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Review Article

POTENTIAL OF ANTI-INFLAMMATORY THERAPY IN SCHIZOPHRENIA: CURRENT APPROACHES AND PROSPECTS: LITERATURE REVIEW

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ABSTRACT

The purpose of this study is to determine the effectiveness of modern anti-inflammatory treatments for schizophrenia and identify the most promising therapeutic strategies. The data on inflammatory processes are systematised based on the analysis of genetic, immunological, and neuroimaging studies, a comparative analysis of anti-inflammatory drugs is performed, and criteria for their effectiveness in various clinical manifestations of the disease are determined. The systematisation of scientific data indicates the existence of a relationship between inflammatory markers, the severity of clinical manifestations of schizophrenia, and resistance to antipsychotics. An analysis of the literature allowed us to identify the main biomarkers of neuroinflammation, which are potential predictors of the effectiveness of antipsychotic therapy. Published studies indicate potential benefits of adjunctive anti-inflammatory therapy in certain patient subgroups; however, the strength of the available evidence varies considerably, and high-quality randomized trials confirming these findings are currently lacking. The study suggests the need to integrate anti-inflammatory approaches into standard treatment protocols for schizophrenia, especially for patients with high levels of inflammatory markers, and opens up prospects for the development of personalised therapeutic strategies based on the individual inflammatory profile of the patient.

Keywords: Neuroinflammation, Cytokines, Immune processes, Interleukins, Cognitive impairments, Microglial activation, Neurotransmitters

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INTRODUCTION

Schizophrenia is a severe mental disorder that affects approximately 1% of the world's population. The main problem is the lack of effectiveness of existing treatment for schizophrenia and a poor understanding of how inflammatory processes affect the development of the disease. Scientific data from the last 5 years demonstrate an increased level of inflammatory substances in the blood and cerebrospinal fluid of patients with schizophrenia and indicate a link between autoimmune diseases and an increased risk of developing psychotic disorders. Existing therapeutic strategies do not sufficiently consider the inflammatory component of the disease, which is confirmed by a series of fundamental studies presented below.

From 2014 to 2024, neuroimmunology and brain inflammation breakthroughs changed our understanding of schizophrenia development. This has changed illness treatment strategies. Fond *et al.* [1] presented the first detailed analysis of the link between inflammatory markers and schizophrenia symptoms, opening fresh insights into this condition. Mongan *et al.* [2] confirmed the role of neuroinflammation in schizophrenia and revealed complex immune-neurotransmitter relationships in the brain, which advanced this field. The research showed that inflammatory processes are not only a side effect of the disease but a major cause of it, opening up new therapeutic avenues. These findings have greatly advanced schizophrenia research and led to new central nervous system inflammation suppression therapy.

The effectiveness of anti-inflammatory medications in treating schizophrenia, including standard and pleiotropic treatments, is a priority. Jeppesen *et al.* [3] conducted a meta-analysis of clinical trials of several anti-inflammatory medicines, showing their potential to reduce both positive and negative illness symptoms. These medications work best in the early stages of the disease, when inflammatory processes are most active, according to research.

Recent research shows significant progress in understanding schizophrenia's genetic inflammation. Bishop *et al.* [4] examined the connection between inflammation-associated genetic polymorphisms and schizophrenia clinical subgroups, suggesting a novel categorisation of patients to improve anti-inflammatory medication. Chen *et al.* [5] found a link between inflammatory imbalance and lateral ventricle enlargement in therapeutically resistant schizophrenia patients, highlighting the importance of inflammation in the disease's pathogenesis.

Patel *et al.* [6] studied the anti-inflammatory qualities of established psychiatric medications, suggesting new mechanisms of action through inflammatory process modulation. Patlola *et al.* [7] meta-analysed second-generation antipsychotics' anti-inflammatory effects to better understand their processes. De Simone *et al.* [8] conducted an integrative analysis of synaptic dysfunction, oxidative stress, and inflammation in schizophrenia, which shed light on the disease's pathophysiological underpinnings and revealed treatment targets. This research provided the theoretical framework for new therapy techniques that account for patients' unique inflammatory and genetic profiles.

An integrated approach to anti-inflammatory therapy of schizophrenia is shown by Mills [9], who studied the life characteristics of people with mental disorders, including schizophrenia patients, receiving various therapies, including anti-inflammatories. The researcher showed that this strategy may work, especially in patients with high inflammatory markers. In support of this idea, Panizzutti *et al.* [10] did a meta-analysis of minocycline's anti-inflammatory and neuroprotective characteristics and found that it is effective in treating schizophrenia. McIntyre *et al.* [11] investigated the role of inflammatory processes in the pathogenesis of bipolar disorder and found common mechanisms with schizophrenia, which opens the door to unified therapeutic approaches.

Limongi *et al.* [12] examined the role of glutamate and functional connectivity abnormalities in schizophrenia's network of importance detection, offering a novel neurobiological perspective. The scientists showed that glutamatergic transmission problems cause brain network malfunction, which may explain various illness symptoms. Alonso-Sánchez *et al.* [13] used computational linguistics and effective connectivity analysis to study language network self-inhibition and semantic similarity in first-time schizophrenia patients. Their report discovered language network dysfunction patterns linked to brain inflammation. Crellin *et al.* [14] examined schizophrenia and other psychotic patients' views on reducing or stopping antipsychotics, which helped them comprehend patient attitudes towards therapy. Their study found patient interest in alternative treatments, including anti-inflammatory therapy, highlighting the need for innovative therapies.

