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Schizophrenia in the modern era: advancing neurobiological understanding and therapeutic innovation

Abstract

Schizophrenia is a chronic, severe, and disabling neuropsychiatric disorder that affects approximately 20 to 24 million people globally. Characterized by a wide spectrum of positive, negative, cognitive, and affective symptoms, its etiology and pathophysiology remain multifaceted and influenced by multiple interacting factors. Advances in brain science and neurological research have shifted the traditional dopamine-centric model to incorporate glutamatergic and GABAergic dysfunctions, neurodevelopmental disruptions, immune dysregulation, and oxidative stress. Genetic and epigenetic factors further contribute to disease vulnerability, interacting dynamically with environmental risk factors such as perinatal complications, psychosocial stress, and substance use. Modern diagnostic approaches now explore molecular, imaging, genetic, and proteomic biomarkers alongside emerging tools like digital phenotyping and artificial intelligence (AI) based analysis to improve early detection and individualized care. Neuroimaging studies consistently reveal gray matter loss, altered connectivity, and ventricular enlargement, while Electroencephalograph and event-related potentials have identified potential endophenotypes. Despite the availability of first- and second-generation antipsychotics, approximately 20% to 30% of patients experience treatment-resistant schizophrenia (TRS), for which clozapine remains the most effective option. Emerging pharmacotherapies targeting glutamate, gamma-aminobutyric acid (GABA), and inflammatory pathways are under investigation to address cognitive and negative symptoms more effectively. Non-pharmacological interventions, such as cognitive behavioral therapy (CBT), family-based psychosocial programs, digital therapeutics, and virtual reality (VR)-based treatments, are being increasingly integrated into comprehensive care plans. These approaches aim to enhance coping, reduce the likelihood of relapse, and improve overall quality of life. While significant challenges persist, including stigma, unequal access to care, and translational gaps between research and practice, the future of schizophrenia management lies in precision psychiatry and the development of personalized, integrative treatment strategies. This review highlights the current neurological and pathophysiological insights into schizophrenia, explores novel diagnostic and therapeutic innovations, and underscores the urgent need to bridge research with real-world clinical practice for improved patient outcomes.

Keywords: neurotransmitters, neurochemical signaling, prefrontal cortex, dopamine hypothesis, gabaergic systems, clozapine, virtual reality, artificial intelligence

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Abbreviations: DSM, diagnostic and statistical manual of mental disorders; ICD, international classification of diseases; WHO, world health organization; GABA, gamma-aminobutyric acid; DNA, deoxyribonucleic acid; NMDA, N-methyl-D-aspartate; AI, artificial intelligence; 5-HT2A, 5-hydroxytryptamine 2A; CSF, cerebrospinal fluid; fMRI, functional magnetic resonance imaging; TRS, treatment-resistant schizophrenia; CBT, cognitive behavioral therapy; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; DT, digital therapeutics; VR, virtual reality

Introduction

Schizophrenia is a complex, chronic, and disabling neuropsychiatric disorder that significantly affects how an individual thinks, feels, and behaves.[1] It is characterized by a combination of positive symptoms such as hallucinations and delusions, negative symptoms including emotional blunting and social withdrawal, and cognitive deficits that impair memory, attention, and decision-making abilities. These symptoms typically emerge during late adolescence or early adulthood, disrupting the individual's ability to lead a productive and socially engaged life.[2] Despite common misconceptions, schizophrenia does not signify a split or multiple personality disorder; rather, the term, derived from the Greek words *schizo* (split) and *phren* (mind), refers to a fragmentation of thought processes and emotional responsiveness. The etiology of schizophrenia is multifactorial, involving a combination of genetic vulnerability, neurodevelopmental disruptions, environmental stressors, and biochemical imbalances-especially in dopamine, glutamate, and serotonin pathways.[3] Although there is no definitive cure, advances in pharmacological and psychosocial interventions have considerably improved long-term outcomes, especially when the disorder is diagnosed early and treated continuously. The modern view of schizophrenia has shifted toward understanding it as a spectrum disorder, reflecting the heterogeneity in symptom presentation, progression, and treatment response. This perspective has paved the way for more personalized, patient-centered care and targeted research.[4]

Historically, the conceptualization of schizophrenia has evolved significantly. Ancient civilizations such as those in Egypt, India, and Greece documented behaviors resembling psychosis, often attributing

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them to supernatural or spiritual causes.[5] The Greek physician Hippocrates proposed a natural explanation, linking mental illness to imbalances in bodily fluids. However, it was not until the late 19th century that schizophrenia began to be understood in clinical terms. Emil Kraepelin, a German psychiatrist, first described the condition as *dementia praecox*, distinguishing it from bipolar disorder based on its early onset and progressive decline in cognitive functioning.[6] This was a crucial step in the medical classification of psychiatric illnesses. Later, in 1911, Swiss psychiatrist Eugen Bleuler introduced the term 'schizophrenia' to better reflect the splitting of mental functions observed in patients. He proposed four core features-affective blunting, autism (social withdrawal), ambivalence, and associative disturbances, now known as Bleuler's 'four A's'.[7] Over the decades, definitions and diagnostic frameworks have continued to evolve, especially with the development of standardized manuals like the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD).[8] Notably, the DSM-III, introduced in 1980, moved toward a symptom-based, operational approach that allowed for more standardized diagnoses.[9] Currently, schizophrenia is classified in both DSM-5 and ICD-11 as a severe mental disorder marked by specific core symptoms lasting at least six months and significantly impairing daily functioning.[10] The characterization of schizophrenia as a spectrum ranging from mild to severe, episodic to chronic, has been further supported by neuroimaging, genetic, and neurobiological research.[11] These scientific advances continue to reshape our understanding of schizophrenia, moving beyond traditional diagnostic boundaries toward models that account for overlapping features with other psychiatric conditions, especially within the framework of initiatives like the National Institute of Mental Health's Research Domain Criteria.[12]

