https://doi.org/10.52645/MJHS.2024.4.09

UDC: 616.895.8-07

REVIEW ARTICLE

Mechanisms of niacin skin test pathogenesis in patients at clinical high risk for psychosis and schizophrenia

Igor Nastas*, Larisa Boronin

Department of Mental Health, Medical Psychology and Psychotherapy, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

ABSTRACT

Introduction. Elevated or imbalanced levels of markers of oxidative stress and inflammation are often observed in various somatic pathologies and mental disorders, including schizophrenia.

Purpose of the study. This study aims to investigate the mechanisms of pathogenesis and the evidence supporting the use of niacin skin and oral tests in patients with schizophrenia.

Materials and methods. A literature review was conducted on the specific reactions to the niacin skin or oral test in patients with schizophrenia, first-episode psychosis, and those at clinical high risk for psychosis (CHR-P). Evidence-based data up to and including 2024 were reviewed, with 48 literary sources selected.

Results. An attenuated niacin-induced flush, coupled with low vitamin B3 levels, an imbalance in the Redox-Ratio and omega-3/omega-6 fatty acids, and elevated phospholipase A2 levels, are the main evidence-based findings associated with schizophrenia.

Conclusions. The niacin skin and oral tests in patients with schizophrenia and those at high risk for psychosis are characterized by an abnormal response to niacin. Additional markers may further validate positive test results for niacin.

Keywords: niacin, skin test, pathogenesis, psychotic disorders, high-risk populations, schizophrenia.

Cite this article: 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;11(4):54-61. https://doi.org/10.52645/MJHS.2024.4.09.

Manuscript received: 02.09.2023

Accepted for publication: 20.11.2024

Published: 10.12.2024

***Corresponding author: Igor Nastas,** PhD, MD, associate professor, Department of Mental Health, Medical Psychology and Psychotherapy, *Nicolae Testemițanu* State University of Medicine and Pharmacy, 165, Ștefan cel Mare și Sfânt blvd, Chișinău, Republic of Moldova, MD 2025
e-mail: igor.nastas@usmf.md

Authors' ORCID IDs
Igor Nastas – https://orcid.org/0000-0001-8751-9101
Larisa Boronin – https://orcid.org/0000-0001-8180-8711

Key messages

What is not yet known on the issue addressed in the submitted manuscript

There are ongoing challenges in the timely diagnosis of schizophrenia, particularly during prodromal states. Current diagnostic criteria are primarily based on assessment tools that are applicable only when
symptoms of schizophrenia are well manifested, leaving a gap in early detection.

The research hypothesis

The use of the niacin test as a diagnostic method may provide additional insights, especially in the pre-psychotic stage, potentially aiding in earlier diagnosis.

The novelty added by manuscript to the already published scientific literature

This manuscript introduces the novelty of exploring inflammatory imbalance, phospholipid dysregulation, and NAD+ deficiency in schizophrenia. These factors may contribute to enhanced diagnostic strategies and offer possibilities for adjuvant treatment options for schizophrenia.

