REVIEW ARTICLE

Promising Advances in Schizophrenia Treatment

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Abstract: Schizophrenia is a severe mental illness affecting perception, cognition, and emotions. It is the most common functional psychotic condition and ranks in the top 10 worldwide disease burdens. The disease is caused by genetic predisposition, neurotransmitter imbalance, and risk factors like overweight, insufficient exercise, smoking, hyperglycemia, hypertension, and hyperlipidemia. Schizophrenia increases mortality risk by 12 times due to somatic disorders, heightened instances of suicide, and a poor lifestyle. Brain damage during pre-onset or early post-onset periods is associated with negative symptoms. The molecular pathology of schizophrenia is being increasingly understood, with a focus on changes to proteins and pathways. Diagnosis is made after a mix of symptoms for a minimum of one month. Despite its challenges, pharmacological treatment for schizophrenia is advancing, with promising new therapies targeting GABAergic signaling, inflammatory pathways, and epigenetic mechanisms. Novel drugs like cariprazine and brilaroxazine have shown efficacy in treating negative symptoms and clozapine-resistant schizophrenia. Other emerging treatments include asenapine transdermal system, lumateperone, paliperidone, olanzapine/samidorphan, pimavanserin, risperidone ISM, roluperidone, and TAAR-1 agonists. With a better understanding of the disease pathophysiology and development of targeted therapies, the outlook for schizophrenia management is improving.

Keywords: Schizophrenia; Genetic factors; Cariprazine; Brilaroxazine; Asenapine; Lumateperone; TAAR-1 agonist.

1. Introduction

Schizophrenia is a severe and complex mental illness characterized by a diverse array of symptoms that profoundly affect an individual's perception, cognitive functions, and emotional responses. As the most prevalent functional psychotic disorder, it poses a significant challenge to global health systems. The World Health Organization has consistently ranked schizophrenia among the top 10 causes of disability worldwide, underscoring its substantial impact on individuals, families, and societies [1-4].

The management of schizophrenia is multifaceted and aims to address various aspects of the condition throughout its course. Key objectives include early diagnosis to identify the disorder in its initial stages and minimize its potential long-term impact, prompt treatment initiation to begin appropriate interventions as soon as possible, relapse prevention to reduce the frequency and severity of psychotic episodes, rehabilitation programs offering comprehensive support to help individuals develop or regain essential life skills, and social reintegration to assist affected individuals in re-establishing their roles within their communities and pursuing as normal a life as possible [5].

The onset of schizophrenia typically occurs during a critical period of personal and professional development. Diagnosis is most commonly made between the ages of 16 and 30, often following the individual's first psychotic episode. This initial episode, characterized by a marked break from reality, serves as a crucial turning point in the course of the illness. Research has consistently demonstrated that initiating therapy promptly after this first episode is paramount for achieving optimal recovery outcomes [6]. The impact of schizophrenia extends beyond its well-known effects on thought processes and behavior. Extensive research has unveiled a wide range of sensory and perceptual impairments associated with the disorder. These deficits include difficulties in verbal communication, challenges in face and object perception, impaired sound discrimination, reduced contrast sensitivity, and problems with tone matching [7]. Individuals with schizophrenia often struggle to express thoughts coherently and understand complex language, recognize and interpret facial expressions, identify objects accurately, differentiate between various auditory stimuli, perceive differences in visual contrast, and identify and replicate auditory tones. These diverse impairments highlight the pervasive nature of schizophrenia and underscore the need for comprehensive treatment approaches. Effective management strategies must address not only the primary symptoms but also the broader range of cognitive and perceptual deficits associated with the disorder.

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1.1. Pathological changes in schizophrenia

1.1.1. Brain Changes

Schizophrenia is associated with significant structural and functional brain alterations, which contribute to the diverse symptomatology of the disorder. These changes are observed from the early stages of the illness and evolve throughout its course, providing insights into the underlying neurobiology of schizophrenia.

1.1.2. Pre- and Early Post-onset Changes

Neuroimaging studies have revealed reduced gray matter volume and compromised white matter integrity in individuals with schizophrenia, detectable even before or shortly after the onset of psychotic symptoms [8]. These structural alterations are not uniform across the brain but show regional specificity. Notably, severe negative symptoms have been linked to white matter loss in specific brain regions, including the cingulate cortex, temporal cortex, and insular cortex. These findings suggest a potential neuroanatomical basis for the negative symptom domain of schizophrenia.