Globally, schizophrenia affects approximately 20 to 24 million people, or about 1% of the population, with a lifetime prevalence estimated between 0.3% and 0.7%.[13] Onset typically occurs between the ages of 16 and 30, with males often showing symptoms slightly earlier than females.[14] While its prevalence appears relatively similar across cultures and regions, the impact of the disorder varies dramatically due to differences in healthcare infrastructure, cultural attitudes, and stigma.[15] Schizophrenia significantly impairs social, occupational, and personal functioning, often resulting in a lifelong struggle with disability. Individuals may face enduring challenges in completing education, maintaining employment, building relationships, and achieving independent living. In addition to the primary symptoms, many patients suffer from comorbidities such as depression, anxiety, substance use disorders, and metabolic or cardiovascular diseases, all of which contribute to a higher mortality rate.[16] Life expectancy for individuals with schizophrenia is estimated to be 10 to 20 years shorter than the general population, largely due to preventable health issues and suicide.[17] Families and caregivers often bear the emotional and economic burden of the illness, providing long-term support amidst considerable stress. The stigma surrounding schizophrenia remains a significant barrier to treatment, early diagnosis, and social participation. Misconceptions and fear can lead to social isolation, discrimination, and human rights violations in some communities.[18]

Economically, schizophrenia causes a substantial burden on societies worldwide. Costs arise not only from direct healthcare expenses-hospitalizations, medications, outpatient care but also from indirect factors like lost productivity, disability benefits, and caregiver time. The World Health Organization (WHO) ranks schizophrenia among the leading causes of disability adjusted life years globally.[19] However, the growing recognition of mental health as a public health priority has led to initiatives aimed at improving access to care, particularly in low- and middle-income countries. The WHO's mental health gap action programme is one such effort, advocating for the coordination of mental health services into primary care settings to reduce the treatment gap.[20] At the same time, the paradigm of care is shifting from institutionalization toward community-based mental health services, emphasizing rehabilitation, recovery, and social engagement.[21] Recovery-oriented approaches highlight not only symptom control but also personal empowerment, autonomy, and hope principles that resonate with a more humane and inclusive understanding of schizophrenia. Innovations in digital health, telepsychiatry, and early psychosis intervention programs further support this transition by enhancing access, monitoring, and personalized care.[22] Though much remains to be done, especially in addressing stigma and ensuring equal access to services, the progress of schizophrenia research and management is increasingly promising.[23,24]

Etiology

The etiology of schizophrenia, according to current perspectives, is complex and not fully understood. It is now widely accepted that there is no single, exact cause of schizophrenia. Instead, it is the result of a multifactorial interaction involving genetic, neurobiological, developmental, and environmental factors. Modern research emphasizes that individuals may have varying combinations of risk factors, and these may contribute differently to the onset and progression of the disorder.[25]

Genetic studies have shown that schizophrenia has a strong hereditary component, with a high co-occurrence rate among monozygotic twins and increased risk among direct biological relatives. However, no single gene has been identified as the definitive cause. Instead, the disorder is associated with multiple genetic variants, each contributing a small amount to the overall risk. Epigenetic mechanisms, such as deoxyribonucleic acid (DNA) methylation and histone modification, also influence gene expression and may help explain how environmental exposures can affect the risk of developing schizophrenia without altering the DNA sequence itself.[26]

Neurochemical theories have evolved beyond the original dopamine hypothesis, which suggested that overactivity of dopamine pathways was responsible for positive symptoms such as hallucinations and delusions. Current perspectives also highlight the roles of glutamate, the brain's major excitatory neurotransmitter, and GABA, the main inhibitory neurotransmitter.[27] Dysregulation of these neurotransmitters may contribute to cognitive deficits and negative symptoms.

Neuroimaging studies have revealed structural brain abnormalities in individuals with schizophrenia, including reduced gray matter volume, enlarged ventricles, and altered connectivity between brain regions. These findings support the view that schizophrenia is a neurodevelopmental disorder, potentially rooted in disruptions during early brain development. Such disruptions may be triggered by prenatal factors like maternal infections, malnutrition, obstetric complications, or perinatal hypoxia.[28]

Environmental factors further complicate the etiology. Psychosocial stressors, urban living, childhood trauma, and substance abuse (especially cannabis during adolescence) have been linked to increased risk. These environmental factors may act by modifying neural circuitry or interacting with genetic predispositions to initiate the disorder.[29] Contemporary models, such as the diathesis-stress model and the gene-environment interaction framework, illustrate

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how inherited vulnerabilities may interact with external stressors to trigger schizophrenia. These models support the hypothesis that while many individuals may carry genetic risk factors, the disorder often develops only when these are combined with environmental factors.[30]

Pathophysiology

The pathophysiology of schizophrenia is complex and multifactorial, involving dysregulation in neurochemical signaling, structural brain abnormalities, neurodevelopmental disruptions, and impaired connectivity among brain regions. Although the exact mechanisms remain unclear, several interconnected systems contribute to the development and progression of the disorder.[31]

Dopaminergic dysfunction: The classical dopamine hypothesis remains central, proposing hyperactivity of dopamine transmission in the mesolimbic pathway (linked to positive symptoms such as hallucinations and delusions) and hypoactivity in the mesocortical pathway (associated with negative and cognitive symptoms).[32]

