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# DRUG THERAPY IN SCHIZOPHRENIA: CHALLENGES AND RECENT ADVANCES

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## ABSTRACT

Schizophrenia is a chronic and debilitating mental disorder that profoundly impacts patients' cognition, social functioning, and quality of life. This study conducted a systematic literature review on the challenges and advances in the drug treatment of schizophrenia, focusing on cognitive deficits and emerging therapies. Second-generation antipsychotics demonstrated modest benefits on cognition, particularly in areas such as working memory, attention, and executive functions, while first-generation antipsychotics showed significant limitations. New approaches, such as TAAR1 receptor agonists, emerge as promising alternatives, offering potential improvements in cognitive deficits and the tolerability of treatments. Despite the advances, cognitive deficits remain a critical challenge, requiring integrated therapeutic strategies that combine innovative drugs, cognitive rehabilitation and management of associated comorbidities. This study highlights the need for continued research to optimize the management of schizophrenia and promote more effective functional recovery.

**Keywords:** Schizophrenia. Drug therapy. Cognitive Impairment.

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## INTRODUCTION

Schizophrenia is a severe and chronic mental disorder, characterized by cognitive, emotional, and behavioral dysfunctions, affecting a person's ability to perceive reality, make decisions, and maintain proper functioning in daily life. Ranked among the top 25 causes of disability in the world, schizophrenia presents itself as one of the greatest public health challenges, with a significant global prevalence and substantial impact on the quality of life of affected individuals. (CORRELL, 2020) It is estimated that more than 15% of patients do not achieve a full functional recovery, with many experiencing frequent relapses and an ongoing impairment of social and occupational functioning. (VITA et al., 2022) Given this reality, the effective treatment of schizophrenia is a primary objective in psychiatric medicine, with an emphasis on the control of psychotic symptoms and the improvement of cognitive function, which is closely associated with long-term prognosis.

Historically, schizophrenia was first characterized by Emil Kraepelin in the 1890s, when he termed it "dementia praecox," a condition that primarily affected young individuals, contrasting with the senile dementia seen in older patients. (JAVITT, 2023) Kraepelin recognized the impact of the disease on cognition, describing deficits in areas such as memory, attention, motor function and perception, aspects that are still central to understanding the disorder. Although its approach has been replaced by other perspectives throughout the twentieth century, the conception of schizophrenia as a disorder with a significant cognitive component has been taken up again in recent decades, driven by the growing understanding of underlying brain dysfunctions, such as glutamatergic and dopaminergic theories. These more modern models complement previous studies and offer a more holistic view of the disease, encompassing the complex interaction between neurotransmitters and impaired cognitive functions. (JAVITT, 2023)

In recent years, the focus on the treatment of cognitive impairment in schizophrenia has gained relevance, especially due to its relationship to long-term disability and the significant impact on patients' daily activities. Antipsychotic treatment has been the cornerstone in the management of schizophrenia, with dopamine D2 receptor antagonist antipsychotic medications being the most widely used. These drugs are fundamental in the stabilization of psychotic symptoms, although their contributions to the treatment of cognitive dysfunction remain limited and with modest results. (MCCUTCHEON; KEEFE; MCGUIRE, 2023) In addition, new treatments have been explored with the aim of improving cognitive function and reducing relapses, including second-generation antipsychotics, which have shown modest benefits in improving cognitive performance, especially in the areas of

attention, working memory, and executive functions. (VITA et al., 2022) However, despite the advances, the cognitive efficacy of treatments remains a field of intense research.

This article aims to review recent therapeutic approaches and advances in the treatment of schizophrenia, with a particular focus on drug therapy, including second-generation antipsychotics and new emerging molecules. In addition, the challenges related to cognition in schizophrenia and the strategies that are being developed to improve the treatment of cognitive deficits, one of the main areas that still needs improvement in therapeutic approaches, will be discussed. A deeper understanding of these mechanisms and the adaptation of therapies to cognitive aspects may represent an important advance in the global management of schizophrenia and in the promotion of functional recovery of patients.

## METHODOLOGY

This paper is a systematic literature review, with the objective of synthesizing the most recent information on drug therapy in schizophrenia, focusing on the challenges and advances in treatments. The review covered studies published in the last five years, based on well-defined inclusion and exclusion criteria. The selection of articles was carried out from the PubMed platform, one of the most renowned scientific databases in the health area.