1.1.3. Basal Ganglia Dysfunction

The basal ganglia, a group of subcortical structures crucial for motor control and learning, play a significant role in schizophrenia pathophysiology. Dopamine receptors in the basal ganglia mediate different aspects of reward learning: D1 receptors are involved in positive reward learning, while D2 receptors contribute to negative reward learning. Dysfunction in both cortical regions and the basal ganglia, resulting from a dysregulated reward system, is thought to underlie the negative symptoms of schizophrenia [1,4,8]. This connection between reward processing and symptomatology offers potential targets for novel therapeutic approaches.

1.1.4. Neurochemical Alterations

Recent research has uncovered more subtle neurochemical changes in schizophrenia. For instance, decreased expression of sodium/hydrogen exchangers (NHE6/7) in neurons may lead to alterations in organellar pH, protein modifications, and intracellular trafficking [2, 3]. Additionally, higher levels of lactate in the anterior cingulate cortex have been observed, inversely correlating with cognitive function and frontal lobe emotional withdrawal. These lactate levels tend to increase with the duration of illness, suggesting a progressive neurochemical disturbance in schizophrenia.

2. Types of Schizophrenia

Schizophrenia is a complex mental disorder that manifests in various forms, each with its distinct characteristics and challenges. While the classification of schizophrenia subtypes has evolved over time, understanding these different presentations can provide valuable insights into the diverse nature of the condition and inform tailored treatment approaches. This section explores the various types of schizophrenia, their defining features, and their implications for diagnosis and management.

2.1. Paranoid Schizophrenia

Paranoid schizophrenia is widely recognized as the most common subtype of the disorder. It is characterized primarily by the presence of persistent delusions and hallucinations, which often revolve around themes of persecution, grandiosity, or both. Despite these severe symptoms, individuals with paranoid schizophrenia typically maintain relatively preserved cognitive functions, particularly in areas of communication and emotional expression. This preservation of certain abilities can sometimes mask the severity of the condition, leading to delayed diagnosis or treatment [8].

2.2. Hebephrenic (Disorganized) Schizophrenia

Hebephrenic schizophrenia, also known as disorganized schizophrenia, usually emerges between the ages of 15 and 25, a critical period of personal and social development. The hallmark of this subtype is the profound disorganization of thought processes, which manifests in speech patterns that are often incoherent, fragmented, or difficult to follow. This communication barrier can significantly impair social and occupational functioning. Another defining feature of hebephrenic schizophrenia is the marked lack of emotional expressiveness, often referred to as "flat affect." This emotional blunting can further complicate interpersonal relationships and contribute to social isolation [8].

2.3. Catatonic Schizophrenia

Catatonic schizophrenia is a unique and complex neuropsychiatric syndrome characterized by distinct abnormalities in movement and behavior. These can range from extreme immobility (stupor) to excessive and purposeless motor activity. Interestingly, catatonic symptoms can mimic other neurological conditions, coexist with them, or even be induced by neuroleptic medications in chronic schizophrenia patients. This overlap and potential iatrogenic cause underscore the importance of careful differential diagnosis and medication management in treating this subtype [9].

2.4. Undifferentiated Schizophrenia

Undifferentiated schizophrenia presents a diagnostic challenge as it encompasses a range of symptoms that may overlap with paranoid, hebephrenic, and catatonic types, yet does not fully meet the criteria for any single subtype. This classification acknowledges the heterogeneous nature of schizophrenia and the fact that many individuals with the disorder may exhibit a mix of symptoms that defy neat categorization. The undifferentiated subtype highlights the need for flexible and individualized treatment approaches that address the specific symptom constellation of each patient [10].

2.5. Residual Schizophrenia

Residual schizophrenia refers to a state in which an individual retains some symptoms of the disorder after an acute psychotic episode, but these symptoms are less severe than during the active phase. A notable characteristic of this subtype is the tendency for affected individuals to absorb and interpret information selectively, often in ways that align with their preexisting beliefs about their condition. This selective information processing can pose challenges for treatment adherence and recovery, necessitating tailored psychoeducational approaches [11].

