**JANICKA, Urszula, BOGDAN, Klaudia, JANKOWSKI, Mikołaj, CIEPLUCH, Natalia, SŁOMIŃSKI, Szymon Stanisław, TOCZEK, Wiktoria Oliwia, OLSZÓWKA, Magdalena, and DZIUGIEŁ, Sonia. Targeting Schizophrenia: A Review of Pharmacological and Psychosocial Innovations. Quality in Sport. 2026;49:67583. eISSN 2450-3118.**
**https://doi.org/10.12775/QS.2026.49.67583**
**https://apcz.umk.pl/QS/article/view/67583**

**The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).**
**Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2025.**

**The authors declare that there is no conflict of interest regarding the publication of this paper.**
**Received: 17.12.2025. Revised: 24.12.2025. Accepted: 05.01.2026. Published: 07.01.2026.**

# Targeting Schizophrenia: A Review of Pharmacological and Psychosocial Innovations

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**ABSTRACT**

**Background.** Paranoid schizophrenia is the most common subtype of schizophrenia, characterized by both positive symptoms, such as hallucinations and delusions, and negative symptoms like reduced motivation and social withdrawal. While pharmacological advances have improved symptom control, challenges remain in treating negative symptoms and ensuring long-term adherence and recovery.

**Aim of the study**. This review analyzes recent literature (2020–2025) on pharmacological and psychosocial treatment strategies for paranoid schizophrenia, with attention to effectiveness, tolerability, and integration.

**Materials and methods.** PubMed and Google Scholar were searched for meta-analyses, RCTs, and guidelines published in the last 5 years using terms like “paranoid schizophrenia”, “antipsychotics”, “long-acting injectables”, “CBT”, “treatment”.

**Current stage of knowledge.** Modern antipsychotics, particularly SGAs and LAIs, reduce relapse risk and enhance adherence. Cariprazine and newer agents like Cobenfy show promise in treating negative and treatment-resistant cases. Integration with psychosocial strategies—especially CBT and family interventions—enhances functional recovery, though results for negative symptoms remain mixed. Novel treatments target glutamatergic and cholinergic systems beyond traditional dopaminergic focus.

**Conclusions.** A multimodal approach is essential. Future treatment should emphasize personalized strategies, early intervention, targeting of non-dopaminergic pathways, and better access to integrated care, particularly for patients with persistent negative or cognitive symptoms.

**Keywords**: schizophrenia, antipsychotics, dopamine, treatment, CBT, cariprazine, symptoms in schizophrenia, dopamine receptors

**Content**



## 1. Introduction

Schizophrenia is a severe mental illness that affects around 1% of the global population and is associated with significant functional impairment [1]. Schizophrenia arises from a combination of genetic vulnerability and environmental influences. Genetically, it is a polygenic disorder, with many common variants contributing small effects to overall risk. Environmental risk factors include childhood trauma, cannabis use, obstetric complications, and growing up in urban settings. Recent findings also emphasize the role of gene–environment interactions and correlations, where genetic predisposition may shape an individual's exposure to certain environments or alter their sensitivity to environmental stressors [9]. According to ICD-10 and DSM-IV criteria, paranoid schizophrenia is the most commonly diagnosed subtype, accounting for approximately 40–50% of cases. Other subtypes such as undifferentiated, disorganized, and catatonic are significantly less frequent. Although DSM-5 and ICD-11 have discontinued the use of subtypes due to concerns about their diagnostic validity and consistency, ICD-10 continues to recognize them in current clinical practice in many regions [2]. Schizophrenia usually emerges during early adulthood and is defined by a combination of positive and negative symptoms. Positive symptoms encompass experiences such as

hallucinations, delusional thinking, and disorganized language or communication. Negative symptoms may include reduced emotional expression (blunted affect), limited speech output (alogia), lack of motivation (avolition), social withdrawal (asociality), and diminished ability to experience pleasure (anhedonia). For a diagnosis to be made, these symptoms must persist for a minimum of six months, with a phase of more intense symptoms lasting at least one month [3]. Cognitive impairment in schizophrenia is generally divided into neurocognitive and social cognitive domains, both of which have a substantial impact on patients' ability to function socially and maintain an adequate quality of life [4]. It substantially impairs social and occupational functioning and carries a high relapse rate, particularly when adherence is inconsistent. Due to its disabling nature, schizophrenia requires prompt initiation of antipsychotic treatment, as early intervention is associated with improved long-term outcomes. Management should be personalized to the patient's clinical profile, with regular assessment of both therapeutic response and potential side effects. [3]. Current pharmacological treatment primarily relies on dopamine- receptor antagonists, which are generally effective for managing positive symptoms but demonstrate limited efficacy in alleviating cognitive and negative symptoms. [7]. Second-generation antipsychotics (SGAs), including agents such as olanzapine, risperidone, aripiprazole, and paliperidone, significantly reduce relapse and hospitalization risk compared to first-generation antipsychotics (FGAs) and no-treatment conditions [5]. Maintenance using long-acting injectable (LAI) formulations has been shown to improve adherence and further reduce relapse rates compared to oral medication [6]. Emerging therapies targeting non-dopaminergic mechanisms are currently under investigation. In addition, integrated care models that combine antipsychotic medication with psychosocial interventions—such as cognitive behavioral therapy and psychoeducation—offer a more comprehensive approach to improving functional outcomes and quality of life. [1]