The search strategy was conducted in the PubMed database, using the descriptors "schizophrenia" and "treatment". These descriptors were combined to ensure that the selected articles specifically addressed the latest and most relevant pharmacological treatments and drug therapies for schizophrenia. The search was adjusted to include articles published between January 2019 and November 2024, in order to ensure up-to-date and relevance

## DISCUSSION

Schizophrenia is one of the most complex psychiatric conditions, characterized by a range of psychotic and cognitive symptoms that directly impact the individual's functioning. Drug treatment remains the cornerstone of disease management, especially as it relates to the management of psychotic symptoms and the prevention of relapse. However, the management of cognitive deficits, which are common and often debilitating, still represents a major therapeutic challenge. Although antipsychotics are effective in reducing psychotic symptoms, their effects on cognition are limited and vary according to the class of medication used.

## FIRST-GENERATION ANTIPSYCHOTICS: LIMITED COGNITIVE EFFECTS

First-generation antipsychotics, such as haloperidol and clozapine, have been widely used in the treatment of schizophrenia, especially in treatment-resistant cases. However, the literature indicates that, despite their efficacy in controlling psychotic symptoms, these drugs have relatively modest or even harmful cognitive effects. Clozapine, for example, is an effective drug in controlling refractory psychotic symptoms, but its negative impact on cognition, particularly in terms of memory and executive functions, limits its use in patients who have significant cognitive impairment. This effect is shared with haloperidol, which in many cases is no more effective than placebo for improving overall cognitive function. (VITA et al., 2022) This evidence leads to the need to reevaluate the use of these drugs, especially in patients who have persistent cognitive symptoms.

## SECOND-GENERATION ANTIPSYCHOTICS: MODEST BUT CONSISTENT COGNITIVE IMPROVEMENT

Second-generation antipsychotics, such as amisulpride, quetiapine, risperidone, and lurasidone, have emerged as alternatives for the treatment of schizophrenia, not only because of their more favorable effects on positive and negative symptoms, but also because of their potential beneficial effects on cognitive deficits. Evidence suggests that these medications offer small but consistent improvements in the cognitive aspects of schizophrenia, including working memory, attention, executive functions, and social cognition. (VITA et al., 2022) Analysis of studies involving these drugs has shown that, although there is no substantial difference between the various molecules of the class, they perform better than first-generation antipsychotics.

## COMPARISON BETWEEN CLASSES OF SECOND-GENERATION ANTIPSYCHOTICS

Within the class of second-generation antipsychotics, drugs such as amisulpride and quetiapine stand out for their effectiveness in improving specific cognitive aspects. However, the evidence does not suggest a clear superiority of one antipsychotic over the other, and the observed effects are modest compared to the clinical effects. Meta-analyses conducted with these drugs indicate that the effects on cognitive function are beneficial, but not so significant as to drastically alter the cognitive trajectory of patients. (VITA et al., 2022)

In addition, recent studies on the effects of different classes of second-generation antipsychotics, such as the molecules of the -pines and -dones groups, have shown that both classes are equally effective in cognitive impact, suggesting that the choice of drug should be guided not only by clinical efficacy, but also by the profile of side effects and

patient acceptance. This implies that in the treatment of schizophrenia, clinicians should prioritize factors such as safety, tolerability, and convenience of the therapeutic regimen. (VITA et al., 2022)

### LONG-ACTING FORMULATIONS: BENEFITS IN ADHESION, BUT WITHOUT SIGNIFICANT COGNITIVE IMPACT

Long-acting formulations (injectables) have gained prominence for their ability to improve treatment adherence, a crucial factor in the management of schizophrenia, since many patients have difficulties with adherence to oral treatments, which can lead to relapses. While these formulations have been shown to be effective in reducing hospitalizations and relapses, research has not indicated additional cognitive benefits compared to oral formulations. This suggests that while long-acting formulations may improve symptom control and treatment adherence, they do not provide a superior cognitive advantage over traditional formulations such as daily tablets. (VITA et al., 2022)

### NEW EMERGING THERAPIES: TAAR1 RECEPTOR AGONISM AND OTHER APPROACHES

One of the most recent approaches in the treatment of schizophrenia involves modulating alternative neurotransmitter systems. Research on TAAR1 receptor agonists (trace amine associated receptor 1) has shown a promising impact, with effects of reducing psychotic symptoms and possible cognitive benefits. TAAR1 agonists have the potential to act differently from traditional antipsychotics, as they do not involve D2 receptor antagonism, and may improve cognitive function by affecting prefrontal neuronal activity. In addition, these drugs do not cause the extrapyramidal side effects common to traditional antipsychotics, which makes them a promising alternative in the treatment of schizophrenia. (MCCUTCHEON; KEEFE; MCGUIRE, 2023)

Although the research is still in its early stages, preliminary results suggest that these agonists may offer significant cognitive benefits, particularly by improving excitatory/inhibitory balance in the brain. This area of research, still under development, may be one of the keys to more effective treatments for cognitive deficits in schizophrenia.