2.6. Cenesthopathic Schizophrenia

Cenesthopathic schizophrenia is a less commonly recognized subtype characterized by pathological bodily sensations, known as cenesthopathies. These abnormal bodily perceptions are intimately linked to the mental illness and can significantly impact an individual's quality of life. The presence of these somatic symptoms in the context of schizophrenia highlights the complex interplay between mind and body in mental health disorders and underscores the need for comprehensive treatment approaches that address both psychological and physical symptoms [12].

2.7. Unspecified Schizophrenia

The category of unspecified schizophrenia acknowledges that some individuals may meet the overarching diagnostic criteria for schizophrenia but present with symptom patterns that do not neatly fit into other established subtypes. This classification ensures that individuals with atypical presentations are not excluded from diagnosis and treatment. It also reflects the evolving nature of our understanding of schizophrenia and the potential for identifying new subtypes or refining existing classifications as research in this field progresses [8]].

3. Signs and Symptoms

Schizophrenia is characterized by a diverse array of symptoms, typically categorized into positive and negative symptoms. These manifestations can significantly impact an individual's perception, cognition, and behavior, leading to substantial impairments in daily functioning and quality of life.

3.1. Positive Symptoms

Positive symptoms in schizophrenia represent an exaggeration or distortion of normal cognitive and perceptual processes. These symptoms include delusions, hallucinations, and various verbal and behavioral anomalies [13]. Delusions are fixed, false beliefs that persist despite contradictory evidence, often involving themes of persecution, grandiosity, or control. Hallucinations, most commonly auditory, involve perceiving sensory experiences in the absence of external stimuli. Verbal anomalies may manifest as disorganized speech or thought processes, while behavioral anomalies can include catatonia or inappropriate emotional responses.

3.2. Negative Symptoms

Negative symptoms, in contrast, reflect a diminution or loss of normal functions. These symptoms include alogia (poverty of speech), avolition (lack of motivation), affective blunting (reduced emotional expressiveness), asociality (reduced social engagement), and anhedonia (inability to experience pleasure) [14]. Negative symptoms affect approximately 60% of individuals with schizophrenia and can significantly impair everyday functioning, social behavior, and the ability to live independently [15]

4. Causes/Etiology

The etiology of negative symptoms is complex and can be classified as either primary or secondary. Primary negative symptoms are intrinsic to the pathophysiology of schizophrenia, while secondary negative symptoms may arise from comorbidities, medication side effects, or external factors such as social isolation. Differentiating between primary and secondary negative symptoms presents a significant clinical challenge. Notably, reducing antipsychotic medication dosage may alleviate secondary negative symptoms but potentially exacerbate primary negative symptoms, highlighting the delicate balance required in treatment [16]

4.1. Genetics

Genetic factors play a substantial role in the development of schizophrenia, with studies suggesting that genetic predisposition can increase the risk of developing the disorder by up to 80%. The heritability of schizophrenia is evident in twin studies, which show that if one identical twin is affected, the other has a 48% chance of developing the disorder. This risk decreases to 17% for fraternal twins, 13% if one parent has schizophrenia, and 9% if a sibling is affected [17]. These findings underscore the significant genetic component in schizophrenia etiology while also highlighting the role of environmental factors in disease manifestation.

4.2. Neurotransmitter imbalance

Dysregulation of neurotransmitter systems, particularly dopamine, has been implicated in the pathophysiology of schizophrenia. The dopamine hypothesis suggests that positive symptoms arise from excessive dopamine activity in the mesolimbic pathway, while negative symptoms may result from dopamine deficits in the prefrontal cortex. However, the neurobiology of schizophrenia extends beyond dopamine, involving other neurotransmitters such as serotonin, GABA, and adrenaline [17]. This complex neurochemical landscape underscores the challenges in developing effective pharmacological treatments that address the full spectrum of schizophrenia symptoms.

5. Pathophysiology

The growing understanding of schizophrenia's molecular pathology and the protein/pathway changes involved has paved the way for the development of novel symptom-treating drugs [18-20]. Several key areas of research have emerged, offering new insights into the complex pathophysiology of the disorder.

5.1. GABAergic Theory

The GABAergic theory of schizophrenia posits that abnormalities in GABAergic signaling contribute to the disorder's symptoms. Mouse models have successfully captured various GABAergic abnormalities observed in schizophrenia, providing valuable tools for studying these mechanisms. Recent research has uncovered an emerging link between GABAergic signaling, microglia, and neuroinflammation, suggesting a unique pathway through which disease progression may influence GABA function [21-23]. This interplay between neurotransmission and immune processes opens up new avenues for therapeutic intervention.

