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NASTAS IGOR

„ CLINICAL EFFECTS OF ADJUVANT TREATMENT ON THE SYMPTOMS OF SCHIZOPHRENIA”

321.06 PSYCHIATRY AND NARCOLOGY

HABILITATED DOCTORAL THESIS IN MEDICAL SCIENCES

ABSTRACT

Chișinău, 2026

The thesis was developed within the Department of Mental Health, Medical Psychology and Psychotherapy "Alexandru Nacu" at the Nicolae Testemițanu State University of Medicine and Pharmacy.

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The public defence will take place on 4 June 2026, at 14:00, at Nicolae Testemițanu State University of Medicine and Pharmacy, 165 Ștefan cel Mare și Sfânt Blvd., Office 205, during the meeting of the Public Defence Committee for the Doctor Habilitatus thesis, approved by the decision of the Nicolae Testemitanu State University of Medicine and Pharmacy Senate, Minutes No. 4/6 of 22 April 2026.

Composition of the Public Defence Committee for the Doctor Habilitatus thesis:

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1. INTRODUCTION

1.1 Relevance and Importance of the Research Topic

Schizophrenia affects approximately 23 million people worldwide, corresponding to 1 in 345 individuals (0.29%). Among adults, the prevalence is estimated at 1 in 233 individuals (0.43%) [1]. The onset most commonly occurs in late adolescence and early adulthood, typically around the age of 20 years, with an earlier onset observed in males compared to females. A meta-analysis including 4,536,447 patients with schizophrenia (1957–2021) reported a life expectancy deficit of approximately 15–20 years, with a weighted average of 14.5 years of potential life lost and a mean life expectancy of around 60 years[2]. According to the Global Burden of Disease (GBD) study, one of the most comprehensive global epidemiological assessments conducted by the Institute for Health Metrics and Evaluation (IHME), which provides detailed estimates of incidence, prevalence, mortality, and disability impact for over 360 diseases, the burden of schizophrenia has increased substantially between 1990 and 2021. Specifically, prevalence rose from 13.62 million to 23.18 million cases, incidence increased from 883,000 to 1.223 million cases, and age-standardized disability rates (ASDR) increased from 8.76 million to 14.82 million, representing increases of over 70.1%, 38.5%, and 69.2%, respectively. The male-to-female burden ratio has remained relatively constant over the past three decades, with males exhibiting a higher risk. As life expectancy continues to increase globally, the burden of schizophrenia is expected to rise further, with projections indicating continued increases in prevalence, incidence, and overall disease burden by 2050 . The economic burden of schizophrenia varies across studies; however, indirect costs related to productivity losses among patients and caregivers consistently represent the largest proportion (48.9%–81.4%), followed by direct medical costs (19.5%–36.8%) and direct non-medical costs such as legal expenses, social benefits, and housing (4.0%–18.2%) . These considerations highlight the necessity for improved disease management strategies, taking into account the clinical and pathogenetic heterogeneity of schizophrenia, available resources, and accumulated scientific knowledge. Current treatment approaches are multimodal, based on multifactorial etiological theories, and include pharmacological, social, and psychotherapeutic interventions aimed at achieving a biopsychosocial balance. Antipsychotic therapy remains the cornerstone of treatment, primarily through dopamine D2 receptor blockade, which effectively reduces positive symptoms such as hallucinations and delusions. However, this mechanism is also associated with adverse effects, limiting the therapeutic window and dose individualization. Antipsychotics demonstrate limited efficacy in addressing negative and cognitive symptoms, which are major determinants of long-term disability. Furthermore, approximately 60–70% of patients experience treatment failure, including relapse despite ongoing pharmacotherapy. While some antipsychotics exhibit improved relapse prevention profiles, no ideal medication exists. Adverse effects, including metabolic syndrome, extrapyramidal symptoms, sedation, and cardiovascular risks, reduce tolerability and contribute to poor treatment adherence. Additionally, higher plasma drug levels in females may increase the risk of adverse effects, complicating dose adjustment. Clozapine, recommended for treatment-resistant schizophrenia, shows a response rate of only approximately 33% after three months of treatment. In this context, there is a pressing need for novel therapeutic approaches that integrate etiopathogenetic mechanisms and target systemic and molecular alterations associated with schizophrenia.

1.2 Aim of the Research

To evaluate the efficacy of adjunctive therapies in patients with schizophrenia receiving maintenance antipsychotic treatment in reducing clinical symptoms and improving quality of life.

1.3 Research Objectives

Objective 1:
To analyze the anti-inflammatory, neuroprotective, antioxidant, and neuromodulatory effects of adjunctive therapies and their efficacy on schizophrenia symptoms.

Objective 2:
To investigate the efficacy of adjunctive treatment according to patient age.

Objective 3:
To evaluate the dose–response relationship of adjunctive treatments in patients with schizophrenia.

Objective 4:
To analyze the impact of treatment duration on clinical parameters.

Objective 5:
To assess changes in clinical parameters depending on the type of adjunctive treatment.

Objective 6:
To evaluate the impact of adjunctive treatment on social and economic aspects in patients with schizophrenia.

Objective 7:
To determine the effects of adjunctive therapies on patients' quality of life.

Objective 8:
To develop an intervention algorithm aimed at reducing clinical symptoms and improving quality of life in patients with schizophrenia.

Research Hypothesis

The research hypothesis is based on cellular pathobiological mechanisms identified in schizophrenia, including reduced mitochondrial membrane potential, decreased activity of complex I (the largest enzymatic complex of the mitochondrial respiratory chain), reduced adenosine triphosphate (ATP) production, increased production of reactive oxygen species and nitric oxide, activation of intrinsic apoptotic pathways, reduced neuronal and glial density in specific brain regions (as demonstrated in postmortem studies), increased vulnerability to oxidative stress, impaired neuroplasticity, and altered cerebral energy metabolism. These cellular dysfunctions are particularly associated with dopaminergic system dysregulation and only partial symptom control under antipsychotic treatment, especially due to the persistence of negative and cognitive symptoms, which represent the primary contributors to long-term disability and impaired social reintegration. Based on these premises, adjunctive pharmacological interventions targeting these pathobiological mechanisms may represent a promising therapeutic strategy in schizophrenia.

To test this theoretical hypothesis, the statistical hypothesis was based on the null hypothesis (H0): "There are no statistically significant differences between groups in terms of clinical symptom severity, global functioning, and quality of life at the end of the intervention." Rejection of the null hypothesis would indicate statistically significant differences between groups.

Summary of Research Methodology and Justification of Methods

The overall research methodology is based on the compilation and integration of results obtained from the author's scientific publications, complemented by additional statistical analyses and comparative interpretations. The research was grounded in a general hypothesis supported by relevant bibliographic sources and statistical data analysis. PRISMA criteria served as the foundation for selecting and including bibliographic sources. Each chapter, addressing distinct components of schizophrenia pathophysiology, was analyzed separately through systematic reviews, umbrella reviews, or original meta-analyses, with appropriate conclusions drawn for each. The justification of the research direction is based on the results obtained.

Scientific Novelty and Originality of the Results

1. Identification and statistical analysis of pro- and anti-inflammatory processes related to the onset and progression of schizophrenia.
2. Analysis of mitochondrial dysfunction and cellular membrane pathological processes as pathogenetic substrates in schizophrenia, with the proposal of targeted adjunctive interventions.
3. Proposal of specific biological and clinical biomarkers for psychosis risk assessment and prediction of treatment response, including analysis of the role of exosomes in diagnosis and personalized intervention.
4. Evaluation of the neuromodulatory effects of estradiol in postmenopausal female patients with schizophrenia, supporting its protective and antidopaminergic role in early disease development.
5. Development of a screening, diagnostic, and intervention algorithm for the prodromal stage of schizophrenia based on clinical syndrome type.

Major Applied Scientific Problem Solved

This work provides an innovative approach to schizophrenia management, proposing criteria for early screening and diagnosis, as well as targeted pathogenetic interventions addressing underlying disease mechanisms. This approach contributes to symptom reduction and improvement in quality-of-life indicators among patients with schizophrenia, as demonstrated by statistical analysis.

Theoretical Significance

The research contributes to highlighting the complex pathobiological mechanisms underlying schizophrenia. In particular, it provides a detailed analysis of the molecular, metabolic, inflammatory, and mitochondrial dysfunctions associated with this disorder, emphasizing their role at different stages of disease progression, including the prodromal phase and high-risk states for psychosis.

The study also proposes a conceptual framework that integrates these mechanisms into a unified pathogenetic model, linking cellular dysfunctions with clinical symptomatology. The proposed adjunctive therapeutic approaches go beyond the classical dopaminergic paradigm, targeting additional biological pathways involved in schizophrenia and thereby contributing to the consolidation of the theoretical basis for future research and the development of new therapeutic strategies.

Applied Value of the Work

1. The research establishes clinical criteria and biological markers applicable in the prodromal stage, where current classification systems, such as DSM-5 and ICD-11, provide limited guidance for intervention.
2. The identification of high-risk states for psychosis and the implementation of the proposed intervention algorithm provide solutions aimed at reducing clinical symptoms and decreasing the risk of disease onset.
3. Improved control of schizophrenia symptoms, particularly negative symptoms through adjunctive therapy, contributes to reducing hospitalization rates, facilitating social reintegration, and improving patients' quality of life.

Validation of Scientific Results

International Conferences

1. The 38th Congress of the European College of Neuropsychopharmacology (ECNP), 11–14 October 2025, Amsterdam, the Netherlands.
2. The 7th International Conference on Nanotechnologies and Biomedical Engineering, 7–10 October 2025, Chișinău, Republic of Moldova.
3. The 37th Congress of the European College of Neuropsychopharmacology (ECNP), 21–24 September 2024, Milan, Italy.
4. European Congress of Psychiatry, 6–9 April 2024, Budapest, Hungary.
5. The 4th International Congress of the Society of Psychiatrists, Narcologists, Psychotherapists and Clinical Psychologists of the Republic of Moldova (SPNPPC) and the 8th Eastern European Mental Health Conference "In and Out of Your Mind", Chișinău, Republic of Moldova, 10–13 October 2024.
6. International Congress "Together for Mental Health: Trauma and Its Costs for Humanity", 3rd Edition, 12–15 October 2023.

International Conference of the Society of Psychiatrists, Narcologists, Psychotherapists and Clinical Psychologists of the Republic of Moldova (SPNPPC), “Mental Health for All: Developing Resilience and Quality Services”, 24–26 November 2022, Chișinău, Republic of Moldova.

National Conferences with International Participation

8. Satellite Conference “New Horizons in Mental Health”, held within the Anniversary Congress with international participation “80 Years of Innovation in Health and Medical Education”, 20–23 October 2025, Chișinău, Republic of Moldova.

National Conferences Abroad

9. The 9th National Congress of Psychiatry, 19–23 March 2025, Sibiu, Romania.
10. National Conference “NoAddict”, 24–27 April 2024, Iași, Romania.
11. National Conference “Depression – Psychopathological Perspectives and Its Social Reflection”, held within the Days of the “Socola” Institute of Psychiatry, 2–5 October 2024, Iași, Romania.

Publications Relatedt to the Thesis Topic

A total of 46 scientific works related to the research topic have been published, including: 13 articles in journals indexed in Web of Science and Scopus databases; 1 article in a peer-reviewed journal abroad; 2 articles in journals included in the National Register of specialized journals, Category B; 4 papers in the proceedings of international scientific conferences abroad; 9 papers in the proceedings of international scientific conferences held in the Republic of Moldova; 1 paper in the proceedings of a national scientific conference with international participation; 1 single-author monograph; and 1 multi-author monograph coordinated by the author. In addition, the following were obtained: 1 invention patent, 4 copyright certificates, 1 innovator certificate, and 1 implementation act.

Volume and Structure of the Thesis

The thesis comprises 154 pages of main text and includes 57 tables and 31 figures. It consists of an introduction, 7 chapters presenting the author’s original results and discussion, conclusions and synthesis for each chapter, general conclusions, and practical recommendations. The bibliography includes 353 sources, and the thesis contains abstracts in Romanian and English.

The general conclusions and practical recommendations are based on the results obtained in the research and reflect the components of the thesis outlined in the aim and proposed objectives.

Favorable Approval of the Research Ethics Committee: 25 March 2025, No. 1, related to No. 7 of 23 December 2024.

The research was carried out within the Department of Mental Health, Medical Psychology and Psychotherapy, Nicolae Testemițanu State University of Medicine and Pharmacy.

Keywords: schizophrenia, adjunctive therapy, inflammation, cytokines, negative symptoms, prodromal symptoms, estradiol, oxidative stress, lipid metabolism, exosomes.

2. RESEARCH METHODOLOGY

The thesis was developed as a synthesis-based work, grounded in the compilation, critical analysis, and integration of published studies, including research conducted with the participation of the thesis author, addressing etiopathogenetic mechanisms, biomarkers, and adjunctive therapeutic strategies in schizophrenia. Through this structure, the research methodology aims to connect different levels of analysis, namely from molecular and cellular mechanisms to clinical expression, functional impact, and quality of life, and ultimately to evaluate the role of adjunctive therapies based on the analyzed mechanisms in the context of maintenance treatment with antipsychotics.

General Research Design and Thematic Axes

The synthesized research directions are structured into five thematic axes, presented in the chapters containing the research results:

I. Inflammation and immune activation in the pathogenesis of schizophrenia, including cerebral neurotransmission and cytokines in the acute state and remission, the influence of antipsychotics on cytokines, types of correlations between clinical symptoms and cytokine levels, the relationship between cytokine levels and cognitive function, anti-inflammatory substances in schizophrenia, and substances acting on negative and cognitive symptoms in schizophrenia.

II. Mitochondrial dysfunction and phospholipid imbalance as pathogenetic mechanisms in schizophrenia, with emphasis on the role of polyunsaturated fatty acids, niacin, and oxidative stress in the transition to psychosis.

III. The neuromodulatory, neuroprotective, and thymostabilizing effects of estradiol, its relationship with mitochondrial function, and the use of estradiol as adjunctive therapy in schizophrenia.

IV. The importance of exosomes as biomarkers in the diagnosis, course, and treatment of schizophrenia, including their potential in predicting severity, prognosis, and therapeutic response.

V. Challenges in the early diagnosis of schizophrenia: characteristics of the prodromal state, risk of transition to psychosis, and development of a screening and diagnostic algorithm.

The scientific literature used was identified through systematic searches in the main biomedical and interdisciplinary databases relevant to the thesis topic. PubMed/MEDLINE, Web of Science Core Collection, Scopus, and PsycINFO were accessed, while Cochrane Library and major publishing platforms - including Elsevier/ScienceDirect, Wiley Online Library, SpringerLink, Nature Publishing Group, Frontiers, BMJ, JAMA Network, and Oxford Academic - were consulted to identify meta-analyses and high-level evidence syntheses.

The selection of studies was performed using combinations of keywords and MeSH terms related to schizophrenia, inflammation, cytokines, oxidative stress, mitochondrial dysfunction, polyunsaturated fatty acids, niacin, estradiol, exosomes, adjunctive treatment, negative symptoms, cognitive symptoms, high-risk states for psychosis, and quality of life. The bibliography also includes publications in which the author was either co-author or sole author and which were subject to the same criteria of methodological rigor and reporting during the publication process in journals indexed in PubMed, Scopus, or Web of Science.

Study Selection Criteria

The selection and reporting of studies included in systematic reviews and meta-analyses were guided by the PRISMA recommendations - Preferred Reporting Items for Systematic Reviews and Meta-Analyses - to ensure the replicability of the systematic analyses.Original studies, randomized clinical trials, postmortem studies, meta-analyses, systematic reviews, umbrella reviews, and evidence syntheses relevant to pathogenetic mechanisms, biomarkers, and adjunctive treatments were included. The results of four double-blind randomized clinical trials on adjunctive treatment in schizophrenia, conducted with the participation of the thesis author and published in journals with impact factor, were also included. Studies without statistical relevance, isolated case reports, publications without peer review, and studies that did not generally comply with PRISMA methodological criteria were excluded.

Methods of Analysis and Instruments Used

The evidence synthesis included an integrative narrative analysis, complemented by secondary statistical analyses based on data published in the selected studies. The research included the development of original systematic reviews, the performance of meta-analyses of randomized clinical trials, as well as an umbrella review based on previously published meta-analyses.

The statistical evaluation included analyses of correlation coefficients, linear regression models, and comparative analyses of differences between groups. Meta-analysis was used as the central statistical method for combining and analyzing data from several independent clinical studies, particularly randomized clinical trials, with the aim of obtaining a more precise estimate of the effect of adjunctive interventions.

The main stages followed in conducting the author’s meta-analyses were: defining the research question using the PICO framework; establishing eligibility criteria; defining the methodological design; selecting studies; assessing quality and risk of bias; performing statistical analysis, including heterogeneity assessment; and interpreting the results. Risk of bias was assessed using the Cochrane Risk of Bias Tool, RoB 2, in Review Manager Web developed by the Cochrane Collaboration. In addition to meta-analyses of primary clinical studies, an umbrella review approach was also used to clarify the consistency and coherence of evidence regarding the role of inflammation, oxidative stress, mitochondrial dysfunction, and adjunctive interventions in schizophrenia. Where numerical information allowed, secondary ANOVA-type comparisons were performed, as well as estimations of standardized effects through aggregation of published results and visual comparative analyses, including forest plots, heatmaps, and multicriteria analyses. For each thematic axis, the main results of the studies and meta-analyses were summarized; convergences and discrepancies between sources were highlighted; and changes in biomarkers — inflammation, oxidative stress, mitochondrial function, and exosomes — were correlated with clinical expression, including positive, negative, and cognitive symptoms, quality of life, and the effects of adjunctive therapies. This approach allowed not only the description of the clinical effects of adjunctive treatment but also their integration into a pathobiological model supporting the proposed algorithms for screening, diagnosis, and early intervention presented in the subsequent chapters.

Data processing, effect estimation, and diagram generation were performed using MATLAB R2025b Update 1 — The MathWorks, Inc.; license No. 41294434 — and Review Manager Web developed by the Cochrane Collaboration. For additional calculations, including correlations, effects, and confidence intervals, validated online statistical tools were used, including gigacalculator.com.

Limitations Related to the Design and Integration of Thesis Results

1. As a synthesis-based work, the methodology of the thesis is dependent on the quality and design of the included studies, over which direct control was not possible.
2. Umbrella reviews and secondary meta-analyses are limited by the availability of numerical data, the heterogeneity of adjunctive interventions - doses, duration, and study populations - and, in some cases, by the variability of clinical assessment instruments.
3. Some estimates required indirect calculation or statistical conversions due to the absence of primary indicators.
4. Most of the included studies originate from different geographical regions and may reflect possible genetic or enzymatic differences within the investigated populations

3. INFLAMMATION AND IMMUNE ACTIVATION IN THE PATHOGENESIS OF SCHIZOPHRENIA

3.1 Introduction

Cytokines represent one of the key components of the response to infectious agents or other harmful exogenous factors. Patients with schizophrenia show increased levels of pro-inflammatory cytokines in the blood and cerebrospinal fluid, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF), and C-reactive protein (CRP). IL-6 and TNF are involved in cytotoxicity processes and influence dopaminergic, glutamatergic, and cognitive pathways implicated in the pathophysiology of schizophrenia [15]. Particularly at the onset of schizophrenia and during recurrent psychotic episodes, blood levels of pro-inflammatory cytokines such as IL-1, IL-6, and TNF tend to increase, while IL-6 levels are associated with an unfavorable prognosis in schizophrenia [16]. Variations in TNF-α are correlated with psychopathological inflammatory processes in patients with treatment-resistant schizophrenia and in those receiving chronic treatment [17]. Cytokines are considered key markers of immune system activation, and there is evidence that multiple cytokines are elevated in patients with mental disorders [18].

In addition, an important question concerns how anti-inflammatory agents influence the clinical parameters of schizophrenia when used as adjunctive treatment compared with antipsychotic treatment alone.

3.2 Material and Methods

Methods of analysis and instruments used

The statistical analysis methods included the assessment of relationships between variables using Pearson, Spearman, and Kendall correlation coefficients, calculated with the gigacalculator.com platform. To compare differences between groups and assess the influence of treatment on cytokine levels, one-way ANOVA tests were applied using the ANOVA Calculator. Graphical analyses and linear regression models, including the scatter plot of the relationship between treatment duration and effect size, for example Figure 10, were generated using MATLAB R2025b Update 1. The mean difference at the end of the study and the pooled effect estimates were calculated using Review Manager Web, RevMan Web. Within this chapter, the author also performed secondary meta-analyses based on data published in randomized clinical trials, as well as an umbrella review derived from existing meta-analyses in the literature. Heterogeneity was assessed using I^2, τ^2, and χ^2 statistics, and the results were illustrated through forest plots and other comparative graphs.

3.3 Results and Discussion

3.3.1 Cytokines in the acute episode

Following patient selection, the first study group included 3,710 patients with schizophrenia and 5,190 controls for the group of patients with acute states. Using the correlation calculator, we calculated the Pearson coefficient, which, according to the data from the sources, confirms the presence of a correlation between the presence of inflammatory cytokines in the plasma of patients with schizophrenia and the magnitude of the effect in acute cases with psychotic exacerbation. The results demonstrated statistically significant indicators: P value = 0.04004379 (≤ 0.05), z score = -1.75017767, 95% confidence interval = [-0.6803, 0.0469], where the linear regression is described by the formula: $y = -0.00140227x + 0.44566987$. According to Evans' scale (1996), the Pearson coefficient r, calculated for 23 selected items from Table A1.4.1 for the acute state, was r = -0.37252487, representing a moderate negative linear correlation [19].

Conclusions

The significant association indicates that, in acute schizophrenia, the greater the dysregulation of cytokines, the more variable the study results become. This suggests that inflammation in schizophrenia is real but heterogeneous, influenced by multiple biological and clinical factors. This would imply that some patients with acute schizophrenia may have a much more pronounced inflammatory profile than others, supporting the concept of an "inflammatory subgroup" in schizophrenia.

3.3.2 Variability of cytokines after treatment with antipsychotics

The analysis of the data suggests that inflammation-associated cytokines, such as IL-1β, TGF-β, and IFN-γ, show a reduction after treatment with antipsychotics. This suggests that antipsychotic medications may have an anti-inflammatory effect, as they appear to reduce the levels of pro-inflammatory markers in the blood.

Table 7.1.1. F test — Fisher test — for assessing differences between levels of pro-inflammatory cytokines in patients receiving antipsychotic treatment

Statistical indicator	**Value**
F statistic	35.983
P value	0.00003

The ANOVA analysis applied both to the group of patients receiving antipsychotic treatment and to the control group revealed statistically significant differences between the levels of pro-inflammatory cytokines in both groups.

Table 7.2.1. F test — Fisher test — for assessing differences between levels of pro-inflammatory cytokines in patients without antipsychotic treatment

Statistical indicator	**Value**
F statistic	8.134
P value	0.02910

Discussion and conclusions

According to the obtained results, there are statistically significant differences between the analyzed cytokines in the control group. The ANOVA analysis applied both to the group of patients receiving antipsychotic treatment and to the control group revealed statistically significant differences between the levels of pro-inflammatory cytokines in both groups. The correlation analysis between pro-inflammatory cytokine levels and antipsychotic treatment revealed a moderate positive relationship, confirmed by the nonparametric Spearman and Kendall tests, both showing statistical significance. These data suggest that changes in the levels of pro-inflammatory cytokines are associated with antipsychotic treatment, supporting the hypothesis of an immunomodulatory effect of antipsychotics.

3.4 Relationship between cytokine levels and cognitive function

The data indicate that immunoinflammatory activation represents a relevant mechanism in the impairment of cognitive function in schizophrenia, with variable intensity depending on the stage of the disease and the clinical profile of the patients. Pro-inflammatory cytokines, particularly IL-6, TNF-α, and IL-1β, are consistently associated with cognitive deficits in domains such as attention, working memory, executive function, and information processing speed, both in first-episode psychosis and in chronic or treatment-resistant forms.

3.5 Adjunctive anti-inflammatory therapies in schizophrenia

Inflammatory processes in the central nervous system contribute to the clearance of inflammatory mediators, with cytokines showing a direct concordant relationship between different stages of schizophrenia and quantitative changes.