Introduction

Many mechanisms of the pathogenesis of mental and somatic disorders share common points of contact, related to the increase in markers of oxidative stress and inflammation. Oxidative stress and decreased antioxidant activity play important roles in the development of these disorders. Violations of mitochondrial functions, depletion of NAD+ (Nicotinamide adenine dinucleotide oxidized form), NAD+ -induced signaling cascades, and increases in levels of reactive oxygen and nitrogen species are the basis of this process [1]. Zapata-Pérez R. et al. (2021) describe the relationship between the oxidized (NAD+) and reduced (NADH) forms of nicotinamide adenine dinucleotide, the redox balance, and the biosynthesis of fatty acids and nucleic acid [2]. The balance between the synthesis and breakdown of NAD+ is required to maintain cellular homeostasis and physiological functioning. It is known that NAD+ deficiency, which can be genetically determined and also due to low levels of its precursors as a result of dietary deficiencies and synthesis issues, leads to serious somatic and mental disorders. For example, niacin deficiency is associated with pellagra symptoms such as diarrhea, dermatitis, and dementia [3]. Sitarz R. et al. (2023), describe the mechanisms underlying metabolic imbalances due to fatty acid and vitamin B3 deficiency. The authors reported the effectiveness of omega-3 fatty acids in the onset of mental disorders, even when there are no clear indications for the initiation of psychotropic therapy [4]. The nicotinate phosphoribosyl transferase gene (NAPRT1) encodes a key enzyme for niacin metabolism. According to Periyasami S. et al. (2019), niacin deficiency is associated with schizophrenia-like symptoms [5]. Therefore, the antioxidant and anti-inflammatory properties of some food additives, such as omega-3 fatty acids, vitamin B3, and NAD (Nicotinamide adenine dinucleotide), can be used as alternative or adjuvant therapies for mental diseases and comorbid somatic pathology caused by inflammatory reactions and oxidative stress. Such therapies may include the use of NAD+ precursors like nicotinamide mononucleotide and nicotinamide ribose, which quickly increase NAD+ levels in the brain and periphery [1, 6]. The disturbances of neurotransmission constitute one of the pathogenetic elements of the membrane phospholipid hypothesis in schizophrenia [7]. Impaired prostaglandin signaling in schizophrenia is established, with several pathways explaining this mechanism: reduced levels of arachidonic acid, a precursor of prostaglandins; increased activity of the enzyme phospholipase A2, and abnormal expression of niacin receptors in cutaneous capillary walls. Skin flushing in response to niacin administration is also considered to be influenced by prostaglandins [8]. David F. Horrobin, the proponent of the prostaglandin signaling imbalance hypothesis in schizophrenia, stated in 1977 that it "does not necessarily contradict modern theories of the transmitters of schizophrenia, since prostaglandins alter the secretion and action of mediators." He supported his hypothesis with clinical observations, noting that the increased pain threshold and decreased inflammation in patients with schizophrenia could be attributed to prostaglandins. Additionally, he noted that the increase in prolactin due to antipsychotic treatment might be associated with prostaglandin synthesis. However, it remains unclear why "all effective antischizophrenic drugs stimulate prolactin secretion" but "high doses of drugs recently shown to be prostaglandin antagonists cause schizophrenia-like syndromes [9]. Clinical practice shows that high doses of antipsychotics are less associated with symptom exacerbation. Another important metabolic criterion and risk factor is the omega-3 index, which represents the percentage of red blood cells with omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in erythrocytes [10, 11]. According to David F. Horrobin et al. (1994), "in schizophrenia, the metabolism of phospholipids may be impaired both in the brain and in red blood cells" [12]. The authors note that the patients with negative symptoms have had "the concentrations of arachidonic acid (AA) and DHA in erythrocyte membrane phospholipids deviated sharply from the norm"[12]. Ya-Hui Yu et al. (2022) also report the membrane hypothesis of schizophrenia, according to which low levels of polyunsaturated fatty acids, including omega-3 arachidonic acid (AA), lead to dysfunctional signaling, changes in the structure, rigidity, and conformation of cell membranes, and pathology of receptor activity, proteins, prostaglandins, cyclooxygenases, and ion channels in these patients [13]. Reporting an abnormal response to niacin in patients, Ranpiao Gan et al. (2022) conclude that this response occurs in the "early stage of psychosis" and during "disease progression," linking it to PUFAs (polyunsaturated fatty acids) [14]. Zhang T. et al. (2023) stated a significant correlation between attenuated niacin response and core negative symptoms in patients with first-episode psychosis. According to the authors, this indicates that an attenuated niacin response (ANR) may be a potential biomarker for certain subtypes characterized by negative symptoms and poor symptomatic remission [15].

