**Beyond Dopamine: Exploring Novel Pharmacological Targets for Improved Antipsychotic Outcomes**

**Abstract**

Schizophrenia is a disorder characterized by a multifaceted pathogenic mechanism impacted by numerous genes. The investigation of its pathophysiology is mostly dominated by the dopamine hypothesis. Multi-target therapies represent a viable strategy for addressing polygenic disorders characterized by intricate pathomechanisms, such as schizophrenia. Second-generation or atypical antipsychotics do, target many aminergic G protein-coupled receptors (GPCRs) at the same time. 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. Dopaminergic receptor antagonism, which inhibits dopamine D2 receptors in the brain to produce antipsychotic effects, served as the foundation for the development of the first generation of antipsychotics. Antipsychotics of the second generation work by blocking both dopamine and 5-hydroxytryptamine receptors. From the third generation of antipsychotics onward, therapeutic targets for antipsychotic schizophrenia shifted away from D2 receptor blockage and toward D2 receptor partial agonism and the antipsychotic effects of novel targets such as D3, 5-HT1A, 5-HT7, and mGlu2/3. Various receptors, such as 5-hydroxytryptamine, glutamate, γ-aminobutyric acid, acetylcholine receptors, NMDARs, and norepinephrine, contribute to schizophrenia development. As a result, the goal of developing new antipsychotic medications has shifted toward agonism or inhibition of these receptors. This study intends to present a narrative review of the research on therapeutic targets and drugs for schizophrenia, thereby providing significant insights for both therapy and future research in this area.

**Keywords:** Antipsychotic drugs,Multi target drugs, Neurotransmitter, Schizophrenia

1.0 **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 symptoms (hallucinations, delusions, and thought disorders), negative symptoms (social withdrawal, apathy, and lack of motivation), and cognitive deficits symptoms (memory and learning impairments, attention deficiencies). It is generally agreed that the symptoms of schizophrenia are caused by abnormalities in neurotransmission involving a significant number of receptors and enzymes, especially 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 technique is based on the assumption that single-target drugs are safer since they have fewer side effects due to their selectivity. However, it was shown that this is only true for single-gene illnesses, and the number of early single-target treatments performed 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).

The multiplicity of psychotic disorders has made it challenging to understand the behavioral signs of psychosis. Symptoms are subjective and based on the patient's personal perspectives (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 knowledge of psychosis fails to account for many of the developing mechanisms or describe multiple interactions.

**1.1 Pathophysiology of Psychosis**

Viewing psychosis through a neuroendocrine-immunomodulation lens has shown a complicated etiology, which has filled some 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. Neurobiological mechanisms that contribute to psychosis include neurotransmitter dysregulation (dopamine, glutamate, serotonin), neuroinflammation, the hypothalamic-pituitary-adrenal (HPA) axis, gut-brain axis (GBA), oxidative stress, and mitochondrial dysfunction.

**1.1.1 Neurotransmitter Dysregulation**

**(i) Dopamine**

“Although several hypotheses have been offered to explain the neurobiological mechanisms that drive the onset of psychosis, the dopamine hypothesis remains the most prevalent. 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 pathway is a dopaminergic system that starts in the ventral tegmental area (VTA) and travels to the nucleus accumbens. The route transmits dopamine signals to several specialized locations, including the amygdala, hippocampus, ventral and associative striatum, thalamus, and the prefrontal cortex” (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 associated with goal-directed behavior, research has demonstrated that mesolimbic dopamine transmission also integrates homeostatic tasks, responding to physiological changes through 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**