3.5.1 Acetylsalicylic acid

Meta-analytic data suggest that aspirin administered as adjunctive treatment in schizophrenia may have a modest beneficial effect on global symptomatology, expressed by the total PANSS score. However, the lack of statistical significance and the variable level of heterogeneity across studies indicate that the clinical efficacy of aspirin has not been conclusively demonstrated at the population level, but may be relevant only for certain subgroups of patients, possibly characterized by an increased inflammatory profile.

3.5.2 Celecoxib

Discussion and conclusions: Celecoxib is emerging as a promising adjunctive treatment in schizophrenia, particularly for improving positive and general symptoms, with a favorable safety profile and good tolerability. Its efficacy appears to be more evident in the early stages of the disorder and in first-episode psychosis, suggesting the involvement of early inflammatory activation in the pathogenesis of schizophrenia. Clinical and meta-analytic data support the hypothesis of an inflammatory subgroup of patients in whom selective COX-2 inhibition may modulate neuroinflammatory processes and glutamatergic excitotoxicity. In this context, pro-inflammatory cytokines may represent not only markers of severity but also potential predictors of therapeutic response to anti-inflammatory interventions.

3.5.3 Minocycline

Conclusion regarding total symptoms: Statistical analyses revealed significant differences in the total PANSS score between the analyzed groups, as well as a strong positive association between adjunctive minocycline administration and symptom improvement in patients with schizophrenia compared with the control group.
Conclusion regarding negative symptoms: The ANOVA analysis performed for PANSS negative scores did not reveal statistically significant differences between the analyzed groups ($F = 2.085$; $P = 0.147$). These results suggest that adjunctive treatment with minocycline does not lead to a significant improvement in negative symptoms compared with the control group within the analyzed data.
Conclusion regarding positive symptoms: The ANOVA analysis revealed statistically significant differences in PANSS positive symptom scores between the analyzed groups ($F = 10.877$; $P = 0.00083$). These results indicate that adjunctive treatment with minocycline is associated with a significant improvement in positive symptoms in patients with schizophrenia compared with the control group. The high statistical significance suggests that minocycline exerts a beneficial effect on positive symptoms, possibly through anti-inflammatory mechanisms and modulation of microglial activation, supporting the hypothesis of the involvement of immunoinflammatory processes in the expression of positive symptoms in schizophrenia.
Conclusion regarding general symptoms: The ANOVA analysis demonstrated statistically significant differences in PANSS general symptom scores between the analyzed groups ($F = 5.276$; $P = 0.016$). These data suggest that adjunctive treatment with minocycline is associated with a significant improvement in the general symptoms of schizophrenia compared with the control groups.
General discussion: Overall, the data support the conclusion that minocycline administered as adjunctive treatment has a significant beneficial effect on total, positive, and general symptoms of schizophrenia, while its impact on negative symptoms remains limited. This highlights the need for differentiated therapeutic strategies and further studies specifically targeting this symptomatic domain.

Table 15. Results of randomized clinical trials on the clinical effects of anti-inflammatory therapies in schizophrenia [20–38].

Author	**Number of patients**	**Duration**	**Dose**	**Results**
Aspirin(ASP)				
Attari, 2017	60 SSD: 20 ASP(325 mg)+ APD, 20 PL + APD	6 weeks.	ASP 325 or 500 mg/day	The positive, negative, and general PANSS scores were lower in the aspirin group than in the placebo group. Omeprazole, 20 mg/day, was administered to all patients to reduce gastrointestinal adverse effects. No significant side effects were reported
Laan, 2010	70 SCZ: 33 ASP + APD, 37 PL + APD	3 months	ASP 1000 mg/day	The total PANSS score showed improvement. Pantoprazole, 40 mg/day, was administered to all patients for gastric protection. No significant side effects were reported.

Erlyn Limoa, 2023	46 SCZ: 23 ASP+RIS, 23 PL+RIS	8 weeks	ASP 1 tab/day*	The PANSS score decreased more markedly in the study group (73.46%) compared with the control group (35.5%) ($p < 0.001$).
Celecoxib(CEL)				
Akhondzadeh, 2007	60 SCZ: 30 CEL + RIS, 30 PL + RIS	8 weeks	CEL 400 mg/day; RIS 6 mg/day	The treatment significantly reduced the positive PANSS score and the total PANSS score. No significant benefit was observed for negative PANSS symptoms. No significant side effects were reported
Müller, 2002	50 SCZ: 25 CEL + RIS, 25 PL + RIS	5 weeks	CEL 400 mg/day; RIS 6 mg/day; 5 weeks	No significant improvement was observed in positive or negative PANSS symptoms. The total PANSS score decreased. The cognitive items “difficulty in abstract thinking” and “conceptual disorganization” improved. No significant side effects were reported in the treatment group.
Müller, 2010	50 SCZ: 25 CEL + AMI, 25 PL +AMI	6 day.	CEL 400 mg/day; AMI 200 → 1000 mg/day	A decrease in the PANSS negative symptom score was observed. No significant adverse effects were reported
Rapaport, 2005	35 SCZ: 18 CEL + APD, 17 PL + APD	8 weeks	CEL 400 mg/day	The treatment groups showed no clinical differences at the end of the study. No significant adverse effects were reported.
Wang ,2024	90 SCZ	12 weeks	CEL 400 mg/day	After 12 weeks of treatment, celecoxib significantly improved the total PANSS score and the scores of the three PANSS subscales in patients with schizophrenia
Zarghami, 2024	49 SCZ	5 weeks	CEL 400 mg/day	Over the course of 5 weeks, the celecoxib group showed a significantly greater improvement in total PANSS scores, positive symptom scores, and general psychopathology subscale scores: $t = 2.89$, $P = 0.006$; $t = 2.37$, $P = 0.022$; and $t = 3.34$, $P = 0.002$, respectively
N-acetylcysteine (NAC)				
Berk, 2008	140 SCZ: 69 NAC + APD, 71 PL + APD	24 weeks	NAC 2 g/day	A reduction was observed in the total, negative, and general PANSS scores. The positive PANSS score did not improve significantly. An improvement in the CGI score was observed. No significant side effects were reported
Farokhnia, 2013	42 SCZ: 21 NAC + RIS, 21 PL + RIS	8 weeks	NAC 2 g/day; RIS 6 mg/day	The PANSS negative symptom score improved. No significant side effects were reported
Minocicline (MIN)				
Xiang, 2017	548 SSD: 286 MIN + APD, 262 PL + APD	18.5 ± 13.4 weeks	MIN 171.9 ± 31.2 mg/day	Eight studies were included. The total, positive, negative, and general PANSS and BPRS scores improved.

				No significant improvement in cognitive function was observed. No significant differences in adverse events were found between the study group and the control group.
Interferon-γ-1b (IFN-γ-1b)				
Grüber, 2014	2 SCZ	4 weeks.	1.5 ml/week	A reduction in the total PANSS score was observed
Monoclonal antibodies				
Girgis, 2018	36 SCZ: 19 TOC + APD; 17 PL + APD		Tocilizumab (TOC): 8 mg/kg, 3 infusions per month, for 12 weeks. Tocilizumab (TOC): 4 mg/kg, 2 infusions per month, for 8 weeks. Canakinumab (CNK): 150 mg, single infusion, adjunctive to antipsychotic drugs (APD), for 8 weeks	A significant reduction in PANSS negative symptoms was observed. No significant behavioral changes were reported.
Hoprekstad, 2025	6SCZ+PRD+APD : 6 PL+APD	6 weeks.	PRD, prednisolone tapered from 40 mg/day to 5 mg/day by week 6.	A reduction in the PANSS score was observed over 6 weeks. A statistically significant reduction in the PANSS general psychopathology score was observed over 6 weeks. No change was observed in PANSS negative symptoms
Miller,2016	6SCZ	8 weeks	TOC 4 mg/kg, 2 infusions (weeks. 0, 4)	No significant changes were observed. An improvement in verbal fluency was observed.
Weickert, 2019	27 SCZ + SZA: CNK + APD; PL + APD (nu este specificat nr. pacienți per grup)	8 weeks	CNK 150 mg, 1 infusion; APD	An improvement in positive symptoms was observed. A positive correlation was found between high-sensitivity C-reactive protein and the PANSS positive symptom score. An improvement in PANSS positive symptoms was observed.

				A positive correlation was found between C-reactive protein levels and the PANSS positive symptom score.
Statins (STAs)				
Shen, 2018	339 SCZ: 169 STA + APD, 170 PL + APD	6 weeks.– 6 months	Pravastatin 40 mg/day; lovastatin 20 mg/day; simvastatin 40 mg/day; atorvastatin 20 mg/day	Six studies were included. A reduction in PANSS positive and negative symptom scores was observed. A correlation was found between adjunctive simvastatin treatment and a reduction in PANSS negative symptoms
Fingolimod				
Karbalaee, 2024	80 SCZ	8 weeks.	Fingolimod 0,5 mg/day	Significant time-by-treatment interaction effects were observed for negative symptoms (P = 0.003), general symptoms (P = 0.037), and the total PANSS score (P = 0.035), suggesting greater symptom improvement following adjunctive fingolimod therapy.
Berberine				
Meijuan,2022	32SCZ+27PL	8 weeks	Berberine 900mg/day	Berberine treatment significantly improved the PANSS negative symptom subscale (F = 18.981; p < 0.001). In the berberine group, the change in CRP concentration was significantly positively correlated with the change in the PANSS negative symptom subscale over 8 weeks (r = 0.56; p = 0.002).
Palmitoylethanolamide (PEA)				
Salehi,2022	50 SCZ (25 RIS+25PL)	8 weeks	PEA 1200 mg/day	A significant time-by-treatment interaction effect was observed for negative symptoms (p = 0.012), suggesting greater symptom improvement in the PEA group. In contrast, longitudinal changes in positive symptoms and depressive symptoms were similar between groups (p > 0.05).

Legend: SSD, schizophrenia spectrum disorder; APD, antipsychotic drugs; PL, placebo; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia; RIS, risperidone; AMI, amisulpride; CGI, Clinical Global Impression scale; BPRS, Brief Psychiatric Rating Scale; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PRG, pregnenolone; ESR, estrogen; SERM, selective estrogen receptor modulator; EPO, erythropoietin; DAV, davunetide; MCCB, MATRICS Consensus Cognitive Battery; SCoRS, Schizophrenia Cognition Rating Scale; UPSA, UCSD Performance-Based Skills Assessment; TOC, tocilizumab; SZA, schizoaffective disorder; CNK, canakinumab; CRP, C-reactive protein; PRD, prednisolone.

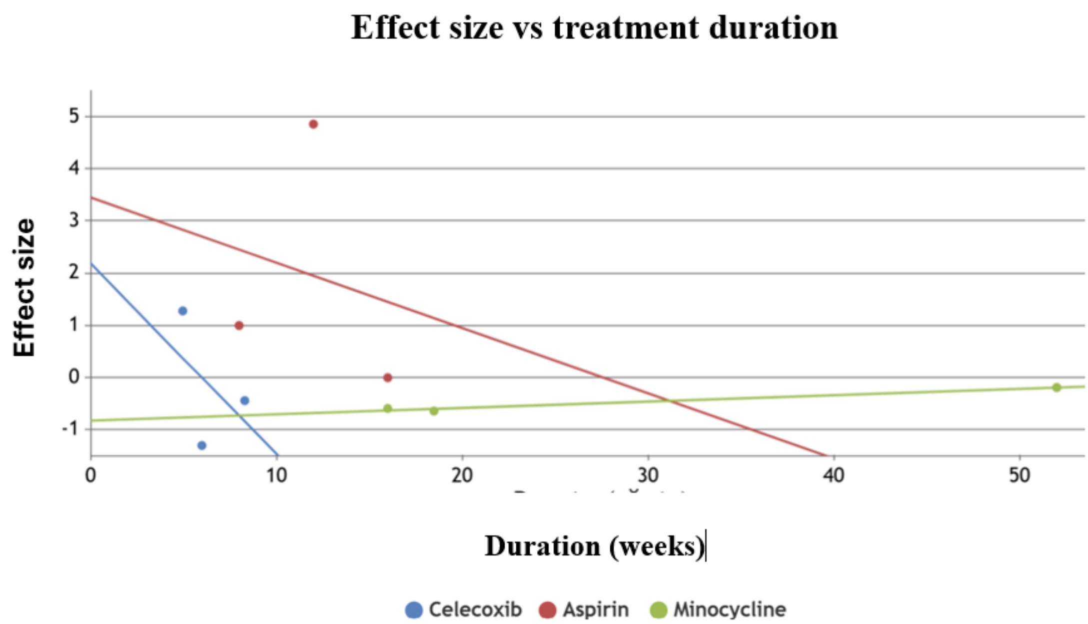
To determine the relationship between two variables, namely the duration and the effect of anti-inflammatory treatment, studies reporting both treatment duration and effect size were selected (Table 16).

Table 16. Statistical data on adjunctive therapy with aspirin, celecoxib, and minocycline

Type of intervention	**Study** *(author, year)*	**Total number of patients**	**Effect measure**	**Duration** *(weeks)*
Aspirin	Laan et al., 2010 [22]	70	4.86	12.0
Aspirin	Weiser et al., 2021 [39]	360	0.0	16.0
Aspirin	Pourghasem et al., 2022 [40]	45	1.0	8.0
Celecoxib	Baheti et al., 2013 [41]	71	-1.3	6
Celecoxib	Zheng et al., 2017 [42]	626	-0.44	8.3
Celecoxib	Zarghami et al., 2024 [43]	49	1.28	5.0
Minocycline	Solmi et al., 2017 [44]	413	-0.59	16.0
Minocycline	Xiang et al., 2017 [29]	548	-0.64	18.5
Minocycline	Deakin et al., 2018 [45]	207	-0.19	52.0
Minocycline	Deakin et al., 2019 [46]	207	-0.186	52.0

Based on these data, a scatter plot was generated using StatsCharts, an online tool for statistical charts and data visualization (StatsCharts. Online statistical charts and data visualization tool. Available from: https://www.statscharts.com).

Figure 15. Scatter plot showing the correlation between treatment duration and treatment effect in adjunctive anti-inflammatory therapy



Conclusions: Based on the scatter plot, aspirin appears to produce a stronger initial therapeutic effect; however, this effect tends to decrease over longer treatment durations. Celecoxib also demonstrates early benefits, particularly during the first weeks of therapy, followed by a subsequent decline in effectiveness. In contrast, minocycline shows a more modest but relatively stable effect over time, suggesting its potential suitability for longer-term adjunctive anti-inflammatory treatment.

3.6 Correlation between duration, dose, and effect of anti-inflammatory therapy

Table 17. Correlation between age, duration, dose, and effect of anti-inflammatory therapy

Medication name, Author	Patient age (years)	Treatment duration	Measured indicators	Results
Aspirin 325 or 500 mg Attari N. et al., 2017 [21]	31.4 – 33.5	6 weeks	PANSS	Results showed that the effect of adding aspirin to antipsychotic treatment was greater in terms of the final outcome, positive and negative symptoms, and general psychopathology four weeks after discontinuing the intervention, compared with the other time points.
Aspirin 1000 mg Laan W. et al., 2010 [22]	—	3 months	PANSS	Aspirin administered as adjuvant therapy to standard antipsychotic treatment reduces symptoms of schizophrenia spectrum disorders. The reduction is more pronounced in individuals with more altered immune function.

Medication name, Author	Patient age (years)	Treatment duration	Measured indicators	Results
Aspirin 325 mg + risperidone Erlyn Limoa et al., 2023 [23]	20–45	8 weeks	PANSS	Greater decrease in serum TNF-α levels compared with those who received risperidone alone. More pronounced clinical effect with combination therapy (73.46% vs. 35.5%).
Celecoxib 400 mg + risperidone 6 mg Akhondzadeh S. et al., 2006 [24]	19–44	8 weeks	PANSS	The combination of risperidone and celecoxib showed significant superiority over risperidone monotherapy in treating positive symptoms, general psychopathology symptoms, as well as in total PANSS scores.
Celecoxib 400 mg + risperidone 2–6 mg Müller N. et al., 2002 [47]	35.9 (SD = 12.8) celecoxib group; 35.5 (SD = 13.6) placebo group	5 weeks	PANSS	Add-on treatment with celecoxib has significant positive effects on the therapeutic action of risperidone in the total psychopathology of schizophrenia.
Celecoxib 400 mg + amisulpride (200–1000 mg) Müller N. et al., 2010 [26]	26.2–30.9	6 weeks	PANSS CGI	A significantly superior therapeutic effect was observed in the celecoxib group compared with placebo in the treatment of early-stage schizophrenia. This is the first time an improvement of negative symptoms in patients has been demonstrated through celecoxib administration.
Celecoxib 400 mg Rapaport H. et al., 2005 [25]	44.1–47.3	8 weeks	—	Augmentation of treatment with celecoxib in outpatients with chronically ill schizophrenia did not improve clinical symptoms or measures of disability.
Minocycline 200 mg Chaudhry IB et al., 2012 [48]	—	48 weeks	PANSS	Adding minocycline to standard treatment in the early stages of schizophrenia leads predominantly to improvement of negative symptoms.
Minocycline 200 mg	31–30.2	8 weeks	PANSS AIMS	The decrease in PANSS score for negative symptoms from baseline to week 8 in the minocycline group was

Medication name, Author	Patient age (years)	Treatment duration	Measured indicators	Results
Ghanizadeh A. et al., 2014 [49]				greater than in the placebo group (4.3 (4.2) vs. 3.2 (3.3)). However, the difference was not statistically significant. No participant discontinued the study because of adverse effects. This study supports the efficacy of minocycline as an adjuvant treatment alongside risperidone for treating negative symptoms in patients with schizophrenia.
Minocycline 200 mg + risperidone max 6 mg Khodaie-Ardakani M. et al., 2013 [50]	41.05–38.95	8 weeks	PANSS AIMS	Minocycline appears to be an effective and well-tolerated short-term adjuvant to risperidone for the treatment of negative symptoms and general psychopathology in schizophrenia.
Minocycline 200 mg + 200–600 mg chlorpromazine equivalent Levkovitz Y. et al., 2009 [51]	25.1–24.7	6 months	SANS CGI	Treatment with minocycline was associated with improvement of negative symptoms and executive functions, both correlated with frontal lobe activity.
Minocycline 200 mg Liu F. et al., 2014 [52]	27.05–27.7	16 weeks	SANS PANSS CGI	The treatment response rate (43.6%) in the minocycline group was significantly higher compared with the placebo group (10.0%) after 16 weeks of treatment. No significant differences were found between the seven cognitive domains ($P > 0.05$), except for the attention domain ($P = 0.044$).

Discussion: Thus, the mean age for aspirin was 33.5 years (range: 20–45 years), for celecoxib 35 years (range: 19–47 years), and for minocycline 31 years (range: 25–41 years). The overall mean age was therefore 33 years (range: 19–47 years). The mean duration of adjunctive aspirin treatment was 8 weeks (range: 6–12 weeks), celecoxib treatment lasted an average of 7 weeks (range: 5–8 weeks), while minocycline had a mean treatment duration of 21 weeks (range: 4–48 weeks). Overall, the response rate for the three anti-inflammatory agents, compared with the control group, was 83% across the total of 12 evaluated studies.

3.7 Central inflammatory markers and their relationship with quality of life

Interleukin-6 (IL-6) and quality of life. IL-6 is the most consistent proinflammatory marker in schizophrenia and shows strong associations with quality-of-life indicators. Increased IL-6 levels are linked to poorer physical and psychological well-being in patients with schizophrenia. Studies demonstrate that IL-6 is significantly correlated with reduced mental and physical well-being [53]. The relationship between IL-6 and quality of life appears to be mediated by several pathways, including metabolic dysfunction, cognitive impairment, and symptom severity.

Tumor necrosis factor-alpha (TNF-α) and functional status. TNF-α levels show strong negative correlations with quality of life in schizophrenia. Baseline peripheral TNF-α levels are negatively associated with remission at 6 months in female patients, suggesting that elevated TNF-α may hinder recovery and functional improvement [54]. TNF-α is positively correlated with adverse symptoms and negatively correlated with several cognitive functions, including attention, verbal memory, and executive functioning [54].

C-reactive protein (CRP) and quality of life. CRP is a useful screening marker for detecting inflammation in patients with schizophrenia and shows consistent associations with quality of life. Patients with elevated CRP levels (>3.0 mg/L) have lower quality of life compared with those with normal CRP levels [55]. After adjustment for sociodemographic and clinical variables, individuals with elevated CRP demonstrated significantly lower quality of life than those with normal CRP levels (OR = 0.57, 95% CI = 0.46–0.68) [56]. Elevated CRP levels are associated with more severe symptoms and poorer quality-of-life outcomes. Studies show that patients with increased CRP have higher scores across different PANSS categories, including total PANSS score, positive symptoms, negative symptoms, and general psychopathology.

Subsequently, from 50 identified sources, we selected 8 studies with well-structured and clearly defined research designs for direct or indirect assessment of quality-of-life indicators. The analyzed data support the existence of consistent bidirectional relationships between proinflammatory markers (IL-6, TNF-α, and CRP) and quality-of-life indicators. Elevated levels of these markers are associated with poorer physical and psychological well-being, impaired social functioning, cognitive deficits, and greater clinical severity, supporting the rationale for targeting inflammation as an adjunctive therapeutic approach.

3.10 Chapter 3 Summary

1. Cytokines in First-Episode Psychosis. Analysis of the correlation between proinflammatory cytokine levels and antipsychotic treatment revealed a moderate positive relationship, confirmed through nonparametric Spearman and Kendall tests, both with statistical significance. These data suggest that changes in proinflammatory cytokine levels are associated with antipsychotic treatment, supporting the hypothesis of an immunomodulatory effect of antipsychotics.

2. Relationship Between Cytokine Levels and Cognitive Function. The data indicate that immunoinflammatory activation represents a relevant mechanism in cognitive impairment in schizophrenia, with variable intensity depending on disease stage and clinical profile of patients. Proinflammatory cytokines, particularly IL-6, TNF-α, and IL-1β, are consistently associated with cognitive deficits in domains such as attention, working memory, executive function, and information processing speed, both in first-episode psychosis and in chronic or treatment-resistant forms. Meta-analytic data confirm the existence of a significant inverse association between inflammatory markers and global cognitive performance.

3. Adjunctive Anti-inflammatory Therapy in Schizophrenia. Integrated analysis of clinical, meta-analytic, and statistical data indicates that the efficacy of adjunctive anti-inflammatory therapy in schizophrenia is heterogeneous, dependent on the substance used, clinical context, and inflammatory profile of patients, without supporting universal use of these interventions. For aspirin, meta-analytic data suggest a potential modest beneficial effect on global symptomatology, expressed through total PANSS score. Celecoxib emerges as a promising adjunctive agent, particularly for amelioration of positive and general symptoms, with favorable safety and tolerability profile. Its efficacy appears more pronounced in early stages of schizophrenia and in first-episode psychosis, supporting the hypothesis of early inflammation involvement in disease pathogenesis. The data support the existence of an inflammatory subgroup in which selective COX-2 inhibition can modulate neuroinflammatory processes and glutamatergic excitotoxicity, and proinflammatory cytokines can function both as severity markers and as predictors of therapeutic response. Adjunctive treatment with minocycline indicates a positive, stable, and statistically significant association between adjunctive minocycline treatment and improvement in total PANSS score. The data suggest a moderate beneficial effect, confirmed through multiple statistical methods, which confers validity to the conclusions. Minocycline efficacy appears to be dependent on clinical context, being more evident in acute or subacute phases of illness and possibly conditioned by baseline inflammatory status.

4. Age-Effect Relationship in Adjunctive Therapy. Therapeutic response remains high regardless of age variation. Patient ages ranged from 19 to 47.3 years; however, clinical response was positive in over 83% of studies, indicating that age is not a major limiting factor in the efficacy of adjunctive anti-inflammatory treatment. Substances such as minocycline and aspirin showed efficacy both in younger patients (20–30 years) and in older patients (40+ years).

5. Duration-Effect Relationship in Adjunctive Therapy. Longer treatment duration does not guarantee a better response. Short-term treatments with aspirin (6–8 weeks) or celecoxib (5–8 weeks) generated positive clinical responses. Optimal duration may depend more on patient profile and selection of inflammatory biomarkers than on treatment length itself. The best response rates were observed in combination therapies. For both aspirin and minocycline, combination with an antipsychotic led to significantly better clinical response rates than monotherapy. This suggests that anti-inflammatory mechanisms can potentiate the effect of antipsychotics, especially in forms with resistant negative symptomatology.

