics may disrupt glutamatergic neurotransmission by regulating glutamate release, modulating glutamatergic receptors, or altering the density or subunit composition of glutamatergic receptors (Zink *et al*., 2014). It has been demonstrated that antipsychotics that inhibit the dopamine D2 receptor increase the phosphorylation of the NMDA receptor's NR1 subunit, promoting its activation and, consequently, gene expression. Dopamine-glutamate interactions take place intraneuronally and intrasynaptically. Certain second-generation antipsychotics have been found to function on NMDA receptors differently than first-generation antipsychotics (Solmi *et al.*, 2017). Abnormalities in glutamatergic neurotransmission are a potential therapeutic target for schizophrenia, particularly for the treatment of cognitive impairment and negative symptoms. Reports of hypoactivity of NMDA receptors in schizophrenia prompted clinical experiments with compounds that stimulated this receptor. Classical NMDA receptor agonists are not considered in this study due to excitotoxicity and cell damage caused by excessive NMDA receptor stimulation. In this context, the glycine modulatory binding site on the NMDA receptor may be an appealing therapeutic target (Pei *et al.*, 2021). Next, positive allosteric modulators of AMPA receptors, as well as orthosteric ligands and modulators of metabotropic glutamatergic receptors, in particular ligands acting on mGluR2/3 receptors, may be considered promising potential medications against schizophrenia in accordance with the glutamatergic hypothesis of this disease (Kondej *et al.*, 2018).

Other potential therapeutic targets under investigation include NMDAR stimulants (D-serine, D-aspartic acid GNE-6901), GABA receptor agonists (Pyrazoloquinolone compound), MGlu receptor modulators, Cholinergic receptor modulators, 5-HT2C receptor agonists (Lorcaserin, Vabicaserin), and noradrenergic alpha-2 receptor modulators (Hanson *et al.,* 2024).

**1.6 Advantages and Disadvantages of Multi-Target Ligands**

The primary advantages of multi-target medications over single-target therapies and combination therapy include:

(i) Enhancing therapy efficacy by understanding the disease's complex pathomechanism.

(ii) Improved treatment safety by avoiding variations in bioavailability, pharmacokinetics, and metabolism of a combination regimen, as well as avoiding medication interactions.

(iii)Multi-target mode of action is advantageous in combating drug resistance and tolerance development, and it can serve as the foundation for medication repurposing efforts.

The drawback of MTDs is the challenge in creating compounds with balanced activity to numerous targets, which sometimes requires compromising activity at some targets (Vlocskó *et al.*, 2022).

Furthermore, molecules obtained, particularly by pharmacophore linkage, are generally not drug-like due to their high molecular mass (Schaller *et al.*, 2020).

**1.7 Conclusion**

As previously stated, most efforts in drug design and discovery during the last two decades have followed the paradigm "one disease, one gene, one molecular target, one drug". However, fresh findings in systems biology and discoveries of the molecular complexity of diseases have significantly shifted current drug discovery efforts toward multi-target medicines. In contrast to the traditional magic bullet method, such compounds are able to exert a wide range of pharmacological activities and have emerged as magic shotguns in the treatment of multifactorial disorders. The main concept of multi-target compound design is to obtain greater treatment efficacy and safety by simultaneously addressing multiple actors in the pathogenic cascade.

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