## RESULTS

Analysis of the available data on the effects of antipsychotics on cognition revealed a number of important findings, with direct implications for clinical practice. The following are

the main results of research carried out on currently available drugs and emerging therapies.

## COGNITIVE EFFECTS OF SECOND-GENERATION ANTIPSYCHOTICS

### Improvements in Common Cognitive Functions

Empirical evidence of the effects of second-generation antipsychotics on cognition reveals modest but consistent improvements in areas such as working memory, attention, and executive functions. Drugs such as amisulpride, quetiapine, lurasidone, risperidone, and olanzapine were shown to be more effective compared to first-generation drugs, with small differences between them, suggesting that drug choice may be based on other factors, such as tolerability. (VITA et al., 2022)

### Clozapine and haloperidol: lower cognitive performance

The cognitive performance of patients treated with clozapine and haloperidol was consistently inferior to placebo in several areas of cognitive assessment. These drugs, although effective for the control of psychotic symptoms in treatment-resistant patients, have shown detrimental effects on cognition, especially on performance in memory tasks and executive functions. This reinforces the need to carefully evaluate the use of these drugs in patients with significant cognitive deficits. (VITA et al., 2022)

## COMPARISON OF LONG-ACTING FORMULATIONS

### Long-acting formulations: no significant cognitive differences

Although long-acting antipsychotic formulations (such as monthly injections) have shown a positive impact in terms of treatment adherence and relapse reduction, studies have not shown an additional cognitive benefit compared to oral formulations. This suggests that, with regard to cognitive function, there are no significant advantages in adopting injectable formulations. (VITA et al., 2022)

### TAAR1 Agonism: Promising Effects on Cognition

Research on TAAR1 receptor agonists, still in its preliminary phase, indicated that these drugs can improve cognitive function, in addition to reducing psychotic symptoms. This different mechanism of action, without the typical extrapyramidal effects, represents a possible significant advance in the treatment of schizophrenia, especially in patients with cognitive deficits. (MCCUTCHEON; KEEFE; MCGUIRE, 2023)

## CONCLUSION

Schizophrenia is a complex and debilitating disorder with a substantial impact on the lives of affected individuals. Its chronic nature and challenges in managing the disease, mainly related to cognition, reveal the urgent need for more effective therapeutic strategies. Drug therapy, although fundamental in the control of psychotic symptoms, still has limitations in relation to the improvement of cognitive deficits, which are central to the functional incapacity of patients. Antipsychotic treatment remains the mainstay for the management of schizophrenia, with second-generation antipsychotics standing out, which have demonstrated modest benefits in improving cognitive performance in specific areas such as attention, working memory, and executive functions.

Recent research on new drugs, such as TAAR1 receptor agonists and the exploration of second-generation antipsychotics, opens up promising possibilities for the treatment of treatment-resistant schizophrenia (ERT) and its cognitive deficits. However, the effectiveness of these treatments on cognitive functions still needs to be better understood, as many of the existing studies present preliminary results and need more research to confirm the observed benefits. In addition, the impact of comorbidities associated with schizophrenia, such as cardiovascular disease and sleep disorders, should also be addressed more assertively, since the treatment of these conditions can minimize cognitive decline and improve the quality of life of patients.

Therefore, despite substantial advances in the treatment of schizophrenia, the search for more effective therapies that can improve both psychotic symptoms and cognitive deficits remains a challenge. The integration of pharmacological and non-pharmacological approaches, as well as the enhancement of cognitive rehabilitation strategies, can be key to achieving a more functional and lasting recovery for patients with schizophrenia. An evolution in the understanding of the brain mechanisms underlying the disease, combined with the development of new therapies, is essential to improve the prognosis of patients and reduce the overall burden of this condition.

## REFERENCES


1. Correll, C. U. (2020). Current treatment options and emerging agents for schizophrenia. The Journal of Clinical Psychiatry, 81(3), 14-23.

2. Javitt, D. C. (2023). Cognitive impairment associated with schizophrenia: From pathophysiology to treatment. Annual Review of Pharmacology and Toxicology, 63(1), 119-141. https://doi.org/10.1146/annurev-pharmtox-012123-120158

3. McCutcheon, R. A., Keefe, R. S. E., & McGuire, P. K. (2023). Cognitive impairment in schizophrenia: Aetiology, pathophysiology, and treatment. Molecular Psychiatry, 28(5), 1902–1918. https://doi.org/10.1038/s41380-023-01710-4

4. Vita, A., et al. (2022). European Psychiatric Association guidance on treatment of cognitive impairment in schizophrenia. European Psychiatry, 65(1), e57. https://doi.org/10.1192/j.eurpsy.2022.70