6. Dose-Effect Relationship in Adjunctive Therapy. Correlative analysis of dose, treatment duration, and clinical response indicates that the efficacy of adjunctive anti-inflammatory therapy in schizophrenia is predominantly determined by the type of substance used and association with baseline antipsychotic. For aspirin, moderate doses (325–1000 mg/day) administered over relatively short periods (6–12 weeks) were associated with significant clinical improvements, including positive symptoms, negative symptoms, and general psychopathology, suggesting that therapeutic benefit appears early and does not require prolonged exposure. For celecoxib, the standard dose of 400 mg/day demonstrated clinical efficacy particularly in early stages of schizophrenia, with observable effects in short intervals (5–8 weeks), while treatment prolongation or use in patients with stabilized chronic illness did not lead to additional benefits, indicating a limited temporal therapeutic window. In contrast, minocycline, administered at a constant dose of 200 mg/day, presented a more modest but more stable effect over time, with sustained benefits on negative symptoms and executive functions in studies with medium and long duration (16–48 weeks), suggesting a profile suitable for longer-term adjunctive interventions.

7. Impact of Adjunctive Anti-inflammatory Therapy on Quality-of-Life Indicators in Schizophrenia. Systemic inflammation represents a relevant biological determinant of quality of life in schizophrenia. Adjunctive anti-inflammatory therapy has the potential to improve quality of life through indirect mechanisms. The effect on quality of life appears to be mediated primarily through reduction of negative symptoms, improvement in cognitive functioning and social adaptation, rather than through a direct influence on subjective perception of well-being. The analyzed data support the existence of consistent and bidirectional relationships between proinflammatory markers (IL-6, TNF-α, CRP) and quality-of-life indicators. Elevated levels of these markers are associated with poorer physical and psychological well-being, impaired social functioning, cognitive deficits, and greater clinical severity, which justifies addressing inflammation as an adjunctive therapeutic target. Adjunctive therapy with anti-inflammatory agents, particularly aspirin and N-acetylcysteine, can contribute to improvement in functional and cognitive status, two essential dimensions of quality of life in patients with schizophrenia.

Overall, these results support the conclusion that adjunctive anti-inflammatory therapy does not represent a uniformly effective strategy in schizophrenia, but rather one that requires careful patient selection based on clinical and biological characteristics. Identification of subgroups with relevant inflammation and use of inflammatory markers as therapeutic stratification tools represent essential directions for optimizing adjunctive anti-inflammatory interventions and for developing personalized approaches in schizophrenia treatment. There is an urgent need for personalized therapeutic approaches that focus on patients presenting relevant peripheral inflammation, rather than adding a nonsteroidal anti-inflammatory drug (NSAID) to every patient with schizophrenia and persistent symptomatology.

4. MITOCHONDRIAL DYSFUNCTION AND PHOSPHOLIPID IMBALANCE AS PATHOGENETIC MECHANISMS OF SCHIZOPHRENIA: THE ROLE OF POLYUNSATURATED FATTY ACIDS, NIACIN, AND OXIDATIVE STRESS IN TRANSITION TO PSYCHOSIS

4.1 Introduction

Mitochondrial pathology is a frequent finding in schizophrenia, evidenced through various techniques in patients, in post-mortem samples, in cell lines, and in animal models [57]. Thus, schizophrenia is not only a disease with synaptic transmission disturbances, but also a condition accompanied by systemic and cellular dysfunctions of energy metabolism. Post-mortem studies indicate a decrease in neuronal and glial density in certain brain regions, suggesting the involvement of apoptosis in the pathogenesis of schizophrenia. In response to intracellular signals generated by cellular stress and mitochondrial dysfunction, the intrinsic apoptotic pathway can be activated through the release of proapoptotic factors from mitochondria [58].

4.2 Mitochondrial Dysfunction, Oxidative Stress, and Dopaminergic Neurotransmission in Schizophrenia

Under physiological conditions, dopamine (DA) is metabolized with the participation of mitochondrial enzymes—monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). This process leads to the formation of hydrogen peroxide (H_2O_2) and other reactive oxygen species (ROS) . Under conditions of dopamine excess or deficient utilization, similar to schizophrenia, there is an increase in the level of reactive oxygen species, which damages the mitochondrial membrane, reduces the electrical potential difference between the two faces of the inner mitochondrial membrane ($\Delta\Psi m$) and the activity of complex I (NADH dehydrogenase) [59][60][61]. The inner mitochondrial membrane potential ($\Delta\Psi m$) is considered the driving force of ATP synthesis and is essential for mitochondrial functions: protein transport, calcium homeostasis, and maintenance of mitochondrial integrity. Dopamine toxicity on mitochondria in neuronal and oligodendrocyte cultures is manifested by reduction of mitochondrial membrane potential ($\Delta\Psi m$), reduction of complex I activity (the largest enzymatic complex in the mitochondrial respiratory chain), decreased adenosine triphosphate (ATP) production, increased levels of reactive oxygen species (ROS), and activation of apoptosis [62][63]. Investigations of patients at first-episode psychosis have identified mitochondrial abnormalities occurring before antipsychotic treatment [64]. Although both typical and atypical antipsychotics can alter mitochondrial function, the mode of action differs between them. In general, typical medications exert a more pronounced inhibition on mitochondrial function and induce greater oxidative stress than atypical ones. This has been evidenced by changes in mitochondrial membrane potential[62][63] .

4.3 Materials and Methods

This chapter analyzed adjunctive interventions with mitochondrial targeting potential in schizophrenia and the role of polyunsaturated fatty acids (omega-3/omega-6) and niacin in pathogenesis and in transition to psychosis. The methodological approach included: (1) synthesis of evidence from secondary sources (umbrella reviews, meta-analyses, systematic reviews) for mitochondrial interventions; (2) an original meta-analysis for the effect of omega-3 on total

PANSS, based on randomized clinical trials that reported homogeneous data (Mean, SD, N) for the omega-3 and placebo groups; (3) a literature review regarding the niacin test and its mechanisms (flushing/prostaglandin–phospholipid–PUFA/NAD axis). The bibliographic search for the niacin/PUFA component and transition to psychosis was conducted in PubMed, MEDLINE, Scopus, Cochrane Library, and Research4Life databases, for literature published up to and including 2024. Statistical analysis and software used: The PANSS meta-analysis (omega-3) was performed in RevMan Web (The Cochrane Collaboration, 2023), using the data (Mean/SD/N) entered for each study and generating a forest plot. Visualizations (forest plot for mitochondrial therapies, heat map, comparative graphs) were created in MATLAB (The MathWorks, Inc., MATLAB R2025b, Natick, MA, 2025). For classification of the level of evidence, compounds were grouped into a standardized operational A-C system. Results were synthesized in the form of tables and figures.

4.4 Results and Discussion

For a comparative evaluation of the evidence, a synthesis in table form of adjunctive interventions with mitochondrial potential in schizophrenia was performed. Based on these data, we visualized the effect size (Standardized Mean Difference, SMD) and 95% confidence intervals for each intervention using a forest plot. The vertical axis lists the interventions, and the horizontal axis represents the SMD. A value of 0 indicates no difference. A negative sign of the SMD corresponds to an improvement in favor of the intervention (decrease in symptom score):

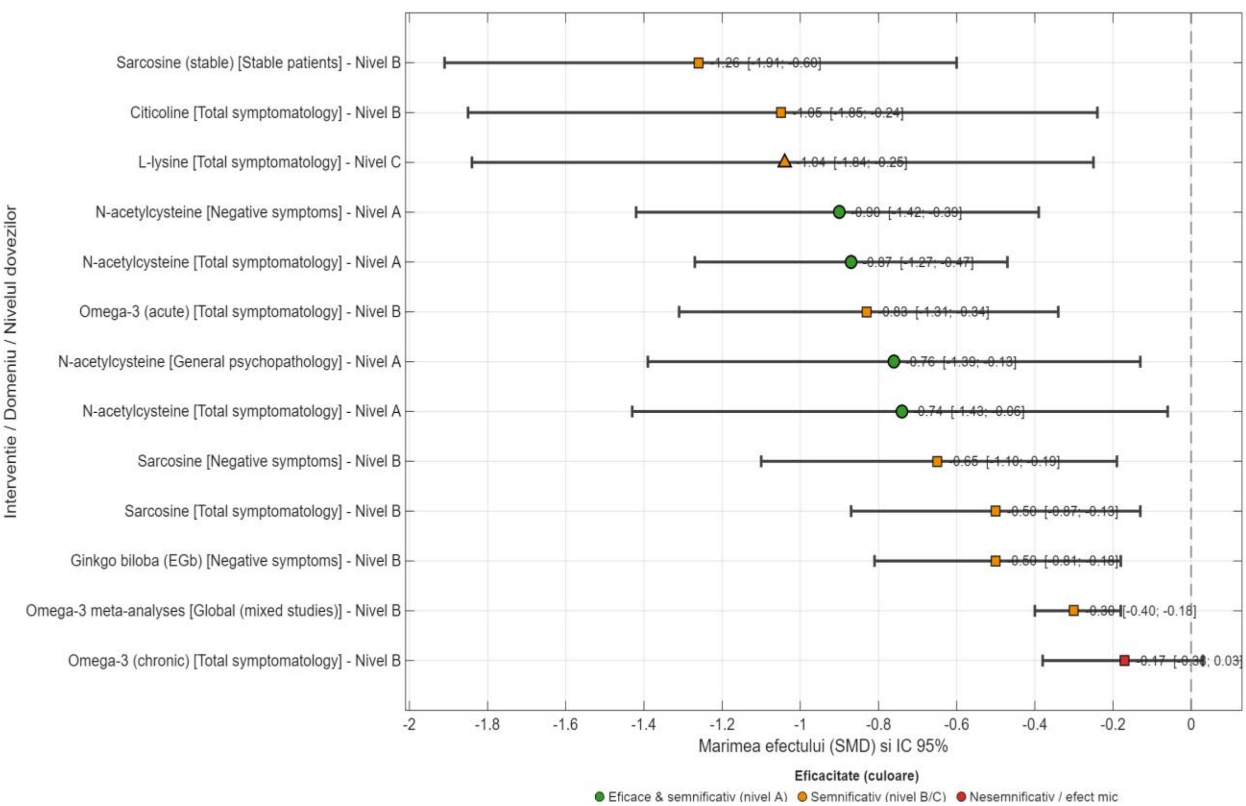


Figure 16. Forest plot of adjunctive mitochondrial-targeted therapies in schizophrenia, showing standardized mean differences (SMDs) and 95% confidence intervals (CIs), coded according to the level of evidence
(The MathWorks, Inc. MATLAB, version R2025b. Natick, MA: The MathWorks, Inc.; 2025).

In conclusion, the forest plot supports the usefulness of N-acetylcysteine (NAC) as an adjunctive intervention with the best combination of effect size and consistency, while sarcosine, citicoline, L-lysine, EGb, and omega-3 remain promising options, but with limitations in study methodology. High heterogeneity between studies, possible influence of publication bias, and design differences (disease stage, doses, duration, inclusion criteria) limit the generalization of conclusions. To facilitate an integrated comparison between adjunctive interventions with mitochondrial potential, a heat map was constructed that simultaneously synthesizes four relevant dimensions: level of evidence (ordinally coded), effect magnitude (SMD), compatibility with antipsychotic treatment, and safety profile. This visual representation allows rapid identification of interventions with favorable overall profiles and highlights areas with missing data (missing cells), contributing to the comparative interpretation of results from existing syntheses. The figure was generated in MATLAB (MathWorks, MATLAB R2025b), using SMD values and evidence levels extracted from previous tables. To allow direct visual comparison between interventions, SMD values were expressed as effect size (absolute value), regardless of the direction of effect.

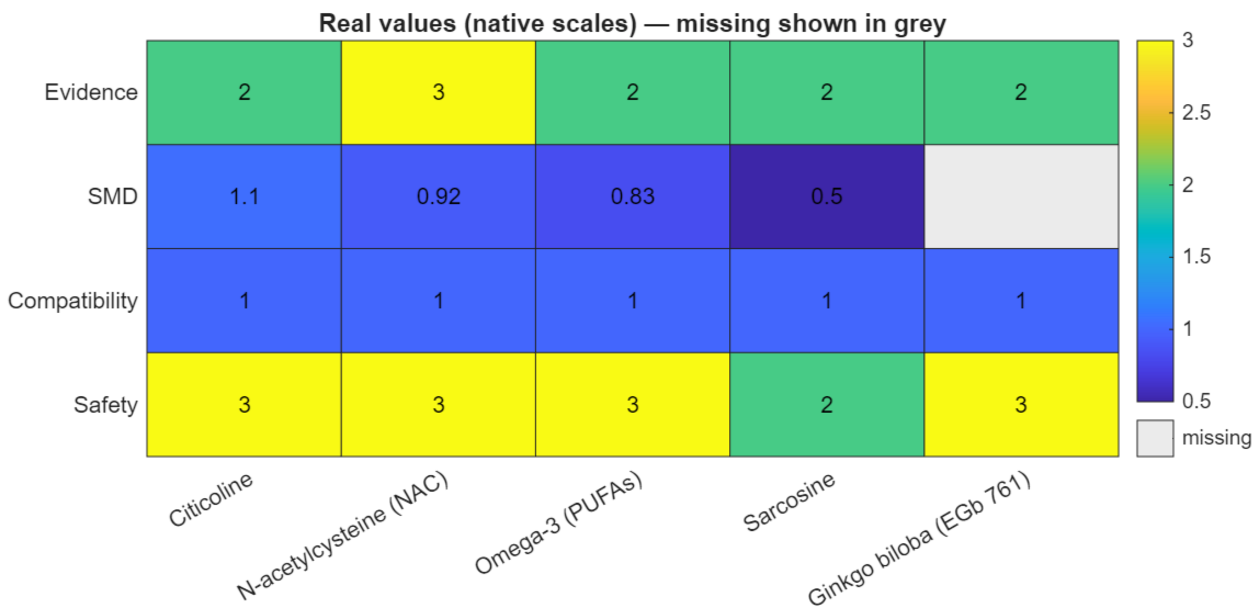


Figure 17. Heat map. Adjunctive mitochondrial interventions: Actual values of indicators (native scales). (MathWorks. MATLAB Release R2025b. Natick, MA: The MathWorks, Inc.; 2025.)

Legend:
Evidence: 0–3 (A = 3, B = 2, C = 1, ns = 0). Ns = no significant evidence (not significant). SMD (efficacy indicator): standardized mean difference (SMD). Compatibility: 0 = No, 1 = Yes. Safety: 1–3 (Low = 1, Moderate = 2, High = 3). Gray cell (Ginkgo, at SMD) indicates missing numerical data.

The figure indicates that citicoline had the highest value of standardized effect value (SMD), moderate evidence level (B), high safety, and good compatibility. NAC remains highest in level of evidence (A = 3), with moderate-to-large SMD and very good safety and compatibility profile. Omega-3 shows moderate efficacy and excellent safety profile, good compatibility with antipsychotics. Sarcosine has lower efficacy and moderate safety (2), but is compatible with antipsychotics. Ginkgo biloba has excellent safety, is compatible, and has evidence level B, but lacks SMD data.

Discussion: Comparative Analysis of Mitochondrial Adjuvants
Compounds with High Level of Evidence: N-Acetylcysteine (NAC)
Efficacy: Consistent evidence regarding amelioration of negative, general, and total symptoms, as well as cognitive domains, in multiple systematic reviews and meta-analyses.
Effect size: Moderate (SMD between -0.41 and -0.92, where reported).
Safety: High. No significant adverse events or drug interactions were reported in available safety studies.
Compatibility: Excellent. Reported as compatible with antipsychotics, including clozapine, olanzapine, and risperidone.
Level of evidence: High (A), although some meta-analyses assess the quality of evidence as low or very low due to heterogeneity and small sample sizes.
Compounds with Moderate Level of Evidence: Citicoline
Efficacy: High efficacy (SMD approximately -1.05) in network meta-analyses.
Quality of evidence: Low, due to limited number of studies and high heterogeneity.
Safety and compatibility: Good. No significant adverse events or drug interactions were reported.
Sarcosine:
Efficacy: Moderate, particularly for negative symptoms in stable, non-refractory patients (SMD between -0.36 and -1.26).
Safety: Moderate to high. Good tolerability has been reported.
Compatibility: Generally good, but efficacy may be reduced in combination with clozapine.
Omega-3 Fatty Acids:
Efficacy: Effective in acute phases (SMD -0.83), with variations in effect sizes and quality of evidence.
Safety and compatibility: High. Favorable safety profile and good compatibility reported.
Level of evidence: Moderate (B).
Ginkgo Biloba Extract (EGb 761):
Efficacy, safety, and compatibility: Not directly evaluated in these 10 studies; however, previous meta-analyses support a moderate effect on negative symptoms, high safety, and good compatibility.
In conclusion, among the included studies, N-acetylcysteine (NAC) stands out as the mitochondrial adjuvant with the most balanced and consistent profile in schizophrenia, supported by constant efficacy, high safety, and excellent compatibility with antipsychotics. Citicoline, sarcosine, and omega-3 fatty acids represent promising alternatives, with moderate evidence regarding efficacy and favorable safety profiles. Ginkgo biloba extract is supported by previous evidence indicating moderate efficacy and high safety.

4.4.1 Polyunsaturated fatty acids, niacin, and transition to psychosis

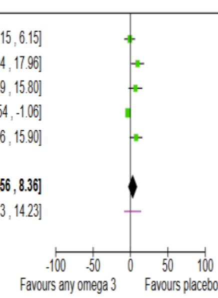
Analyzing the effect of omega-3 fatty acids on factors involved in the pathophysiology of inflammation associated with schizophrenia, an anti-inflammatory effect was observed in 10 of the 12 cases studied. Omega-3 fatty acids act on interleukin metabolism by reducing the levels of IL-1β and IL-6, which are inflammatory mediators [67][68].

Another study, which included 33 clinical trials with a total of 2,068 participants, concluded that a daily intake of 1 g of omega-3 fatty acids significantly reduced IL-6 levels (SMD = –1.17 pg/mL; 95% CI: –1.78 to –0.55; $p < 0.001$; GRADE = moderate) and TNF-α levels (SMD = –2.15 pg/mL; 95% CI: –3.14 to –1.16; $p < 0.001$) [69]. Increased levels of omega-6 polyunsaturated fatty acids (PUFAs) in individuals who progressed to psychosis (CHR-C) may reflect activation of the prostaglandin cascade and a cytokine-induced inflammatory response in the brain.

To evaluate the effect of polyunsaturated fatty acids in schizophrenia, we performed a meta-analysis of data from randomized clinical trials that reported statistically relevant and sufficiently homogeneous data for meta-analysis. Statistical synthesis analyses were performed using RevMan Web software (Review Manager Web, The Cochrane Collaboration, 2023). For each of the five resulting studies included in the analysis, relevant numerical data were manually extracted: the mean total PANSS score, standard deviation (SD), and number of participants (N) for the experimental group (omega-3) and the control group (placebo). These data were entered into RevMan Web, where summary tables and forest plot graphical representations were generated.

In the table below, the total PANSS outcome after intervention with omega-3, administered orally in different forms and doses versus placebo, was analyzed [70][71][72][73][74][75] (Figure 19).

	Any omega 3			Placebo				Mean difference	Risk of Bias					
Study or Subgroup	Mean [PANSS points]	SD [PANSS points]	Total	Mean [PANSS points]	SD [PANSS points]	Total	Weight	IV, Random, 95% CI [PANSS points]	A	B	C	D	E	F
Fenton 2001 – Omega-3 vs Placebo – PANSS total[a]	69	16	43	70	18	44	19.9%	-1.00 [-8.15 , 6.15]	+	+	+	+	?	?
Emsley 2002 Omega 3 supplemental schizophrenia[b]	12.6	14	20	3.1	13.3	20	17.5%	9.50 [1.04 , 17.96]	?	+	+	+	?	+
Bentsen et al., 2013 Omega and vitamins[c]	69.408163	21.330493	49	62.804	25.209514	50	16.3%	6.60 [-2.59 , 15.80]	+	+	?	+	?	?
Jamilian et al., 2014 Omega-3 in schizophrenia	49.13	5.31	30	52.43	3.32	30	28.8%	-3.30 [-5.54 , -1.06]	?	+	+	+	?	?
Qiao, 2020 Omega 3[d]	67.38	16.54	32	59.91	18.67	35	17.6%	7.47 [-0.96 , 15.90]	+	+	+	+	+	?
Total (Wald[e])			**174**			**179**	**100.0%**	**2.90 [-2.56 , 8.36]**						
95% prediction interval								[-8.43 , 14.23]						



Test for overall effect: Z = 1.04 (P = 0.30)

Heterogeneity: Tau² (REML[f], 95% CI) = 25.66 [2.86 , 251.94]; Chi² = 16.31, df = 4 (P = 0.003); I² = 71%

Footnotes

[a]Means and SD were taken directly from the study's original table; Endpoint data (week 16). PANSS total (30–210), lower scores indicate improvement; endpoint at 16 weeks.

[b]Endpoint (week 12). Lower PANSS = improvement. ITT with LOCF; add-on to stable antipsychotics

[c]Endpoint means and SDs for PANSS total were not directly reported in the publication. Values were reconstructed from baseline and modeled change data as presented by the authors.

[d]Week-8 endpoint; final values (not change). PANSS total range 30–210 (higher = worse). Means/SDs from Qiao 2020, Table 2 (week 8). Adjunctive omega-3 540 mg EPA + 360 mg DHA/day vs placebo (vitamin E 10 mg/day). 67 randomized; 47 completed—per-arm completer N nc

[e]CI calculated by Wald-type method.

[f]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

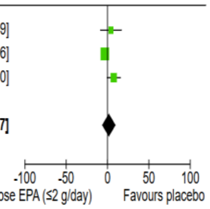
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Figure 19. Forest plot: Effect of omega-3 fatty acids as an adjunct to antipsychotic treatment on PANSS score (Review Manager Web, The Cochrane Collaboration, 2023).

General interpretation: The evidence does not support a clear benefit of omega-3 supplementation in schizophrenia with respect to the total PANSS score. The results are inconsistent: some studies show benefit, one shows a negative effect, and others show no effect. The high heterogeneity reduces confidence in the pooled results. Larger, high-quality randomized clinical trials are needed, ideally stratified by dose, duration, and formulation type.

Subsequently, the studies were divided according to the dose of omega-3 administered (up to 2 g/day vs 3 g/day). The results obtained for the dose of up to 2 g/day are shown in the figure below.

Study or Subgroup	Low dose EPA (≤2 g/day) Mean [PANSS points]	SD [PANSS points]	Total	Placebo Mean [PANSS points]	SD [PANSS points]	Total	Weight	Mean difference IV, Random, 95% CI [PANSS points]
Bentsen et al., 2013 Omega and vitamins[a]	69.408163	21.330493	49	65.3	30	26	20.2%	4.11 [-8.88 , 17.09]
Jamilian et al., 2014 Omega-3 in schizophrenia	49.13	5.31	30	52.43	3.32	30	48.7%	-3.30 [-5.54 , -1.06]
Qiao, 2020 Omega 3[b]	67.38	16.54	32	59.91	18.67	35	31.1%	7.47 [-0.96 , 15.90]
Total (Wald[c])			**111**			**91**	**100.0%**	**1.54 [-5.98 , 9.07]**



Test for overall effect: Z = 0.40 (P = 0.69)

Heterogeneity: Tau² (REML[d]) = 28.97; Chi² = 6.85, df = 2 (P = 0.03); I² = 67%

Footnotes

[a]Endpoint means and SDs for PANSS total were not directly reported in the publication. Values were reconstructed from baseline and modeled change data as presented by the authors.

[b]Week-8 endpoint; final values (not change). PANSS total range 30–210 (higher = worse). Means/SDs from Qiao 2020, Table 2 (week 8). Adjunctive omega-3 540 mg EPA + 360 mg DHA/day vs placebo (vitamin E 10 mg/day). 67 randomized; 47 complete

[c]CI calculated by Wald-type method.

[d]Tau² calculated by Restricted Maximum-Likelihood method.