Cognitive-behavioral therapy for psychosis (CBTp) is widely recommended by clinical guidelines as an adjunct to pharmacotherapy for persistent positive symptoms. However, umbrella reviews indicate that while CBTp may provide small to moderate reduction in delusions, hallucinations, and general psychopathology at the end of treatment, the evidence for sustained effects or relapse prevention is weak or inconsistent. [8]

## 2. Pathophysiology of Schizophrenia

Schizophrenia is marked by a constellation of positive, negative, and cognitive symptoms. A central hypothesis in its pathophysiology involves dysregulated dopamine

transmission within the striatum, which is believed to contribute significantly to the emergence of these symptom domains. [10]

The neurodevelopmental and dopaminergic models represent two of the most widely accepted frameworks for explaining the underlying causes of schizophrenia.[13]

### 2.1 Dopamine role

Dopamine plays a vital role in the central nervous system, where it influences essential functions such as reward processing, motor control, and cognitive activity. Beyond the brain, it also contributes to the regulation of peripheral systems, including blood pressure, kidney function, and gastrointestinal motility. [11] The dopamine hypothesis links the manifestation of positive symptoms to heightened dopaminergic activity in the mesolimbic pathway (also known as reward- pathway) , while reduced dopamine function in the mesocortical pathway is associated with negative and cognitive symptoms.[12]

Multiple lines of evidence—including genetic, postmortem, pharmacological, and neuroimaging studies—indicate that dopaminergic dysregulation is central to the pathophysiology of schizophrenia. All approved antipsychotics exert their effects by antagonizing D2/D3 dopamine receptors. Neuroimaging findings consistently show elevated dopamine synthesis and release capacity in the striatum of individuals with schizophrenia, particularly in areas receiving input from the frontal cortex. This increase correlates with the severity of psychotic symptoms. Similar dopaminergic changes have also been observed in individuals at genetic or clinical high risk for the disorder, especially in those with more prominent prodromal symptoms, although not all high-risk individuals show these alterations—likely due to variability in illness progression.[13] Understanding how dopaminergic dysfunction contributes to the neural circuits involved in psychotic symptoms may offer a more reliable foundation for developing objective markers in both basic neuroscience and clinical research [14]

Negative symptoms of schizophrenia frequently emerge early in the course of the illness and are highly prevalent and clinically significant in most patients. These symptoms are associated with poorer functional outcomes, leading to challenges in employment, household responsibilities, leisure activities, and interpersonal relationships. Despite their impact, current pharmacological treatments show limited effectiveness in addressing this fundamental aspect of the disorder. Negative symptoms are increasingly acknowledged as a fundamental and enduring component of schizophrenia, affecting up to 60% of individuals diagnosed with the disorder. These symptoms—such as blunted affect, avolition, alogia, anhedonia, and social

withdrawal—often appear early in the course of the illness, sometimes even before the onset of positive symptoms. Their early emergence and persistent nature make them particularly detrimental, as they are closely linked to impairments in real-world functioning. [15]

| **Symptom Type** | **Key Symptoms** | **Brief Characteristic** |
|---|---|---|
| Positive | –Hallucinations-especially auditory<br>– Delusions<br>–Disorganized speech/thought | Added experiences not seen in healthy individuals. Linked to dopamine hyperactivity in the mesolimbic pathway. Usually respond well to antipsychotic medications. |
| Negative | – Avolition (lack of motivation)<br>– Anhedonia<br>– Asociality<br>– Flat affect<br>– Alogia (poverty of speech) | Reductions in normal functions. Harder to treat and strongly linked to long-term disability. Often divided into experiential and expressive domains |
| Cognitive | – Impaired attention<br>– Poor memory<br>– Slowed processing<br>– Deficits in social cognition | Present in around 70% of patients, often before psychotic onset. Affect daily functioning and do not respond well to standard treatment. |

Tab.1 Schizophrenia symptoms comparison.