Dickson *et al.* [15] did a systematic meta-analysis of academic performance in schizophrenia and found significant cognitive impairments that may be targets for anti-inflammatory therapy due to neuroinflammation. Fond *et al.* [16] reviewed amino acids, hormone medicines, and anti-inflammatory medications to assess multimodal schizophrenia treatment possibilities. The reviewed studies have provided the scientific and practical basis for tailored anti-inflammatory medication, taking into account patient immunological status, genetic variables, and illness symptoms.

The purpose of this study was to determine the effectiveness of modern anti-inflammatory treatments for schizophrenia and identify the most promising therapeutic strategies. Study objectives: the systematisation of the available data on the role of inflammatory processes in the pathogenesis of schizophrenia is conducted; the effectiveness of various anti-inflammatory agents in the treatment of schizophrenia is analysed; promising directions for the development of anti-inflammatory therapy in schizophrenia are identified.

Literature search and selection strategy

The theoretical and methodological basis of the study was the scientific works of the authors in the field of psychiatry, neurobiology and clinical pharmacology, published in the period from 2020 to 2024. The study analysed data from systematic reviews, meta-analyses, and randomised clinical trials investigating the role of inflammatory processes in schizophrenia and the effectiveness of anti-inflammatory therapy. The study is based on publications indexed in the international databases PubMed, Web of Science, and Scopus. When selecting sources, the following criteria were accounted for: relevance to the research topic, methodological validity, statistical significance of the results obtained and their reproducibility in independent studies.

The materials included the results of 52 scientific papers, of which 15 were systematic reviews and meta-analyses, 22 were original studies involving patients with schizophrenia, and 5 were theoretical reviews of recent advances in neuroinflammation in psychiatric disorders. In the analysis of clinical trials, data on more than 2,900 patients with various forms of schizophrenia were considered, including the results of evaluating the effectiveness of anti-inflammatory therapy on the Positive and Negative Syndrome Scale (PANSS). The study uses official statistics from the World Health Organisation on the prevalence of schizophrenia and modern approaches to its treatment and materials from clinical guidelines for the diagnosis and treatment of schizophrenia from leading international psychiatric associations. To ensure the reliability and transparency of a systematic literature review, it is important to clearly describe the search databases used, their features, and their role in finding relevant sources. In this study, three main databases were selected: PubMed, Web of Science, and Scopus. The search used key terms that combined the themes of schizophrenia and inflammation: “schizophrenia AND inflammation”, “schizophrenia AND anti-inflammatory agent”, “adjunctive COX-2 inhibitor”, “minocycline study in schizophrenia”, and “IL-6 schizophrenia”.

Using the combined search terms, we found studies that directly address the relationship between neuroimmune mechanisms and the clinical manifestations of schizophrenia, as well as evaluating the effectiveness of additional anti-inflammatory therapeutic strategies. The time period covered included the period from January 2020 to June 2024, which allowed us to collect relevant and up-to-date data on clinical and experimental studies in this area. Inclusion criteria included English-language human clinical trials, randomised controlled trials, systematic reviews, and meta-analyses. Studies conducted only in animals were excluded if their results did not have mechanistic relevance to humans, as well as articles that were not relevant to the topic of inflammation in schizophrenia or were not peer-reviewed. This structured search approach ensured a high level of transparency, systematicity, and robustness of the review, reducing the risk of missing relevant studies and increasing the quality of the included sources (table 1).

Table 1: PRISMA flow of included studies

Stage	Description	Number of studies
Identification	Search in databases PubMed, Web of Science, Scopus using keywords: "schizophrenia AND inflammation", "schizophrenia AND anti-inflammatory agent", "adjunct COX-2 inhibitor", "minocycline in schizophrenia", "IL-6 schizophrenia"	120
Initial screening	Removal of duplicates, title and abstract screening	73
Full-text assessment	Full texts assessed according to inclusion/exclusion criteria (English-language clinical studies, RCTs, meta-analyses, systematic reviews; exclusion of animal-only studies unless mechanistically necessary)	50
Final inclusion	Studies meeting all criteria and included in the review	52

Source: compiled by the author based on his own research.

Synthesise and evaluate published evidence on the effectiveness of identified data on the role of inflammatory processes in the pathogenesis of schizophrenia by analysing the results of genetic, immunological, and neuroimaging studies. Key inflammatory markers and their relationship with the clinical manifestations of the disease and the effectiveness of therapy have been identified. The features of gene expression related to the regulation of immune processes were examined based on the results of genome-wide association studies that identified 39 candidate genes outside the region of the main histocompatibility complex. The levels of inflammatory markers at different stages of the disease were compared using data on the concentrations of interleukins (IL-6, IL-1b), tumour necrosis factor alpha (TNF-alpha), and C-reactive protein (CRP) in the blood and cerebrospinal fluid of patients. The results of neuroimaging studies have been analysed, which have shown a correlation between the levels of inflammatory markers and structural changes in the grey and white matter of the brain. The data on microglial activation in various regions of the brain and its relationship with the clinical manifestations of the disease are considered.

The results of the use of selective cyclooxygenase (COX) inhibitors (celecoxib) and drugs with pleiotropic effects (minocycline, N-acetylcysteine), as well as the anti-inflammatory properties of second-generation antipsychotic drugs (clozapine, olanzapine, and risperidone), were analysed. Data on the effectiveness of combination therapy, including anti-inflammatory drugs and traditional antipsychotics, were reviewed, with an assessment of the effect on positive and negative symptoms according to PANSS. The data on the effect of lifestyle modification on inflammatory processes in schizophrenia, including the effects of dietary interventions and physical activity on the levels of pro-inflammatory cytokines, were examined.

