Dopamine and Serotonin Interactions in Schizophrenia: A Focused Review of Mechanisms and Therapeutic Implications

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Abstract

Schizophrenia is a chronic and complex mental illness that substantially impacts a person's thoughts, emotions, and daily life. It is characterized by a combination of positive symptoms such as hallucinations and delusions, and negative symptoms such as emotional withdrawal, lack of motivation, and cognitive difficulties. Historically, the dopamine system has been the forefront of research on schizophrenia, but serotonin's role has recently come into sharper focus. While serotonin is necessary for regulating emotions and mental processes, dopamine imbalances are known to result in psychotic symptoms and cognitive impairments. Interactions between these neurotransmitters affect brain functions.

Many patients have seen better results due to advancements in treatment, especially second-generation antipsychotics that target both the dopamine and serotonin systems. However, challenges still exist, especially in effectively managing negative and cognitive symptoms. This review highlights key findings that support a more integrative model involving serotonin-dopamine interactions, emphasizing the role of receptors such as dopamine receptor D_1, dopamine receptor D_2, 5-hydroxytryptamine 1A ($5\text{-}HT_{1A}$), and 5-hydroxytryptamine 2A ($5\text{-}HT_{2A}$). It also explores the therapeutic potential of newer agents like brexpiprazole, cariprazine, and pimavanserin, which offer more targeted symptoms control with fewer adverse effects. Additionally, emerging research on the gut-brain axis and glutamatergic modulation presents promising directions for future treatment strategies. In this review, we looked at the research on the roles of dopamine and serotonin in schizophrenia and discussed the therapeutic approaches that could lead to more comprehensive and effective treatment plans.

Introduction

Schizophrenia is a chronic mental illness that may affect the thoughts, behaviors, and feelings of an affected person. The diagnosis of schizophrenia has been around for many years despite changes in its definition and categorization (1). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Version (DSM-5), schizophrenia is a chronic mental illness characterized by the presence of positive and negative symptoms as well as cognitive impairment (2). The positive symptoms associated with schizophrenia refer to the presence of abnormal symptoms, such as hallucinations, thought disorders, delusions, and repetitive movements. These symptoms can cause "significant difficulties in daily functioning, and these difficulties have been associated with impaired executive functions" (3). The negative symptoms of schizophrenia are often described as the absence of normal behavior or function. This may refer to a person's lack of motivation, and interest or verbal and emotional expression (4). Negative symptoms domain in schizophrenia typically includes 5 key constructs: blunted affect, alogia, avolition, asociality, and anhedonia, with up to 60% of patients experiencing prominent, clinically relevant symptoms that require treatment (4). Today, according to the National Alliance on Mental Illness (NAMI), prevalence of schizophrenia ranges from 0.25% to 0.64% of U.S. adults (5). while both males and females are affected by schizophrenia, studies have shown that males tend to experience an earlier onset, more severe negative symptoms, and poorer functional outcomes. In contrast, females are more likely to have a later onset, better treatment response, and relatively improved social function (6). There are standard treatments that exist today, but medicine is always evolving and searching for better treatments. The focus of research in schizophrenia now focuses on the neurotransmitters

underlying brain function, like serotonin and dopamine (7, 8).

Dopamine (DA) and serotonin (also known as 5-hydroxytryptamine or 5-HT) are two of the many neurotransmitters currently under consideration for their potential roles in the pathophysiology of schizophrenia. Dopamine plays major roles in movement, reward, cognition, and sleep. The dopamine hypothesis of schizophrenia was developed in the 1960s as an explanation for the cause of this disease (9). The original hypothesis proposed that dopamine is an inhibitory neurotransmitter involved in the pathology of schizophrenia (10). This led to the advent of many schizophrenia therapies, all targeting the dopaminergic pathways thought to be the sole cause in the etiology of this illness. The original dopamine hypothesis has since been revised, now stating that "dopamine abnormalities in the mesolimbic and prefrontal brain regions exist in schizophrenia" (10). Current schizophrenia medications block the dopamine receptor D_2 in an effort to reduce positive symptoms (9). This mode of treatment has been successful, but in recent years researchers have begun to investigate alternative targets to produce more effective treatments and therapies for schizophrenia (7, 8).