The aim of the research

The aim of this paper was to study the mechanisms of pathogenesis and the evidence supporting the use of niacin skin and oral tests in patients with schizophrenia, first-episode psychosis, and those at clinical high risk for psychosis (CHR-P). Additionally, the research aimed to examine the rationale for the use of vitamin B3 as an additional or preventive therapy in these groups of patients.

Materials and methods

A literature review was conducted on the occurrence of specific reactions to the niacin skin or oral test in patients with schizophrenia, first-episode psychosis, and those at clinical high risk for psychosis (CHR-P). Information was sourced from the PubMed, MEDLINE, Medscape, Scopus, Cochrane Library, and research4life.org databases up to and including 2024, from which 48 sources were selected. The inclusion criteria were studies published in English and human studies only. The literature was analyzed concerning mechanisms of action, risk factors, and evidence supporting the utility of the niacin skin or oral test in high-risk psychosis states and schizophrenia.

Table 1. Niacin or methylnicotinate tests in patients with schizophrenia-control group studies

Author, year	Number of the patients/control	Diagnose	Dose /route of administration	Result
Basant K Puri et al., 2002 [22]	27/26	Schizophrenia	Niacin	Flushing response is reduced in schizophrenia, with a sensitivity of 75% and a specificity of 65%
Nilson B.M.,2006 [23]	30/17	Schizophrenia	200 mg niacin /orally	The patients showed a delayed temperature increase after niacin ingestion (P=0.002) and a higher frequency of electrodermal non-responding (P<0.05).
Karakula-Juchnowicz H. et al., 2020 [24]	56/45	Schizophrenia	Methylnicotinate 0.1M; 0,001M; 0.0001M	The absent response was detected in 60.7% of individuals suffering from schizophrenia, and the proposed method could predict schizophrenia with 71% sensitivity and 66% of specificity.
Arzanlou M., 2021 [25]	36/33	Schizophrenia	Niacin patches 0.1M; 0,001M; 0.0001M	Flush responses to niacin are more impaired in patients with schizophrenia. At 10 min, the highest test accuracy was reported when a 0.001 M niacin solution was used (Sensitivity=94%, specificity=50%, PPV= 51%, and NPV= 94%). At 15 min, the highest test accuracy was observed with a 0.01 concentration (Sensitivity=52%, specificity=92%, PPV=79%, and NPV=77%).
Dan-Dan Wang et al., 2021 [26]	307 schizophrenia /148	Schizophrenia, bipolar disorder	Niacin	Attenuation and a delay of the niacin-induced skin flushing were characterized in the largest cohort of patients with schizophrenia. Patients with either schizophrenia or affective disorders were identified from the healthy control group with a sensitivity of 55.28%, a specificity of 83.56%, and a positive predictive value of 93.66%.
Ya-Hui Yu et al., 2022 [13]	46/37	Schizophrenia	Methyl nicotinate 0.1M; 0,001M; 0.0001M before and after 2 months follow-up period	Healthy controls exhibited enhanced niacin-induced flush at the 2-month follow-up, whereas patients with schizophrenia did not show significant changes in their flushing response.
Gan Ranpiao, 2022 [14]	105CHR/57FES/ 52 HCs	CHR FES	Methylnicotinate 0.1M; 0,001M; 0.0001M	CHR individuals showed attenuated niacin-induced flushing responses characterized by a modest level of severity that was intermediate between those of HCs and patients with FES. The niacin flush response is more blunted in CHR converters to full psychosis at 2 years of follow-up compared to non-converters.
Carena F. et al., 2023 [27]	21/20	Schizophrenia	375 mg crystalline niacin orally	Abnormal niacin response was observed in 90,5% of the patient group and 0% in the control group (non-randomized clinical trial).
TianHong Zhang et al., 2023 [28]	60/60	Clinically high-risk psychosis (CHR)	Methylnicotinate	The CHR group exhibited significantly higher half-maximal blood flow response - LogEC_{50} (t = 3.650, P < .001) and minimal blood flow response - Span (t = 2.657, P = .009) values than the HC group. These findings indicate a significant association between niacin response and psychosis conversion outcomes in individuals with CHR.