Figure 20. Forest plot of the effect of EPA ≤2 g/day administered as an adjunct to antipsychotics on PANSS score, compared with placebo (meta-analysis, random-effects model).

High dose of EPA (>2 g/day)

- Included study: only Emsley 2002 (n = 14 vs. n = 20 placebo).
- Mean difference: +9.50 PANSS points (95% CI: 1.04 to 17.96; p = 0.03).

Interpretation: A statistically significant benefit was observed in favor of the high dose of omega-3. Heterogeneity could not be calculated.

The role of niacin in the pathogenesis of schizophrenia

Several pathological metabolic mechanisms have been identified in schizophrenia, including reduced levels of arachidonic acid, increased phospholipase A2 enzyme activity, and abnormal expression of niacin receptors in the walls of cutaneous capillaries. In addition, skin flushing in response to niacin administration is considered to be influenced by prostaglandins [76]. According to R. Gan et al. (2022), the abnormal response to niacin observed in patients with schizophrenia appears in the "early stage of psychosis" and throughout the "course of the disease," linking it to polyunsaturated fatty acids (PUFAs) [77].

To study the pathogenic mechanisms and the evidence supporting the use of the cutaneous and oral niacin test in patients with schizophrenia, first-episode psychosis, and individuals at clinical high risk for psychosis (CHR-P), as well as to analyze the rationale for using vitamin B3 as an adjunctive or preventive therapy in these patient groups, a literature review was conducted on the occurrence of specific responses to the cutaneous or oral niacin test in patients with schizophrenia, first-episode psychosis, and CHR-P. Information was collected from PubMed, MEDLINE, Medscape, Scopus, the Cochrane Library, and Research4Life.org up to and including 2024, with a total of 48 sources selected. The inclusion criteria were studies conducted on human subjects and published in English. The literature was analyzed in terms of mechanisms of action, risk factors, and evidence supporting the utility of the cutaneous or oral niacin test in high-risk states for psychosis and in schizophrenia [78]. In conclusion, an abnormal niacin response in schizophrenia was found to be associated with metabolic disturbances, imbalance of the omega-3/omega-6 ratio and NAD^+/NADH balance, and low levels of vitamin B3. Vitamin B3, niacin, and its derivatives, together with omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), show potential as adjunctive therapies in schizophrenia by reducing oxidative stress and inflammatory responses and by improving cell membrane fluidity [78][79].

Another systematic review was conducted by the author on the diagnostic value of the niacin test in patients with schizophrenia. PubMed, MEDLINE, Scopus, the Cochrane Library, and Research4Life databases were used to search for information. A total of 61 sources published between 1997 and 2022 were identified. Based on the inclusion criteria, 19 sources reporting sensitivity and specificity indicators of the niacin test in patients with schizophrenia were selected for statistical analysis, including 1,283 patients and 854 control subjects. The absence of these indicators was considered an exclusion criterion.

According to the data calculated from the 19 sources, the cutaneous niacin test can predict, with a probability of 78.5%, that patients with a positive test result will have the disease, schizophrenia, and, with a probability of 71.09%, that healthy individuals with a negative test result will not have the disease. The Pearson correlation coefficient, $r = –0.5408$, confirms the existence of a moderate negative correlation between the sensitivity and specificity of the cutaneous niacin test, based on data from the 19 sources. The strength of the association was statistically significant, with $P = 0.00773690$ (≤ 0.05), $z = –2.42109578$, and a 95% confidence interval ranging from –0.7988 to –0.1148. Linear regression was described by the formula: $y = –0.22274884 \cdot x + 97.80636210$ [80].

4.5 Chapter 4 Summary:

1. In patients with schizophrenia, mitochondrial dysfunction represents an essential pathogenetic element, and cognitive and negative symptoms are associated with these pathological mechanisms. Mitochondrial dysfunctions are evidenced by increased production of reactive oxygen species (ROS) and nitric oxide (NO), increased brain vulnerability to oxidative stress, activation of the intrinsic apoptotic pathway, decreased neuronal and glial density in specific brain regions (proven postmortem), dysregulation of neuroplasticity and cerebral energy metabolism.

2. Atypical antipsychotics (olanzapine, risperidone) appear to have a less harmful impact on essential cellular functions because they affect cellular compartments involved in processing and transport, not directly the nucleus or cellular stress mechanisms. These mechanisms affected by typical antipsychotics are more sensitive and more important for cellular integrity, suggesting a potentially greater negative impact compared to atypical ones.

3. Peripheral benzodiazepine receptor ligands exhibit anti-apoptotic effects, counteracting the effects of ROS, decreased mitochondrial potential, and mitochondrial structural alterations. They stimulate the expression of anti-apoptotic genes and proteins and inhibit the expression of pro-apoptotic ones, which confers neuroprotective potential.

4. Overproduction of reactive oxygen species (ROS), collapse of mitochondrial potential, increased lysosomal membrane permeability, glutathione (GSH) depletion, and lipid peroxidation represent the target of adjuvant therapies needed in schizophrenia. These therapies

are intended to reduce both the mitochondrial pathobiological processes connected to the acute phase of schizophrenia and those caused by antipsychotic treatment. As adjuvant treatment acting on the mitochondrial system in addition to standard antipsychotic therapy in schizophrenia, N-acetylcysteine (NAC) stands out with a profile with the maximum degree of evidence and safety on total, negative, and general symptoms in schizophrenia.

5. Omega-3 fatty acid consumption has been associated with a reduced probability of transition to psychosis, in a dose-dependent manner. A statistically significant benefit is observed in favor of the higher dose of 2 g/day of omega-3.

6. According to calculations performed, the positive predictive value of the niacin test is 78.5%, and the negative predictive value is 71.09%, which makes it an easy-to-use and cost-effective screening tool for identifying individuals at clinical high risk for psychosis (CHR), patients with schizophrenia, or those at risk of developing schizophrenia .

5. THE ROLE OF ESTRADIOL IN SCHIZOPHRENIA: NEUROBIOLOGICAL MECHANISMS, MITOCHONDRIAL FUNCTION, AND ADJUNCTIVE CLINICAL IMPLICATIONS

5.1 Introduction

The hypothesis of the protective role of estradiol proposes that psychotic disorders may worsen during phases of the menstrual cycle characterized by low estradiol levels, particularly around menstruation. Several sources support this hypothesis [81][82][83]. Similarly, clinical cases have been reported in which women with chronic schizophrenia experienced symptomatic improvement during pregnancy, when estrogen, particularly estradiol, levels are markedly elevated [82]. After childbirth, when estrogen levels decline sharply, increased vulnerability to psychosis has been observed [84]. Higher mean estrogen levels have also been associated with better cognitive performance, including executive functioning, verbal memory, spatial memory, attention/processing speed, and global cognitive functioning [85].

5.2 Estradiol and the Severity of Psychotic Symptoms in Schizophrenia

The working hypothesis of the present research is that sex hormones may directly or indirectly modulate the expression of psychotic symptoms. Estradiol has been hypothesized to act as a protective factor in schizophrenia, potentially providing relative protection to women at risk of developing a psychotic episode during phases characterized by higher estradiol levels, namely before menopause and during the peri- and post-ovulatory phases of the menstrual cycle [86]. It has also been concluded that the hypoestrogenism observed in patients with schizophrenia is not related to antipsychotic treatment [86]. Furthermore, the idea has been proposed that the longer the brain is exposed to sufficient estradiol levels before illness onset, the more “protected” it may be, potentially delaying the emergence of psychotic symptoms [87]. Psychiatric admissions are also significantly more frequent during the perimenstrual phase of the cycle. Studies have demonstrated not only a significant excess of admissions during this phase, but also an inverse correlation between blood estradiol concentrations and the severity of symptomatology [88].

5.2.2 Estrogen and Neuroinflammation

Of particular interest are the effects of estrogens on cognitive abilities that are most commonly impaired in schizophrenia, especially working memory and verbal memory, as well as executive functioning [89]. It has been suggested that estrogen plays a role in maintaining verbal memory in women, while findings from treatment with gonadotropin-releasing hormone agonists indicate that estrogen may be important for preserving memory during the postmenopausal period [90]. There is a general consensus regarding the capacity of estrogens to limit the proinflammatory activation of microglia following short-term exposure to bacterial cell debris, viral agents, or hypoxia [91]. Another mechanism through which estradiol may influence microglia involves the G protein–coupled estrogen receptor 1, also known as GPER1 [92]. Activation of GPER1 by estradiol may reduce neuroglial inflammation by decreasing the production of proinflammatory cytokines and protecting neurons. This effect is rapid and does not depend on gene transcription, unlike the actions mediated through estrogen receptors alpha and beta, ERα and ERβ.

5.2.3 Neuroprotective and Regenerative Properties of Estradiol: Influence on Mitochondrial Function

It is particularly significant that mitochondria are involved in steroidogenesis, since the first step in this process consists of cholesterol transport into these organelles, with cholesterol serving as the primary substrate for estrogen synthesis. Estrogens may influence a broad range of cellular mechanisms, which in turn may affect genetic or metabolic components associated with schizophrenia. Genomic mechanisms represent one of the pathways involved and include the regulation of gene expression through the activation of estrogen receptors, ERα and ERβ, by estrogens. These receptors act as transcription factors, activating or inhibiting the transcription of specific genes. The result is the stimulation or suppression of protein synthesis involved in neuronal functioning, energy metabolism, and protection against oxidative stress.

Estradiol may also improve mitochondrial activity directly, by enhancing mitochondrial function through the promotion of mitochondrial DNA gene transcription, and indirectly, by promoting the transcription of nuclear genes involved in mitochondrial and metabolic regulation [93]. In general, the brains of young females tend to show lower levels of oxidative damage compared with those of males. This has been attributed to stronger antioxidant mechanisms and better mitochondrial function in females, a pattern associated with neuroprotection. However, these differences usually diminish with aging, while the incidence of brain pathologies increases in women with advancing age. Sex hormones, whose levels decline during normal aging, have therefore been proposed as key factors involved in these mechanisms [94].

Estradiol has been attributed the capacity to enhance neurogenesis, angiogenesis, synaptic density, neuronal plasticity and connectivity, axonal growth, remyelination, and the expression of neurotrophic factors through the activation of extranuclear estrogen receptors and rapid intracellular signaling pathways [95][96].

5.2.4 Estradiol and Cerebral Neurotransmission

The effects of estrogen on the nigrostriatal system have been established, and dopaminergic neurons are considered direct targets of estrogen. Estrogen stimulates neurite extension and branching, as well as the expression of tyrosine hydroxylase, the key enzyme involved in dopamine synthesis [97]. Estradiol has been shown to increase dopamine release in females, but not in males, within the striatal region [98]. Its effects on serotonergic neurotransmission are reflected in increased 5-HT2A receptor binding in prefrontal regions of the human brain [99]. Estrogens also increase the dopaminergic sensitivity of D2/D3 receptors in the ventral tegmental area, which is part of the mesolimbic pathway associated with positive symptoms and the mesocortical pathway associated with negative and cognitive symptoms [100][101][102]. The stimulatory effect of estrogen on the activity of dopaminergic neurons, particularly in the striatum and nucleus accumbens, is well documented [103].

5.2.5 Estrogens and Cognitive Functions

The interaction between estrogen and glutamate may influence cognitive domains such as working memory and executive functions. The brain regions thought to underlie these cognitive domains are the prefrontal cortex and the hippocampus [104].

In one study, the global dementia score assessed using the Clinical Dementia Rating scale increased more slowly in patients who used estrogen therapy (n = 71) compared with those who did not use estrogen therapy (n = 1,004), with annual CDR increases of 0.194 versus 0.298, respectively (p = 0.045). These findings suggest that estrogen treatment may exert a protective effect on the progression of dementia [105].

Another study involving 731 women aged over 60 years found that participants with higher estradiol levels had higher scores on the Digit Symbol Substitution Test, reflecting better processing speed, sustained attention, and working memory. These findings suggest that serum estradiol may serve as a potential biomarker of cognitive decline in older women [106].

5.3 Materials and Methods

A quantitative analysis was conducted to evaluate the effect of transdermal estradiol administered as an adjunct to antipsychotic treatment on symptom severity in female patients with schizophrenia, using data reported in randomized controlled clinical trials. The statistical synthesis was performed in Review Manager Web, developed by The Cochrane Collaboration (2023).

Studies were included according to the PICO criteria: women diagnosed with schizophrenia; transdermal estradiol as adjunctive therapy to antipsychotics; placebo as comparator; and changes in PANSS scores as the outcome. For the primary meta-analyses assessing the effect of estradiol, the mean, standard deviation (SD), and number of participants (N) were extracted for each study, separately for the estradiol and placebo arms, for the PANSS subscales and the PANSS total score.

The intervention effect was expressed as the mean difference (MD) between groups, with a 95% confidence interval (95% CI), since all studies used the same assessment scale. The systematic and meta-analytic synthesis was performed using a random-effects model. Heterogeneity was assessed using I^2, Chi^2, and Tau^2 statistics.

In the absence of direct reporting of quality-of-life indicators in the included studies, quality of life was estimated indirectly by converting PANSS scores into EQ-5D-5L utility values using the Singapore model proposed by Abdin et al. (2019). Risk of bias was assessed using the Cochrane Risk of Bias tool available in RevMan Web, and the results were integrated into the interpretation of the findings and conclusions.

5.4 Results and Discussion

5.4.1 Effects of Adjunctive Estrogen Treatment on Symptoms of Schizophrenia

With regard to clinical outcomes, women with schizophrenia appear to have a more favorable course of illness than men; however, they seem to be more vulnerable to psychotic states after childbirth and during the menopausal period. Since these periods of vulnerability are associated with estrogen deficiency, estrogen has been proposed as a potential therapeutic option for schizophrenia in women.

Weiser et al. (2019), in a study of estradiol conducted in the Republic of Moldova found a significant improvement in PANSS total scores, as well as in the PANSS positive, PANSS negative, and PANSS general psychopathology subscales, from baseline to the end of the study. A significant improvement was also observed in the CGI-S scale, Clinical Global Impression–Severity, and the MADRS, Montgomery–Åsberg Depression Rating Scale. However, the beneficial effects of estradiol were observed only in women aged 38 years and older [107].

An important conclusion of this study is that estradiol may be beneficial primarily for women with unstable or declining estradiol levels, or with reduced sensitivity of estrogen receptors. To analyze the effect of estradiol on symptoms of schizophrenia, the thesis selected studies that met the following inclusion criteria: double-blind randomized clinical trials; homogeneity of data, including the use of identical assessment scales; availability of data required for meta-analysis, including mean values, sample size, standard deviation, or other parameters from which the standard deviation could be derived, such as variance, 95% confidence interval, or standard error; and accessibility of the reported data. As a result, only two studies met these criteria [108][107].

Presented below are the meta-analysis and subgroup analysis of randomized clinical trials that met the inclusion criteria for evaluating the effect of estradiol on symptoms of schizophrenia. The analysis was performed using Review Manager Web, developed by The Cochrane Collaboration, 2023. Available at: https://revman.cochrane.org.

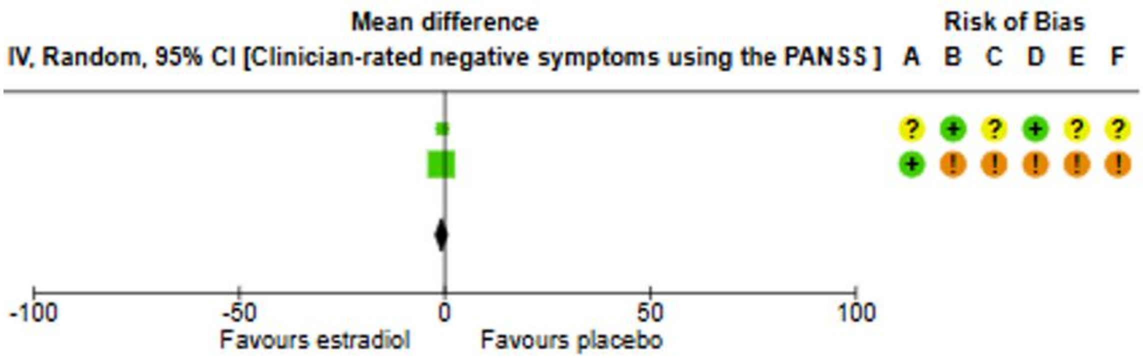


Figure 22. Effect of estradiol on PANSS negative symptoms: forest plot and PANSS risk-of-bias assessment (Review Manager Web, The Cochrane Collaboration, 2023).

Table 23. Meta-analysis of the effect of adjunctive transdermal estradiol on PANSS positive symptoms compared with placebo (Kulkarni et al., 2014; Weiser et al., 2019)

	Estradiol			Placebo				Mean difference
Study or Subgroup	Mean [PANSS score]	SD [PANSS score]	Total	Mean [PANSS score]	SD [PANSS score]	Total	Weight	IV, Random, 95% CI [PANSS score]
Kulkarni 2014[a]	15.177797	5.346096	118	16.36	5.39	62	18.6%	-1.18 [-2.83 , 0.47]
Weiser 2019[b]	13.4	2.5	95	14.4	3	93	81.4%	-1.00 [-1.79 , -0.21]
Total (Wald[c])			**213**			**155**	**100.0%**	**-1.03 [-1.75 , -0.32]**

Mean difference IV, Random, 95% CI [PANSS score]: -100 -50 0 50 100; Favours estradiol / Favours placebo

Test for overall effect: Z = 2.84 (P = 0.004)

Heterogeneity: Tau² (REML[d]) = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%

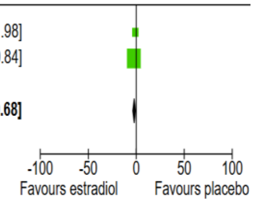
Footnotes
[a]SDs calculated from variances reported in the source article.
[b]Overall sample
[c]CI calculated by Wald-type method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.

Table 24. Meta-analysis of the effect of adjunctive transdermal estradiol on PANSS general psychopathology symptoms compared with placebo (Kulkarni et al., 2014; Weiser et al., 2019).

Study or Subgroup	Estradiol Mean [PANSS score]	Estradiol SD [PANSS score]	Estradiol Total	Placebo Mean [PANSS score]	Placebo SD [PANSS score]	Placebo Total	Weight	Mean difference IV, Random, 95% CI [PANSS score]
Kulkarni 2014[a]	32.585085	9.104288	118	33.52	9.18	56	24.4%	-0.93 [-3.85 , 1.98]
Weiser 2019[b]	34	5.1	95	36.5	6.4	93	75.6%	-2.50 [-4.16 , -0.84]
Total (Wald[c])			**213**			**149**	**100.0%**	**-2.12 [-3.56 , -0.68]**

Test for overall effect: Z = 2.88 (P = 0.004)

Heterogeneity: Tau² (REML[d]) = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%



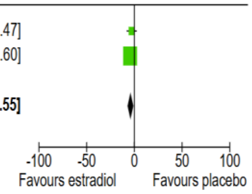
Footnotes
[a]SDs calculated from variances reported in the source article.
[b]Overall sample
[c]CI calculated by Wald-type method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.

Table 25. Meta-analysis of the effect of adjunctive transdermal estradiol on the PANSS total score compared with placebo (Kulkarni et al., 2014; Weiser et al., 2019).

Study or Subgroup	Estradiol Mean [PANSS score]	Estradiol SD [PANSS score]	Estradiol Total	Placebo Mean [PANSS score]	Placebo SD [PANSS score]	Placebo Total	Weight	Mean difference IV, Random, 95% CI [PANSS score]
Kulkarni 2014[a]	63.502373	17.061243	118	66.28	17.09	62	23.4%	-2.78 [-8.03 , 2.47]
Weiser 2019[b]	61.8	9.1	95	66.3	11.1	93	76.6%	-4.50 [-7.40 , -1.60]
Total (Wald[c])			**213**			**155**	**100.0%**	**-4.10 [-6.64 , -1.55]**

Test for overall effect: Z = 3.16 (P = 0.002)

Heterogeneity: Tau² (REML[d]) = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%

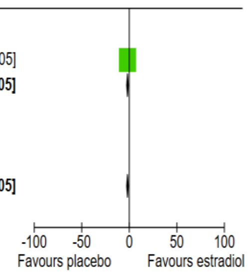


Footnotes
[a]SDs calculated from variances reported in the source article.
[b]Overall sample
[c]CI calculated by Wald-type method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.

Table 26. Subgroup analysis according to age (≥38 years): effect of estradiol compared with placebo on PANSS scores (Weiser et al., 2019).

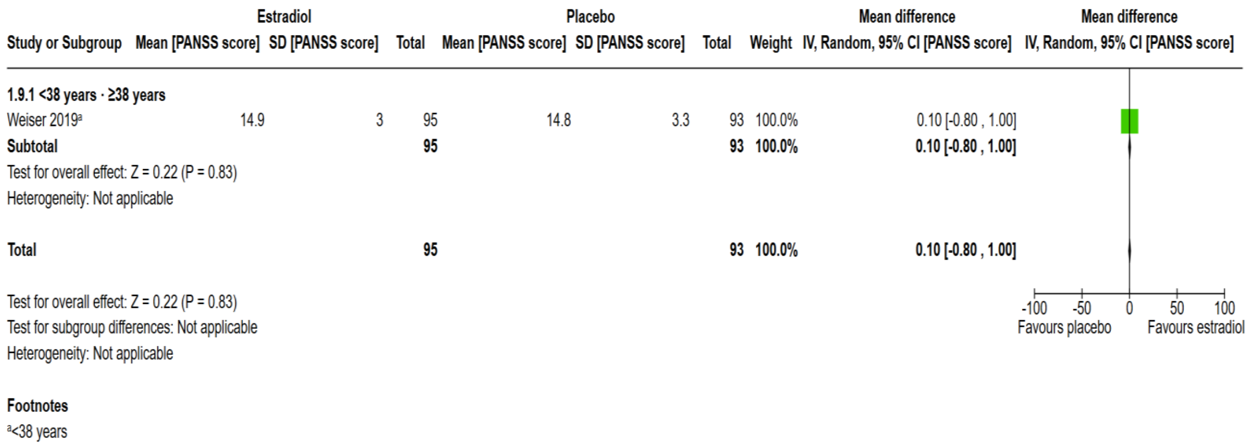
Study or Subgroup	Estradiol Mean [PANSS score]	Estradiol SD [PANSS score]	Estradiol Total	Placebo Mean [PANSS score]	Placebo SD [PANSS score]	Placebo Total	Weight	Mean difference IV, Random, 95% CI [PANSS score]
1.8.1 <38 years · ≥38 years								
Weiser 2019[a]	14	2.6	95	15.9	3.3	93	100.0%	-1.90 [-2.75 , -1.05]
Subtotal			**95**			**93**	**100.0%**	**-1.90 [-2.75 , -1.05]**
Test for overall effect: Z = 4.38 (P < 0.0001)								
Heterogeneity: Not applicable								
Total			**95**			**93**	**100.0%**	**-1.90 [-2.75 , -1.05]**

Test for overall effect: Z = 4.38 (P < 0.0001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Footnotes
[a]≥38 years

Table 27. Subgroup analysis according to age (<38 years): effect of estradiol compared with placebo on PANSS scores (Weiser et al., 2019).



5.4.4 Quality-of-Life Indicators Associated with Adjunctive Estradiol Treatment

To determine the relationship between PANSS scores and quality of life, the Singapore model proposed by Abdin et al. (2019) was used, according to the following formula:

EQ-5D-5L = 1.3103 − 0.0044 × PANSS positive + 0.0025 × PANSS negative − 0.0146 × PANSS general − 0.0029 × age + 0.0149 × female [109].

According to the formula, if the patient is female, the coefficient is coded as 1, whereas if the patient is male, it is coded as 0. For the Weiser et al. (2019) study, the data were calculated as shown in Table 31.

Table 31. Calculation of EQ-5D values based on PANSS positive, negative, and general psychopathology scores according to the Singapore model (Weiser et al., 2019).

Group	Assessment time point	PANSS Positive	PANSS Negative	PANSS General	EQ-5D Utility
Estradiol	Baseline	19.4	19.0	43.8	0.546
	Final	13.4	14.4	34.0	0.704
	Δ (Final − Baseline)	—	—	—	+0.158
Placebo	Baseline	19.8	18.9	44.7	0.531
	Final	14.4	15.3	36.5	0.666
	Δ (Final − Baseline)	—	—	—	+0.135
Between-group effect	**Δ Estradiol − Δ Placebo**	**—**	**—**	**—**	**0.023**

Note: In the Weiser et al. (2019) study, both treatment arms consisted exclusively of female participants. Accordingly, the sex variable was coded as female = 1 for all observations, and the corresponding coefficient (+0.0149) was applied uniformly across all EQ-5D utility calculations.