Serotonin is often targeted in pharmaceutical therapies, especially for the treatment of depression and anxiety. Class of medications like selective serotonin re-uptake inhibitors (SSRI) have been proven safe and effective and are widely prescribed. These medications increase serotonin availability in the synaptic cleft by blocking the reuptake of this neurotransmitter into the presynaptic neuron (11, 12). As a neurotransmitter, serotonin functions primarily in the mood and memory areas of the brain, and it also has a role in sleep, pain, and movement (11). Treatments that decrease the availability of serotonin have been shown to generally enhance motor activity, particularly spontaneous movement in familiar environments, and may also increase behaviors related to sexuality or aggression (11). In the pathophysiology of schizophrenia, serotonin is thought to play a role, as seen in hallucinogens as well as antipsychotic medications (12, 13). Some researchers have suggested that serotonin abnormalities may be linked to certain characteristic of schizophrenia, such as negative symptoms, progressive brain changes, and chronicity. This perspective proposes that serotonin dysfunction could underlie negative syndrome schizophrenia and may involve increased sensitivity of postsynaptic serotonin receptors. As a result, it has been proposed that treatments for schizophrenia should target both dopamine and serotonin systems by including agents that block 5-HT receptors. Further research is encouraged to better understand the impact of this selective serotonin receptor hypersensitivity in schizophrenia (12). Building on this, recent studies have explored how serotonin interacts with glutamate, furthering our understanding of schizophrenia's biological complexity (13). These interactions involve functional crosstalk between serotonin and glutamate systems, particularly through 5-hydroxytryptamine receptor 2A (5-HT_{2A}) and metabotropic glutamate receptors such as metabotropic glutamate receptor 2 ($mGlu_2$). This receptor-level interaction has been shown to regulate glutamate release and cortisol signaling in brain regions implicated in schizophrenia, including the prefrontal cortex (13). Alterations in this pathway may contribute to disrupted perceptions, cognition, and behavior observed in preclinical models of the disorder (13). Early intervention has also been emphasized as crucial in improving outcomes for patients, highlighting the importance of addressing psychosis promptly (14). On a broader level, genetic studies have revealed the intricate hereditary nature of schizophrenia, which may explain its diverse symptoms (15). Additionally, disruptions in brain development during key periods, such as infancy and childhood, may play a significant role in the disorder's onset. The role of serotonin in shaping psychiatric treatment strategies has been critical, as has the evolution of diagnostic tools and therapeutic approaches in managing schizophrenia (16–19).

The Role of Dopamine in Schizophrenia

Evidence Supporting the Role of Dopamine

The dopamine hypothesis has been a central framework for understanding schizophrenia for decades. The original hypothesis proposed that excessive dopamine activity in the mesolimbic pathway influences the positive symptoms of schizophrenia, such as hallucinations and delusions (21). The dopamine hypothesis has evolved to incorporate mesocortical hypodopaminergia as well. Hypodopaminergic activity in the mesocortical pathway accounts for cognitive deficits and negative symptoms, including reduced motivation (20, 21). Neuroimaging evidence also supports this hypothesis.

Positron emission tomography (PET) studies reveal increased dopamine synthesis and release in the striatum of individuals with schizophrenia, correlating with psychotic symptom severity (20–22).

Genetic studies further substantiate dopamine's central role. Polymorphisms in the dopamine receptor D2 gene (DRD2), which encodes the D_2 receptor, are strongly associated with schizophrenia and influence receptor density and sensitivity. Variations in the catechol-O-methyltransferase gene (COMT), which affects dopamine degradation, influence dopamine availability in the prefrontal cortex and decision-making (23, 24). Postmortem studies also exposed changes in dopamine receptor density in the striatum and prefrontal cortex that relate to the positive and negative symptoms of schizophrenia (25).

Another potential interaction worth noting is environmental factors such as prenatal adversity, early-life trauma, and urban upbringing work alongside genetic predispositions to compound dopaminergic dysregulation. These stressors increase the sensitivity of the dopamine system, enhancing its responsiveness and contributing to the abnormal salience attribution often observed in psychosis (23).