Although the neurodevelopmental and dopamine hypotheses were initially developed independently, recent findings increasingly support their convergence. Advances in neurobiology have clarified how disruptions in synaptic refinement and cortical excitation–inhibition (E/I) balance during development may contribute to schizophrenia. Genetic studies link the disorder to variants affecting glutamatergic and GABAergic signaling, as well as neurodevelopmental pathways. Additionally, in vivo imaging and stem cell research point to reduced synaptic density in individuals with schizophrenia. Stress during critical developmental periods has also been shown to accelerate synaptic pruning. These findings support a model in which dysregulated frontal cortical circuits—particularly those with impaired E/I balance—may drive subcortical dopaminergic abnormalities, contributing to the emergence of psychotic symptoms. [13]

## 3. Pharmacological treatment

### 3.1 Antipsychotics therapy

Currently approved treatments for schizophrenia often show limited efficacy across the full spectrum of symptoms and are frequently accompanied by adverse effects such as extrapyramidal symptoms, sedation, weight gain, endocrine disturbances, and metabolic abnormalities. [16] Pharmacological management of schizophrenia is primarily based on antipsychotic therapy. [17] In cases where patients exhibit suboptimal therapeutic response, clinicians may adopt alternative strategies, including increasing the dosage, switching to a different antipsychotic, or augmenting treatment with a second psychotropic agent—such as antidepressants, mood stabilizers, anxiolytics, stimulants, or even another antipsychotic. [16]

Antipsychotic medications have been in clinical use since the mid-1950s, with the earlier compounds classified as typical or first-generation antipsychotics (for example: chlorpromazine, haloperidol). In the 1990s, a new class of antipsychotics, termed second-generation or atypical antipsychotics (SGAs), was introduced. Clozapine was the first SGA developed, followed by others including risperidone, olanzapine, ziprasidone, quetiapine, amisulpride, sertindole, lurasidone, paliperidone, iloperidone, asenapine, aripiprazole, and more recently, brexpiprazole, cariprazine, and zotepine (the latter not approved in the USA). Several SGAs, such as paliperidone, aripiprazole, olanzapine, and risperidone, are also available in long-acting injectable (LAI) formulations. Current clinical guidelines recommend SGAs as the preferred first-line treatment both for initial psychotic episodes and during exacerbations. This preference is supported by evidence indicating a reduced incidence of adverse effects, which contributes to improved treatment adherence and
lower rates of therapy discontinuation. Nonetheless, SGAs are associated with side effects including weight gain and metabolic disturbances, which may elevate the risk of diabetes mellitus and hypercholesterolemia. [23]

Although the classical dopamine hypothesis has long provided a framework for understanding psychosis in schizophrenia, it has since been expanded to include multiple neurotransmitter systems. Emerging research highlights the involvement of glutamatergic, GABAergic, serotonergic, and cholinergic dysfunctions in the disorder's pathophysiology. While all approved antipsychotic medications primarily target dopamine D2 receptors—either through antagonism or partial agonism—many also interact with other receptor systems, which influences both their therapeutic effects and side-effect profiles. However, current evidence

does not strongly support the combined use of antipsychotics with additional psychotropic agents to enhance symptom control. This underscores the urgent need for innovative pharmacological strategies that move beyond the limitations of dopamine-centered treatments. [16] Although a range of psychotropic medications is available, achieving optimal clinical outcomes remains a significant challenge. Emerging evidence, consistent with clinical observations, indicates that newer atypical antipsychotics may offer greater efficacy in addressing the negative and cognitive symptoms of schizophrenia. [18] Extrapyramidal symptoms (EPS) from antipsychotics primarily result from dopamine D2 receptor blockade in the nigrostriatal pathway. All antipsychotics bind to D2 receptors, but vary in affinity and receptor profiles. D2 occupancy around 80% is typically sufficient for clinical efficacy, while higher levels increase EPS risk. Other receptors—such as 5-HT1A, 5-HT2A, 5-HT2C, and M1—also contribute to side effect profiles. Second-generation antipsychotics generally carry a lower risk of EPS due to their broader receptor activity. [20] They are typically recommended as first-line therapy due to their lower risk of side effects compared to first-generation agents. However, their use is associated with an elevated risk of cardiovascular complications. Therefore, individuals receiving these medications should undergo regular metabolic monitoring—at least annually—and be provided with lifestyle counseling aimed at preventing weight gain and supporting smoking cessation [3].