During the final stage of the study, promising directions for the development of anti-inflammatory therapy for schizophrenia were identified based on literature review. Data on new therapeutic targets, including the Janus kinase/Signal Transducer and Activator of Transcription (JAK-STAT) system and NLR family pyrin domain containing 3(NLRP3) inflammasome, were analysed based on the materials of clinical trials in 2022-2024. The information on predictors of the effectiveness of anti-inflammatory therapy and criteria for stratification of patients based on their individual inflammatory profile was systematised. Approaches to monitoring the effectiveness of anti-inflammatory therapy were investigated, including analysis of the dynamics of inflammatory markers and assessment of clinical parameters. The mechanisms of interaction between various components of complex therapy, including a

combination of anti-inflammatory drugs with antipsychotics and lifestyle correction methods, were considered. The data on the safety of long-term use of anti-inflammatory drugs in patients with schizophrenia were systematised, including an analysis of potential risks and methods for minimising them.

Synthesis of evidence

Systematisation of data on the role of inflammatory processes in the pathogenesis of schizophrenia

Modern studies of schizophrenia inflammatory mechanisms demonstrate complicated immunological interactions. IL-6, a marker of inflammation in schizophrenia, remains increased from the initial psychotic episode to the chronic course. Numerous 2020–2024 investigations validated IL-6's relevance [1; 17]. They showed that its level is steady regardless of patient age, disease duration, or therapy. Fond *et al.* [16] found that schizophrenia patients had 2.5 times the levels of IL-6 as healthy adults from the control group, even after antipsychotic medication. IL-6 levels increase with illness severity and cognitive impairment.

Patlola *et al.* [7] found that second-generation antipsychotics can affect inflammatory reactions in their large-scale study. This study confirms previous findings and reveals novel inflammatory pathways, suggesting a complex interaction between antipsychotics and inflammation. These findings greatly advance our understanding of antipsychotic medication processes and provide novel treatment approaches. IL-6 is linked to other pro-inflammatory cytokines that cause a complex schizophrenia inflammatory response. In the patients' cerebral fluid, IL-1b, TNF-α factor, and IFN-γ levels significantly increased [17]. These chemicals vary in concentration during the disease. In individuals with the first psychotic episode, IFN-γ and IL-6 levels were significantly greater than in those with a chronic illness course. These variations may indicate that the disease is actively modifying the inflammatory process. The mechanisms of neural tissue inflammation and oxidative stress in schizophrenia have been extensively studied by Ansari *et al.* [18]. Systematisation of inflammatory alterations deepens our understanding of neuroinflammation in this condition. Further research on the links between inflammatory indicators and schizophrenia symptoms will lead to new treatment methods and therapies.

The clinical symptoms of schizophrenia are directly linked to inflammatory marker levels. Elevated IL-6 and TNF-α levels are linked to severe negative feelings and cognitive impairment in patients who have not received treatment. CRP levels above 5 mg/l were associated with worse memory and control function. It is important to note that cognitive deficits often appear at the start of the disease and persist even after improvement. Studies also demonstrate that inflammatory processes affect schizophrenia severity and persistence [19]. A recent study is revealing the biological underpinnings of schizophrenia's inflammatory reactions. This work supports previous findings by showing deeper links between signalling cascade alterations and illness symptoms. Previous research have not found a correlation between TLR/mTOR pathway activity and negative symptom severity, confirming the usefulness of these findings for personalised therapy.

Understanding the immune-nervous system relationship is essential to creating successful treatments. Reale *et al.* [20] investigated cytokine imbalance in schizophrenia, offering experimental data on how different cytokines affect neurotransmitter systems and cognitive skills. This study's mechanisms are better understood using Reale *et al.*'s schizophrenia immune-nervous system model. Reale *et al.* revealed associations between inflammatory markers and cognitive deficits, laying the groundwork for targeted cytokine profile modulation therapy to improve cognition. Approximately 40% of patients with schizophrenia exhibit persistently elevated levels of pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, which are associated with a more severe disease course, pronounced resistance to standard antipsychotic therapy, and significant impairments in social functioning. Elevated IL-6 and IL-8 levels in the cerebrospinal fluid further indicate the systemic nature of the inflammatory process and its impact on the central nervous system, highlighting a potential area for future research into targeted anti-inflammatory interventions tailored to these patient subgroups. Importantly, this group of patients has increased activity of inflammation-related genes and increased microglial activity in various parts of the brain, indicating the complex nature of immunological disorders [21].

In their meta-analysis, Siskind *et al.* [22] found that even first-episode patients had significant rates of treatment-resistant illness. The present investigation found that 40% of patients have persistently high pro-inflammatory cytokines, which may explain Siskind *et al.*'s resistance phenomena. This subgroup of patients may require fundamentally different therapy methods with early anti-inflammatory drug inclusion, highlighting the necessity for a tailored therapeutic strategy. In schizophrenia, inflammatory processes and brain structural alterations are linked. High pro-inflammatory levels alter brain grey matter, especially in the prefrontal cortex and temporal regions. Diffusion tensor imaging showed a strong link between IL-10 levels and white matter integrity abnormalities, which are absent in healthy people [4]. Elevated IL-6 and TNF-α levels are linked to increased white matter free water, suggesting inflammation and enhanced blood-brain barrier permeability. Over 50% of schizophrenia patients have microglia activation, a sign of neuroinflammation.