“Evidence suggests that the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) plays a role in psychotic etiology. 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 cause excessive glutamate release in the cortex. Blocking serotonin 5-HT2A receptors has been shown to be effective in reducing 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 causes an over activation of downstream glutamate transmission to the VTA and, presumably, dopamine release in the mesolimbic pathway” (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 importance of glutamate in psychosis, there has been a lot of research in recent years into the potential role of the amino acid D-serine, a strong co-agonist at the glycine position on the NMDAR. Schizophrenia has been linked to abnormal D-serine levels and/or enzyme activity involved in its generation and degradation. D-serine and inhibiting its catabolism have been suggested to be beneficial in treating 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) shields the brain, the impacts of neuro-immune interactions are typically overlooked. 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 modest cytokine production is required for homeostasis, the intensity of clinical symptoms in schizophrenia has been associated 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 immunological cells located 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 CNS homeostasis by regulating neuronal nutrition, neurotransmitters (particularly glutamate), ion and water homeostasis, synaptic formation and modulation, cerebral blood flow and metabolism, blood-brain barrier development, maintenance, and function, 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). Astrocytes use glutamate transporters to recover around 80% of the glutamate from the synaptic cleft (Schousboe, 2019). Astrocytes express GABA-A and GABA-B receptors, as well as GAT-1 and GAT-3 transporters, which can release and regulate GABA concentrations. Astrocytes secrete thrombospondins, hevin, and TGF-β1, which enhance synaptic function. 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). Cerebrospinal fluid (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 seen in clinical diseases defined by a disruption in normal myelination, indicating abnormal oligodendrocyte activity. In normal physiological circumstances, oligodendrocytes are the myelinating cells of the CNS, hence they are critical 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 people with myelin-related disorders have also experienced psychosis, it has been argued that disturbances in myelination in specific regions such as the frontotemporal, callosal, and periventricular fiber tracts may be at the root of psychotic behavior. Oligodendrocytes are also susceptible to glutamate's excitotoxic effects. These cells are also known to have immune-inflammatory capabilities, which can mitigate 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, implying that dysfunction in psychosis may extend to changes in the gut microbiota, which play critical roles in the control of host homeostasis. The gut microbiome's activities have a direct impact on myelination, neurotransmission, BBB organization, the HPA axis, and neural-immune interactions. The gut microbiome can produce inflammatory compounds that pass the blood-brain barrier. However, inflammatory activities influence 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 produce neurotransmitters such as dopamine, noradrenaline, glutamate, GABA, acetylcholine, and serotonin. The gut microbes produce a large amount of tryptophan (the precursor to serotonin) and other tryptophan metabolites such as 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 production is a natural process of aging that is impacted by both environmental and genetic factors. However, in pathological circumstances such as psychosis, oxidative stress worsens and accelerates brain damage through mitochondrial dysfunction and pro-apoptotic processes. 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 perform important functions in neurochemical communication and have a high metabolic demand, making them more susceptible to oxidative stress and severe damage.

**1.1.4 Mitochondrial Dysfunction**

Mitochondria, which play essential roles in energy metabolism, oxidative stress, and synaptic activity modulation, produce virtually all of the cellular ATP in the body through oxidative phosphorylation, which is carried out by the electron transport chain's complexes I–IV. Under normal circumstances, 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 important treatment for schizophrenia. They are split into two types: conventional / typical 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 result from diminished activity in the mesocortical dopaminergic pathway (the projection from the VTA to regions of the prefrontal cortex), where D1 receptors are predominant. Other dopaminergic pathways in the central nervous system (such as the nigrostriatal and tuberoinfundibular) appear to operate normally in schizophrenia. Thus, in terms of treatment, it would be preferable to inhibit dopaminergic transmission in the limbic system while enhancing 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. Second-generation antipsychotics, which are currently the primary treatment for schizophrenia and bipolar disorder, are essentially multi-target chemicals. Second-generation antipsychotics mostly block D2 and 5-HT2A receptors. Their blocking of D2 receptors is far lower than that of regular antipsychotics, decreasing the associated adverse effects while maintaining 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 drugs (excluding third-generation) function by blocking 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 is evidence that antagonizing the serotonin 5-HT2A receptor may have a favorable impact on the incidence of extrapyramidal side effects, as well as the reduction of negative and cognitive symptoms in schizophrenia. Clozapine is a classic example of a "dirty" medication that is nonetheless regarded as a "gold standard" atypical antipsychotic due to its absence of extrapyramidal syndrome (EPS), superiority in the treatment of drug-resistant schizophrenia, and capacity 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 considered beneficial, with a low frequency of EPS and a moderate elevation in prolactin during acute-phase studies. 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). Blocking adrenergic receptors may help to stabilize dopaminergic neurotransmission in schizophrenia. Activating α2A adrenergic receptors in the prefrontal cortex may improve cognitive performance (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 common off-target for antipsychotics since inhibiting it causes drowsiness and may lead to weight gain. Weight gain and metabolic irregularities can also be linked to adrenergic or cholinergic receptor inhibition, but histamine H1 receptor antagonism is thought to be the principal cause of second-generation antipsychotic-induced obesity. In contrast, the histamine H3 receptor is an emerging target for new antipsychotics since selective antagonists or inverse agonists of this histamine receptor subtype are useful in addressing cognitive deficits in schizophrenia” (Sadek *et al.*, 2016).