Dopamine Receptors and Their Implications

The dysfunction of different dopamine receptors is key to the variety of schizophrenia symptoms. D_2 receptors, primarily expressed in the striatum, are commonly linked to positive symptoms and are often found to be hyperactive in schizophrenia. Antipsychotics mainly act to reduce dopamine activity in this pathway (D_2 receptor antagonists), alleviating symptoms of psychosis (21, 26). However, excessive D_2 blockade can result in motor problems such as rigidity and tremors, also known as extrapyramidal symptoms, and impairments in reward processing and cognitive function (27).

Conversely, dopamine receptors D_1, predominantly expressed in the prefrontal cortex, are critical for cognitive functions such as working memory and executive function. Hypoactivity of D_1 receptors correlates with the cognitive deficits observed in schizophrenia, which are among the most disabling aspects of the disorder. These impairments remain inadequately addressed by current treatments (28). Experimental therapies that selectively enhance D_1 receptor activity have shown promise in preclinical studies but have yet to achieve widespread clinical application (29).

Emerging evidence suggests that additional receptor subtypes may have key roles in schizophrenia. These additional subtypes include dopamine receptors D_3 and D_4 receptors. D_3 receptors, expressed in limbic regions, influence motivation and reward processing, making them potential targets for negative symptom treatment (6). D_4 receptors are related to cortical excitability and may contribute to cognitive impairments (30). These findings highlight the need for a nuanced understanding of receptor-specific contributions to schizophrenia symptomatology, allowing for advancements in targeted therapeutics (26, 30).

Cognitive Deficits, Positive and Negative Symptoms

The hallmark symptoms of schizophrenia can be classified as positive symptoms, negative symptoms, and cognitive deficits. The positive symptoms of schizophrenia are linked to hyperdopaminergic activity in the mesolimbic pathway. Some of the positive symptoms associated with this disorder are hallucinations and delusions (20). Negative symptoms, on the other hand, can arise from hypodopaminergic activity in the mesocortical pathway, which disrupts motivation and goal-directed behavior. Some negative symptoms seen in schizophrenia are diminished emotional expression and social withdrawal (22). Cognitive deficits, encompassing impairments in working memory, attention, and executive function, are attributed to prefrontal D_1 receptor hypoactivity (28,29).

Preclinical models have demonstrated that striatal D_2 hyperactivity induces psychosis-like behaviors, while prefrontal D_1 hypoactivity impairs decision-making and working memory (31). These studies bridge molecular dysfunctions with clinical manifestations, providing a translational framework for understanding the disorder (22).

Despite these pathways operating primarily independently, their interplay is critical for understanding schizophrenia's complex symptomatology. For example, dopaminergic disruptions in one region can indirectly influence activity in others, creating a cascade of dysfunctions that collectively contribute to the disorder (20).

Antipsychotic Treatments and Emerging Therapies

Antipsychotics have been the cornerstone of schizophrenia treatment for decades, primarily targeting dopamine pathways. First-generation

antipsychotics (FGAs), such as haloperidol, achieve their effects through robust D_2 receptor antagonism. While effective for positive symptoms, these medications are associated with significant side effects, including extrapyramidal symptoms and tardive dyskinesia, limiting their long-term utility (27, 32, 33). Second-generation antipsychotics (SGAs), such as clozapine and aripiprazole, incorporate serotonin receptor modulation to demonstrate enhanced efficacy. Clozapine, in particular, is regarded as the gold standard for treatment-resistant schizophrenia (20). However, its mechanism of action remains incompletely understood and may involve glutamatergic or immune pathways alongside dopamine antagonism (22–24).

Emerging treatments seek to refine the therapeutic approach to dopamine dysregulation. Partial D_2 agonists aim to balance receptor activity without inducing complete antagonism, potentially reducing side effects (33). Similarly, D_1 receptor modulators are being explored for their ability to address cognitive deficits, a domain poorly served by existing therapies (28, 29). A shift toward precision medicine can be seen as treatments are tailored to address the full spectrum of schizophrenia symptoms while minimizing adverse effects.