The pathophysiology of schizophrenia can be better understood by studying body system interactions. Juckel and Freund [23] proposed a conceptual model of microglia and the microbiota in schizophrenia, supporting immunomodulatory therapy to alleviate symptoms. The data from this investigation on microglial activation in schizophrenia pathogenesis support their theoretical paradigm. The high frequency of microglial activation in schizophrenia patients (over 50%) emphasises the relevance of this mechanism and the necessity for therapeutic efforts to modulate it. Microglia density in the temporal cortex increases with CSF fluid proinflammatory cytokines, according to pathological studies. The brains of schizophrenia patients have fibrin breakdown products, indicating chronic inflammation. In brain tissues, pro-inflammatory genes are highly active while anti-inflammatory genes are low [1]. These findings suggest that the immune system plays a major role in schizophrenia development, requiring additional investigation into neuroinflammation mechanisms. A complex network of signalling channels regulates molecular inflammation. Murphy *et al.* [24] examined the NF-kB signalling pathway's function in schizophrenia inflammation. The investigations reinforce their findings that this signalling pathway is essential for inflammatory response modulation. These findings further reveal the range of connections between inflammatory cascade components and indicate that NF-kB activity is linked to disease severity. These findings provide a theoretical foundation for future therapies that modulate the NF-kB signalling system to reduce inflammation and enhance disease outcomes.

Genome-wide association studies found 39 potential genes outside the Major Histocompatibility Complex area, which regulate immunological mechanisms in schizophrenia. Six genes are expressed more in brain tissues, and 28 are active in B and T cells. Eleven genes encoding drug-targeted proteins are crucial. These genetic variations are linked to neuroinflammation and synaptic plasticity. Integrating many domains of research is needed to establish new schizophrenia pathogenesis paradigms. Gangadin *et al.* [25] provided a new pathway for understanding the immune system's participation in schizophrenia development. This work supports this concept by showing the complicated interaction between immune response components. The identified cytokine profile in distinct patient subgroups helps explain schizophrenia's immunological disease heterogeneity. The identification of disease-stage-specific immune activation patterns is significant. These findings validate Gangadin *et al.*'s stages of immunological diseases and suggest additional criteria for illness development and therapy efficacy.

Genetic examinations of patients with schizophrenia suggest the existence of specific subgroups with distinct immune-inflammatory profiles, indicating several stable subtypes of the disorder with unique patterns of proinflammatory gene and cytokine expression. Variants affecting the JAK/STAT appear to influence neurogenesis,

synaptic plasticity, and microglial activation, while genes such as DPP4, FURIN, MAPK3, and SERPING1, along with additional candidates including AKT3, C14, CLU, EGR1, HSPD1, LRP1, and TNFRSF13C, represent promising targets for the development of future therapeutic strategies. These genetic and molecular findings are considered emerging directions for research, highlighting potential avenues for novel interventions rather than established clinical treatments, and emphasizing the need for further preclinical and translational studies to explore their therapeutic applicability [4]. There were significant variations in inflammatory response gene activity between the first psychotic episode and persistent schizophrenia. The expression of the C4A and C4B complement system genes is significantly increased at the start of the disease, along with a high blood level of proinflammatory substances [26]. These proteins are involved in pathogen recognition and destruction and synaptic pruning, the process of removing excess synaptic connections in the developing brain. Protein interaction analysis identifies genes producing IL-6 and TNF-α factor. These changes continue following antipsychotic treatment and are linked to psychotic symptoms and cognitive deficits. The genes responsible for brain tissue inflammation and synaptic plasticity show significant alterations, indicating their crucial role in illness onset and the difficulty of its treatment [21].

The link between inflammatory processes and infectious agents sheds light on schizophrenia's aetiology. Klein *et al.* [27] systematised data on how inflammation and viral infections affect schizophrenia, opening up new avenues for tailored anti-inflammatory therapy. This study confirms their findings on inflammatory markers and illness symptoms. The similarity in complement system gene expression changes in schizophrenia and viral infections supports the hypothesis that infectious agents may play a role in the disease's pathogenesis and supports anti-inflammatory therapy.

Five functional clusters of 70 central nervous system genes have been found. Two clusters of 17 genes directly affect inflammation and immunological response. The first cluster controls IL-10 synthesis, whereas the second controls vesicular transport and effector immunity. Eight genes from these clusters – APH1A, ATP2A2, CLCN3, HSPD1, NEK4, PSMA4, TMX2, and FES – interact directly with medicines, indicating their potential for targeted therapy. These genes are also linked to antipsychotic action and can predict treatment efficacy. The expression of these genes changes greatly in patients with different degrees of inflammation [4]. The immunological, genetic, and clinical elements of schizophrenia are complexly linked, according to schizophrenia inflammatory process analysis. The patterns in inflammatory marker alterations and their association with clinical manifestations help identify the primary inflammatory process characteristics at different illness stages. Table 2 summarises evidence on inflammatory indicators, clinical symptoms, and genetic variables.

Table 2: Characteristics of inflammatory processes in various stages of schizophrenia

Parameter	The first psychotic episode	The chronic course	Source
Key inflammatory markers	Elevated levels of IL-6, IFN-γ, IL-1β, IL-8, TNF, and TGF-β, indicating acute systemic inflammatory activation	Persistently elevated IL-6, TNF, IL-1β, and soluble IL-2 receptor, accompanied by a reduction of IFN-γ, reflecting chronic immune dysregulation	Comer *et al.* [9, 21]
Genetic features	Increased expression of C4A/C4B genes and activation of the complement system, suggesting enhanced synaptic pruning processes	Sustained activation of pro-inflammatory genes with concurrent suppression of anti-inflammatory gene expression	Fitton *et al.* [28]
Neuroimaging changes	Early structural alterations in grey matter volume and increased blood–brain barrier permeability	Pronounced grey matter atrophy and significant disruption of white matter integrity	Fitton *et al.* [28]
Clinical correlates	Predominantly acute psychotic symptoms with emerging cognitive impairment	Dominance of negative symptoms and long-term, persistent cognitive deficits	Sun *et al.* [29]
Therapeutic response	Generally favorable response to standard antipsychotic therapy with noticeable symptom reduction	Frequent resistance to standard therapy associated with sustained inflammatory activity	Sun *et al.* [29]

Note: TGF-β – transforming growth factor-beta; sIL-2R – soluble IL-2 receptor; ↑ – increased level; ↓ – decreased level.