Glutamate and GABA abnormalities: Emerging evidence highlights the role of glutamatergic hypofunction, particularly involving N-methyl-D-aspartate (NMDA) receptor dysregulation, contributing to cognitive deficits and excitotoxicity. GABAergic interneuron dysfunction also disrupts inhibitory control, leading to abnormal cortical activity and impaired neuronal connectivity.[33]

Neurodevelopmental and neurodegenerative changes: Prenatal and early life insults (e.g., maternal infection, obstetric complications, or malnutrition) may interfere with brain development, creating vulnerability. This is compounded by synaptic elimination abnormalities during adolescence and progressive gray matter loss in adulthood.[34]

Brain structure and connectivity: Neuroimaging studies frequently show reduced gray matter volume, especially in the prefrontal cortex, hippocampus, and temporal lobes. There is also evidence of disrupted white matter integrity and altered functional connectivity between brain networks, impairing cognitive and emotional regulation.[35]

Inflammation and oxidative stress: Increased levels of pro-inflammatory cytokines and oxidative stress markers have been observed in patients, suggesting a role of immune dysregulation and impaired cellular homeostasis in pathogenesis.[36]

Genetic and epigenetic factors: Schizophrenia has a strong genetic basis, with polygenic risk profiles indicating contributions from multiple susceptibility genes (e.g., DISC1, NRG1, COMT). Epigenetic modifications influenced by the environment may alter gene expression without changing the DNA sequence.[37]

Neurobiological basis of schizophrenia

Schizophrenia is increasingly recognized as a brain disorder involving complex neurobiological mechanisms. Current research focuses on disrupted brain development, progressive neural changes, neurotransmitter imbalances, and cellular-level dysfunctions, all contributing to the onset and progression of the disorder.[38]

Neurodevelopmental and neuroprogressive models: The neurodevelopmental model suggests that schizophrenia originates from disturbances in brain development during prenatal or early postnatal life. Factors such as genetic mutations, in-utero infections, maternal malnutrition, or obstetric complications can interfere with key neurodevelopmental processes like neuronal migration, synaptogenesis, and myelination.[39] The neuroprogressive model complements this by indicating that schizophrenia progressively develops after its initial onset, with further degeneration in brain structure and function. Progressive loss of gray matter, cognitive dysfunction, and worsening of symptoms over time indicate an active pathological process rather than a static developmental abnormality.[40] These two models together explain how early brain injuries may set the stage for the disorder, while later environmental factors and biological changes contribute to its progression.[41]

Structural and functional brain abnormalities

Gray matter loss: Neuroimaging studies repeatedly demonstrate reduced gray matter volume, especially in the prefrontal cortex, temporal lobes, and hippocampus. This loss is associated with impairments in cognitive functions, working memory, emotional regulation, and cognitive processing. Gray matter reduction is more significant in patients with longer illness duration, supporting the neuroprogressive nature of the disease.[42]

Ventricular enlargement: Patients with schizophrenia often exhibit enlarged lateral and third ventricles, a marker of brain tissue loss or atrophy. This is considered one of the most reliable structural findings and is thought to indicate abnormal brain development or degeneration.[43]

Prefrontal cortex and hippocampal changes: The prefrontal cortex, responsible for planning, decision-making, and social behavior, shows hypoactivity, especially during cognitive tasks. This may explain the negative symptoms and executive dysfunctions in schizophrenia.[44]

The hippocampus, essential for memory and emotional regulation, often appears shrunken and displays abnormal neuronal activity. Hippocampal dysregulation may contribute to sensory misprocessing and the formation of delusions.[45]

Neurotransmitter dysregulation

Schizophrenia involves complex imbalances in multiple neurotransmitter systems:

Dopamine: The dopamine hypothesis remains central. Overactivity in the mesolimbic pathway is linked to positive symptoms (hallucinations, delusions). Underactivity in the mesocortical pathway contributes to negative symptoms and cognitive deficits.[46]

Glutamate: The glutamate hypothesis suggests that NMDA receptor hypofunction leads to decreased excitatory transmission, particularly in cortical circuits. This may result in disorganized thinking, memory impairment, and affective disturbances.[47]

Gamma-aminobutyric acid: GABAergic interneurons, particularly parvalbumin-positive cells, are reduced in schizophrenia. This leads to cortical disinhibition and impaired neural coordination, contributing to cognitive dysfunction.[48]

Serotonin: The serotonin system is linked, particularly through 5-hydroxytryptamine 2A (5-HT2A) receptor involvement. Second-generation antipsychotics that inhibit both dopamine and serotonin receptors highlight the therapeutic significance of this system.[49]

Advances in biomarkers and diagnostic tools in schizophrenia

Efforts to establish valid biomarkers and advanced diagnostic methods in schizophrenia have gained attention in recent years. Early detection, objective diagnosis, and personalized treatment strategies depend primarily on the development and validation of biological and technological markers. Current efforts span molecular biology, neuroimaging, genetics, and AI.[50]

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Molecular and imaging biomarkers: Molecular biomarkers include measurable biological substances in blood, cerebrospinal fluid (CSF), or tissues that indicate physiological or pathological processes. In schizophrenia, research has identified alterations in: Inflammatory markers (e.g., IL-6, TNF-α, C-reactive protein); Oxidative stress markers (e.g., reduced glutathione); Neurotrophic factors (e.g., decreased brain-derived neurotrophic factor); Neurotransmitter metabolites in CSF or plasma (e.g., homovanillic acid for dopamine).[51]

Imaging biomarkers refer to structural or functional changes visible through neuroimaging techniques that correlate with clinical symptoms or disease progression. These may include reduced gray matter, enlarged ventricles, and altered brain connectivity. Biomarkers are still largely in the research phase, and none have yet been adopted into routine clinical practice. However, combining molecular and imaging biomarkers may enhance early detection and prognosis.[52]