Limitations of the Dopamine Hypothesis

The dopamine hypothesis explains many core features of schizophrenia but fails to account for the disorder's full complexity. For instance, cognitive deficits and negative symptoms often persist despite dopamine activity being normalized (21). This suggests the involvement of more or potentially different neurotransmitter systems, such as glutamate and gamma-aminobutyric acid (GABA). The relationship between dopamine and serotonin is also particularly relevant, forming the basis for the efficacy of atypical antipsychotics. This interaction underscores the necessity of integrated models that encompass multiple neurotransmitter systems. Future research must expand out of dopamine-centric paradigms to fully capture schizophrenia's neurobiology and develop more comprehensive treatment approaches (21).

The Role of Serotonin in Schizophrenia

Understanding Serotonin's Role in Schizophrenia

Although dopamine has long been at the center of schizophrenia research, serotonin is increasingly recognized as a key factor, especially in understanding negative symptoms and cognitive challenges (10, 12, 35).

Studies have shown that serotonin imbalances in areas like the prefrontal cortex and hippocampus can lead to symptoms such as emotional withdrawal, apathy, and cognitive difficulties, issues that are particularly difficult to treat (13, 28, 36). Research also points to variations in serotonin receptors (e.g., $5\text{-}HT_{2A}$) and transporters (e.g., solute carrier family 6 member 4, also known as SLC6A4) as influential factors in the development of schizophrenia and individual responses to treatment (13,28,36). Additionally, environmental factors like prenatal adversity or early-life trauma may disrupt serotonin pathways during critical stages of brain development, increasing vulnerability to the disorder (20, 36). The importance of serotonin became more apparent with the development of SGAs which antagonize both dopamine and serotonin receptors. This dual action has provided broader symptom relief and highlighted serotonin's important role in the disorder (10, 12, 35).

Serotonin Receptors: Key Players in Schizophrenia

Serotonin plays a vital role in the brain, influencing mood, cognition, and emotional balance. In schizophrenia, serotonin's effects are largely mediated by specific receptors that affect how the brain regulates critical neurotransmitters like dopamine and glutamate. Understanding these mechanisms has led to advancements in treating the disorder, particularly with medications targeting serotonin receptors. The $5\text{-}HT_{2A}$ receptor is perhaps the most well-studied in schizophrenia. Found abundantly in the prefrontal cortex, this receptor modulates dopamine and glutamate activity, which are crucial for cognitive and emotional balance. When overactivated, it can contribute to hallucinations, delusions, and cognitive disturbances. Medications like risperidone and olanzapine, commonly used second-generation antipsychotics, work by blocking $5\text{-}HT_{2A}$ receptors, reducing these symptoms while enhancing dopamine function in key brain regions (37). Clozapine, given for treatment-resistant schizophrenia, also blocks $5\text{-}HT_{2A}$ receptors but has the added benefit of partially activating 5-Hydroxytryptamine Receptor 1A ($5\text{-}HT_{1A}$), which are known to regulate mood, anxiety, and emotional processing. This unique combination makes clozapine especially effective for severe cases and patients with suicidal ideation (38, 39).

Another key serotonin receptor is 5-HT_{1A}, which influences the release of serotonin itself and plays a significant role in mood and emotional regulation. Activating this receptor has shown promise in alleviating negative symptoms of schizophrenia, such as apathy and emotional withdrawal. Aripiprazole, a third-generation antipsychotic, combines partial activation of $5HT_{1A}$ receptors with $5HT_{2A}$ receptor antagonism. This dual action helps manage symptoms effectively while minimizing side effects like motor rigidity (39).

The 5-hydroxytryptamine receptor 2C (5-HT_{2C}) also contributes to the broader understanding of serotonin's role in schizophrenia. Located in the limbic system, it helps regulate dopamine in reward pathways. However, its activity is linked to metabolic side effects, such as weight gain, often seen with medications like olanzapine (40). Meanwhile, emerging research on 5-hydroxytryptamine receptor 6 (5-HT_6) and 5-hydroxtryptamine receptor 7 (5-HT_7) highlight their involvement in cognition and memory. These receptors have become promising targets for experimental therapies aimed at improving cognitive deficits in schizophrenia, with drugs like pimavanserin showing potential in early studies (41, 42). Lastly, serotonin's role extends beyond the brain. Most serotonin in the body exists in the peripheral system, particularly in the gut. Receptors like 5-hydroxytryptamine receptor 3 (5-HT_3) and 5-hydroxytryptamine receptor 4 (5-HT_4), while not directly related to schizophrenia symptoms, play a critical role in managing the side effects of antipsychotic medications, such as nausea and constipation. Additionally, emerging research into the gut-brain axis suggests that peripheral serotonin may indirectly influence mental health, opening new avenues for holistic treatment approaches (40, 41).