Δ indicates the change from baseline to final assessment; PANSS = Positive and Negative Syndrome Scale; EQ-5D = EuroQol five-dimension health utility measure.

Discussion

Both groups showed a significant improvement in EQ-5D scores. Adjunctive estradiol was associated with a small additional improvement compared with placebo (+0.023). According to

the criteria proposed by Leucht et al. [110][111][112], changes in PANSS scores may be interpreted using the following formula:
Percentage change = (Baseline score − Final score) / (Baseline score − 7) × 100,
where "7" represents the minimum possible score for each PANSS subscale.
The interpretation thresholds proposed by Leucht et al. (2005, 2006) are as follows: **≥25% = minimally improved**, **≥50% = much improved**, and **≥75% = very much improved**.
For the estradiol group, the PANSS positive subscale showed the following result:
(19.4 − 13.4) / (19.4 − 7) = 6.0 / 12.4 = 0.484, corresponding to approximately **48% improvement**, which approaches the threshold for "much improved".
For the PANSS negative subscale in the estradiol group:
(19.0 − 14.4) / (19.0 − 7) = 4.6 / 12.0 = 0.383, corresponding to approximately **38% improvement**, indicating a change between "minimally improved" and "much improved".
For the PANSS general psychopathology subscale in the estradiol group:
(43.8 − 34.0) / (43.8 − 7) = 9.8 / 36.8 = 0.266, corresponding to approximately **27% improvement**, which meets the criterion for "minimally improved".
In the placebo group, the PANSS positive subscale showed the following result:
(19.8 − 14.4) / (19.8 − 7) = 5.4 / 12.8 = 0.422, corresponding to approximately **42% improvement**, exceeding the threshold for "minimally improved".
For the PANSS negative subscale in the placebo group:
(18.9 − 15.3) / (18.9 − 7) = 3.6 / 11.9 = 0.303, corresponding to approximately **30% improvement**, which also meets the criterion for "minimally improved".
For the PANSS general psychopathology subscale in the placebo group:
(44.7 − 36.5) / (44.7 − 7) = 8.2 / 37.7 = 0.217, corresponding to approximately **22% improvement**.
Overall, both groups demonstrated clinical improvement. However, the estradiol group showed greater improvement across all symptom dimensions, particularly in positive symptoms (**48% vs. 42%**) and general psychopathology symptoms (**27% vs. 22%**).

Table 32. Calculation of EQ-5D values based on PANSS positive, negative, and general psychopathology scores according to the Singapore model, stratified by age group (Weiser et al., 2019).

Group (age group and treatment)	PANSS Positive	PANSS Negative	PANSS General	PANSS Total	Baseline EQ-5D	Endpoint EQ-5D
<38 years, estradiol	19.2 → 13.8	18.9 → 14.9	43.3 → 34.9	81.3 → 63.6	0.566	0.702
<38 years, placebo	19.6 → 13.8	19.0 → 14.8	44.6 → 35.5	83.2 → 64.1	0.545	0.693
≥38 years, estradiol	19.6 → 13.0	19.1 → 14.0	44.3 → 33.3	83.1 → 60.2	0.520	0.697
≥38 years, placebo	20.0 → 15.1	18.9 → 15.9	44.7 → 37.8	83.6 → 68.8	0.512	0.627

Note: Values for PANSS scores are presented as baseline → endpoint. EQ-5D utility values were calculated according to the Singapore model. The mean age for the group younger than 38 years was 31.1 years. The mean age for the group aged 38 years and older was 41.3 years. The mean age was calculated by the author based on the original study data from Weiser et al. (2019), in which the author was a co-author.

Table 33 presents the percentage improvement in PANSS scores according to age group and treatment.

Table 33. Percentage improvement in PANSS scores according to Leucht criteria, stratified by age group and treatment.

Group (age group, treatment)	PANSS positive	PANSS negative	PANSS general
<38 years, estradiol	44% – minimally improved	34% – minimally improved	23% – below threshold
<38 years, placebo	46% – minimally improved	35% – minimally improved	24% – below threshold
>38 years, estradiol	**52% – much improved**	42% – minimally improved	30% – minimally improved
>38 years, placebo	38% – minimally improved	25% – minimally improved	18% – below threshold

Figure 30 visually summarizes the data presented in the previous tables and enables an immediate assessment of the clinical relevance of changes in EQ-5D values in relation to MIC thresholds. The graphical visualization was generated using MATLAB R2025b (MathWorks), based on EQ-5D values calculated according to the minimum important change (MIC) criteria.

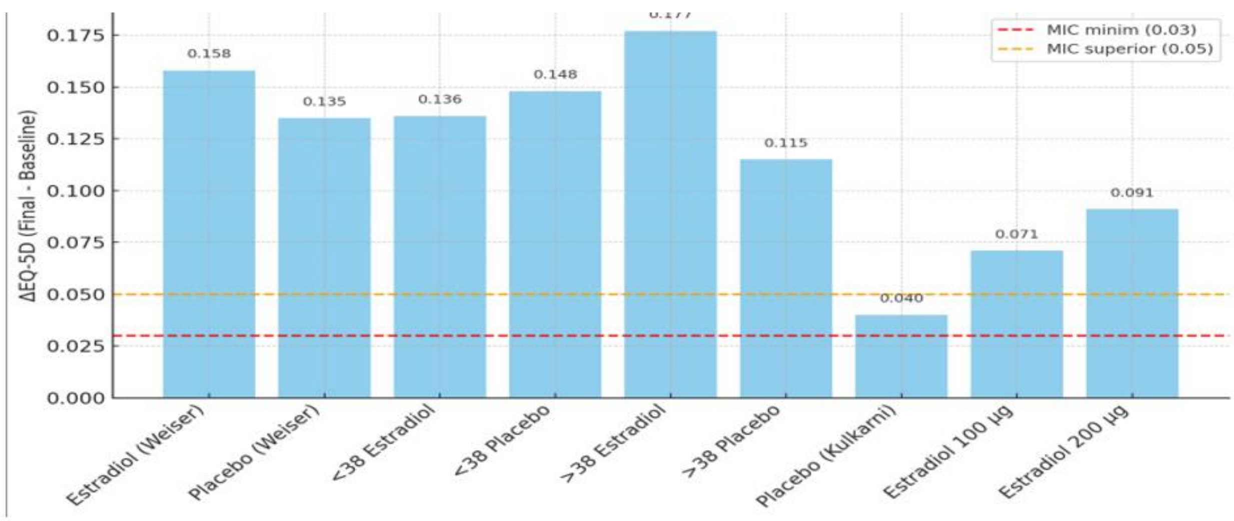


Figure 30. Changes in EQ-5D utility values (ΔEQ-5D) among patients with schizophrenia receiving adjunctive estradiol versus placebo, stratified by age group and estradiol dose

5.5 Synthesis of Chapter 5

1. The results of the meta-analysis indicate that adjunctive transdermal estradiol has a modest but significant beneficial effect on PANSS positive, general psychopathology, and total scores, with high consistency across studies and no statistical heterogeneity. Negative symptoms showed only limited improvement, confirming the therapeutic difficulty of this symptom domain in schizophrenia.

2. The therapeutic effect of estradiol appears to be dose-dependent, with the 200 μg/day dose being associated with the most consistent symptomatic improvements and the greatest gain in quality of life, thereby supporting a dose–response relationship. Overall, these findings support the use of estradiol as an adjunctive therapy in schizophrenia, particularly for the improvement of positive symptoms and the reduction of overall illness severity.
3. Patients' age appears to influence treatment response, with benefits being more pronounced in women aged over 38 years, especially in the positive symptom domain. In this subgroup, the reduction in PANSS positive symptoms reached the threshold of "much improved" according to Leucht criteria (52% vs. 38% in the placebo group), while general psychopathology and negative symptoms improved at a minimal level. These changes were associated with an increase in the EQ-5D score of +0.177, with the difference compared with placebo (+0.062) exceeding the threshold for clinical significance, as defined by the minimum important change (MIC). In patients younger than 38 years, estradiol and placebo produced similar improvements, with no meaningful differences between treatment arms.
4. Selective estrogen receptor modulators appear to represent useful agents as adjunctive treatment in schizophrenia, with raloxifene showing positive effects particularly on general psychopathology and negative symptoms.
5. Overall, the analyzed data indicate that transdermal estradiol administered as an adjunct to antipsychotic treatment produces modest but clinically relevant short-term improvements, both in psychotic symptomatology, as assessed by PANSS, and in quality of life, as estimated by EQ-5D, over an 8-week treatment period. The reduction in PANSS scores, interpreted according to Leucht criteria, corresponds to increases in EQ-5D utility values that exceed the minimum clinically important threshold, MIC/MID, thereby confirming the clinical relevance of the observed changes.
6. The available evidence suggests an association between estrogen levels and psychological stability in female patients, supporting the hypothesis that estrogens may exert a modulatory effect on response to antipsychotic treatment. In women with schizophrenia, particularly those with limited therapeutic response or symptom exacerbation during the postmenopausal period, adjunctive estrogen therapy may be considered as an individualized complementary strategy, guided by the clinical profile and by careful assessment of the benefit–risk ratio.

6. EXOSOMES IN SCHIZOPHRENIA: MOLECULAR MECHANISMS AND THEIR UTILITY AS BIOMARKERS IN DIAGNOSIS, DISEASE COURSE, AND TREATMENT

6.1 Introduction

Exosomes are classified as small extracellular vesicles (30–150 nm) released by both prokaryotic and eukaryotic cells for the purposes of intercellular communication and signaling. Cellular components, including proteins, lipids, metabolites, small molecules, DNA, RNA, and membrane surface proteins, are encapsulated within exosomes during their formation and subsequently delivered to recipient cells through processes such as endocytosis and plasma membrane invagination [113]. Due to their multifaceted roles in intercellular information transfer, exosomes play a crucial role in physiological regulation, disease progression, immune responses, and the development of pathological conditions [113]. They are involved in various processes related to inflammation, central nervous system communication, immune modulation, and tissue repair [114]. Exosomes may therefore be considered important tools for both therapeutic applications and early disease detection. Traditional methods for exosome isolation and purification primarily include density gradient centrifugation, chromatography, and immunoaffinity purification. Ultracentrifugation remains one of the most widely used techniques for exosome isolation [115][116][117]. Recent evidence indicates that, in schizophrenia, alterations have been identified in profiles of microRNAs, circular RNAs (circRNAs), metabolites, and complement system proteins, which are associated with symptom severity and treatment resistance [118]. In first-episode psychosis, microRNAs demonstrate high diagnostic value, with reported sensitivity ranging from 76% to 96%, specificity from 78% to 96%, and area under the curve (AUC) values up to 0.94. Additionally, analyses of brain-derived exosomes have revealed disruptions in signaling pathways and mitochondrial function, which correlate with clinical manifestations [118]. The relevance and informativeness of extracellular vesicles, particularly exosomes, are attributed to several key characteristics: their involvement in cellular communication, their ability to cross the blood–brain barrier, and their accessibility for quantification in peripheral body fluids.

6.2 Diagnostic and Therapeutic Potential of Exosomal microRNAs

Nastas I. and Boronin I. (2025), evaluating nine bibliographic sources reporting the sensitivity and specificity of exosomes as biomarkers in schizophrenia, estimated a positive predictive value (PPV) of 80%, a negative predictive value (NPV) of 77.71%, and an area under the curve (AUC) of 0.678. The authors also highlighted limitations of the analyzed studies, including small sample sizes and variability in diagnostic methodologies. Nevertheless, preliminary findings suggest that exosomes may serve, at minimum, as components of a multimarker panel for the diagnosis of schizophrenia [119].

Intranasal administration of exosomes derived from olfactory mucosa mesenchymal stem cells has been shown to effectively ameliorate schizophrenia-like behaviors in laboratory mice, particularly social withdrawal and sensory gating deficits induced by methylazoxymethanol acetate (MAM). Moreover, this intervention resulted in a reduction of neuroinflammatory markers and suppression of microglial activation in the hippocampus [120].

6.3 Materials and Methods

The analysis included 56 clinical studies investigating exosomal biomarkers in schizophrenia, of which 6 were synthesized in a descriptive table, while 3 studies (Du 2019, Du 2021, and Xue 2024) provided quantitative data on sensitivity, specificity, and AUC. For these studies, the corresponding values were extracted, and the Youden index was calculated. Diagnostic performance was summarized using medians and interquartile ranges (Q1–Q3), which describe the distribution of central values and provide a robust estimate less influenced by extreme values. Differences between diagnostic indicators were evaluated using one-way analysis of variance (ANOVA), and the nonparametric Kruskal–Wallis test was applied to verify the consistency of the results.

6.4 Results and Discussion

A total of six clinical studies were selected from the 56 bibliographic sources on exosomes as biomarkers in schizophrenia analyzed by the author. The aim of the subsequent statistical analysis was to integrate published data on the sensitivity, specificity, and diagnostic accuracy (area under the curve, AUC) of exosomal biomarkers used in the diagnosis of schizophrenia. For this purpose, sensitivity, specificity, and AUC parameters were analyzed based on the following sources [121][122][123].

Table 36. Diagnostic performance of exosomal biomarkers in schizophrenia: sensitivity, specificity, AUC, and Youden index (synthesis of data derived from 56 bibliographic sources).

Sensitivity (%)	Specificity (%)	AUC (%)	Youden index*	Author/source
86.9	87.1	91.0	74.0	Du et al. (2021)
73.1	80.3	82.7	53.4	Du et al. (2021)
97.9	95.2	99.0	93.1	Du et al. (2021)
76.9	78.3	75.3	55.2	Du et al. (2019)
85.3	82.0	89.5	67.3	Xue T. et al. (2024)

Note: * Calculation performed by the author.

For analytical accuracy, all training datasets, including internal validation datasets, were excluded, as they tend to produce overly optimistic results due to threshold selection being performed on the same data. Medians and interquartile ranges (IQRs) were used to describe biomarker performance because the distribution of sensitivity, specificity, and AUC values was heterogeneous across studies. The median provides a more robust estimate and is less influenced by extreme values than the mean. In addition, the Youden index (J) was calculated, integrating sensitivity and specificity into a single measure and providing an overall, comparable assessment of diagnostic test accuracy.

Diagnostic performance of exosomal biomarkers in schizophrenia: median values and interquartile ranges (IQRs). AUC values ranged from 75.3% to 99.0%, with a median of 89.5%. The interquartile range included the central half of AUC values, indicating that 50% of exosomal tests had AUC values between 82.7% and 91.0%. These relatively narrow limits suggest good homogeneity across studies, without substantial dispersion. The median sensitivity was 85.3% (IQR 76.9–86.9), indicating that exosomal biomarkers showed good ability to detect patients with schizophrenia, with approximately 85 of 100 cases correctly identified. The median specificity was 82.0% (IQR 80.3–87.1), indicating a solid ability to exclude healthy individuals, with approximately 82–87 healthy individuals correctly classified per 100. Specificity was generally slightly lower than sensitivity, but remained above the 80% threshold, supporting diagnostic accuracy. The median Youden index was 67.3 (IQR 55.2–74.0). This integrated score confirms an appropriate balance between sensitivity and specificity. Lower values indicate that some biomarker panels had more modest accuracy; however, most values were within a favorable diagnostic range, approaching or exceeding 70.

The following table presents statistical indicators calculated for four data samples.

Table 38. Analysis of distribution normality: skewness, kurtosis, and normality test (StatsKingdom. *Online Statistical Tests and Calculators*. Available from: https://www.statskingdom.com. Accessed 2025).

Skewness:	0.48071	1.166904	-0.206172	-0.206172
Excess kurtosis:	-0.221077	0.72423	-0.139712	-0.139712
Normality	0.9489	0.5319	0.9996	0.9996
Outliers				
Mean	84.02	84.58	0.875	0.875
S	9.65049	6.77399	0.089496	0.089496

Although the normality tests did not reveal statistically significant deviations ($p > 0.05$), the small sample size and methodological heterogeneity across studies limit the statistical power of these tests. In this context, describing diagnostic performance using the median and interquartile range remains a more robust and appropriate approach than relying exclusively on mean-based parameters.

6.5 Synthesis of Chapter 6

The synthesized results indicate that exosomal biomarkers demonstrate overall good diagnostic performance in schizophrenia, with median AUC values approaching 0.90 and sensitivity and specificity values exceeding the 80% threshold. These values suggest a strong capacity to discriminate between patients with schizophrenia and healthy controls, particularly when biomarkers are used as part of multiparametric panels. Overall, the available data support the potential utility of exosomes as diagnostic and prognostic biomarkers in schizophrenia. The integration of exosomal markers with other clinical or biological data may improve patient stratification and the personalization of therapeutic interventions. Future prospective, multicenter studies with large samples would contribute to clarifying the specificity of multiple exosomal markers.

7. CHALLENGES IN THE EARLY DIAGNOSIS OF SCHIZOPHRENIA: THE PRODROMAL STATE AND RISK FOR PSYCHOSIS. SCREENING AND INTERVENTION ALGORITHM

7.1 Introduction

There are several challenges associated with the early identification of schizophrenia, primarily related to the lack of specific symptoms in the initial stages of the disorder. For early diagnosis and prediction of psychotic onset, the following criteria may be utilized: characteristic prodromal signs, neuropsychological deficits identified through standardized testing, predictive biological markers, and patterns of disease progression. Based on the latter parameter, the availability of an electronic patient record containing the clinical history may allow the development of predictive algorithms for disease evolution, thereby facilitating the transition toward personalized medicine in mental health care.

7.3 Materials and Methods

Chapter 7 was developed as an integrative and comparative analysis aimed at evaluating the performance of screening and diagnostic instruments used in individuals at clinical high risk for psychosis (Clinical High Risk for Psychosis, CHR-P) and at proposing a clinical management algorithm based on psychometric assessment and biological biomarkers. The analysis included data extracted from the scientific literature and combined descriptive, analytical, and statistical modeling approaches. Diagnostic performance was assessed through receiver operating characteristic (ROC) curve modeling, using sensitivity and specificity values reported in the literature. The modeling was conducted in MATLAB (MathWorks, R2025b), and the area under the curve (AUC) was used as a global indicator of discriminative ability. Based on the obtained results, a stepwise clinical algorithm for managing CHR-P cases was proposed: initial screening using PRODscreen, diagnostic confirmation through the Structured Interview for Prodromal Syndromes (SIPS), and the integration of biological markers, followed by the initiation of appropriate early intervention.

7.4 Results and Discussion

Key instruments used for screening and diagnosis of high-risk syndromes for psychosis and first-episode psychosis were compiled. To evaluate the effectiveness of screening and diagnostic tools in the prodromal stage of schizophrenia, sensitivity and specificity parameters were used.

Subsequently, ROC curves were modeled to compare the discriminative performance of the main screening and diagnostic instruments used in the prodromal stage of schizophrenia, based on sensitivity and specificity values reported in the literature. The aim was to perform a comparative evaluation of their ability to differentiate between individuals at risk for psychosis and those not at risk (Figure 31).

Receiver Operating Characteristic (ROC) Analysis of Psychosis Risk Assessment Instruments Using Sensitivity–Specificity Data

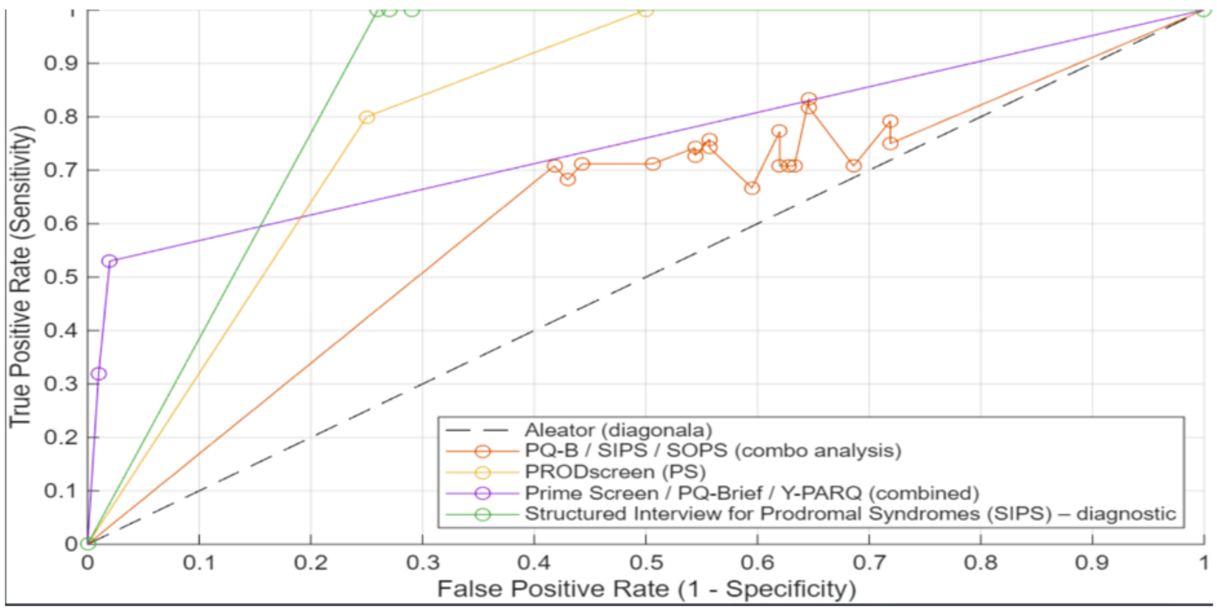


Figure 31. Comparative ROC curves of screening and diagnostic instruments used in the prodromal stage of schizophrenia, modeled based on sensitivity and specificity values reported in the literature. *(MathWorks. MATLAB [computer program]. R2025b, licensed version. Natick, MA: MathWorks, Inc.; 2025).*

Discussion The diagonal line represents the "guessing" model, i.e., random performance (AUC = 0.5). Any instrument positioned above this line demonstrates true diagnostic value, whereas instruments located close to the diagonal indicate poor discriminative ability.

The **Structured Interview for Prodromal Syndromes (SIPS)** (green) shows data points concentrated in the upper-left region of the graph, reflecting an excellent balance between sensitivity and specificity. The curve approaches the ideal ROC shape, suggesting very strong clinical performance in detecting prodromal syndromes.

The **PQ-B / SIPS / SOPS combination** (orange) exhibits substantial variability, as it integrates data from multiple studies with different thresholds and clinical contexts. The points are widely dispersed, with some approaching the diagonal, particularly in the central region. This variability indicates that while combined instruments are sensitive, their precision is inconsistent. Nevertheless, most points lie clearly above the diagonal, supporting their utility as screening tools, though not necessarily as definitive diagnostic instruments.

PRODscreen (yellow) demonstrates a relatively steep curve, indicating high sensitivity relative to specificity, which supports its use as an effective initial screening tool.

The **Prime Screen / PQ-Brief / Y-PARQ combined instruments** (purple), which are self-report measures, show high sensitivity but at the cost of an increased rate of false positives, reflecting a trade-off between sensitivity and specificity.

Conclusions

The comparative analysis of screening and diagnostic instruments in the prodromal stage of schizophrenia revealed significant differences between structured clinical interview–based tools and self-report instruments. The **Structured Interview for Prodromal Syndromes (SIPS)** demonstrated the highest overall diagnostic accuracy, with an AUC of 0.87 and consistently reported sensitivity values approaching 100%, accompanied by specificities ranging from 71% to 74%.

PRODscreen also showed high performance, with an AUC of 0.83, supporting its utility as an initial clinical triage tool. The combination of self-report instruments (Prime Screen, PQ-Brief, and Y-PARQ) yielded an intermediate AUC of 0.76, indicating an acceptable balance between sensitivity and specificity.

In contrast, analysis of multiple variants of the **PQ-B/SIPS/SOPS combination** demonstrated considerable variability (AUC = 0.61), with data points dispersed around the random diagonal line, reflecting inconsistent diagnostic performance.