5.2. Developmental Neuroinflammation

Studies using rodent models of maternal immune activation (e.g., the PolyI:C model) have demonstrated that developmental neuroinflammation can have far-reaching effects on neurotransmitter systems implicated in schizophrenia. This inflammatory insult impacts the expression of genes related to GABA, glutamate, and serotonin receptors. Importantly, these effects can be modified by histone acetylation, establishing a link between neurotransmission, inflammation, and epigenetic regulation [24-26]. This multifaceted interaction highlights the complex nature of schizophrenia pathophysiology and suggests potential targets for intervention at various levels.

5.3. MicroRNA Regulation

MicroRNAs have emerged as important regulators of gene expression in schizophrenia. For instance, miR-25-3p has been shown to regulate salt-inducible kinase 1 (SIK1), a protein involved in various cellular processes relevant to schizophrenia pathophysiology. This regulation affects macrophage activity, cytokine production, circadian rhythms, sleep patterns, and metabolism [27,28]. The involvement of microRNAs in such diverse processes underscores their potential as both biomarkers and therapeutic targets in schizophrenia.

5.4. Epigenetic Therapeutic Targets

The role of epigenetic mechanisms in schizophrenia has gained increasing attention. Histone acetylation and microRNAs have emerged as key epigenetic regulators that may be targeted for more efficacious therapies [24]. These epigenetic processes offer the potential for modulating gene expression patterns without altering the underlying DNA sequence, providing a flexible approach to addressing the complex and heterogeneous nature of schizophrenia.

6. Diagnosis

The diagnosis of schizophrenia remains a complex process, as there is no single definitive test to confirm the presence of the disorder. Instead, clinicians rely on a comprehensive clinical examination that assesses a range of behavioral and biological changes. These may include insomnia, loss of appetite, and social disinterest. The diagnostic process also involves consulting with the patient's relatives to gather additional information about the individual's behavior and functioning. To meet the diagnostic criteria for schizophrenia, a patient must exhibit a specific combination of symptoms for at least one month [29].

The evolution of diagnostic tools in schizophrenia reflects the growing understanding of the disorder's complexity. Historic clinical evaluation scales played a crucial role in standardizing the assessment of schizophrenia symptoms: In the 1960s and 1970s, the Brief Psychiatric Rating Scale (BPRS) and the Psychopathology Rating Schedule (PRS) were widely used to evaluate psychiatric symptoms, including those associated with schizophrenia. These scales provided a structured approach to symptom assessment, improving the consistency of diagnoses across different clinicians and research settings. The 1980s saw a shift towards a multi-dimensional approach to schizophrenia, as proposed by Crow. This led to the development of more specialized scales, such as the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) [30]. These scales allowed for a more nuanced evaluation of the distinct symptom domains in schizophrenia, recognizing the importance of both positive and negative symptoms in the disorder's presentation.

Currently, two scales are considered the gold standards in schizophrenia research:

- The Positive and Negative Syndrome Scale (PANSS) is widely acknowledged as the premier tool for assessing schizophrenia symptoms. It provides a comprehensive evaluation of positive, negative, and general psychopathology symptoms, offering a nuanced picture of the disorder's manifestation in each individual.
- The Brief Psychiatric Rating Scale (BPRS), despite its earlier origins, continues to be commonly used alongside PANSS [30]. Its enduring relevance speaks to its utility in providing a quick yet informative assessment of psychiatric symptoms, making it valuable in both clinical and research settings. These diagnostic tools, combined with clinical judgment and a thorough patient history, form the basis of schizophrenia diagnosis in modern psychiatric practice.

7. Pharmacological Treatment

The pharmacological management of schizophrenia presents numerous challenges, reflecting the complex nature of the disorder and the limitations of current treatment options. Only about 20% of patients experience successful treatment outcomes, and nonadherence rates range from 37% to 74%. Treatment withdrawal significantly increases the risk of relapse, underscoring the importance of continuous medication management. Older antipsychotic drugs, such as chlorpromazine, haloperidol, trifluoperazine, and fluphenazine, are associated with serious adverse effects, including neuroleptic malignant syndrome. These challenges highlight the pressing need for improved treatments that enhance cognition, promote adherence, minimize adverse effects, and address treatment-resistant cases [31].