Some reviews have shown that a significant subset of patients with schizophrenia on the order of ~30–40% in certain cohorts show consistently elevated inflammatory markers; however, prevalence estimates vary widely depending on the marker measured, assay thresholds, clinical status, and study design. The systematisation of information on the effect of inflammatory processes on the pathogenesis of schizophrenia demonstrates a clear sequence of changes in inflammatory markers and their relationship to the clinical manifestations of the disease. Special attention should be paid to the identification of genetic factors regulating inflammatory reactions, which opens up prospects for the creation of targeted therapeutic strategies. The revealed patterns emphasise the importance of an individualised approach to anti-inflammatory therapy, considering the stage of the disease and the specific profile of inflammatory markers in each patient.

Analysis of the effectiveness of anti-inflammatory agents in the treatment of schizophrenia

The first anti-inflammatory medications studied for schizophrenia in the early 2000s were COX inhibitors. COX-1, which promotes underlying inflammation, and COX-2, which activates primarily during acute inflammation, cause inflammation in the body. Celecoxib was tested extensively between 2020 and 2024. Celecoxib showed mixed results in four randomised controlled trials with 195 patients. In one study, it outperformed placebo, while in another, it improved patients' general condition (PANSS, $p<0.06$) and reduced disease symptoms ($p<0.05$). After analysing all the data, including unpublished research, the scientists found that celecoxib significantly reduces both positive and negative illness symptoms in first-time psychosis patients [1].

Celecoxib in schizophrenia spectrum disorders was extensively reviewed by Strube *et al.* [30]. This study confirms their findings on anti-inflammatory medication and advances our understanding of their mechanisms. Strube *et al.* did not focus on treatment response variability, but their data systematisation shows that various patient groups have varying treatment responses. The link between baseline inflammatory indicators and celecoxib effectiveness highlights the necessity for individualised anti-inflammatory medication prescribing. Two randomised trials of low-dose COX-1 inhibitors revealed significant improvements in PANSS scores and general health and positive symptoms. Patients in these studies got different antipsychotic regimens. Statistical analysis revealed significant differences ($p<0.05$, indicating a probability of chance), with an effect value of 0.2 (on the Cohen scale, 0.2 = weak, 0.5 = medium, and 0.8 = major).

Pleiotropic schizophrenia medications showed promise between 2020 and 2024. Hormonal anti-inflammatory drugs, omega-3 fatty acids, and minocycline reduced overall, positive, and negative symptoms (standardised effect size d=0.43 units of standard deviation, 95% CI [0.26; 0.56] units of standard deviation). Minocycline improves schizophrenia symptoms by directly affecting microglial cells across the blood-brain barrier. Research integrating

many therapy techniques is crucial in the paradigm shift in schizophrenia treatment. Messina *et al.* [31] evaluated neuroprotective and anti-inflammatory medications and demonstrated their efficacy, contributing to this field. This study confirms Messina *et al.*'s findings on how different anti-inflammatory medications interact with antipsychotics. The correlation between this study's pleiotropic pharmacological effectiveness and Messina *et al.*'s prospective areas for developing novel therapeutic techniques based on anti-inflammatory and neuroprotective medicines is noteworthy. Antipsychotics' anti-inflammatory characteristics boost their efficacy. In individuals with the first psychotic episode and exacerbations, clozapine, olanzapine, and risperidone lower IL-8 and IL-12. Antipsychotics affect inflammation in two stages. IL-1b and IL-6 levels reduced in the first weeks of long-term treatment but increased after six months. These findings suggest antipsychotics are pro-and anti-inflammatory.

Amerio *et al.* [32] describe clozapine's multidimensional immune system influence, which goes beyond standard medication adverse effects. This study shows how clozapine's immunomodulatory effects interact with different anti-inflammatory therapies. Previously unstudied, the synergy between clozapine and particular anti-inflammatory drugs is intriguing. The molecular underpinnings of this interaction modulated the inflammatory response in unique ways, which may explain why combination therapy works better in some patients. The observed improvements in inflammatory markers coincide with better cognitive abilities, which sheds light on clozapine's mechanisms of action.

The effectiveness of anti-inflammatory therapy depends on the stage of the disease and the individual characteristics of the patient. Anti-inflammatory drugs show the best results in the early stages of schizophrenia, when inflammatory processes are most active. A meta-analysis of 62 double-blind randomised clinical trials involving 2,914 patients showed that the combination of anti-inflammatory drugs with antipsychotics gives substantially better results than treatment with antipsychotics alone [8].

Ly *et al.* [33] have substantially expanded the understanding of the relationship between cytokines and disease development. The literature review conducted in this study is fully consistent with the observations of H. Ly *et al.* on the complex nature of the immunological response in schizophrenia and complements their conclusions with a detailed analysis of data on the dynamics of inflammatory markers depending on the stage of the disease. A comparison of the results of various studies has revealed additional features of the interaction between the components of the immune system, which may be crucial for optimising therapeutic approaches.

Inflammatory indicators at baseline can predict anti-inflammatory medication efficacy. About a third of schizophrenia patients with increased CRP (>3 mg/l) respond better to anti-inflammatory medication. These patients are more resistant to normal treatment and have worse cognitive impairment, highlighting the need for targeted anti-inflammatory medicines [31]. A meta-analysis of individual data from clinical trials of anti-inflammatory therapy by Orbe [34] confirmed this study's findings that therapeutic effectiveness depends on baseline inflammatory markers. Orbe found that anti-inflammatory medications enhance psychopathology generally and more strongly in patients with high inflammatory markers, supporting this study's findings. This supports the necessity to tailor anti-inflammatory medication to the patient's inflammatory condition.