**(ii) Third-Generation Antipsychotics**

Aripiprazole, a third-generation antipsychotic, causes partial agonism of D2 and 5-HT1A receptors. It ameliorates negative, positive, cognitive, and depressive symptoms. Aripiprazole, brexpiprazole, and cariprazine are all third-generation antipsychotic medications. The mechanism of action of these drugs remains essentially related to dopaminergic neurotransmission, although not to dopamine receptor antagonism, but to partial or biased agonism (functional selectivity) (Ricci *et al*., 2024). Because of its partial agonism properties, aripiprazole is classified as a "dopamine stabilizer". Aripiprazole was one of the first functionally selective D2 receptor ligands found, and it may help stabilize dopaminergic transmission via the D2 receptor. Although aripiprazole was initially classified as a partial D2 receptor agonist, it was later shown that it might operate as a full agonist, partial agonist, or antagonist at the D2 receptor depending on the signaling readout and cell type used. Aripiprazole is a partial agonist that reduces cAMP accumulation through the D2 receptor. However, aripiprazole has also been shown to be an antagonist in GTPS binding tests 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 antipsychotic properties of D2 receptor partial agonists have been established. D2 receptor partial agonists (DRPAs) have considerable D2 receptor occupancy, however DRPAs have intrinsic D2 receptor activity lower than that of dopamine, and therefore may minimize the chance of EPS while maintaining clinical efficacy, which can be particularly useful in minimizing 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 study of therapeutic targets for antipsychotic medications is based on the concept of neurotransmitter abnormalities in schizophrenia, with the goal of creating antipsychotic effects by blocking or stimulating the function of certain receptors. Previous research on antipsychotic drugs has largely focused on dopamine; however, certain individuals treated with dopamine antagonists may develop dopamine hyper sensitivity, hence lowering treatment effectiveness. Blocking dopamine receptors can produce extra-vertebral systemic responses, metabolic challenges, and hyperprolactinemia (Diamanti-Kandarakis *et al.,* 2019). “Researchers have focused on finding new antipsychotic drug targets that do not include dopamine D2 receptors. Several research was carried out to confirm the effectiveness 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 is interesting to note that “muscarinic receptor antagonists worsen cognitive and negative symptoms in schizophrenia patients, but xanomeline, a muscarinic receptor agonist, improves all symptoms in schizophrenia patients and animal models. Based on these and other findings, the muscarinic theory of schizophrenia was proposed. The role of nicotinic cholinergic receptors in schizophrenia pathogenesis may explain why persons with schizophrenia are frequently smokers. It is theorized that smoking lowers particularly unfavorable 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). Abnormal glutamatergic neurotransmission is a promising therapeutic target for schizophrenia, particularly for cognitive impairment and negative symptoms. Reports of hypoactivity of NMDA receptors in schizophrenia motivated clinical trials with drugs that stimulated this receptor. This study does not include classical NMDA receptor agonists because of the excitotoxicity and cell damage induced by excessive NMDA receptor stimulation. In this scenario, the glycine modulatory binding site on the NMDA receptor may be an attractive 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 noted, most efforts in drug design and discovery during the last two decades have followed the paradigm of "one disease, one gene, one molecular target, one drug". However, recent advances in systems biology and discoveries about the molecular complexity of disorders have considerably redirected current drug research efforts toward multi-target treatments. Unlike the classic magic bullet technique, these chemicals can exhibit a wide range of pharmacological effects and have emerged as magic shotguns in the treatment of multiple illnesses. The primary goal of multi-target drug design is to improve efficacy and safety by simultaneously targeting multiple players in the pathogenic cascade.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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