Role of neuroimaging: Neuroimaging has significantly advanced our understanding of schizophrenia by providing non-invasive insights into brain structure and function. Functional magnetic resonance imaging (fMRI) reveals reduced prefrontal cortex activity, disrupted connectivity in key networks, and abnormal responses to stimuli.[53] Positron emission tomography scans confirm increased dopamine synthesis in the striatum, while diffusion tensor imaging shows white matter abnormalities, particularly between the frontal and temporal lobes. These techniques not only aid in diagnosis but also help track disease progression and treatment response.[54]

Genetic and proteomic markers: Genetic studies using genome-wide association studies have identified several susceptibility genes for schizophrenia, including DISC1, COMT, NRG1, ZNF804A, and MIR137, which are involved in synaptic development, neurotransmission, and brain structure.[55] However, each gene contributes only a small risk, highlighting the polygenic nature of the disorder. Additionally, proteomic research has revealed abnormal protein expression related to inflammation, oxidative stress, and neuronal signaling, with potential use as diagnostic, prognostic, or treatment-response biomarkers.[56]

Digital phenotyping and AI-based diagnostics: Digital phenotyping uses smartphones and wearable devices to continuously collect behavioral and physiological data, such as speech patterns, social interactions, sleep cycles, and movement, offering early detection of psychotic episodes or treatment response.[57] Complementing this, AI-based diagnostics apply machine learning to analyze neuroimaging and genetic data, detect subtle behavioral patterns, predict relapse, and personalize treatment. Tools like natural language processing and AI-enhanced fMRI analysis show promise for more objective, data-driven approaches to diagnosing and managing schizophrenia, though they remain in early developmental stages.[58]

Symptom Domains and Clinical Subtypes in Schizophrenia

Schizophrenia is a heterogeneous disorder characterized by diverse symptom domains and clinical presentations. Understanding these domains helps in diagnosis, treatment planning, and identifying potential subtypes within the disorder.[59]

Positive, Negative, Cognitive, and Affective Symptoms

Schizophrenia presents with a range of symptoms categorized as positive, negative, cognitive, and affective. Positive symptoms are the most recognizable and include hallucinations (often auditory), delusions, and disorganized speech or behavior, typically responsive to dopamine D2 receptor antagonists.[60] Negative symptoms involve reduced emotional expression and behavioral functions such as affective flattening, alogia, anhedonia, and avolition, and are often persistent, disabling, and less responsive to treatment. Cognitive symptoms include deficits in attention, working memory, and executive function, significantly impacting daily functioning and long-term outcomes, with limited treatment options.[61] Affective symptoms, such as depression, anxiety, and emotional instability, are common and can worsen prognosis, increase suicide risk, and affect treatment adherence.[62]

Emerging endophenotypes: Emerging endophenotypes in schizophrenia are heritable, measurable characteristics that bridge genetic risk and clinical symptoms, helping to uncover biological mechanisms and subtypes. Key examples include impaired smooth-pursuit eye movements, cognitive deficits (e.g., working memory), altered P300 EEG signals, and reduced prepulse inhibition. These features are often found in unaffected relatives and may aid in early detection and personalized interventions.[63]

Treatment-resistant Schizophrenia: TRS is characterized by inadequate response to at least two antipsychotic trials at proper doses and durations, affecting 20% to 30% of patients.[64,65]

TRS is associated with persistent symptoms, functional impairment, increased hospitalization, and suicide risk, and limited treatment options.[66] Clozapine is the most effective therapy, but is underused due to the required blood monitoring and serious side effects. Emerging strategies include glutamatergic agents, anti-inflammatory drugs, and non-pharmacological approaches like CBT, transcranial magnetic stimulation**,** and digital therapeutics (DT).[67]

Current and emerging therapeutic strategies

Current and emerging therapeutic strategies for schizophrenia aim to address the diverse symptom domains and biological mechanisms underlying the disorder.[68]

Pharmacological treatments: Pharmacological treatments remain the mainstay of management: First-generation antipsychotics (FGAs) such as haloperidol primarily target dopamine D2 receptors and are effective for positive symptoms but often cause extrapyramidal side effects. Second-generation antipsychotics (SGAs) like risperidone, olanzapine, and aripiprazole have broader receptor profiles, including serotonin 5-HT2A antagonism, and are generally better tolerated with lower motor side effects, though they may lead to metabolic issues.[69]

Emerging pharmacological treatments: Emerging pharmacological targets are focused on the glutamatergic and GABAergic systems, which are increasingly recognized as key contributors to schizophrenia's pathophysiology: Glutamatergic modulation involves targeting NMDA receptor hypofunction, a proposed mechanism for cognitive and negative symptoms.[70] Agents like glycine, D-serine, and glycine transporter inhibitors aim to enhance NMDA receptor activity, though results have been mixed. GABAergic approaches explore the role of GABA interneuron dysfunction, particularly in the prefrontal cortex. GABA-A receptor modulators are being investigated to restore inhibitory-excitatory balance, which may improve cognitive deficits and reduce cortical hyperactivity (Table 1).[71]

Non-pharmacological therapies: CBT helps individuals with schizophrenia identify and reframe maladaptive thoughts related to delusions and hallucinations, offering coping strategies and improving insight. It is effective as an add-on to medication, particularly in reducing positive symptoms and enhancing quality of life.[76] Family and psychosocial interventions, including psychoeducation, communication training, and social skills development, support long-