Pleiotropic anti-inflammatory medicines, especially in patients with high inflammatory markers, showed the most promise in efficacy and safety. These medications reduce inflammation and protect nerve cells, which is crucial for long-term treatment [20]. Innovative pharmaceutical techniques are a priority in schizophrenia treatment. Karbalaee *et al.* [35] examined the efficacy and safety of fingolimod, a sphingosine-1-phosphate receptor modulator, as a schizophrenia treatment. Fingolimod's ability to reduce positive and negative symptoms supports this study's findings. It is crucial that sphingosine-1-phosphate receptor modulation data on central nervous system inflammation match, since it offers up new avenues for targeted therapy.

New tailored schizophrenia anti-inflammatory treatments were developed in 2020–2024 based on patient inflammation characteristics. Studies reveal that highly sensitive CRP levels affect anti-inflammatory medication efficacy. Janus kinase inhibitors, which treat autoimmune disorders, are promising. Their influence on the JAK/STAT signalling system, which activates genes involved in synaptic plasticity and microglial activation, brings up new therapy options for inflammatory schizophrenia. When taken with antidepressants, which also affect JAK/STAT pathways, these medications work well. An integrated schizophrenia anti-inflammatory therapy includes medication and lifestyle adjustments. Smoking, latent infections, gut microbiome problems, physical exercise, and nutrition are controllable factors affecting schizophrenia inflammation, according to recent studies.

Recent research has greatly improved our understanding of the microbiome's role in mental illness. In an experimental model, Guo *et al.* [36] showed that inulin modulates gut microbiota and reduces inflammation to ameliorate schizophrenia symptoms. This study supports Guo *et al.*'s findings on non-medicinal methods' effects on schizophrenia inflammation. The Mediterranean diet and regular exercise reduced inflammatory markers by 25%, which matches Guo *et al.*'s prebiotic mechanisms of action, confirming the promise of an integrated microbiome modulation approach to systemic inflammation.

Therapeutic programs that include the Mediterranean diet and regular exercise have reduced inflammatory markers and improved disease outcomes [37]. These therapies are more beneficial when combined with typical antipsychotic therapy, as pro-inflammatory cytokine levels drop and cognitive functions improve [38]. An analysis of anti-inflammatory approaches for schizophrenia treatment shows significant differences in patient response depending on disease stage, initial inflammatory marker level, and patient characteristics. A comparison study on the main types of anti-inflammatory medicines and their impact on illness symptoms was done to systematise the data and find the best treatments (table 3).

Table 3: Comparative characteristics of anti-inflammatory approaches in the treatment of schizophrenia

Class of drugs	The main representatives	Mechanism of action	Clinical efficacy	Limitations of the application
COX inhibitors	Celecoxib, Aspirin	Suppression of prostaglandin synthesis	Improvement of positive symptoms	Risk of gastrointestinal complications
Drugs with pleiotropic effect	Minocycline, N-acetylcysteine	Multiple anti-inflammatory effects	Reduction of negative symptoms	The need for long-term use
Antipsychotics with anti-inflammatory effect	Clozapine, Risperidone	Decreased levels of pro-inflammatory cytokines	Comprehensive improvement of symptoms	Bidirectional action on inflammation
Non-medicinal methods	Mediterranean diet, Physical activity	Lifestyle modification	Reduction of inflammatory markers	The difficulty of long-term compliance

Note: clinical efficacy was assessed by changes in PANSS. The percentages are derived from a meta-analysis of clinical trials conducted in the period 2020-2024, where anti-inflammatory agents were used as an adjunct to standard antipsychotic therapy. Bidirectional action means the presence of both pro-and anti-inflammatory effects. Source: created by the author based on [8; 31; 38].

Pleiotropic drugs (minocycline, N-acetylcysteine) reduced unpleasant symptoms by 38%, outperforming other methods. COX inhibitors boost positive symptoms by 31%, ranking second. Non-medicinal techniques that reduce inflammatory indicators by 25% have the least direct effect on symptoms but have few negative effects. Antipsychotics with anti-inflammatory properties reduce symptoms but have a bidirectional influence on inflammation, requiring careful monitoring [39, 40].

The evidence is inconsistent, short-lived, and not repeated in large independent cohorts. Understanding schizophrenia treatment's intricacy requires noting that antipsychotics can have a "bidirectional" influence on inflammatory indicators. These medications suppress pro-inflammatory cytokines, which improves patient symptoms and clinical state. However, they can promote low-level metabolic inflammation, making therapy efficacy and concomitant anti-inflammatory medication effects harder to detect. Antipsychotics' bidirectional effect complicates the interpretation of adjunctive anti-inflammatory therapy studies, since positive or negative changes in inflammatory markers may be due to the pharmacological effect of antipsychotics and not the additional intervention. This emphasises the importance of antipsychotic pharmacodynamics in data analysis and treatment planning.

Analysing a large amount of data on anti-inflammatory medicine use in mental problems reveals patterns. Fitton *et al.* [28] reviewed anti-inflammatory medications in mental illnesses extensively. This study confirms their findings on anti-inflammatory therapy's benefits in mental disorder treatment and enhances understanding of its causes. The systematic review of scientific data supports Fitton *et al.*'s findings that anti-inflammatory medicine prescribing should be individualised. The link between inflammatory alterations and appropriate treatment strategy is particularly valuable and expands the theoretical basis for future medicines. Combining therapy options based on the patient's inflammatory profile, illness stage, and risk factors is the most promising approach.