By targeting serotonin receptors, modern antipsychotics have significantly improved the lives of patients with schizophrenia, addressing both core symptoms and the side effects of treatment. Ongoing research continues to expand our understanding of serotonin's complex role, paving the way for more effective and personalized therapies.

Medications Targeting Serotonin Receptors

Antipsychotic medications play a critical role in managing schizophrenia by targeting serotonin receptors to improve symptoms and minimize side effects. Medications like risperidone and olanzapine block 5-HT_{2A} receptors, which not only help reduce hallucinations and delusions but also enhance dopamine activity in the prefrontal cortex, improving motivation and emotional withdrawal (37, 40). For individuals with treatment-resistant schizophrenia, clozapine is often the go-to medication. Its success lies in its ability to block 5-HT_{2A} receptors while also partially activating 5-HT_{1A} receptors, making it particularly effective for severe cases, especially those involving suicidal thoughts (38, 39, 44).

Aripiprazole, a newer antipsychotic, takes a slightly different approach. It works by partially activating both D_2 and 5-HT_{1A} receptors, while simultaneously blocking 5-HT_{2A} receptors. This unique mechanism allows it to treat symptoms effectively while reducing side effects like muscle stiffness, which can occur with older antipsychotics (39, 45).

Similarly, newer medications like brexpiprazole and cariprazine offer a balanced approach by targeting both dopamine and serotonin systems, allowing them to manage both the positive symptoms (like hallucinations) and the negative symptoms (like apathy and social withdrawal) of schizophrenia (40).

Another medication, pimavanserin, was initially developed for treating psychosis in Parkinson's disease, however, it is now being explored for its ability to reduce hallucinations in schizophrenia via an antagonist effect on 5-HT_{2A} receptors. Early research shows promise for its use in this area (41).

Schizophrenia represents a significant challenge both for individuals living with it and for healthcare systems globally. The burden of the disease highlights the need for innovative, effective treatment strategies that address core symptoms while improving overall quality of life (46). As we continue to learn more about how serotonin receptors influence the brain, the development of targeted therapies offers hope for improving outcomes and restoring balance for those affected by this complex condition.

Beyond the Brain: Serotonin's Broader Impact

Interestingly, the majority of the body's serotonin is not in the brain, it is in the gut and blood platelets. Among the serotonin receptors found outside the brain, 5-HT_3 and 5-HT_4 stand out for their unique roles in schizophrenia treatment. While these receptors do not directly affect core symptoms like hallucinations or delusions, they play a significant role in managing side effects of antipsychotic medications. For example,

5-HT_3 receptors help regulate gut motility and control nausea, making them key players in addressing nausea caused by antipsychotic drugs. Similarly, 5-HT_4 receptors are involved in improving gut movement, which can help relieve constipation, a common and uncomfortable side effect of many schizophrenia treatments (47). But their role may go beyond just easing side effects. Emerging research suggests that these receptors could indirectly contribute to managing schizophrenia itself. For example, 5-HT_4 receptors have been linked to better cognitive flexibility, which means they could help address cognitive difficulties often experienced by people with schizophrenia. Meanwhile, blocking 5-HT_3 receptors may influence dopamine pathways in a way that complements existing treatments (47).

Even more intriguing is the growing research on the gut-brain axis, which highlights how the gut and brain are deeply connected. Serotonin produced in the gut and metabolites from the gut microbiome, like short-chain fatty acids (SCFAs), might influence brain function and behavior. This connection has sparked interest in exploring how targeting gut serotonin, especially through receptors like 5-HT_3 and 5-HT_4, could help not only with side effects but also with improving the overall mental health of people living with schizophrenia (47).