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term management by reducing relapse, improving adherence, and enhancing daily functioning.[77] DT uses apps, wearables, and online platforms to monitor symptoms, promote treatment adherence, and deliver therapy remotely, offering scalable, accessible support. VR provides immersive environments to practice social and cognitive skills, reduce paranoia, and improve social functioning, holding promise as a future therapeutic tool in schizophrenia care (Table 2).[78]

Table 1 Classes of pharmacological treatments for schizophrenia with examples, mechanisms of action, and target symptoms.[72–75]

S. No.	Class	Example drugs	Mechanism of action	Target symptoms
1	First-Generation Antipsychotics	Haloperidol, Chlorpromazine	Potent D2 receptor antagonism → reduces dopaminergic neurotransmission in the mesolimbic pathway	Mainly positive symptoms
2	Second-Generation Antipsychotics	Risperidone, Olanzapine, Quetiapine, Aripiprazole	D2 receptor antagonism + 5-HT2A antagonism (modulates dopamine release in various brain regions)	Positive and some negative symptoms
3	D2 Partial Agonists	Aripiprazole, Brexpiprazole	Partial agonist at D2 receptors → stabilizes dopamine levels (agonist in low dopamine areas, antagonist in high dopamine areas)	Both positive and negative symptoms
4	Clozapine (for TRS)	Clozapine	Weak D2 antagonism, strong 5-HT2A, D4, and muscarinic receptor binding	Treatment-resistant positive & negative symptoms
5	Glutamatergic Agents (experimental)	D-serine, Glycine, Sarcosine	Enhance NMDA receptor function (co-agonists or glycine transporter inhibitors)	Cognitive and negative symptoms
6	GABAergic Agents (experimental)	GABA-A $\alpha 2/\alpha 3$ modulators (e.g., MK-0777)	Positive allosteric modulators of GABA-A receptors → restore inhibitory neurotransmission	Cognitive and negative symptoms (experimental)
7	Adjunctive Therapies	Selective serotonin reuptake inhibitors, Mood stabilizers, Anti-inflammatory agents	Modulate serotonin, mood, or inflammation pathways	Comorbid depression, mood instability, and inflammation

Table 2 Overview of non-pharmacological therapies for schizophrenia, including descriptions and clinical benefits.[79–82]

S. No.	Therapy	Description	Clinical benefits
1	Cognitive Behavioral Therapy	A structured, time-limited psychological intervention aimed at changing maladaptive thoughts and behaviors	Reduces distress from delusions/hallucinations; improves coping and insight
2	Family and Psychosocial Interventions	Education and support for family members include social skills training and vocational rehabilitation	Reduces relapse rates, improves medication adherence, and enhances social functioning
3	Digital Therapeutics	Use of mobile apps, web-based tools, or software for symptom tracking, self-management, and therapy	Increases access to care, supports monitoring, and promotes engagement.
4	Virtual Reality Approaches	Immersive simulations to train social interaction or exposure to anxiety-provoking situations	Enhances real-life skills, reduces paranoia, and improves cognitive and social outcomes

Challenges and future directions in schizophrenia care

Bridging the gap between research and clinical practice: Bridging the gap between research and clinical practice remains a major challenge, as many advancements in neurobiology and digital health have yet to be adopted into routine care.[83] Translating complex findings into accessible, evidence-based interventions requires improved clinician training, interdisciplinary collaboration, and streamlined healthcare systems.[84]

Reducing stigma and improving access to care: Reducing stigma and improving access to care are essential for better outcomes. Stigma often delays diagnosis and treatment, while disparities in mental health services, especially in low-resource settings, limit recovery potential. Public education, policy reforms, and culturally sensitive interventions are needed to promote early engagement and sustained support.[85]

Innovations in early diagnosis and prevention: Innovations in early diagnosis and prevention, such as digital phenotyping, genetic risk profiling, and neuroimaging, provide potential for identifying at-risk individuals before fully developed symptoms emerge. Early intervention strategies can delay or reduce illness severity, emphasizing the importance of preventive approaches.[86]

Future targets for drug development: Future targets for drug development include glutamatergic and GABAergic systems, inflammatory pathways, and neuroplasticity-enhancing agents.[87] Precision psychiatry aims to tailor treatments based on individual biomarkers, leading to more effective, personalized therapies. As research advances, combining pharmacological and non-pharmacological strategies will be key to transforming schizophrenia care.[88]

Conclusion

Schizophrenia remains a chronic and impairing mental disorder, characterized by a complex interaction of genetic, neurobiological, and environmental factors. Recent advances in neuroscience have redefined our understanding, moving beyond the traditional dopamine hypothesis to include glutamatergic dysfunction, GABAergic imbalance, neuroinflammation, oxidative stress, and abnormal neurodevelopment. While current antipsychotic medications effectively target positive symptoms, TRS and the burden of cognitive and negative symptoms remain significant challenges. Incorporating pharmacological innovations, such as agents targeting glutamate and GABA pathways, with non-pharmacological strategies like cognitive behavioral therapy, psychosocial support, and emerging DT offers a

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more holistic approach to care. Advances in neuroimaging, genetic studies, and AI have improved diagnostic precision and may soon personalize treatment pathways. However, bridging the gap between cutting-edge research and clinical practice, reducing stigma, and expanding access to care, especially in low-resource settings, are critical steps forward. The future of schizophrenia management lies in precision psychiatry, using biomarkers, digital monitoring, and comprehensive care models customized to individual needs. Continued interdisciplinary research, patient-centered interventions, and global mental health initiatives are essential to improving quality of life and long-term outcomes for those affected by this complex disorder.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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References