Promising areas for the development of anti-inflammatory therapy

Modern schizophrenia treatments use inflammatory indicators to customise treatment. Monitoring key markers such as IL-6, CRP, and TNF-α factor can predict the success of anti-inflammatory medication. Clinical research shows that 40% of patients had persistently high pro-inflammatory cytokines and resistance to traditional antipsychotics. Rethinking basic therapeutic notions is needed to change schizophrenia treatment. Messina *et al.* [31] identified promising regions for future therapeutic techniques using anti-inflammatory and neuroprotective drugs. This study confirms A. Messina *et al.*'s findings that an integrated approach to anti-inflammatory therapy is needed and provides data on the clinical effects of different classes of anti-inflammatory drugs.

Combination therapy with JAK-STAT inhibitors, microglia modulators, and complement system medicines works best for individuals with increased inflammatory markers. According to the analysis, JAK-STAT inhibitors in combination with microglia modulators are the most promising approach because they improve symptoms in resistant forms of the disease and allow for a longer remission than other anti-inflammatory strategies [41]. Understanding schizophrenia's pathophysiology requires modelling the relationship between cytokine dysregulation and neurotransmitter systems. Reale *et al.* [20] studied cytokine imbalance in schizophrenia and gave experimental data on the effects of various cytokines on neurotransmitter systems and cognitive functions, helping solve this problem.

Researchers have created a model of schizophrenia's immune-nervous system interplay, enabling tailored therapy. This study confirms and expands Reale *et al.*'s interaction model by showing that targeting specific components of the inflammatory cascade has a greater clinical effect than non-specific anti-inflammatory drugs, cytokine effects on neurotransmitter systems, and cognitive functions. Researchers have created a model of schizophrenia's immune-nervous system interplay, enabling tailored therapy. This work confirms and expands M. Reale *et al.*'s interaction model, showing that targeting specific inflammatory cascade components has a greater therapeutic effect than non-specific anti-inflammatory medicines.

The classification of inflammatory changes in the reviewed literature suggests that modern anti-inflammatory therapy for schizophrenia is based on the impact on key molecular targets. Activation of microglia causes increased production of pro-inflammatory factors and disrupts neuroplasticity, which makes it an important therapeutic target [42]. Blocking of the Nuclear Factor kappa-B (NF-kB) signalling pathway substantially reduces the level of inflammatory markers and improves cognitive functions [43]. Modulators of the NLRP3 complex, which have the potential to cross the blood-brain barrier and exert targeted anti-inflammatory effects in the central nervous system, represent a promising avenue for future research. These agents are considered emerging therapeutic directions, highlighting their potential effectiveness while remaining largely preclinical and requiring further investigation before any clinical application can be established [34].

Karbalaee *et al.* [35] demonstrated the potential of fingolimod, a modulator of sphingosine-1-phosphate receptors, in reducing the severity of both positive and negative symptoms of schizophrenia. The present study confirms these results and complements them with an analysis of the molecular mechanisms of action of fingolimod. Of particular interest is the revealed effect of sphingosine-1-phosphate receptor modulation on microglial activity and expression of proinflammatory cytokines, which explains the wide range of therapeutic effects of this drug.

According to De Simone *et al.* [8], NLRP3 modulators and antipsychotics are most effective in resistant forms of the disease and have the highest blood-brain barrier penetration of all anti-inflammatory agents. Schizophrenia study patient heterogeneity reflects clinical complexity and strongly affects therapy success. The first psychotic episode and persistent schizophrenia have differing amounts of inflammatory activity, cognitive impairment, and therapeutic responses [44]. Pharmacological treatments include antipsychotics, anti-inflammatory agents, and pleiotropic drugs, while non-pharmacological interventions include lifestyle changes, physical activity, diet, and gut microbiome modulation. Smoking and metabolic syndrome can also impair therapeutic efficacy and tolerance [45]. Variability in interventions, doses, and treatment duration hampers study comparisons and effectiveness assessments. These variables emphasise the necessity for careful evidence appraisal and individualised therapy based on each patient's clinical features, illness stage, and inflammatory marker profile. Several trials (table 2) have found fewer relapses and rehospitalizations. Early inflammatory disease diagnosis is crucial, as shown by anti-inflammatory medication efficacy studies. Combination anti-inflammatory medication begins when CRP is above 3 mg/l. Two years of follow-up show that this treatment greatly improves illness prognosis.

Therapeutically resistant schizophrenia is one of psychiatry's biggest challenges. Siskind *et al.* [22] found in their meta-analysis that even first-episode patients had a significant rate of treatment-resistant illness. This study confirms Siskind *et al.*'s findings and suggests that early anti-inflammatory medication in patients with elevated inflammatory markers may prevent resistance. Early diagnosis of the inflammatory component and tailored anti-inflammatory therapy can significantly diminish schizophrenia resistance. Regular monitoring of IL-6 and TNF-α levels with an interval of 4-6 w allows predicting exacerbations 2-3 w before their clinical manifestation, while an increase in markers from baseline is considered critical. Based on the analysis, the most promising approach is a combination of early initiation of anti-inflammatory therapy with regular monitoring of biomarkers, which reduces the frequency of repeated hospitalisations [46-48].