### 3.2 Long-acting injectable antipsychotics

Long-acting injectable (LAI) antipsychotics serve as an alternative to oral antipsychotic (OAP) formulations and may offer particular benefits for individuals in the early phases of schizophrenia, including improved adherence and relapse prevention. [19] LAI formulations of second-generation antipsychotics (SGAs) are an important component of treatment for individuals with schizophrenia-spectrum disorders, offering improved medication adherence and a reduced risk of relapse. [21] They may also provide therapeutic advantages for patients with schizophrenia during acute phases of illness.[7]

LAI antipsychotics offer several advantages over oral formulations, particularly in addressing issues related to medication adherence. These benefits include improved monitoring of adherence through missed or delayed injection appointments, reduced pill burden, and mitigation of the clinical consequences associated with treatment interruptions, such as relapse, hospitalization, and increased mortality. Additionally, the pharmacokinetic properties of LAI antipsychotics influence their absorption rate, the frequency and severity of adverse effects, and

the potential for drug–drug interactions, all of which are important considerations in optimizing individualized treatment plans [27].

### 3.3 Clozapine

The first second generation antipsychotic drug- clozapin, is the only approved treatment for treatment-resistant schizophrenia (TRS), yet it is effective in only 30–60% of patients. Its exact mechanism remains unclear, though it may modulate glutamatergic activity via astrocytes in responders. Despite its efficacy, clozapine carries serious risks—including agranulocytosis and myocarditis—necessitating regular blood monitoring during treatment. [22]

### 3.4 Cariprazine

Most second-generation antipsychotics, which primarily exert their effects through dopamine D2 receptor antagonism, are effective in alleviating the positive symptoms of schizophrenia. However, managing negative symptoms remains more challenging, and to date, cariprazine has been recognized for its therapeutic potential in targeting these negative symptoms. Cariprazine's unique pharmacological profile is defined by its partial agonist activity at dopamine D2 and D3 receptors, exhibiting a higher affinity for the D3 subtype, along with agonism at serotonin 5-HT1A receptors. This distinct receptor interaction pattern differentiates cariprazine from other antipsychotics and is believed to contribute to its efficacy in improving negative symptoms of schizophrenia as well as its antidepressant effects. [24]

### 3.5 New Directions in Antipsychotic Therapy

While current antipsychotic medications for schizophrenia are primarily centered around dopamine D2 receptor antagonism or partial agonism, they often engage with a range of other neurotransmitter receptors, influencing both efficacy and tolerability. These treatments are largely effective in alleviating positive symptoms, though residual symptoms may persist in some patients. Despite these therapeutic effects, a substantial proportion of individuals struggle with treatment adherence, often due to burdensome side effects. Increasingly, schizophrenia is understood as a disorder involving complex neurochemical dysregulation beyond dopamine, which has led to growing interest in adjunctive therapies that could enhance symptom control by targeting additional pathways. [16]

Recently, Cobenfy—a novel antipsychotic composed of xanomeline and trospium chloride—received approval from the United States Food and Drug Administration (FDA), representing a significant advancement in the pharmacological management of schizophrenia. As a first-in-

class agent, Cobenfy exerts its therapeutic effects through cholinergic receptor activation, offering an alternative to traditional dopamine antagonists. This mechanism enables the reduction of psychotic symptoms while potentially limiting adverse effects typically associated with dopaminergic blockade. Data from pivotal trials, including the EMERGENT-2 and EMERGENT-3 studies, demonstrated that Cobenfy significantly improved both positive and negative symptoms of schizophrenia, as evidenced by greater reductions in Positive and Negative Syndrome Scale (PANSS) total scores compared to placebo. The drug also displayed a favorable safety profile, with lower incidences of weight gain and extrapyramidal symptoms. Nonetheless, side effects such as nausea, dyspepsia, and constipation were reported, and caution is advised in patients with hepatic or renal impairment. Overall, Cobenfy represents a promising therapeutic option, particularly for individuals with treatment-resistant schizophrenia or those who are unable to tolerate conventional antipsychotics. Ongoing research is necessary to evaluate its long-term efficacy and safety, especially in vulnerable patient populations.[25]

Effective management of schizophrenia necessitates a combination of antipsychotic pharmacotherapy and psychosocial interventions. [26]

## 4. Psychosocial and integrated treatment.

Clinical practice supports the integration of non-biological therapies alongside pharmacological treatment in patients with schizophrenia. Cognitive-behavioral therapy (CBT) was the first psychotherapeutic approach to gain widespread approval and receive recommendations from both the American Psychiatric Association (APA) and the National Institute for Health and Care Excellence (NICE). However, most studies to date have focused on addressing positive symptoms and preventing relapse, while considerably less attention has been directed toward the treatment of negative symptoms. [28]

Based on the systematic review and network meta-analysis by Bighelli et al. (2021), family interventions, family psychoeducation, and cognitive behavioral therapy demonstrated robust efficacy in reducing relapse risk and should be prioritized as first-line psychosocial interventions in the long-term management of schizophrenia.