These findings open the door to a more holistic approach to treating schizophrenia. By addressing both the brain and the gut, we are moving toward therapies that tackle core symptoms while improving overall quality of life. It is a promising step forward for those living with this complex condition (40,46).

Challenges and Opportunities in Targeting Serotonin Receptors for Schizophrenia

Serotonin receptors have a lot of potential for treating schizophrenia, but there are also particular challenges. One major obstacle is the widespread presence of serotonin receptors throughout various parts of the brain. This makes it difficult to precisely target them without affecting other systems, leading to unintended side effects such as weight gain or metabolic issues. Additionally, serotonin does not work in isolation, it interacts closely with dopamine and glutamate systems, further complicating treatment strategies. These complexities highlight the need for a more integrated approach to managing schizophrenia (47, 48).

Looking to the future, research is shifting toward the development of more selective treatments, such as serotonin-dopamine modulators. These therapies aim to address the full range of schizophrenia symptoms while minimizing side effects (48).

Challenges in Serotonin Modulation

One challenge in serotonin-focused therapies is finding the right balance between treating symptoms and avoiding unwanted side effects. For example, a recent case report highlighted a rare side effect in a patient taking cariprazine, a medication that works as a partial agonist at 5-HT_{1A} receptors and modulates 5-HT_7 receptors. While cariprazine helped improve the patient's cognitive and psychotic symptoms, it also caused hypersexual behavior, a rare and disruptive side effect. This behavior was likely tied to the medication's complex interactions with serotonin receptors and its influence on dopamine pathways related to reward processing. Once the medication was discontinued, the hypersexuality resolved. This case underscores the importance of monitoring patients carefully and highlights the delicate balance needed in developing serotonin-targeted treatments (49).

Opportunities in Serotonin-Dopamine Modulation

Another promising direction involves combining serotonin and dopamine modulation. A case report involving a patient with treatment-resistant schizophrenia and dopamine supersensitivity psychosis (DSP) sheds light on this approach. After prolonged use of high-dose antipsychotics, the patient was switched to asenapine, a medication with strong 5-HT_{2A} receptor antagonism (50). This switch led to significant improvements in psychotic symptoms such as hallucinations and delusions, while also enhancing cognitive functioning. Unlike other antipsychotics, asenapine's serotonergic properties helped restore dopamine balance without worsening DSP. This case demonstrates the potential of serotonin-dopamine activity modulators to address even the most difficult-to-treat forms of schizophrenia while reducing dopamine-related side effects (50).

Adjunctive Serotonin Therapies for Negative Symptoms

Treating the negative symptoms of schizophrenia, such as apathy, emotional withdrawal, and lack of motivation, is still a challenge. These symptoms often do not respond well to standard dopamine-focused treatments. A narrative review discussed the use of serotonergic strategies to target these symptoms,

emphasizing the potential of combining serotonin-focused therapies with antipsychotics for better outcomes. For instance, SSRIs like escitalopram have shown modest but meaningful improvements in negative symptoms. These treatments offer clinicians a safe and effective way to enhance serotonergic tone while avoiding other side effects like sedation or metabolic issues (51).

Interactions Between Dopamine and Serotonin Systems

The interaction between DA and 5-HT plays a critical role in regulating mood, cognition, and behavior, making it highly relevant to understanding and treating schizophrenia. These two neuromodulators influence each other through intricate pathways. DA, originating from the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), interacts with 5-HT, which arises from the dorsal and median raphe nuclei (DRN and MRN). These systems maintain a bidirectional relationship: dopamine regulates serotonin signaling in the raphe nuclei, while serotonin projections to dopamine-rich regions like the SNc and VTA modulate dopamine activity (52,53,55,59).

Dopamine exerts its effects primarily through D_1 and D_2 receptor families, which are crucial for regulating motor, emotional, and behavioral functions. For instance, D_2 receptors in the striatum suppress neuronal excitability to regulate motor control, and their dysfunction can lead to motor impairments and emotional disturbances (57,58). Similarly, serotonin receptors, organized into families like 5-HT_1, 5-HT_2, and 5-HT_3, are key to signaling processes that influence mood and cognition. Among them, the 5-HT_{2A} receptor plays a pivotal role in modulating dopamine activity, underscoring the intricate relationship between these neurotransmitters in schizophrenia (52,54,55,58).