Limitations

The plotted points are derived from heterogeneous studies and thresholds and therefore do not represent a true ROC curve for a single instrument within a defined population. Rather, they provide a comparative visualization.

7.4.1 Screening, Diagnostic, and Intervention Algorithm for Clinical High-Risk States for Psychosis

Considering that **PRODscreen** is a screening instrument, whereas **SIPS** is a diagnostic instrument, an algorithm was proposed for the management of cases at clinical high risk for psychosis (CHR-P):

Phase 1: Initial screening: Administration of PRODscreen.

Phase 2: Confirmation: Patients with a positive PRODscreen result, defined as ≥2 symptoms, are referred for SIPS assessment by a trained clinician.

Phase 3: Diagnosis: Based on SIPS, the diagnosis is established, APS/APSS, BIPS, GRD, or POPS, and early intervention is initiated, including psychoeducation, monitoring, psychotherapy, and pharmacotherapy when clinically indicated.

Phase 4: Post-SIPS clinical decision-making.

According to this algorithm, the PRODscreen self-report questionnaire will be administered in at-risk groups [124]. The clinical significance and recommended actions are presented in Table 41.

Table 41. PRODscreen thresholds and recommended clinical actions in the assessment of prodromal risk for psychosis, phases 1–2.

PRODscreen Criterion (out of 12 specific symptoms)	Clinical Significance	Recommended Action
≥ 2/12 specific symptoms	Official threshold validated in the original study; sensitivity 80%, specificity 75%. Indicates probable presence of prodromal symptoms.	Diagnostic evaluation using SIPS (Structured Interview for Prodromal Symptoms)
≥ 3/12 specific symptoms	Alternative validated threshold; increases positive predictive value but reduces	SIPS evaluation + Niacin Skin Flush Test (NSFT) as an

	sensitivity. Indicates higher risk for an APS-type prodromal syndrome.	additional biomarker for psychosis vulnerability

Note: APS = Attenuated Psychotic Symptoms

The diagnostic criteria according to the SIPS questionnaire are presented in the following table (Table 42) (Phase 3).

Table 42. Main Clinical High Risk (CHR) syndromes for psychosis according to SIPS (APSS/APS, BIPS, GRD) [125][126].

Syndrome (Abbreviation)	**Full Name**	**Clinical Significance (SIPS Criteria)**	**Diagnosis by SIPS**
APS / APSS	Attenuated Positive Symptom Syndrome	• At least one positive symptom (P1–P5) scored 3, 4, or 5 (attenuated, subpsychotic severity) • Frequency: ≥ once per week in the past month • Not better explained by another disorder (attribution criterion) • Includes: unusual thought content, suspiciousness, perceptual abnormalities, conceptual disorganization	CHR – Clinical High Risk (attenuated but persistent positive symptoms with clinical-functional impact)
BIPS	Brief Intermittent Psychotic Syndrome	• At least one positive symptom at psychotic level = score 6 on P1–P5 • Duration: minutes per day • Frequency: ≥ once per month • Does not meet duration/urgency	High CHR / intermittent psychosis (real but brief psychotic episodes without duration criteria)

		criteria for full psychosis	
GRD	Genetic Risk and Deterioration Syndrome	• Genetic risk: first-degree relative with psychotic disorder OR DSM-5 schizotypal personality criteria • Functional decline ≥30% in GAF within one year • Both criteria required: genetic risk + recent deterioration	CHR – Clinical High Risk (biological vulnerability + recent functional decline = high transition risk)

To establish a diagnosis of a current psychotic episode according to SIPS, both **Criteria A and B** must be fulfilled.

Criterion A — Severity of Positive Symptoms
At least one positive symptom (P1–P5) must be present at a **psychotic level (score = 6)**:

- Delusional ideas (fully formed delusional conviction)
- Persecutory suspiciousness of psychotic intensity
- Grandiose ideas with psychotic conviction
- Hallucinations (perceptual abnormalities of hallucinatory intensity)
- Severely disorganized or incoherent speech

Criterion B — Duration and Frequency of Psychotic Symptoms
For a psychotic-level symptom to qualify as a current psychotic episode, one of the following criteria (B1 or B2) must be met:

B1. Duration–frequency criterion:

- The psychotic symptom has been present for ≥1 hour per day,
- On average ≥4 days per week,
- For a duration of at least 1 month.

B2. Urgency criterion:

- Even if the duration is less than one month, the episode is considered psychotic if the symptom is:
    - Severely disorganizing, or
    - Dangerous to the patient or others.

Post-SIPS Clinical Decision-Making (Phase 4)
For **APS / BIPS / GRD**, patients are included in a **psychosis prevention program**, consisting of early intervention, psychotherapy, and monitoring at least every 3 months.
For **POPS (Presence of Psychotic Symptoms)**, initiation of **antipsychotic treatment** and **multidisciplinary management** is required.

A **positive niacin test** (i.e., absence of a skin flush response to niacin) will trigger the subsequent steps outlined in the integrated clinical algorithm.

Table 43. Integrated clinical algorithm for the identification and management of psychosis risk states (based on SIPS and biological markers).

SIPS Result **Interpretation** **Final Diagnosis**			**Recommended clinical management**		
			Step 1	**Step 2 (if positive niacin test)**	**Step 3 (if ≥1 positive biomarker)**
APS	Attenuated symptoms	Clinical High Risk (CHR)	No antipsychotic; CBT, monitoring	Evaluate hs-CRP (>3 mg/L – systemic inflammation risk), optional omega-3 index, redox ratio, ISO. Adjunctive intervention up to 3 months	Continue adjunctive intervention up to 3 months OR minimal-dose antipsychotic for a limited period
BIPS	Clear psychotic symptoms	Transient psychosis	Monitoring at least every 3 months; possible minimal-dose antipsychotic; repeat testing after 3 months	Minimal-dose antipsychotic + adjunctive intervention up to 3 months; repeat testing	Minimal-dose antipsychotic + adjunctive intervention; SCID-5 or MINI evaluation
GRD	Genetic risk + functional decline	Clinical High Risk	Psychosocial interventions, monitoring	Evaluate hs-CRP (optional omega-3 index, redox ratio); adjunctive intervention; reassess after 3 months	If no effect after 3 months → minimal-dose antipsychotic; SCID-5 or MINI evaluation

POPS	Clear psychotic symptoms	Established psychosis	Initiate antipsychotic treatment and full management	Minimal-dose antipsychotic + adjunctive intervention up to 3 months	Antipsychotic treatment + adjunctive intervention; SCID-5 or MINI evaluation

Note: Adjunctive intervention refers to treatment with nicotinamide (up to 3 g/day), omega-3 fatty acids (2–4 g/day), N-acetylcysteine, minocycline, and other evidence-based agents, selected according to biomarker profiles.
hs-CRP – high-sensitivity C-reactive protein;
redox ratio – NAD^+/NADH ratio;
SCID-5 – Structured Clinical Interview for DSM-5 Disorders;
MINI – Mini International Neuropsychiatric Interview.

7.5 Synthesis of Chapter 7

1. The integrative analysis of screening and diagnostic instruments used in the prodromal stage of schizophrenia highlights clear differences in performance between self-report–based methods and those based on structured clinical interviews.
2. The Structured Interview for Prodromal Syndromes **(SIPS)** emerged as the instrument with the highest diagnostic accuracy for individuals at clinical high risk for psychosis.
3. The integration of validated thresholds from the **PRODscreen questionnaire**, SIPS diagnostic criteria, and relevant biological markers enabled the development of a stepwise clinical algorithm for screening, diagnosis, and clinical management of patients at risk for psychosis.
4. The findings support the concept that risk assessment for schizophrenia should be multidimensional, and that an integrated approach contributes to improved early diagnosis, reduction in transition to overt psychosis, and optimization of prevention and early intervention strategies.

GENERAL CONCLUSIONS

1. Schizophrenia is associated with a heterogeneous inflammatory profile, characterized by pronounced inflammatory activation in a subset of patients. This supports the existence of a distinct inflammatory subgroup, clinically relevant to psychotic and prepsychotic symptoms and potentially important for treatment stratification. Treatment-related changes in proinflammatory cytokine levels support the hypothesis that antipsychotics may exert immunomodulatory effects, which could be further enhanced by adjunctive therapies. Adjunctive anti-inflammatory interventions have shown higher clinical response rates when combined with antipsychotics than when used as monotherapy. In parallel, mitochondrial dysfunction represents a central pathogenic mechanism in schizophrenia, particularly in relation to negative and cognitive symptoms.
2. The efficacy of adjunctive therapies appears to be preserved across age groups, with favorable clinical responses reported both in younger patients aged 20–30 years and in patients older than 40 years. However, adjunctive estrogen therapy appears to show an age-dependent response. The benefits were more pronounced in women aged over 38 years, particularly regarding improvement in PANSS positive symptoms and quality of life, whereas no clinically relevant differences compared with placebo were observed in women younger than 38 years.
3. Comparative analysis of adjunctive therapies with anti-inflammatory, antioxidant, and neuromodulatory effects demonstrates consistent dose–response relationships, with doses close to standard therapeutic ranges that are well tolerated and clinically relevant. These doses appear sufficient to modulate pathogenic mechanisms in schizophrenia without requiring excessive pharmacological escalation. Moreover, adjunctive therapy may reduce the need for increasing antipsychotic doses, thereby lowering the risk of adverse effects
4. The statistical analysis confirms a significant inverse association between inflammatory marker levels and overall clinical functioning, supporting the hypothesis of an interrelationship between inflammation and clinical symptomatology. The data suggest that the minimum effective duration of adjunctive intervention is relatively short, approximately 5–8 weeks, with statistically demonstrable clinical effects that vary according to the type of adjunctive treatment. These findings support the concept of targeted, biomarker-guided pathophysiological intervention, in which patient selection and timing of treatment initiation may be more important determinants of clinical response than prolonged treatment duration.
5. Atypical antipsychotics appear to have a less detrimental impact on essential cellular functions, primarily affecting cellular compartments involved in processing and transport, without directly impairing nuclear function or cellular stress-response mechanisms. In contrast, typical antipsychotics may affect fundamental cellular processes, including nuclear homeostasis and the cellular stress response, which are essential for maintaining cellular integrity and viability, suggesting a greater cytotoxic potential. The efficacy of adjunctive therapy in schizophrenia is largely determined by the type of agent used and its interaction with the baseline antipsychotic regimen. N-acetylcysteine, minocycline, omega-3 fatty acids, estradiol, and selective estrogen receptor modulators act through anti-inflammatory, antioxidant, and immunomodulatory mechanisms, reduce oxidative stress and mitochondrial dysfunction, and may contribute to improved clinical outcomes.

6. Reduction in psychotic symptoms, as measured by PANSS following adjunctive interventions, is consistently associated with improvements in global and social functioning, assessed using the Personal and Social Performance Scale (PSP) and the Global Assessment of Functioning (GAF). These associations have been documented in validation studies and longitudinal follow-up studies of patients with schizophrenia. When integrated with quality-of-life indicators, such as EQ-5D, these functional gains are associated with preservation of social and occupational roles, reduced hospitalization and relapse rates, and consequently lower direct and indirect costs of treatment and care.
7. Improvements in quality of life are largely associated with reductions in negative symptoms, enhanced cognitive functioning, and better social adaptation. The analyzed data support consistent and potentially bidirectional relationships between proinflammatory markers, including IL-6, TNF-α, and CRP, and quality-of-life indicators. Elevated levels of these markers are associated with poorer physical and social functioning, cognitive impairment, and greater clinical severity, supporting inflammation as a relevant therapeutic target in adjunctive treatment. The data further indicate that combining such therapies with antipsychotic treatment may improve both clinical outcomes and EQ-5D quality-of-life measures after a relatively short intervention period, approximately 8 weeks. Reductions in PANSS scores, interpreted according to Leucht criteria, correlate with increases in EQ-5D utility values exceeding the minimum clinically important difference (MIC/MID), thereby confirming the clinical relevance of these findings.
8. Based on the calculations performed, the niacin test demonstrated a positive predictive value of 78.5% and a negative predictive value of 71.09%, supporting its potential utility as a practical and cost-effective screening tool for identifying individuals at clinical high risk for psychosis or at increased risk of developing schizophrenia.
9. The synthesized results indicate that exosomal biomarkers demonstrate good overall diagnostic performance in schizophrenia, with median AUC values approaching 0.90 and sensitivity and specificity values exceeding 80%. These findings support the potential utility of exosomes as diagnostic and prognostic biomarkers. Their integration with clinical and other biological data may improve patient stratification and support the personalization of therapeutic interventions.
10. By integrating the validated PRODscreen screening tool, the SIPS structured clinical interview, and relevant biological markers, this research enabled the development of an integrated clinical algorithm for the identification, stratification, and management of psychosis risk states. The findings support the concept that schizophrenia risk assessment should rely on a multidimensional framework and that such an integrated approach may improve early diagnosis. The proposed algorithm also supports early intervention, treatment personalization, and optimization of prevention strategies.

RECOMMENDATIONS

1. **1.** It is recommended to implement the assessment of systemic inflammatory markers involved in the pathogenic mechanisms of schizophrenia, including hs-CRP or, alternatively, IL-6 and TNF-α, markers of lipid and phospholipid imbalance, such as the omega-3 index and niacin test, oxidative stress markers, including the oxidative stress index (OSI), markers of energetic and mitochondrial dysfunction, such as the NAD^+/NADH ratio, and neuroimmune communication markers, including exosomal microRNAs. These biomarkers may serve as complementary biological indicators in the diagnosis of prodromal states and in the assessment of psychosis risk.
2. **2.** Adjunctive therapies should be implemented in a personalized manner, guided by each patient's biological and clinical profile, using safe dosing regimens and treatment durations supported by meta analytic evidence and robust statistical analyses.
3. **3.** The proposed integrated clinical algorithm for the identification and management of psychosis risk states ought to be clinically validated and incorporated into national clinical protocols and routine practice.

REFERENCES

1. Schizophrenia [Internet]. World Health Organization. 2025 [cited 2025 Nov 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/schizophrenia
2. Correll CU, Solmi M, Croatto G, Schneider LK, Rohani-Montez SC, Fairley L, et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry. 2022 Jun;21(2):248–71.
3. Zhan Z, Wang J, Shen T. Results of the Global Burden of Disease study for schizophrenia: trends from 1990 to 2021 and projections to 2050. Front psychiatry. 2025;16:1629032.
4. Martins R, Kadakia A, Williams GR, Milanovic S, Connolly MP. The Lifetime Burden of Schizophrenia as Estimated by a Government-Centric Fiscal Analytic Framework. J Clin Psychiatry. 2023 Aug;84(5).
5. Markota M, Morgan RJ, Leung JG. Updated rationale for the initial antipsychotic selection for patients with schizophrenia. Schizophrenia [Internet]. 2024;10(1):74. Available from: https://doi.org/10.1038/s41537-024-00492-y
6. Nastas I. Schizofrenia. Mecanisme patobiologice și strategii de diagnostic precoce. Chișinău: [S. n.]; 2025. 118 p.
7. Boronin L, Nastas I. Prognozarea riscului de apariţie al stărilor reziduale până în 3 ani de la debutul schizofreniei paranoide. Bul Psihiatr Integr. 2008;XIII(3 (38)):32–8.
8. Revenco M, Boronin L, Nastas I, Coșciug I, Deliv I. Debutul schizofreniei paranoide: Criterii evolutive și de pronostic. Rom J Psychopharmacol. 2010;10(Suppl. 2):41–2.
9. Boronin L, Revenco M, Nastas I, Sinița E. Psihopatologia și evoluția stărilor reziduale în schizofrenie. Rom J Psychopharmacol. 2010;10(Suppl.2):12–3.
10. Hamina A, Taipale H, Lieslehto J, Lähteenvuo M, Tanskanen A, Mittendorfer-Rutz E, et al. Comparative Effectiveness of Antipsychotics in Patients With Schizophrenia Spectrum Disorder. JAMA Netw Open [Internet]. 2024 Oct 9;7(10):e2438358–e2438358. Available from: https://doi.org/10.1001/jamanetworkopen.2024.38358
11. Boronin L, Nastas I. Criterii clinice de rezistență în schizofrenie. In: Culegere de lucrări. Tipografia „Printline"; 2019. p. 13.
12. Campbell M, Young PI, Bateman DN, Smith JM, Thomas SH. The use of atypical antipsychotics in the management of schizophrenia. Br J Clin Pharmacol. 1999 Jan;47(1):13–22.
13. Andrade C. Antipsychotic Medication Continuation vs Taper and Discontinuation in Patients With Schizophrenia and Other Nonaffective Psychotic Disorders. J Clin Psychiatry. 2024 May;85(2).
14. Fond G, Lançon C, Korchia T, Auquier P, Boyer L, Guillaume Fond CL, et al. The Role of Inflammation in the Treatment of Schizophrenia. Front psychiatry [Internet]. 2020;11. Available from: https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2020.00160/full
15. Girgis RR, Kumar SS, Brown AS. The cytokine model of schizophrenia: emerging therapeutic strategies. Biol Psychiatry. 2014 Feb;75(4):292–9.
16. Lin A, Kenis G, Bignotti S, Tura GJ, De Jong R, Bosmans E, et al. The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophr Res. 1998 Jun;32(1):9–15.

17. Yang H, Peng R, Yang M, Zhang J, Shi Z, Zhang X. Association between elevated serum matrix metalloproteinase-2 and tumor necrosis factor-α, and clinical symptoms in male patients with treatment-resistant and chronic medicated schizophrenia. BMC Psychiatry. 2024 Mar;24(1):173.
18. Baganz NL, Blakely RD. A dialogue between the immune system and brain, spoken in the language of serotonin. ACS Chem Neurosci. 2013 Jan;4(1):48–63.
19. Georgiev G.Z. No Title [Internet]. “Correlation Coefficient Calculator.” Available from: https://www.gigacalculator.com/calculators/correlation-coefficient-calculator.php
20. Hong J, Bang M. Anti-inflammatory Strategies for Schizophrenia: A Review of Evidence for Therapeutic Applications and Drug Repurposing. Clin Psychopharmacol Neurosci Off Sci J Korean Coll Neuropsychopharmacol. 2020 Feb;18(1):10–24.
21. Attari A, Mojdeh A, Khalifeh Soltani F A S NMR. Aspirin Inclusion in Antipsychotic Treatment on Severity of Symptoms in Schizophrenia: A Randimized Clinical Trial. Iran J Psychiatry Behav Sci [Internet]. 2017;(11(1):):e5848. Available from: https://brieflands.com/articles/ijpbs-5848.html
22. Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010 May;71(5):520–7.
23. Erlyn Limoa, Jauhari Lutfi, Saidah Syamsuddin, Andi Alfian Zainuddin, Andi Tenri Esa & STL. c. ournal Popul Ther Clin Pharmacol. 2023;30(16):612–619.
24. Akhondzadeh S, Tabatabaee M, Amini H, Ahmadi Abhari SA, Abbasi SH, Behnam B. Celecoxib as adjunctive therapy in schizophrenia: A double-blind, randomized and placebo-controlled trial. Schizophr Res [Internet]. 2007;90(1):179–85. Available from: https://www.sciencedirect.com/science/article/pii/S0920996406004956
25. Rapaport MH, Delrahim KK, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D. Celecoxib Augmentation of Continuously Ill Patients with Schizophrenia. Biol Psychiatry [Internet]. 2005;57(12):1594–6. Available from: https://www.sciencedirect.com/science/article/pii/S0006322305001897
26. Müller N, Krause D, Dehning S, Musil R, Schennach-Wolff R, Obermeier M, et al. Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. Schizophr Res. 2010 Aug;121(1–3):118–24.
27. Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-Acetyl Cysteine as a Glutathione Precursor for Schizophrenia—A Double-Blind, Randomized, Placebo-Controlled Trial. Biol Psychiatry [Internet]. 2008;64(5):361–8. Available from: https://www.sciencedirect.com/science/article/pii/S0006322308002709
28. Farokhnia M, Azarkolah A, Adinehfar F, Khodaie-Ardakani MR, Hosseini SMR, Yekehtaz H, et al. N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: a randomized, double-blind, placebo-controlled study. Clin Neuropharmacol. 2013;36(6):185–92.
29. Xiang YQ, Zheng W, Wang SB, Yang XH, Cai DB, Ng CH, et al. Adjunctive minocycline for schizophrenia: A meta-analysis of randomized controlled trials. Eur Neuropsychopharmacol [Internet]. 2017;27(1):8–18. Available from:

https://www.sciencedirect.com/science/article/pii/S0924977X16320028
30. Lena Grüber, MD; Tilmann Bunse, MD; Elif Weidinger, MD; Heidi Reichard, MD; and Norbert Müller M. Adjunctive Recombinant Human Interferon Gamma-1b for Treatment-Resistant Schizophrenia in 2 patients. J Clin Psychiatry [Internet]. 2014;75(11):1266–7. Available from: https://www.psychiatrist.com/jcp/adjunctive-recombinant-human-interferon-gamma-b-treatment/
31. Girgis RR, Ciarleglio A, Choo T, Haynes G, Bathon JM, Cremers S, et al. A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Tocilizumab, An Interleukin-6 Receptor Antibody, For Residual Symptoms in Schizophrenia. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2018 May;43(6):1317–23.
32. Brian J. Miller, MD, PhD, MPH; James K. Dias, PhD; Henrique P. Lemos, PhD; and Peter F. Buckley M. An Open-Label, Pilot Trial of Adjunctive Tocilizumab in Schizophrenia. J Clin Psychiatry [Internet]. 2016;77(2):275–6. Available from: https://www.psychiatrist.com/jcp/open-label-pilot-trial-adjunctive-tocilizumab-schizophrenia/
33. Weickert T, Jacomb I, Lenroot R, Lappin J, Weinberg D, Brooks W, et al. S33. Reduction in peripheral c-reactive protein levels with canakinumab administration is related to reduced positive symptom severity in patients with schizophrenia and inflammation. Vol. 45, Schizophrenia Bulletin. 2019. p. S318.
34. Shen H, Li R, Yan R, Zhou X, Feng X, Zhao M, et al. Adjunctive therapy with statins in schizophrenia patients: A meta-analysis and implications. Psychiatry Res [Internet]. 2018;262:84–93. Available from: https://www.sciencedirect.com/science/article/pii/S0165178117315445
35. Wang DM, Chen DC, Xiu MH, Wang L, Kosten TR, Zhang XY. S-a demonstrat că citokinele proinflamatorii, inclusiv IFN-β1b și IFN-γ (cu efect sinergic al TNF-α), reduc disponibilitatea triptofanului, care este necesar pentru sinteza 5-HT,iar modificările triptofanului, influențează 5-HT cerebrală. În cele din urmă. Neuropsychopharmacology. 2024 Apr;49(5):893–902.
36. Karbalaee M, Jameie M, Amanollahi M, TaghaviZanjani F, Parsaei M, Basti FA, et al. Efficacy and safety of adjunctive therapy with fingolimod in patients with schizophrenia: A randomized, double-blind, placebo-controlled clinical trial. Schizophr Res. 2023 Apr;254:92–8.
37. Li M, Qiu Y, Zhang J, Zhang Y, Liu Y, Zhao Y, et al. Improvement of adjunctive berberine treatment on negative symptoms in patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci [Internet]. 2022;272(4):633–42. Available from: https://doi.org/10.1007/s00406-021-01359-4
38. Salehi A, Namaei P, TaghaviZanjani F, Bagheri S, Moradi K, Khodaei Ardakani MRR, et al. Adjuvant palmitoylethanolamide therapy with risperidone improves negative symptoms in patients with schizophrenia: A randomized, double-blinded, placebo-controlled trial. Psychiatry Res. 2022 Oct 1;316:114737.
39. Weiser M, Zamora D, Levi L, Nastas I, Gonen I, Radu P, et al. Adjunctive Aspirin vs Placebo in Patients with Schizophrenia: Results of Two Randomized Controlled Trials. Schizophr Bull. 2021;47(4).
40. Pourghasem M, Sadighi G, Mirabzadeh A. Comparing the Effects of Adjunct Aspirin and

Simvastatin on Psychopathology Among Inpatients With Schizophrenia TT -. Iranian-Rehabilitation-Journal [Internet]. 2022 Mar 1;20(1):33–42. Available from: http://irj.uswr.ac.ir/article-1-1566-en.html

41. Baheti T, Nischal A, Nischal A, Khattri S, Arya A, Tripathi A, et al. A study to evaluate the effect of celecoxib as add-on to olanzapine therapy in schizophrenia. Vol. 147, Schizophrenia research. Netherlands; 2013. p. 201–2.