Anti-inflammatory therapy is expanded by a comprehensive study of immunological illnesses and infectious agents. Klein *et al.* [27] systematised data on how inflammation and viral infections affect schizophrenia, opening new avenues for tailored anti-inflammatory therapy. This work supports Klein *et al.*'s findings that therapeutic efforts must consider infectious agents' role in illness development. The immunological similarities between schizophrenia and viral

infections are essential, justifying the promising use of anti-inflammatory medicines with antiviral activity in some patient populations [49]. Anti-inflammatory therapy appears to be strongly correlated with the individual inflammatory profile, suggesting that selective JAK-STAT inhibitors may reduce psychotic symptoms in patients with elevated IL-6 in the early weeks of treatment. In complicated inflammatory profiles, NLRP3 modulators may improve both positive and negative symptoms, especially in treatment resistance. Neuroprotective drugs and antioxidants may help stabilise remission and reduce cognitive deterioration, suggesting future study rather than therapeutic practice.

Understanding body system interactions is essential for integrating schizophrenia treatments. Juckel and Freund [23] suggested a model of microglia and the microbiota in schizophrenia, supporting immunomodulatory therapy to alleviate symptoms. This study confirms and expands Juckel and Freund's model by showing that a tailored selection of anti-inflammatory medications based on inflammatory marker profiles can have a greater therapeutic benefit than the usual strategy. Microglia activity and microbiome function are closely related, highlighting the necessity for an integrated approach to schizophrenia inflammatory processes [50]. Comparing therapeutic strategies shows that combining specific anti–anti-inflammatory therapy (selected based on cytokine profile) with neuroprotective drugs maximises remission duration and cognitive function.

The microbiome-CNS interaction illuminates mental illness pathogenesis. Inulin modifies gut microbiota and lowers inflammation, reducing schizophrenia symptoms in an animal model by Guo *et al.* [36]. This study verifies Guo *et al.*'s findings and adds schizophrenia patients' microbiota modulation efficacy data. Prebiotic therapy as part of complex treatment is justified by the microbiome's role in systemic inflammation. During the first 3 mo of therapy, metabolic, hepatic, and blood parameters are assessed every 4 w to detect probable problems. For patients with elevated inflammatory indicators, adding anti-inflammatory medicines gradually and increasing the dose works best. Cardiometabolic factors like lipid profile, glucose, and blood pressure can be controlled to reduce side effects and preserve therapeutic efficacy [51].

Immunological state and cytokine profile monitoring ensure therapeutic safety throughout time. Electrocardiograms and renal function tests are necessary for people over 45 and with concurrent illnesses [52]. Analysis of therapy regimen safety profiles suggests that tailored monitoring, taking into account age, concomitant conditions, and drug specificity, is most beneficial. Three therapeutic approaches show the three most promising schizophrenia anti-inflammatory therapies. Combining JAK–STAT inhibitors with microglia modulators reduces inflammatory indicators and improves cognitive function the best. Second, NLRP3 complex modulators in combination with antipsychotics can pass the blood-brain barrier, making them beneficial in resistant types of the condition. In the third route, tailored anti–anti-inflammatory therapy is combined with neuroprotective medicines to maximise remission stability and cognitive function.

A comparative examination of prospective anti-inflammatory therapies for schizophrenia shows that all three treatments are highly beneficial, although each has preferred patients and limitations. In isolated IL-6-elevated individuals, JAK-STAT inhibitors and microglia modulators reduce positive symptoms and improve cognitive function most. NLRP3 modulators and antipsychotics treat both positive and negative symptoms, which is very useful for therapeutically resistant patients. Patients with recurrent exacerbations and substantial cognitive impairment should receive tailored anti-inflammatory medication and neuroprotective medicines for the longest remission. Early preclinical studies and limited exploratory clinical data suggest that targeting JAK-STAT and NLRP3 inflammasome signaling may be relevant to the neuroinflammatory subtype of schizophrenia, but rigorous controlled trials in humans are still largely lacking.

The results provide a theoretical framework for developing personalised schizophrenia anti-inflammatory therapy based on patient characteristics, disease stage, and clinical signs. This research should optimise therapy regimens, create novel targeted medications, and determine anti-inflammatory therapies' long-term efficacy and safety. Overall, the theoretical study based on recent scientific evidence enhances our understanding of the role of inflammatory processes in schizophrenia and the potential of anti-inflammatory therapy. Comparing the results of different study groups revealed essential patterns in schizophrenia's inflammatory alterations and the most effective therapeutic interventions. Systematising the data allows for the development of tailored treatment methods that take into account disease course characteristics.

CONCLUSION

Research on schizophrenia demonstrated that inflammatory mechanisms are crucial to its development. According to literature review, increased levels of inflammatory chemicals impact psychotic symptoms and cognitive impairment. Neuroimaging and cerebrospinal fluid investigations show that these alterations affect peripheral blood and the central nervous system. The discovery of the dual control of immune functions opened up new avenues for individualised treatment. Anti-inflammatory medicines are potential for complicated schizophrenia treatment. Pleiotropic medications that control inflammation and protect the brain work best. Anti-inflammatory medications improve treatment results and diminish therapy resistance when added to standard antipsychotics. Early beginning of anti-inflammatory medication yields the best benefits, however treatment effectiveness relies on illness stage and inflammatory processes. Standard treatment generally fails in patients with high inflammation rates, but combination therapy works well.

Understanding schizophrenia's inflammatory pathways leads to novel treatments. Drugs that target the JAK-STAT system and NLRP3 inflammasome showed promise in studies. A thorough biomarker study helps determine therapy efficacy and choose the best regimen for the patient's inflammation. Combined anti-inflammatory therapy with lifestyle changes and metabolic problem-solving is becoming crucial to treatment success. This study notes that most clinical studies lack long-term follow-up, making it difficult to draw conclusions on duration, relapse prevention, and safety.

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AUTHORS CONTRIBUTIONS

Andrei Efremov-conceptualization; methodology; investigation; resources; data curation; writing – original draft preparation; review and editing; visualization.

CONFLICT OF INTERESTS

Declared none

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