Despite these challenges, several promising advances have emerged in the pharmacological treatment of schizophrenia:

7.1. Cariprazine

Cariprazine is a potent D2/D3 partial agonist that has shown promising results, particularly when combined with olanzapine, which has a weaker D2/D3 interaction. This combination has demonstrated effectiveness in treating both negative symptoms and residual positive symptoms of schizophrenia. Cariprazine is generally well-tolerated, normalizes prolactin levels, and does not induce significant metabolic or cardiac changes. Studies have shown improvements in Clinical Global Impression-Severity (CGI-S) scores and a reduction in hospitalizations after 60 days of treatment [32].

The unique pharmacological profile of cariprazine, particularly its D2/D3 partial agonism, suggests potential efficacy in treatment-resistant schizophrenia. The drug's high affinity for D3 receptors may enhance cognition, mood, executive function, and negative symptoms while reducing the risk of extrapyramidal symptoms (EPS) [33]. An 18-month study demonstrated significant improvements, including a 29.8% reduction in negative symptoms, a 25% improvement in CGI scores, and a 29.5% improvement in global functioning [34]. Cariprazine also shows promise in combination therapy, particularly with clozapine. The low risk of drug interactions between cariprazine and clozapine, due to the secondary involvement of CYP3A4 in clozapine metabolism, makes this combination potentially valuable for treatment-resistant cases [35].

7.2. Brilaroxazine

Brilaroxazine is a novel serotonin-dopamine modulator with affinity for the serotonin transporter (SERT) and high affinity for 5-HT2A/2B/7 and D2/3/4 receptors. Phase 1 and 2 trials have shown positive results in terms of efficacy, safety, and pharmacokinetics. The drug demonstrates rapid absorption, dose-dependent maximum concentration (Cmax), and no excess accumulation. Its 40-hour half-life allows for once-daily dosing, potentially improving adherence [36].

In single-dose studies, the most common treatment-emergent adverse events (TEAEs) were orthostatic hypotension, nausea, and dizziness. Multi-dose studies reported somnolence and akathisia as the primary TEAEs. Importantly, brilaroxazine did not induce major metabolic or cardiac changes. The drug's pharmacokinetics showed dose-proportional increases in Cmax and area under the curve (AUC∞), with enhanced absorption when taken with food [37]. At its highest dose (50mg), brilaroxazine demonstrated a lower dropout rate (2%) compared to aripiprazole 15mg (10%). The drug also showed favorable effects on metabolic parameters, decreasing lipids, glucose, and prolactin levels. No significant changes in weight, ECG, or orthostatic measurements were observed [37].

7.3. Other Emerging Treatments

The field of schizophrenia pharmacology continues to evolve, with several other promising treatments in development [31]:

- Asenapine transdermal system: A novel delivery method that may improve adherence and reduce side effects.
- Lumateperone: A new antipsychotic with a unique mechanism of action targeting multiple neurotransmitter systems.
- Paliperidone: Long-acting injectable formulations offering extended dosing intervals.
- Olanzapine/samidorphan combination: Aims to mitigate the metabolic side effects associated with olanzapine.
- Pimavanserin: A selective serotonin inverse agonist showing promise in treating schizophrenia symptoms.
- Risperidone ISM: A long-acting injectable formulation of risperidone.
- Roluperidone: A novel compound targeting negative symptoms of schizophrenia.
- TAAR-1 agonists: A new class of drugs targeting trace amine-associated receptor 1, showing potential in managing schizophrenia symptoms..

8. Conclusion

Schizophrenia is a severe mental illness causing significant disease burden worldwide. Characterized by positive and negative symptoms affecting perception, cognition and emotion, it reduces life expectancy and functioning without proper management. While historically challenging to treat, our growing molecular understanding of schizophrenia pathophysiology is enabling development of promising novel pharmacotherapies. Drugs like cariprazine and brilaroxazine are showing efficacy for negative symptoms and treatment-resistant cases by targeting dopamine and serotonin systems. Epigenetic mechanisms involving histone acetylation and microRNAs are emerging as key therapeutic targets. Continued research into the underlying biology of schizophrenia will be crucial for developing more effective diagnostic and treatment strategies to improve outcomes and quality of life for patients with this complex condition.

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Author's short biography

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