42. Zheng W, Cai DB, Yang XH, Ungvari GS, Ng CH, Müller N, et al. Adjunctive celecoxib for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials. J Psychiatr Res [Internet]. 2017;92:139–46. Available from: https://www.sciencedirect.com/science/article/pii/S0022395617302467

43. Zarghami M, Dodangi N, Azari P, Khalilian A. Antipsychotic Effects of Celecoxib Add-On Haloperidol in Schizophrenia: A Randomized Double-Blind Placebo-Controlled Clinical Trial. IJ Psychiatry Behav Sci. 2024;18(1:e138643).

44. Solmi M, Veronese N, Thapa N, Facchini S, Stubbs B, Fornaro M, et al. Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia. CNS Spectr. 2017 Oct;22(5):415–26.

45. Deakin B, Suckling J, Barnes TRE, Byrne K, Chaudhry IB, Dazzan P. The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial [Internet]. Vol. 5. 2018. p. 885–94. Available from: https://doi.org/10.1016/S2215-0366(18)30345-6

46. Deakin B, Suckling J, Dazzan P, Joyce E, Lawrie SM, Upthegrove R, et al. Minocycline for negative symptoms of schizophrenia and possible mechanistic actions: the BeneMin RCT [Internet]. Vol. 6. 2019. p. 7. Available from: https://doi.org/10.3310/eme06070

47. Müller N, Riedel M, Scheppach C, Brandstätter B, Sokullu S, Krampe K, et al. Beneficial Antipsychotic Effects of Celecoxib Add-On Therapy Compared to Risperidone Alone in Schizophrenia. Am J Psychiatry [Internet]. 2002 Jun 1;159(6):1029–34. Available from: https://doi.org/10.1176/appi.ajp.159.6.1029

48. Chaudhry IB, Hallak J, Husain N, Minhas F, Stirling J, Richardson P, et al. Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J Psychopharmacol. 2012 Sep;26(9):1185–93.

49. Ghanizadeh A, Dehbozorgi S, OmraniSigaroodi M, Rezaei Z. Minocycline as add-on treatment decreases the negative symptoms of schizophrenia; a randomized placebo-controlled clinical trial. Recent Pat Inflamm Allergy Drug Discov. 2014;8(3):211–5.

50. Khodaie-Ardakani MR, Mirshafiee O, Farokhnia M, Tajdini M, Hosseini SMR, Modabbernia A, et al. Minocycline add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: randomized double-blind placebo-controlled study. Psychiatry Res. 2014 Mar;215(3):540–6.

51. Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry. 2010 Feb;71(2):138–49.

52. Liu F, Guo X, Wu R, Ou J, Zheng Y, Zhang B, et al. Minocycline supplementation for treatment of negative symptoms in early-phase schizophrenia: a double blind,

randomized, controlled trial. Schizophr Res. 2014 Mar;153(1–3):169–76.

53. Lee EE, Hong S, Martin AS, Eyler LT, Jeste D V. Inflammation in Schizophrenia: Cytokine Levels and Their Relationships to Demographic and Clinical Variables. Am J Geriatr psychiatry Off J Am Assoc Geriatr Psychiatry. 2017 Jan;25(1):50–61.

54. Kim H, Baek SH, Kim JW, Ryu S, Lee JY, Kim JM, et al. Inflammatory markers of symptomatic remission at 6 months in patients with first-episode schizophrenia. Schizophrenia [Internet]. 2023;9(1):68. Available from: https://doi.org/10.1038/s41537-023-00398-1

55. M. F, J.A. MF, M. A, R. R, C. FA, P. A, et al. Quality of life is associated with chronic inflammation in schizophrenia: a cross-sectional study. Sci Rep [Internet]. 2015;5(1):10793. Available from: https://doi.org/10.1038/srep10793

56. Kachouchi A, Ahmed L, Saadia K, Imane A, Fatiha M. Quality of Life and C-Reactive Protein in Patients with Schizophrenia: A Cross-Sectional Study. Alpha psychiatry. 2024 Mar;25(2):256–61.

57. Roberts RC. Mitochondrial dysfunction in schizophrenia: With a focus on postmortem studies. Mitochondrion. 2021 Jan;56:91–101.

58. Vringer E, Tait SWG. Mitochondria and cell death-associated inflammation. Cell Death Differ. 2023 Feb;30(2):304–12.

59. Xu H, Yang F. The interplay of dopamine metabolism abnormalities and mitochondrial defects in the pathogenesis of schizophrenia. Transl Psychiatry. 2022 Nov;12(1):464.

60. Ben-Shachar D, Zuk R, Glinka Y. Dopamine Neurotoxicity: Inhibition of Mitochondrial Respiration. J Neurochem [Internet]. 1995 Feb 1;64(2):718–23. Available from: https://doi.org/10.1046/j.1471-4159.1995.64020718.x

61. Brenner-Lavie H, Klein E, Zuk R, Gazawi H, Ljubuncic P, Ben-Shachar D. Dopamine modulates mitochondrial function in viable SH-SY5Y cells possibly via its interaction with complex I: Relevance to dopamine pathology in schizophrenia. Biochim Biophys Acta - Bioenerg [Internet]. 2008;1777(2):173–85. Available from: https://www.sciencedirect.com/science/article/pii/S0005272807002320

62. Bergman O, Ben-Shachar D. Mitochondrial Oxidative Phosphorylation System (OXPHOS) Deficits in Schizophrenia: Possible Interactions with Cellular Processes. Can J Psychiatry. 2016 Aug;61(8):457–69.

63. Bagnoli E, Diviney T, FitzGerald U. Dysregulation of astrocytic mitochondrial function following exposure to a dopamine metabolite: Implications for Parkinson's disease. Eur J Neurosci. 2021 May;53(9):2960–72.

64. Martins-de-Souza D, Guest PC, Mann DM, Roeber S, Rahmoune H, Bauder C, et al. Proteomic analysis identifies dysfunction in cellular transport, energy, and protein metabolism in different brain regions of atypical frontotemporal lobar degeneration. J Proteome Res. 2012 Apr;11(4):2533–43.

65. Shinoda Y, Tagashira H, Bhuiyan MS, Hasegawa H, Kanai H, Fukunaga K. Haloperidol aggravates transverse aortic constriction-induced heart failure via mitochondrial dysfunction. J Pharmacol Sci. 2016 Jul;131(3):172–83.

66. Eftekhari A, Azarmi Y, Parvizpur A, Eghbal MA. Involvement of oxidative stress and mitochondrial/lysosomal cross-talk in olanzapine cytotoxicity in freshly isolated rat

hepatocytes. Xenobiotica. 2016;46(4):369–78.

67. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JW, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med. 1989 Feb;320(5):265–71.

68. Khalfoun B, Thibault F, Watier H, Bardos P, Lebranchu Y. Docosahexaenoic and eicosapentaenoic acids inhibit in vitro human endothelial cell production of interleukin-6. Adv Exp Med Biol. 1997;400B:589–97.

69. Amiri Khosroshahi R, Heidari Seyedmahalle M, Zeraattalab-Motlagh S, Fakhr L, Wilkins S, Mohammadi H. The Effects of Omega-3 Fatty Acids Supplementation on Inflammatory Factors in Cancer Patients: A Systematic Review and Dose-Response Meta-Analysis of Randomized Clinical Trials. Nutr Cancer. 2024;76(1):1–16.

70. Fenton WS, Dickerson F, Boronow J, Hibbeln JR, Knable M. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. Am J Psychiatry. 2001 Dec;158(12):2071–4.

71. Emsley R, Myburgh C, Oosthuizen P, van Rensburg SJ. Randomized, Placebo-Controlled Study of Ethyl-Eicosapentaenoic Acid as Supplemental Treatment in Schizophrenia. Am J Psychiatry [Internet]. 2002;159(9):1596–8. Available from: http://dx.doi.org/10.1176/APPI.AJP.159.9.1596

72. Bentsen H, Osnes K, Refsum H, Solberg DK, Bøhmer T. A randomized placebo-controlled trial of an omega-3 fatty acid and vitamins E+C in schizophrenia. Transl Psychiatry [Internet]. 2013;3(12):e335–e335. Available from: http://dx.doi.org/10.1038/tp.2013.110

73. Jamilian H, Solhi H, Jamilian M. Randomized, Placebo-Controlled Clinical Trial of Omega-3 as Supplemental Treatment in Schizophrenia. Glob J Health Sci [Internet]. 2014;6(7). Available from: http://dx.doi.org/10.5539/gjhs.v6n7p103

74. Qiao Y, Liu CP, Han HQ, Liu FJ, Shao Y, Xie B. No Impact of Omega-3 Fatty Acid Supplementation on Symptoms or Hostility Among Patients With Schizophrenia. Front psychiatry. 2020;11:312.

75. Collaboration TC. Review Manager Web (RevMan Web) [Internet]. London: The Cochrane Collaboration; 2023. Available from: https://revman.cochrane.org/

76. Messamore E, Hoffman WF, Yao JK. Niacin sensitivity and the arachidonic acid pathway in schizophrenia. Schizophr Res. 2010 Sep;122(1–3):248–56.

77. Gan R, Wei Y, Wu G, Zeng J, Hu Y, Xu L, et al. Attenuated niacin-induced skin flush response in individuals with clinical high risk for psychosis. Gen psychiatry. 2022;35(2):e100748.

78. : Nastas I BL. Mechanisms of niacin skin test pathogenesis in patients at clinical high risk for psychosis and schizophrenia. Mold J Heal Sci. 2024;11(4):54–61.

79. Nastas I, Boronin L. Results of skin tests and the effects of niacin in patients with schizophrenia. Neurosci Appl [Internet]. 2024;3:105050. Available from: https://www.sciencedirect.com/science/article/pii/S2772408524011153

80. Boronin L., Spinei L. NI. NIACIN SKIN TEST IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW. Arch Balk Med Union [Internet]. 2025;60(2):284–94.

Available from: https://umbalk.org/niacin-skin-test-in-schizophrenia-a-systematic-review/
81. Riecher-Rössler A. Oestrogens, prolactin, hypothalamic-pituitary-gonadal axis, and schizophrenic psychoses. The lancet Psychiatry. 2017 Jan;4(1):63–72.
82. Seeman M V. Menstrual exacerbation of schizophrenia symptoms. Acta Psychiatr Scand. 2012 May;125(5):363–71.
83. Clare AW. The relationship between psychopathology and the menstrual cycle. Women Health. 1983;8(2–3):125–36.
84. Seeman M V. The role of estrogen in schizophrenia. J Psychiatry Neurosci. 1996 Mar;21(2):123–7.
85. Shahini N, Salimi Z, Kiani D, Raftari A, Ziaee M. Relationship of serum estradiol and progesterone with symptoms and sex difference in schizophrenia: A cross-sectional study in Iran. Front Psychiatry [Internet]. 2023;Volume 14. Available from: https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2023.1075780
86. Bergemann N, Mundt C, Parzer P, Jannakos I, Nagl I, Salbach B, et al. Plasma concentrations of estradiol in women suffering from schizophrenia treated with conventional versus atypical antipsychotics. Schizophr Res. 2005 Mar;73(2–3):357–66.
87. Cohen RZ, Seeman M V, Gotowiec A, Kopala L. Earlier puberty as a predictor of later onset of schizophrenia in women. Am J Psychiatry. 1999 Jul;156(7):1059–64.
88. Reilly TJ, Sagnay de la Bastida VC, Joyce DW, Cullen AE, McGuire P. Exacerbation of Psychosis During the Perimenstrual Phase of the Menstrual Cycle: Systematic Review and Meta-analysis. Schizophr Bull. 2020 Jan;46(1):78–90.
89. McGregor C, Riordan A, Thornton J. Estrogens and the cognitive symptoms of schizophrenia: Possible neuroprotective mechanisms. Front Neuroendocrinol [Internet]. 2017;47:19–33. Available from: https://www.sciencedirect.com/science/article/pii/S0091302217300341
90. Sherwin BB, Tulandi T. "Add-back" estrogen reverses cognitive deficits induced by a gonadotropin-releasing hormone agonist in women with leiomyomata uteri. J Clin Endocrinol Metab. 1996 Jul;81(7):2545–9.
91. Villa A, Vegeto E, Poletti A, Maggi A. Estrogens, Neuroinflammation, and Neurodegeneration. Endocr Rev. 2016 Aug;37(4):372–402.
92. Gagne C, Piot A, Brake WG. Depression, Estrogens, and Neuroinflammation: A Preclinical Review of Ketamine Treatment for Mood Disorders in Women. Front Psychiatry [Internet]. 2022;Volume 12. Available from: https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.797577
93. Brand BA, de Boer JN, Sommer IEC. Estrogens in schizophrenia: progress, current challenges and opportunities. Curr Opin Psychiatry. 2021 May;34(3):228–37.
94. Torrens-Mas M, Pons DG, Sastre-Serra J, Oliver J, Roca P. Sexual hormones regulate the redox status and mitochondrial function in the brain. Pathological implications. Redox Biol. 2020 Apr;31:101505.
95. Yang L cai, Zhang QG, Zhou C feng, Yang F, Zhang Y dong, Wang R min, et al. Extranuclear estrogen receptors mediate the neuroprotective effects of estrogen in the rat hippocampus. PLoS One. 2010 May;5(5):e9851.
96. Trenti A, Tedesco S, Boscaro C, Trevisi L, Bolego C, Cignarella A. Estrogen,

Angiogenesis, Immunity and Cell Metabolism: Solving the Puzzle. Int J Mol Sci. 2018 Mar;19(3).

97. Küppers E, Ivanova T, Karolczak M, Beyer C. Estrogen: a multifunctional messenger to nigrostriatal dopaminergic neurons. J Neurocytol. 2000;29(5–6):375–85.

98. Shams WM, Cossette MP, Shizgal P, Brake WG. 17β-estradiol locally increases phasic dopamine release in the dorsal striatum. Neurosci Lett. 2018 Feb;665:29–32.

99. Kugaya A, Epperson CN, Zoghbi S, van Dyck CH, Hou Y, Fujita M, et al. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. Am J Psychiatry. 2003 Aug;160(8):1522–4.

100. Vandegrift BJ, You C, Satta R, Brodie MS, Lasek AW. Estradiol increases the sensitivity of ventral tegmental area dopamine neurons to dopamine and ethanol. PLoS One. 2017;12(11):e0187698.

101. Weinstein JJ, Chohan MO, Slifstein M, Kegeles LS, Moore H, Abi-Dargham A. Pathway-Specific Dopamine Abnormalities in Schizophrenia. Biol Psychiatry. 2017 Jan;81(1):31–42.

102. Lewis DA, Lieberman JA. Catching up on schizophrenia: natural history and neurobiology. Neuron. 2000 Nov;28(2):325–34.

103. Sánchez MG, Bourque M, Morissette M, Di Paolo T. Steroids-dopamine interactions in the pathophysiology and treatment of CNS disorders. CNS Neurosci Ther. 2010 Jun;16(3):e43-71.

104. Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front Neurosci [Internet]. 2015;Volume 9-(FEB). Available from: https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2015.00037

105. Li F, Oh I, Kumar S, Eteleeb A, Gupta A, Buchser W, et al. Loss of estrogen unleashing neuro-inflammation increases the risk of Alzheimer's disease in women. bioRxiv [Internet]. 2022 Jan 1;2022.09.19.508592. Available from: http://biorxiv.org/content/early/2022/09/20/2022.09.19.508592.abstract

106. Xu Q, Ji M, Huang S, Guo W. Association between serum estradiol levels and cognitive function in older women: a cross-sectional analysis. Front Aging Neurosci [Internet]. 2024;Volume 16. Available from: https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2024.1356791

107. Weiser M, Levi L, Zamora D, Biegon A, Sangiovanni JP, Davidson M, et al. Effect of Adjunctive Estradiol on Schizophrenia among Women of Childbearing Age: A Randomized Clinical Trial. JAMA Psychiatry. 2019;76(10):1009–17.

108. Kulkarni J, Gavrilidis E, Wang W, Worsley R, Fitzgerald PB, Gurvich C, et al. Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age. Mol Psychiatry [Internet]. 2015;20(6):695–702. Available from: https://doi.org/10.1038/mp.2014.33

109. Abdin E, Chong SA, Seow E, Verma S, Tan KB, Subramaniam M. Mapping the Positive and Negative Syndrome Scale scores to EQ-5D-5L and SF-6D utility scores in patients with schizophrenia. Qual life Res an Int J Qual life Asp Treat care Rehabil. 2019 Jan;28(1):177–86.

110. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? [Internet]. Vol. 79. 2005. p. 231–8. Available from: https://doi.org/10.1016/j.schres.2005.04.008

111. Leucht S, Davis JM, Engel RR, Kissling W, Kane JM. Definitions of response and remission in schizophrenia: recommendations for their use and their presentation. Acta Psychiatr Scand Suppl. 2009;(438):7–14.

112. Leucht S, Kane JM, Etschel E, Kissling W, Hamann J, Engel RR. Linking the PANSS, BPRS, and CGI: clinical implications. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2006 Oct;31(10):2318–25.

113. Chen YF, Luh F, Ho YS, Yen Y. Exosomes: a review of biologic function, diagnostic and targeted therapy applications, and clinical trials. J Biomed Sci [Internet]. 2024;31(1):67. Available from: https://doi.org/10.1186/s12929-024-01055-0

114. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol. 2014;30:255–89.

115. Greening DW, Xu R, Ji H, Tauro BJ, Simpson RJ. A protocol for exosome isolation and characterization: evaluation of ultracentrifugation, density-gradient separation, and immunoaffinity capture methods. Methods Mol Biol. 2015;1295:179–209.

116. Zarovni N, Corrado A, Guazzi P, Zocco D, Lari E, Radano G, et al. Integrated isolation and quantitative analysis of exosome shuttled proteins and nucleic acids using immunocapture approaches. Methods [Internet]. 2015;87:46–58. Available from: https://www.sciencedirect.com/science/article/pii/S1046202315002340

117. Kenigsberg S, Wyse BA, Librach CL, da Silveira JC. Protocol for Exosome Isolation from Small Volume of Ovarian Follicular Fluid: Evaluation of Ultracentrifugation and Commercial Kits. Methods Mol Biol. 2017;1660:321–41.

118. Desmeules C, Corbeil O, Huot-Lavoie M, Béchard L, Brodeur S, Demers MF, et al. Psychotic Disorders and exosomes: An overview of current evidence and future directions. Psychiatry Res. 2024 Sep;339:116066.

119. Nastas I, Boronin L. Statistical Analysis of Exosome Diagnostic Methods in Patients with Schizophrenia BT - 7th International Conference on Nanotechnologies and Biomedical Engineering. In: Sontea V, Tiginyanu I, Railean S, editors. Cham: Springer Nature Switzerland; 2025. p. 3–13.

120. Zhong XL, Huang Y, Du Y, He LZ, Chen Y wen, Cheng Y, et al. Unlocking the Therapeutic Potential of Exosomes Derived From Nasal Olfactory Mucosal Mesenchymal Stem Cells: Restoring Synaptic Plasticity, Neurogenesis, and Neuroinflammation in Schizophrenia. Schizophr Bull [Internet]. 2024 May 1;50(3):600–14. Available from: https://doi.org/10.1093/schbul/sbad172

121. Du Y, Yu Y, Hu Y, Li XW, Wei ZX, Pan RY, et al. Genome-Wide, Integrative Analysis Implicates Exosome-Derived MicroRNA Dysregulation in Schizophrenia. Schizophr Bull. 2019 Oct;45(6):1257–66.

122. Du Y, Chen L, Li XS, Li XL, Xu XD, Tai SB, et al. Metabolomic Identification of Exosome-Derived Biomarkers for Schizophrenia: A Large Multicenter Study. Schizophr Bull. 2021 Apr;47(3):615–23.

123. Xue T, Liu W, Wang L, Shi Y, Hu Y, Yang J, et al. Extracellular vesicle biomarkers for complement dysfunction in schizophrenia. Brain. 2024 Mar;147(3):1075–86.

124. Heinimaa M, Salokangas RKR, Ristkari T, Plathin M, Huttunen J, Ilonen T, et al. PROD-screen--a screen for prodromal symptoms of psychosis. Int J Methods Psychiatr Res. 2003;12(2):92–104.
125. McGlashan TH, Walsh BC, Woods SW, McGlashan, Thomas H.; Walsh, Brian C.; Woods SW. Structured Interview for Psychosis-Risk Syndromes (SIPS), Version 5.5 [Internet]. New Haven, CT, USA; 2023. Available from: https://easacommunity.org/resources/sips/
126. McGlashan, Thomas H.; Walsh, Brian C.; Woods SW. Structured Interview for Psychosis-Risk Syndromes (SIPS), Version 5.5 [Internet]. New Haven, CT, USA; 2014. Available from: https://easacommunity.org/resources/sips/
127. Cho M, Lee TY, Kwak Y Bin, Yoon YB, Kim M, Kwon JS. Adjunctive use of anti-inflammatory drugs for schizophrenia: A meta-analytic investigation of randomized controlled trials. Aust New Zeal J Psychiatry [Internet]. 2019 Mar 13;53(8):742–59. Available from: https://doi.org/10.1177/0004867419835028
128. Buchanan RW, Weiner E, Kelly DL, Gold JM, Chen S, Zaranski J, et al. Anti-inflammatory Combination Therapy for the Treatment of Schizophrenia. J Clin Psychopharmacol [Internet]. 2020;40(5). Available from: https://journals.lww.com/psychopharmacology/fulltext/2020/09000/anti_inflammatory_combination_therapy_for_the.6.aspx
129. Chandra A, Miller BJ, Goldsmith DR. Predictors of successful anti-inflammatory drug trials in patients with schizophrenia: A meta-regression and critical commentary. Brain Behav Immun [Internet]. 2023;114:154–62. Available from: https://www.sciencedirect.com/science/article/pii/S0889159123002246
130. Sommer IE, van Westrhenen R, Begemann MJH, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. Schizophr Bull. 2014 Jan;40(1):181–91.
131. Mongan D, Ramesar M, Föcking M, Cannon M, Cotter D. Role of inflammation in the pathogenesis of schizophrenia: A review of the evidence, proposed mechanisms and implications for treatment. Early Interv Psychiatry. 2020 Aug;14(4):385–97.
132. Jeppesen R, Christensen RHB, Pedersen EMJ, Nordentoft M, Hjorthøj C, Köhler-Forsberg O, et al. Efficacy and safety of anti-inflammatory agents in treatment of psychotic disorders – A comprehensive systematic review and meta-analysis. Brain Behav Immun [Internet]. 2020;90:364–80. Available from: https://www.sciencedirect.com/science/article/pii/S0889159120311557
133. de Boer J, Prikken M, Lei WU, Begemann M, Sommer I. The effect of raloxifene augmentation in men and women with a schizophrenia spectrum disorder: a systematic review and meta-analysis. npj Schizophr [Internet]. 2018;4(1):1. Available from: https://doi.org/10.1038/s41537-017-0043-3
134. Li Z, Wang Y, Wang Z, Kong L, Liu L, Li L, et al. Estradiol and raloxifene as adjunctive treatment for women with schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials [Internet]. Acta Psychiatrica Scandinavica John Wiley and Sons Inc; Apr 1, 2023 p. 360–72. Available from: https://pubmed.ncbi.nlm.nih.gov/36585771/
135. Zhu XM, Zheng W, Li XH, Cai DB, Yang XH, Ungvari GS, et al. Adjunctive raloxifene for postmenopausal women with schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials. Schizophr Res. 2018 Jul;197:288–93.

136. Zhang S, Liao A, Wang Y, Liu Q, Ouyang L, Peng H, et al. Profiling expressing features of surface proteins on single-exosome in first-episode Schizophrenia patients: a preliminary study. Schizophrenia [Internet]. 2024;10(1):84. Available from: https://doi.org/10.1038/s41537-024-00510-z

137. Dong Y, Wang S, Li M, Su Q, Bi F, Sun X, et al. The multiomics landscape of plasma exosomes in first-episode drug-naïve of schizophrenia. BMC Psychiatry. 2025 Aug;25(1):764.