### 4.1 Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) is a psychological intervention aimed at modifying the interpretation and evaluation of experiences by helping individuals identify patterns of thinking and emotional responses that contribute to distress. Specialized CBT models for psychosis (CBTp) have been developed for various mental health disorders,

including schizophrenia, and are often considered a valuable adjunct to pharmacological treatment. Although CBTp was originally designed as an individual therapy, its high cost has prompted interest in more cost-effective group-based formats. Group CBTp involves structured sessions focused on managing psychotic symptoms through collaborative strategies such as coping with hallucinations, evaluating delusional beliefs, and enhancing problem-solving and social skills. Despite its theoretical advantages, the current evidence base for the efficacy of group CBTp remains inconclusive and warrants further investigation.[29]

Treating negative symptoms in schizophrenia remains a clinical challenge and requires an individualized, multimodal approach that integrates both pharmacological and non-pharmacological strategies. It is essential to first differentiate between primary negative symptoms and secondary ones, which may result from factors such as depression, sedation, or adverse effects of antipsychotic medication. Many antipsychotics, especially those with strong D2 antagonism or additional antihistaminergic and anticholinergic properties, may exacerbate negative and cognitive symptoms through their sedative effects. In this context, antipsychotics with partial dopamine agonism—such as aripiprazole, brexpiprazole, and particularly cariprazine—are of interest. Cariprazine, due to its high affinity for D3 receptors located in brain regions involved in motivation and emotional regulation, has shown antidepressant and pro-cognitive properties. Notably, it is the only second-generation antipsychotic with clinical trial data demonstrating statistically significant superiority over risperidone in improving predominant negative symptoms in patients with stable schizophrenia. [28]

Historically, psychosocial treatment was viewed with skepticism, based on the belief that the cognitive disorganization associated with psychosis rendered patients unsuitable for psychotherapy. However, this perspective has evolved considerably, giving rise to a broad spectrum of rehabilitation-focused interventions. Today, psychosocial strategies are acknowledged as a critical element of schizophrenia management, particularly when pharmacological treatments are insufficient in addressing negative symptoms. Although often less overt than positive symptoms, negative symptoms—such as social withdrawal, reduced motivation, and affective flattening—are the strongest predictors of long-term disability and functional impairment. While cognitive-behavioral therapy (CBT) has shown consistent benefits in reducing positive symptoms, its efficacy in treating negative symptoms remains variable. Specifically, symptoms related to mood and social motivation continue to pose therapeutic challenges. [30]

Severe mental illnesses are often associated with impairments in daily functioning and social skills, significantly limiting individuals' ability to participate in community life.

Therefore, psychiatric rehabilitation plays a crucial role in treatment by supporting patients in shaping their lives and engaging in various areas of social activity, including self-care, family life, leisure, employment, and interpersonal relationships. It should be an integral component of the overall treatment plan for individuals with severe mental disorders, tailored to their individual needs and preferences. [28]

In summary, while the efficacy of CBT on negative symptoms of schizophrenia remains variable, current evidence suggests it offers meaningful benefits in mitigating these symptoms. Given that negative symptoms significantly impair social functioning and are closely linked to long-term disability, even modest improvements are clinically important. Enhancing negative symptom domains such as motivation, emotional expression, and social engagement may contribute substantially to functional recovery, better rehabilitation outcomes, and potentially slow the progression of the disorder. [30]

## 5. Conclusions

Despite advancements in pharmacotherapy, schizophrenia treatment continues to face challenges, particularly in managing negative and cognitive symptoms. SGAs and LAIs have improved relapse prevention and adherence, and newer agents like cariprazine and Cobenfy offer promise in addressing treatment-resistant and negative symptom domains. Psychosocial interventions, especially when integrated with pharmacotherapy, are essential for functional recovery. Future directions should focus on personalizing treatment, targeting non-dopaminergic pathways, and expanding access to evidence-based psychosocial care.

## Disclosure

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**Funding Statement:** The article received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

**Acknowledgements:** None.

**Conflict of Interest Statement:** Authors declare no conflict of interest.

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