1. Audiffred–Jaramillo RI, Alba–García JEG. Cultural beliefs about the etiology of schizophrenia and expressed emotion in Mexican families. *Rev Colomb Psiquiatr (Engl Ed)*. 2024;53(4):435–442.
2. Wojtalik JA, Mesholam–Gately RI, Hogarty SS, et al. Confirmatory efficacy of cognitive enhancement therapy for early schizophrenia: results from a multisite randomized trial. *Psychiatr Serv*. 2022;73(5):501–509.
3. Dor H, Hertzberg L. Schizophrenia biomarkers: blood transcriptome suggests two molecular subtypes. *Neuromolecular Med.* 2024;26(1):50.
4. Sun J, Zelaya F, Sendt KV, et al. Response to clozapine in treatment resistant schizophrenia is related to alterations in regional cerebral blood flow. *Schizophrenia (Heidelb).* 2024;10(1):122.
5. Yang X. Treating rare and intractable diseases via guan yin citta dharma door. *Health Sci J.* 2024;18(5):1137.
6. Ballasch I, López–Molina L, Galán–Ganga M, et al. Alterations of the IKZF1–IKZF2 tandem in immune cells of schizophrenia patients regulate associated phenotypes. *J Neuroinflammation.* 2024;21(1):326.
7. Rampino A, Garofalo M, Nuzzo T, et al. Variations of blood D–serine and D–aspartate homeostasis track psychosis stages. *Schizophrenia (Heidelb).* 2024;10(1):115.
8. Millat MS, Roy J, Rahman MA, et al. Association of *NOTCH4* and *CYP2E1* genetic variants with schizophrenia in the Bangladeshi population: a case–control study. *Health Sci Rep.* 2024;7(12):e70262.
9. Pontes JGM, Nani JVS, Correia BSB, et al. An investigation of the sodium nitroprusside effects on serum lipids in an animal model of schizophrenia by the magnetic resonance study. *ACS Omega*. 2024;9(49):48480–48487.
10. Sathiya E, Rao TD, Kumar TS et al. A comparative study of wavelet families for schizophrenia detection. *Front Hum Neurosci.* 2024;18:1463819.
11. Siskind D, Orr S, Sinha S, et al. Rates of treatment–resistant schizophrenia from first–episode cohorts: systematic review and meta–analysis. *Br J Psychiatry*. 2022;220(3):115–120.
12. Vita A, Barlati S, Ceraso A, et al. Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: a systematic review and meta–analysis of randomized clinical trials. *JAMA Psychiatry*. 2021;78(8):848–858.
13. Bighelli I, Rodolico A, García–Mieres H, et al. Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network metaanalysis. *Lancet Psychiatry*. 2021;8(11):969–980.
14. Selten JP, van der Ven E, Termorshuizen F. Migration and psychosis: a meta–analysis of incidence studies. *Psychol Med.* 2020;50(2):303–313.
15. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry*. 2020;19(1):15–33.
16. Moura BM, Isvoranu AM, Kovacs V, et al. The puzzle of functional recovery in schizophrenia–spectrum disorders–replicating a network analysis study. *Schizophr Bull.* 2022;48(4):871–880.
17. Ostuzzi G, Vita G, Bertolini F, et al. Continuing, reducing, switching, or stopping antipsychotics in individuals with schizophrenia–spectrum disorders who are clinically stable: a systematic review and network meta–analysis. *Lancet Psychiatry*. 2022;9(8):614–624.
18. Singh A. Xanomeline and Trospium: A potential fixed drug combination (FDC) for schizophrenia–a brief review of current data. *Innov Clin Neurosci*. 2022;19(10–12):43–47.
19. Chien YL, Hwu HG, Hwang TJ, et al. Clinical implications of oxidative stress in schizophrenia: Acute relapse and chronic stable phase. *Prog Neuropsychopharmacol Biol Psychiatry.* 2020;99:109868.
20. Dudzinska E, Szymona K, Bogucki J, et al. Increased markers of oxidative stress and positive correlation low–grade inflammation with positive symptoms in the first episode of schizophrenia in drug–naïve patients. *J Clin Med.* 2022;11(9):2551.
21. Jomova K, Raptova R, Alomar SY, et al. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. *Arch Toxicol.* 2023;97(10):2499–2574.
22. Ma J, Yan L, Guo T, et al. A pilot study of biomarkers of oxidative stress in serum and schizophrenia. *Psychiatry Res.* 2020;284:112757.
23. Chauhan P, Kaur G, Prasad R, et al. Pharmacotherapy of schizophrenia: immunological aspects and potential role of immunotherapy. *Expert Rev Neurother.* 2021;21:1441–1453.
24. Nguyen KD, Amerio A, Aguglia A, et al. Microglia and other cellular mediators of immunological dysfunction in schizophrenia: A narrative synthesis of clinical findings. *Cells.* 2023;12(16):2099.
25. Guo J, He C, Song H, et al. Unveiling promising neuroimaging biomarkers for schizophrenia through clinical and genetic perspectives. *Neurosci Bull.* 2024;40(9):1333–1352.
26. Cummings MA, Arias AW, Stahl SM. What is the neurobiology of schizophrenia? *CNS Spectr*. 2024;30(1):e13.
27. Wiedlocha M, Zborowska N, Marcinowicz P, et al. Oxidative stress biomarkers among schizophrenia inpatients. *Brain Sci.* 2023;13(3):490.
28. Li H, Huang Y, Liang L, et al. The relationship between the gut microbiota and oxidative stress in the cognitive function of schizophrenia: A pilot study in China. *Schizophr Res.* 2024;267:444–450.
29. Çilem Kızılpınar S, Çiğdem Aydemır M, Doğan Ö, et al. Social cognition and oxidative stress in schizophrenia patients and first–degree relatives of patients. *Psychiatr Danub.* 2023;35(4):523–534.
30. Wang K, Xiu M, Su X, et al. Association between changes in total antioxidant levels and clinical symptom improvement in patients with antipsychoticnaive first–episode schizophrenia after 3 months of risperidone monotherapy. *Antioxidants (Basel).* 2022;11(4):646.
31. Goh XX, Tang PY, Tee SF. Effects of antipsychotics on antioxidant defence system in patients with schizophrenia: A meta–analysis. *Psychiatry Res.* 2022;309:114429.