138. Tunset ME, Haslene-Hox H, Van Den Bossche T, Vaaler AE, Sulheim E, Kondziella D. Extracellular vesicles in patients in the acute phase of psychosis and after clinical improvement: an explorative study. PeerJ. 2020;8:e9714.

139. Funahashi Y, Yoshino Y, Iga J ichi, Ueno S ichi. Impact of clozapine on the expression of miR-675-3p in plasma exosomes derived from patients with schizophrenia. World J Biol Psychiatry [Internet]. 2023 Apr 21;24(4):303–13. Available from: https://doi.org/10.1080/15622975.2022.2104924

140. Loewy RL, Pearson R, Vinogradov S, Bearden CE, Cannon TD. Psychosis risk screening with the Prodromal Questionnaire--brief version (PQ-B). Schizophr Res. 2011 Jun;129(1):42–6.

141. Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull. 2003;29(4):703–15.

142. Tikka SK, Malathesh BC, Spoorthy MS, Kusneniwar GN, Agarwal N, d'Avossa G, et al. Identification of youth at clinical high-risk for psychosis: A community-based study from India. Early Interv Psychiatry [Internet]. 2025 Jan 1;19(1):e13581. Available from: https://doi.org/10.1111/eip.13581

143. Fonseca-Pedrero E, Ortuño-Sierra J, Chocarro E, Inchausti F, Debbané M, Bobes J. Psychosis risk screening: Validation of the youth psychosis at-risk questionnaire - brief in a community-derived sample of adolescents. Int J Methods Psychiatr Res. 2017 Dec;26(4).

144. Phalen PL, Rouhakhtar PR, Millman ZB, Thompson E, DeVylder J, Mittal V, et al. Validity of a two-item screen for early psychosis. Psychiatry Res. 2018 Dec;270:861–8.

145. Savill M, Loewy RL, Niendam TA, Porteus AJ, Rosenthal A, Gobrial S, et al. The diagnostic accuracy of screening for psychosis spectrum disorders in behavioral health clinics integrated into primary care. Schizophr Res. 2024 Apr;266:190–6.

LIST OF PUBLICATIONS AND PARTICIPATION IN SCIENTIFIC FORUMS

of Mr. **Igor Nastas**, conducted within the framework of the habilitation thesis in medical sciences,
entitled ***"Clinical Effects of Adjunctive Treatment on the Symptoms of Schizophrenia"***,
Postdoctoral Program 2024–2026

Advisors:
Jana Chihai, MD, PhD, Dr. Habil. in Medical Sciences, Associate Professor
Larisa Spinei, MD, PhD, Dr. Habil. in Medical Sciences, Professor

SCIENTIFIC WORKS

- **Monographs:**

1. **Nastas I**, Boronin L, Coșulean R, Bivol M, Belous M, Jelaga D, Chihai J. Telemedicina în sănătatea mintală. Monografie.Coordonator: Igor Nastas:USMF „Nicolae Testemițanu", Laboratorul de sănătate mintală.-Chișinău:CEP Medicina, 2024.-322 p. ISBN 978-9975-82-399-9.
2. **Nastas I**. Schizofrenia. Mecanisme patobiologice și strategii de diagnostic precoce: Monografie. Chişinău, 2025, p. 118. ISBN 978-5-36241-511-2.

- **Articles in international scientific journals (articles in ISI, SCOPUS and other international databases)**

3. Levi L, Zamora D, **Nastas I**, Gonen I, Radu P, Matei V, et al. Add-on pramipexole for the treatment of schizophrenia and schizoaffective disorder: a randomized controlled trial. J Clin Psychiatry. 2022;83(5):21m14233. doi:10.4088/JCP.21m14233. https://doi.org/10.4088/jcp.21m14233 (Web of Science, IF 4.384)
4. Weiser M, Zamora D, Levi L, **Nastas I**, Gonen I, Radu P, Matei V, Nacu A, Boronin L, Davidson M, Davis JM. Adjunctive aspirin vs placebo in patients with schizophrenia: results of two randomized controlled trials. Schizophr Bull. 2021;47(4):1077–1087. doi:10.1093/schbul/sbaa198 https://academic.oup.com/schizophreniabulletin/article/47/4/1077/6105814 (IF 2020:9.306; SCOPUS)

5. Weiser M, Levi L, Zamora A, Biegon A, SanGiovanni J, Davidson M, Burshtein S, Gonen I, Radu P, Slobodzean Pavalache K, **Nastas I**, Hemi R, Ryan T, Davis J. Effect of adjunctive estradiol on schizophrenia among women of childbearing age: a randomized clinical trial. JAMA Psychiatry. 2019;76(10):1009–1017. doi:10.1001/jamapsychiatry.2019.1842 https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2738766 (Web of Science. IF 2019: 17.471)
6. Weiser M, Levi L, Park J, **Nastas I**, Matei V, Davidson M, Arad I, Dudkiewicz I, Davis JM. A randomized controlled trial of add-on naproxen, simvastatin and their combination for the treatment of schizophrenia or schizoaffective disorder. Eur Neuropsychopharmacol. 2023;73:65–74. doi:10.1016/j.euroneuro.2023.04.007 https://www.sciencedirect.com/science/article/abs/pii/S0924977X23000718 (SCOPUS; IF 2023:5.415).
7. Boronin L, Spinei L, **Nastas I**. Omega-3 fatty acids as adjuvant therapy in mental disorders. Arch Balk Med Union. 2024;59(2):201–210. doi:10.31688/ABMU.2024.59.2.07 https://umbalk.org/omega-3-fatty-acids-as-adjuvant-therapy-in-mental-disorders/ (SCOPUS)
8. Boronin L, Spinei L, **Nastas I.** Niacin skin test in schizophrenia: a systematic review. Arch Balk Med Union. 2025;60(2):284–294. doi:10.31688/ABMU.2025.60.2.13 https://umbalk.org/niacin-skin-test-in-schizophrenia-a-systematic-review/ (SCOPUS)
9. **Nastas I**, Boronin L. Estrogen hormonal therapy, clinical picture, and course of schizophrenia and postpartum disorders: review of the current state of evidence. Arch Psychiatry Res. 2025;61(2):115–124. https://doi.org/10.20471/may.2025.61.02.01 https://hrcak.srce.hr/en/334580 (SCOPUS)

✓ **Articles in peer-reviewed international journals**

10. Boronin L, Spinei L, Chihai J, **Nastas I.** Risks and effects of medicinal plants as an adjuvant treatment in mental disorders during pregnancy. *IgMin Res.* 2025;3:195. doi:10.61927/igmin298. https://www.igminresearch.com/articles/a-pdf/igmin298.pdf

- **Articles in accredited national scientific journals:**

✓ **articles published in Category B journals**

11. Boronin L, **Nastas I**. Terapii alternative în perioada de sarcină și de lactație a pacientelor cu patologie gastro-intestinală în practica psihiatrică. Sănătate Publică Econ Manag Med. 2023;(4):73–80. https://repository.usmf.md/bitstream/20.500.12710/26947/1/TERAPII_ALTERNATIVE_IN_PERIOADA_DE_SARCINA_SI_DE_LACTATIE_A_PACIENTELOR_CU_PATOLOGIE_GASTRO_INTESTINALA_IN_PRACTICA_PSIHIATRICA.pdf
12. **Nastas I**, Boronin L. Mechanisms of niacin skin test pathogenesis in patients at clinical high risk for psychosis and schizophrenia. Mold J Health Sci. 2024;4(11):54–61. doi:10.52645/MJHS.2024.4.09 https://mjhs.md/article/mechanisms-niacin-skin-test-pathogenesis-patients-clinical-high-risk-psychosis-and

- **Articles published in conference proceedings:**

  ✓ international conferences held in the Republic of Moldova

13. **Nastas I,** Boronin L**.** Statistical analysis of exosome diagnostic methods in patients with schizophrenia. In: Sontea V, Tiginyanu I, Railean S, editors. *7th International Conference on Nanotechnologies and Biomedical Engineering (ICNBME 2025)*. IFMBE Proceedings. Vol. 135. Cham: Springer; 2025. p. 3–xx. doi:10.1007/978-3-032-06497-4. https://www.springerprofessional.de/en/7th-international-conference-on-nanotechnologies-and-biomedical-/51501412?pageNo=1 (SCOPUS)
14. Boronin L**, Nastas I.** Statistical analysis of combined screening and diagnostic tests for postpartum and schizophrenia-like disorders. In: Sontea V, Tiginyanu I, Railean S, editors. *7th International Conference on Nanotechnologies and Biomedical Engineering (ICNBME 2025): Proceedings*. IFMBE Proceedings. Vol. 135. Cham: Springer; 2025. p. 39–47. doi:10.1007/978-3-032-06497-4_4 https://www.springerprofessional.de/en/statistical-analysis-of-combined-screening-and-diagnostic-tests-/51501486?searchResult=2.boronin (SCOPUS)

- **Abstracts / summaries / theses published in the proceedings of national and international scientific conferences**

15. **Nastas I**, Coșulean R, Boronin L**.** The effectiveness of remote diagnostic strategies for postpartum depression: integration of structured interviews and screening scales. *Neuroscience Applied*. 2026;5:106670. p. 12–13. (SCOPUS) https://www.sciencedirect.com/search?qs=The+effectiveness+of+remote+diagnostic+strategies+for+postpartum+depression%3A+integration+of+structured+interviews+and+screening+scales.+&authors=Nastas
16. **Nastas I,** Boronin L. Effectiveness of virtual reality methods in schizophrenia: assessment of sensitivity and specificity based on available data. *Neuroscience Applied*. 2026;5:50. (SCOPUS). https://www.sciencedirect.com/search?authors=Nastas&qs=Effectiveness+of+virtual+reality+methods+in+schizophrenia%3A+Assessment+of+sensitivity+and+specificity+based+on+available+data
17. Boronin L, **Nastas I**. Pros and cons of alternative therapy omega-3 fatty acids during pregnancy and lactation for mental problems. European Psychiatry. 2024;67(S1):S803-S803.doi:10.1192/j.eurpsy.2024.1674 https://www.cambridge.org/core/journals/european-psychiatry/article/pros-and-cons-of-alternative-therapy-omega3-fatty-acids-during-pregnancy-and-lactation-for-mental-problems/F3E201F57876C238C2803302EA052744 (SCOPUS)
18. **Nastas I,** Boronin L. Results of skin tests and the effects of niacin in patients with schizophrenia. *Neuroscience Applied*. 2024;3(Suppl 2):105050. https://doi.org/10.1016/j.nsa.2024.105050 https://www.sciencedirect.com/science/article/pii/S2772408524011153 (SCOPUS)

19. Bologan A, Boronin L, **Nastas I**. Tratamente alternative și adjuvante în tulburările mintale din timpul sarcinii și alăptării. Rev Științe Sănătății Mold. 2023;10(3 Suppl 1):371. https://repository.usmf.md/handle/20.500.12710/25841
20. Boronin L, **Nastas I**, Radilova I. Natural medicines as adjunctive treatment in schizophrenia during pregnancy. In: Proceedings of the International Conference of the Society of Psychiatrists, Narcologists, Psychotherapists and Clinical Psychologists of the Republic of Moldova "Mental health for all: developing resilience and quality services". Chișinău; 2022. p. 36–37. https://conferinte.stiu.md/sites/default/files/evenimente/Culegere%2024-26%20noi%202022%2C%20Conf%20S%C4%82N%C4%82TATEA%20MINTAL%C4%82%20PENTRU%20TO%C8%9AI.pdf
21. **Nastas I.** Resistance and patterns of adjunctive therapies in schizophrenia. În: Materialele Conferinței Internaționale a Societății Psihiatrilor, Narcologilor, Psihoterapeuților și Psihologilor Clinicieni din Republica Moldova „Sănătatea mintală pentru toți: dezvoltăm reziliența și servicii de calitate". Chișinău, 2022, pp. 65-66. https://conferinte.stiu.md/sites/default/files/evenimente/Culegere%2024-26%20noi%202022%2C%20Conf%20S%C4%82N%C4%82TATEA%20MINTAL%C4%82%20PENTRU%20TO%C8%9AI.pdf
22. **Nastas I.** Adjunctive aspirin vs estradiol in patients with schizophrenia. În: Culegerea lucrărilor Conferinței Internaționale a Societății Psihiatrilor, Narcologilor, Psihoterapeuților și Psihologilor Clinicieni din Republica Moldova „ Sănătatea mintală: într-o lume plină de provocări". Chișinău, 2021, p. 73. ISBN 978-9975-3493-7-6. https://ibn.idsi.md/vizualizare_articol/164029
23. **Nastas I**. Aspecte ereditare în schizofrenie. În: Culegerea lucrărilor Conferinței Internaționale a Societății Psihiatrilor, Narcologilor, Psihoterapeuților și Psihologilor Clinicieni din Republica Moldova „ Sănătatea mintală: într-o lume plină de provocări. Chișinău, 2018, p. 8. ISBN 978-9975-3493-7-6.
24. **Nastas I.,** Boronin L. Terapii hormonale in schizofrenie. Conferința Națională cu participare internațională „Sănătate Mintală- promovare, intervenție și reabilitare". În: Culegere de lucrări. Chișinău, 2019. Tipog. „Printline", p. 14. ISBN 978-9975-32-74-1-1.
25. Boronin L, **Nastas I.** Possible risks of using medicinal plants as adjuvant therapy during pregnancy and lactation in mental patients. In: International Joint Event: 7th Eastern European Conference of Mental Health "In and Out of Your Mind", 4th International Public Mental Health Conference, 3rd International Congress of the SPNPPC. Abstract book. Chișinău (Republic of Moldova); 12–15 Oct 2023. p. 35. Available from:. https://conferinte.stiu.md/sites/default/files/evenimente/Abstract%20Book%20All%20Together%20for%20Mental%20Health%202023.pdf
26. Boronin L, **Nastas I.** Moringa Oleifera as adjuvant therapy during pregnancy and breastfeeding. In: International Joint Event: 7th Eastern European Conference of Mental Health "In and Out of Your Mind", 4th International Public Mental Health Conference, 3rd International Congress of the SPNPPC. Abstract book. Chișinău (Republic of Moldova); 12–

15 Oct 2023. p. 35. Available from:. https://conferinte.stiu.md/sites/default/files/evenimente/Abstract%20Book%20All%20Together%20for%20Mental%20Health%202023.pdf
27. **Nastas I.** The value of some affective parameters in the additional treatment with estradiol in schizophrenia. In: International Joint Event: 7th Eastern European Conference of Mental Health "In and Out of Your Mind", 4th International Public Mental Health Conference, 3rd International Congress of the SPNPPC. Abstract book. Chișinău (Republic of Moldova); 12–15 Oct 2023. p. 55. Available from:. https://conferinte.stiu.md/sites/default/files/evenimente/Abstract%20Book%20All%20Together%20for%20Mental%20Health%202023.pdf
28. **Nastas I,** Boronin L**.** Markeri predictivi la etapa prodromală a schizofreniei. In: Culegere de rezumate. 80 de ani de inovație în sănătate și educație medicală. Congresul aniversar. Chișinău: Universitatea de Stat de Medicină și Farmacie „Nicolae Testemițanu"; 2025. p. 458. CZU: 616.895.8-07. Available from: https://congres.usmf.md/arhiva/congres-2025/culegere-de-rezumate/

- **Patents, invention patents, registration certificates, and materials presented at invention exhibitions**

29. Boronin L, **Nastas I**, Jucovschi C, Nacu A. 3765(13) F1 Metoda de pronosticare a riscului de apariție a stărilor reziduale precoce în schizofrenia paranoidă. În: Buletin Oficial de Proprietatea Industrială. Chișinău, 2008. Nr.12, p. 23.
30. **Nastas I**. Determination of pathogenetic mechanisms in the niacin skin test for patients with high clinical risk of psychosis and schizophrenia in the Republic of Moldova. Certificat de înregistrare a obiectului dreptului de autor (operă științifică). Seria OS nr. 8139. Agenția de Stat pentru Proprietatea Intelectuală a Republicii Moldova. 26 feb 2025.
31. **Nastas I.** Determinarea mecanismelor patogenetice în testul cutanat cu niacină la pacienții cu risc clinic ridicat de psihoză și schizofrenie în Republica Moldova. Certificat de înregistrare a obiectului dreptului de autor (operă științifică). Seria OS nr. 8138. Agenția de Stat pentru Proprietatea Intelectuală a Republicii Moldova. 26 feb 2025.
32. **Nastas I**. Определение патогенетических механизмов теста на ниацин у пациентов с высоким клиническим риском психоза и шизофрении в Республике Молдова. Certificat de înregistrare a obiectului dreptului de autor (operă științifică). Seria OS nr. 8140. Agenția de Stat pentru Proprietatea Intelectuală a Republicii Moldova. 26 feb 2025.
33. **Nastas I**. Telemedicina ca tratament adjuvant în tulburările mintale severe. Gestionarea schizofreniei. Certificat de înregistrare a obiectului dreptului de autor (operă științifică). Seria OS nr. 8232. Agenția de Stat pentru Proprietatea Intelectuală a Republicii Moldova. 07 iul 2025.
34. **Nastas I.** Metoda de tratament adjuvant cu estradiol la pacientele cu schizofrenie în perioada de premenopauză. Certificat de inovator nr. 6297. Ministerul Sănătății al Republicii Moldova. 13 nov 2024.

- **Presentations at scientific forums:**

✓ **International forums**

35. **Nastas I**. Rezistența și modele de terapii adjuvante în schizofrenie. Comunicare prezentată la: Conferința internațională a Societății Psihiatrilor, Narcologilor, Psihoterapeuților și Psihologilor Clinicieni; 24-26 noiembrie 2022. https://conferinte.stiu.md/sites/default/files/evenimente/Culegere%2024-26%20noi%202022%2C%20Conf%20S%C4%82N%C4%82TATEA%20MINTAL%C4%82%20PENTRU%20TO%C8%9AI.pdf https://conferinte.stiu.md/event_page/657
36. **Nastas I.** Aspirina adjunctivă vs estradiol la pacienții cu schizofrenie. Comunicare prezentată la: Congresul Internațional al Societății Psihiatrilor, Narcologilor, Psihoterapeuților și Psihologilor Clinicieni; 23–26 iunie 2021; Chișinău, Republica Moldova. https://ibn.idsi.md/ro/collection_view/1829
37. **Nastas I**. The value of some affective parameters in the additional treatment with estradiol in schizophrenia. Comunicare prezentată la: International Joint Event: 7th Eastern European Conference of Mental Health "In and Out of Your Mind", 4th International Public Mental Health Conference, 3rd International Congress of the SPNPPC. Chișinău, Republic of Moldova; 12–15 Oct 2023. Available from:. https://conferinte.stiu.md/event_page/792
38. **Nastas I.** Abnormal response to niacin in schizophrenia. Comunicarea prezentată la: A 8-a Conferință Est-Europeană de Sănătate Mintală „In and Out of Your Mind" și al 4-lea Congres Internațional al SPNPPC; 10–13 oct 2024; Chișinău, Republica Moldova. USMF „Nicolae Testemițanu". https://conferinte.stiu.md/event_page/1130
39. **Nastas I.** Markeri predictivi la etapa prodromală a schizofreniei. Comunicarea prezentată la: Conferința-satelit „Noi orizonturi în sănătatea mintală"**;** 20–23 oct 2025; Republica Moldova. https://conferinte.stiu.md/event_page/1584
40. **Nastas I.** Aspecte ereditare în schizofrenie. Comunicare prezentată la: Congresul Internațional al Societății Psihiatrilor, Narcologilor, Psihoterapeuților și Psihologilor Clinicieni din Republica Moldova „Sănătatea mintală – o prioritate, prezentă și necesitate a societății contemporane"; 27–29 iunie 2018; Chișinău, Republica Moldova. Available from: https://sanatatemintala.md/ro/congres-ro/congres-2018-ro

✓ **National forums**

41. **Nastas** I.Terapii hormonale in schizofrenie. Studii clinice.In: Conferința Națională cu participare Internațională "Sănătatea mintală – promovare, intervenție și reabilitare" 14-15 noiembrie 2019. https://sanatatemintala.md/images/conferinta_noiembrie_2019/program_conferinta_14_15_11_2019.pdf
42. **Nastas I.** Intervenții adjuvante în schizofrenie. In: Congresul Național de Psihiatrie – ediția a IX-a; 19–22 martie 2025; Sibiu, România. https://e-psihiatrie.ro/congresul-national-psihiatrie-editia-a-ix-a/

- **Poster presentations at scientific forums:**

  ✓ International forums

43. **Nastas I**, Boronin L. Statistical analysis of exosome diagnostic methods in patients with schizophrenia. In: Sontea V, Tiginyanu I, Railean S, editors. Proceedings of the 7th International Conference on Nanotechnologies and Biomedical Engineering (ICNBME 2025). IFMBE Proc. Cham: Springer; 2025. p. 29. Poster S4-P30. doi:10.1007/978-3-032-06497-4. https://www.springerprofessional.de/en/7th-international-conference-on-nanotechnologies-and-biomedical-/51501412?pageNo=1
44. BoroninL, **Nastas I..** Statistical analysis of combined screening and diagnostic tests for postpartum and schizophrenia-like disorders. In: Sontea V, Tiginyanu I, Railean S, editors. Proceedings of the 7th International Conference on Nanotechnologies and Biomedical Engineering (ICNBME 2025). IFMBE Proc. Cham: Springer; 2025. p. 29. Poster S4-P31. doi:10.1007/978-3-032-06497-4. https://www.springerprofessional.de/en/7th-international-conference-on-nanotechnologies-and-biomedical-/51501412?pageNo=1
45. **Nastas I,** Boronin L. Results of skin tests and the effects of niacin in patients with schizophrenia. In: The 37th ECNP Congress**;** 21–24 Sept 2024; Milan, Italy. Poster P3223. https://www.ecnp.eu/meetings/ecnp-congresses/programme-2024/#!sessiondetails/0000155010_0
46. **Nastas I,** Boronin L. Effectiveness of virtual reality methods in schizophrenia: assessment of sensitivity and specificity based on available data. In: The 38th ECNP Congress; 11–14 Oct 2025; Amsterdam, The Netherlands. Poster EP10-0947. https://www.ecnp.eu/congress2025/programme/provisional-programme/#!sessiondetails/0000172470_0

ABSTRACT

Identification data: Nastas Igor, *Clinical Effects of Adjuvant Treatment on the Symptoms of Schizophrenia*. Habilitation Doctoral Thesis in Medical Sciences. Chișinău, 2026.

Relevance of the research: Schizophrenia affects approximately 23 million people worldwide, representing about 0.29% of the global population. Indirect costs, accounting for 48.9%–81.4% of the total disease-related expenses, constitute a substantial socio-economic burden, while approximately 60–70% of patients experience therapeutic failure.

Purpose of the study: To evaluate the effectiveness of adjuvant therapies in schizophrenia among patients receiving antipsychotic treatment.

Research objectives: To analyze the mechanisms of action of adjuvant therapies; to assess their effectiveness depending on age, treatment duration, and type of adjuvant intervention; to determine social and economic impact; to correlate adjuvant therapies with quality-of-life indicators; and to develop an intervention algorithm.

Scientific novelty and originality: Molecular pathological processes associated with schizophrenia were identified, and biological markers were proposed for the detection of states with a high risk of psychosis.

Major new results obtained: The clinical efficacy of adjuvant therapies in reducing the severity of schizophrenic symptoms and improving patients' quality of life was substantiated.

Theoretical significance: Mitochondrial dysfunction was demonstrated as a common pathogenetic mechanism in schizophrenia, contributing to the expansion of theoretical knowledge regarding the biological basis of the disorder.

Practical applicability: The identification of biological markers provides diagnostic support during the prodromal stages of the disease, while the proposed intervention algorithm offers practical solutions for managing states associated with a high risk of psychosis.

Implementation of scientific results: The research findings were implemented within the Clinical Psychiatric Hospital, in the university teaching process, and in the development of intellectual property objects.

Structure of the thesis: The thesis comprises 7 chapters and includes 153 pages of main text, general conclusions and recommendations, 353 bibliographic sources, 8 appendices, 57 tables, 31 figures, and 36 publications related to the topic of the thesis.

Keywords: schizophrenia, adjuvant therapy, inflammation, cytokines, negative symptoms, prodromal symptoms, estradiol, oxidative stress, lipid metabolism, exosomes.