Impact on Treatment Strategies

Understanding the interplay between dopamine and serotonin systems is essential for developing effective treatments for schizophrenia. Dysregulation in these systems contributes to both positive symptoms (like hallucinations, often linked to mesolimbic dopamine hyperactivity) and negative symptoms (such as social withdrawal, tied to mesocortical dopamine hypofunction) (60, 65). Serotonin, particularly through 5-HT_{2A} receptors, helps modulate dopamine release, making it a valuable target for therapies that address the wide range of schizophrenia symptoms (52, 56).

Clinical Implications: Treatments Focusing on Dopamine-Serotonin Interactions

Modern antipsychotic treatments rely heavily on the dual modulation of dopamine and serotonin systems. SGAs like clozapine and olanzapine effectively manage both positive and negative symptoms by targeting both neurotransmitter systems. These medications partially block dopamine receptors while antagonizing 5-HT_{2A} receptors, which enhances mood and cognitive function (56, 61, 62). For example, clozapine's low affinity for D2 receptors reduces the risk of motor side effects, while its potent antagonism of 5-HT_{2A} receptors improves negative symptoms and cognitive deficits by increasing dopamine release in specific pathways (63, 64).

Olanzapine and other atypical antipsychotics also target both systems, addressing the limitations of earlier, dopamine-centric therapies. By balancing dopamine and serotonin modulation, these treatments are particularly effective for individuals with treatment-resistant schizophrenia, providing relief for a population that often struggles to find effective options (56, 62).

Future Direction in Schizophrenia Research

Future Research Related to Serotonin and Dopamine in Schizophrenia

Research into the serotonin and dopamine systems continues to be pivotal for understanding and treating schizophrenia. A major challenge with current treatments targeting serotonin (e.g., 5-HT_{2A}) and dopamine (e.g., D_2) pathways lies in their limited efficacy for negative and cognitive symptoms, alongside notable off-target effects such as metabolic disturbances and movement disorders (60, 66, 67). Future research aims to refine selective serotonin-dopamine modulators (SDAMs) like brexpiprazole and cariprazine. These drugs leverage partial agonism and antagonism across receptors such as 5-HT_{1A}, 5-HT_{2A}, and D_3, potentially enhancing efficacy for negative and cognitive symptoms while minimizing side effects (68, 69). Additionally, emerging studies are exploring the role of 5-HT_7 receptors in regulating circadian rhythms and cognitive processes, with a focus on dual-action drugs that target both 5-HT_7 and dopamine receptors (70, 71).

Negative symptoms such as apathy, anhedonia, and emotional blunting remain inadequately addressed by existing antipsychotics. These symptoms are linked to

dopamine hypofunction in the prefrontal cortex and serotonin dysregulation in limbic regions. Research is therefore directed toward therapies combining D_1 receptor agonism to enhance prefrontal dopamine signaling with 5-HT_{2A} antagonism to modulate limbic serotonin. Such an approach may restore motivation and improve reward processing (72, 73). Meanwhile, the gut-brain axis and its influence on peripheral serotonin signaling represent an untapped frontier in schizophrenia research. With 90% of serotonin located in the periphery, particularly in the gut, understanding its impact on inflammation, neuroplasticity, and neurotransmitter balance could open pathways for gut- targeted treatments like probiotics or peripheral serotonin inhibitors (48, 74).

Schizophrenia's complexity also lies in its intricate interplay among dopamine, serotonin, and glutamate systems. Glutamate hypofunction in N-methyl-D-aspartate (NMDA) receptor pathways exacerbates serotonin and dopamine imbalances. Future therapeutic strategies may include multi-modal drugs targeting glutamate (via NMDA receptor modulators), serotonin (e.g., 5-HT_{1A}/5-HT_{2A}), and dopamine (e.g., D_1/D_3) to address a broader spectrum of symptoms (75, 76). Additionally, the heterogeneity of receptor sensitivity in patients poses challenges for antipsychotic efficacy. Research into genetic and epigenetic biomarkers, such as polymorphisms in 5-HT_{2A} and DRD2 genes, could inform personalized treatment strategies. Pharmacogenomic advancements may refine drug selection and dosing, reducing adverse effects while improving outcomes (77–79).