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32. Yolland CO, Hanratty D, Neill E, et al. Metaanalysis of randomised controlled trials with N–acetylcysteine in the treatment of schizophrenia. *Aust N Z J Psychiatry.* 2020;54(6):453–466.

33. Okubo Eneni AE, Ben–Azu B, Mayowa Ajayi A, et al. Diosmin attenuates schizophrenia–like behavior, oxidative stress, and acetylcholinesterase activity in mice. *Drug Metab Pers Ther.* 2020;35:20200119.

34. Mizuno Y, McCutcheon RA, Brugger SP, et al. Heterogeneity and efficacy of antipsychotic treatment for schizophrenia with or without treatment resistance: a meta–analysis. *Neuropsychopharmacology.* 2020;45(4):622–631.

35. Northwood K, Pearson E, Arnautovska U, et al. Optimising plasma clozapine levels to improve treatment response: an individual patient data meta–analysis and receiver operating characteristic curve analysis. *Br J Psychiatry.* 2023;222(6):241–245.

36. Kikuchi T, Maeda K, Suzuki M, et al. Discovery research and development history of the dopamine D_2 receptor partial agonists, aripiprazole and brexpiprazole. *Neuropsychopharmacol Rep.* 2021;41(2):134–143.

37. Yang Q, Pan X, Yang J, et al. Advances in MRI research for first–episode schizophrenia: a selective review and NSFC–funded analysis. *Schizophr Bull.* 2025;51(2):352–365.

38. Shenoi N, Alobaidi A, Czelusta KL, et al. Treatment updates in schizophrenia and schizophrenia spectrum disorders. *Psychiatr Ann.* 2025;55(1):e8–e13.

39. Tusconi M, Dursun SM. Editorial: Neuroimaging in psychiatry 2023: schizophrenia. *Front Psychiatry.* 2025;16:1591274.

40. Mello RA, Fernandes–Mello V, Sant'Ana L, et al. A narrative review of nosology and the concept of schizophrenia: criticism and proposal. *Einstein (São Paulo).* 2025;23:89.

41. Jarab A, Al–Qerem W, Khdour A, et al. Novel pharmaceutical treatment approaches for schizophrenia: a systematic literature review. *Eur J Clin Pharmacol.* 2025;81(4):525–541.

42. Begni V, Marchesin A, Riva MA. IUPHAR review – Novel therapeutic targets for schizophrenia treatment: A translational perspective. *Pharmacol Res.* 2025;214:107690.

43. Deicher A, Karl S, Otte ML, et al. Randomized, double–blind, sham–controlled trial to evaluate efficacy and tolerability of electroconvulsive therapy in clozapine–resistant schizophrenia. *BMC Psychiatry.* 2025;25(1):536.

44. Yang Q, Pan X, Yang J, et al. Functional and microstructural changes with paliperidone palmitate vs oral antipsychotics in first–episode schizophrenia: randomized multicenter trial. *Schizophr Bull.* 2025;51(2):352–365.

45. Farrell MS, Werge T, Sklar P, et al. Evaluating historical candidate genes for schizophrenia. *Mol Psychiatry.* 2015;20(5):555–562.

46. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci.* 2015;16(10):620–631.

47. Haring L, Koido K, Vasar V, et al. Antipsychotic treatment reduces psychotic symptoms and markers of low–grade inflammation in first episode psychosis patients, but increases their body mass index. *Schizophr Res.* 2015;169(1–3):22–29.

48. Fond G, d'Albis MA, Jamain S, et al. The promise of biological markers for treatment response in first–episode psychosis: a systematic review. *Schizophr Bull.* 2015;41(3):559–573.

49. Petrides G, Malur C, Braga RJ, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry.* 2015;172(1):52–58.

50. Najjar S, Pearlman DM. Neuroinflammation and white matter pathology in schizophrenia: systematic review. *Schizophr Res.* 2015;161(1):102–112.

51. Czobor P, van Dorn RA, Citrome L, et al. Treatment adherence in schizophrenia: a patient - level meta -analysis of combined CATIE and EUFEST studies. *Eur Neuropsychopharmacol.* 2015;25(7):1158–1166.

52. Fryar-Williams S, Strobel JE. Biomarkers of a five–domain translational substrate for schizophrenia and schizoaffective psychosis. *Biomark Res.* 2015;3:3.

53. Baglivo V, Cao B, Mwangi B, et al. Hippocampal subfield volumes in patients with first - episode psychosis. *Schizophr Bull.* 2018;44(3):552–559.

54. Keshavan MS, Collin G, Guimond S, et al. Neuroimaging in schizophrenia. *Neuroimaging Clin N Am.* 2019;30(1):73–83.

55. Yuan N, Chen Y, Xia Y, et al. Inflammation–related biomarkers in major psychiatric disorders: a cross–disorder assessment of reproducibility and specificity in 43 meta–analyses. *Transl Psychiatry.* 2019;9(1):233.