Future Research Beyond Serotonin and Dopamine

While 5-HT and DA remain central to schizophrenia research, scientists are increasingly exploring other pathways that may play a crucial roles in the disorder. One major area of focus is the glutamate system, particularly the NMDA receptor, which has been linked to cognitive deficits and negative symptoms. Since traditional antipsychotics do not target this pathway, researchers are developing drugs that enhance NMDA receptor activity. Examples include glycine reuptake inhibitors and D-serine analogs, which act as co-agonists to boost cognitive processing (80–82).

Another promising avenue is the immune system, as evidence suggests that schizophrenia may involve chronic low-grade inflammation and immune dysregulation. Anti-inflammatory therapies and immune-modulating agents, such as monoclonal antibodies targeting cytokines like interleukin-6 (IL-6) or tumor necrosis factor alpha (TNF-α), could help reduce neuroinflammation and improve both cognitive and negative symptoms (83, 84).

Dysfunction in the GABAergic system, which disrupts cortical inhibition, is also believed to contribute to cognitive deficits and sensory gating abnormalities in schizophrenia. Future treatments may focus on drugs that target $GABA_A$ receptors, such as positive allosteric modulators, to strengthen inhibitory signaling without causing excessive sedation (87, 88). Social dysfunction, a hallmark of schizophrenia, is still an area of unmet need. Therapies based on oxytocin, a hormone that influences empathy and trust, are being studied for their potential to enhance social bonding and reduce social anxiety. Intranasal oxytocin, in particular, is already being tested in clinical trials and shows promise for improving social interactions (87, 88).

The endocannabinoid system is another emerging target, as its dysregulation has been associated with psychosis and cognitive impairments. Research into CB_1 receptor antagonists and CB_2 receptor agonists aims to reduce psychotic symptoms and inflammation while preserving cognitive function. Cannabidiol (CBD) has drawn particular interest for its neuroprotective and anti-inflammatory properties (89, 90).

Disrupted neural oscillations, especially in gamma and theta frequencies, are linked to impaired cognition and sensory integration in schizophrenia. Neuromodulation therapies, such as transcranial magnetic stimulation (TMS) and direct current stimulation, are being explored to restore normal oscillatory activity. These treatments may also be combined with pharmacological agents to enhance their effects (91, 92).

Finally, environmental risk factors like prenatal stress and childhood trauma may increase susceptibility to schizophrenia through epigenetic modifications. Addressing these changes with treatments such as histone deacetylase inhibitors (HDACi) or microRNA modulators offers the potential to reverse abnormal gene expression and restore neural plasticity (93, 94).

Conclusions

DA and 5-HT are major factors in the onset and management of schizophrenia. Alterations in dopamine activity in various brain regions contribute to the

explanation of the disorder's diverse symptoms, which include motivational and decision-making problems as well as hallucinations. Serotonin, on the other hand, contributes to the emotional and cognitive aspects of schizophrenia, often overlapping with dopamine in its effects. Treatments that target both systems, such as second-generation antipsychotics, have improved symptom management for many patients, but negative symptoms like emotional withdrawal and cognitive deficits are still a major challenge.

The growing focus on emerging therapies, including drugs that modulate both serotonin and dopamine, NMDA receptor-targeting agents, and approaches that explore the gut-brain connection, offers exciting opportunities for more effective treatments. Moving forward, a personalized approach that tailor's treatment to individual needs, based on both biological and genetic insights, could pave the way for improvements in care. By broadening the focus beyond dopamine alone and toward a more holistic understanding of schizophrenia, we can improve not just the clinical outcomes but also the quality of life of individuals living with schizophrenia.

Disclosures

The authors declare no conflicts of interest related to this work. This review was conducted as part of the academic requirements for the Master of Biomedical Sciences program at Geisinger College of Health Sciences. No external funding was received.

Acknowledgments

The authors would like to thank Brian J. Piper, Ph.D. for his mentorship, guidance, and continued support throughout the development of this work. We also acknowledge the Master of Biomedical Sciences program and the Geisinger College of Health Sciences for providing the academic resources and environment that supported the completion of this project.

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