56. Waszkiewicz N. Ordering knowledge in the markers of psychiatric/mental disorders. *J Clin Med.* 2022;11(2):284.

57. Gomes FV, Grace AA. Beyond dopamine receptor antagonism: new targets for schizophrenia treatment and prevention. *Int J Mol Sci.* 2021;22(9):4467.

58. Salavati B, Rajji TK, Price R, et al. Imaging-based neurochemistry in schizophrenia: a systematic review and implications for dysfunctional long-term potentiation. *Schizophr Bull.* 2015;41(1):44–56.

59. Pandey GN, Ren X, Rizavi HS, et al. Proinflammatory cytokines and their membrane-bound receptors are altered in lymphocytes of schizophrenia patients. *Schizophr Res.* 2015;164(1-3):193–198.

60. Nielsen PR, Agerbo E, Skogstrand K, et al. Neonatal levels of inflammatory markers and later risk of schizophrenia. *Biol Psychiatry.* 2015;77(6):548–556.

61. Haring L, Koido K, Vasar V, et al. Antipsychotic treatment reduces psychotic symptoms and markers of low-grade inflammation in first-episode psychosis patients. *Schizophr Res.* 2015;169(1-3):22–29.

62. Tourjman V, Kouassi É, Koué MÈ, et al. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. *Schizophr Res.* 2013;151(1–3):43–47.

63. Gomes FV, Grace AA. Beyond dopamine receptor antagonism: new targets for schizophrenia treatment and prevention. *Int J Mol Sci.* 2021;22(9):4467.

64. Kane JM, Agid O, Baldwin ML, et al. Clinical guidance on the identification and management of treatment–resistant schizophrenia. *J Clin Psychiatry.* 2019;80(2):18com12123.

65. Howes OD, McCutcheon R, Agid O, et al. Treatment–resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry*. 2017;174(3):216–229.

66. Miller BJ, Buckley P, Seabolt W, et al. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry.* 2011;70(7):663–671.

67. Chan CC, Dolgopolskaia ES, Goldstein KE, et al. Childhood trauma across the schizophrenia spectrum: a comparison of schizotypal personality disorder and schizophrenia. *Schizophr Bull.* 2024:sbae209.

68. Vita A, De Peri L, Deste G, et al. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry.* 2012;2:e116.

69. Remington G, Foussias G, Agid O, et al. The neurobiology of relapse in schizophrenia. *Schizophr Res.* 2014;152(1):381–389.

70. Lett TA, Voineskos AN, Kennedy JL, et al. Treating working memory deficits in schizophrenia: a review of the neurobiology. *Biol Psychiatry.* 2014;75(5):361–370.

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71. Parker EM, Kindja NL, DeGiosio RA, et al. Impacts of CACNB4 overexpression on dendritic spine density in both sexes and relevance to schizophrenia. *Transl Psychiatry.* 2024;14(1):484.

72. Citak S, Cakici E, Cakici M, et al. Neuropsychological assessment in patients with paranoid and non-paranoid schizophrenia. *Klin Psikofarmakol Bul.* 2013;23(4):294–304.

73. Sabhesan S, Parthasarathy S. Executive functions in schizophrenia. *Indian J Psychiatry.* 2005;47(1):21–26.

74. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple–treatments meta–analysis. *Lancet.* 2013;382(9896):951–962.

75. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol.* 2011;8(2):114–126.

76. Köster LS, Carbon M, Correll CU. Emerging drugs for schizophrenia: an update. *Expert Opin Emerg Drugs.* 2014;19(4):511–531.

77. Kovaleva K, Kachiyeva Z, Abetova A, et al. Genetic variants in antipsychotic metabolism: polymorphism profiles in kazakh cohort with paranoid schizophrenia. *Georgian Med News.* 2024;(355):99–103.

78. Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci*. 2002;25:409–432.

79. Walker E, Kestler L, Bollini A, et al. Schizophrenia: etiology and course. *Annu Rev Psychol.* 2004;55:401–430.

80. Javitt DC. Glutamate as a therapeutic target in psychiatric disorders. *Mol Psychiatry*. 2004;9(11):984–997.

81. Duncan CE, Holdstock J, van der Heaulme T, et al. The influence of NMDA receptor modulation in schizophrenia treatment strategies. *Br J Pharmacol.* 2005;145(8):1043–1052.

82. Goto Y, Grace AA. The dopamine system and the pathophysiology of schizophrenia: a basic science perspective. *Int Rev Neurobiol*. 2007;78:41–68.

83. Fink–Jensen A. Novel pharmacological approaches to the treatment of schizophrenia. *Dan Med Bull.* 2000;47(3):151–167.

84. Emsley R. Drugs in development for the treatment of schizophrenia. *Expert Opin Investig Drugs.* 2009;18(8):1103–1118.

85. Huxley NA, Rendall M, Sederer L. Psychosocial treatments in schizophrenia: a review of the past 20 years. *J Nerv Ment Dis.* 2000;188(4):187–201.

86. Noetzel MJ, Jones CK, Conn PJ. Emerging approaches for treatment of schizophrenia: modulation of glutamatergic signaling. *Discov Med.* 2012;14(78):335–343.

87. Wassef A, Baker J, Kochan LD. GABA and schizophrenia: a review of basic science and clinical studies. *J Clin Psychopharmacol.* 2003;23(6):601–640.

88. Kantrowitz JT, Javitt DC. N–methyl–d–aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? *Brain Res Bull.* 2010;83(3–4):108–121.

Citation: Gosiya, Anjali, Kumar g, et al. Schizophrenia in the modern era: advancing neurobiological understanding and therapeutic innovation. *J Neurol Stroke.* 2025;15(4):85–92. DOI: 10.15406/jnsk.2025.15.00628