Note: *CHR*- Clinically high-risk psychosis, M- Methylnicotinate, PPV-positive predictive value, NPV-negative predictive value, FES-first episode of schizophrenia, HC-healthy control group.

Results and discussions

„Niacin is a general term used to define vitamin B3 and derivatives, including nicotinic acid, nicotinamide, and related compounds, such as nicotinamide riboside" [2]. Pathological processes at the level of membrane phospholipids are considered an essential factor in the pathophysiology of schizophrenia. These processes are believed to have a direct influence on the imbalance of neurotransmitters within the central nervous system [16]. It is known that niacin and its amide, nicotinamide, are considered precursors of vital coenzymes that participate in metabolic reactions. They play a key role in the Krebs cycle and the recovery of nicotinamide adenine dinucleotides (NAD, NADH, NAD+, and NADP+). These coenzymes are involved in DNA repair, detoxification, and the synthesis of steroid hormones [16]. Abram Hoffer (1998) recommends the use of vitamin B3, specifically niacin, in doses ranging from 1 to 12 grams per day for treating psychotic states, including schizophrenia. If adverse reactions occur with niacin, niacinamide can be administered as an alternative, as it generally produces a more moderate effect [17]. The recommended dose for niacin is 2 to 4 mg for infants, 6 to 8 mg for children, 12 mg for teenagers, 16 mg for men, 14 mg for women, and 17 and 18 mg for lactating and pregnant women [18, 19]. In a randomized clinical trial involving patients with schizophrenia who had negative symptoms, the patients failed to flush and had significantly reduced levels of arachidonic and docosahexaenoic acids. Over a period of six months, supplementation led to a conversion from non-flushing to flushing. This conversion was predicted by an increase in arachidonic acid levels in red blood cell membranes, regardless of the nature of the supplementation [20]. Niacin enters the body through food and can also be synthesized from the amino acid tryptophan with the help of vitamin B6. Studies have shown that 1 mg of nicotinamide is produced from 67 mg of tryptophan [21]

In Table 1, the results of several niacin or methylnicoti-

nate skin flush test studies in patients with schizophrenia can be seen.

Hoffer A. and Osmond H. (1966) proposed the NAD-deficiency hypothesis of schizophrenia, concluding that „schizophrenia is an NAD-deficiency disease". They explained this position by stating that „large doses of nicotinic acid and nicotinamide are effective in schizophrenia", quickly improving the clinical condition of patients. The authors drew a parallel between schizophrenia and pellagra, suggesting that patients with schizophrenia „are not able to synthesize NAD as effectively" as the control group [29]. Sang-Young Kim et al. (2017) provide evidence of "redox disturbances" in schizophrenia and mood disorders. The authors identify elements of pathogenesis in schizophrenia, which, in their opinion, include the "immune-oxidative" pathway, oxidative stress, mitochondrial dysfunction, neuroinflammation, and cell-mediated immune response [30]. Ramachandran P. et al. (2012) propose a hypothesis for the therapeutic treatment of schizophrenia using vitamin B3 (niacin), based on the adrenochrome theory of schizophrenia by Hoffer (1981). According to this theory, a pathological product of oxidative metabolism, an adrenaline derivative called adrenochrome, is involved in the productive symptoms of schizophrenia, which have hallucinogenic properties. Vitamin B3, by limiting the production of adrenaline, reduces the synthesis of adrenochrome [31, 32]. In schizophrenia, a high level of adrenochrome accumulates in the central nervous system. Vitamin B3, as a precursor of nicotinamide adenine dinucleotide (NAD) and its reduced form (NADH), participates in these transformations under normal conditions and in schizophrenia. With sufficient levels of NAD and NADH, coenzyme B3 enables adrenochrome to convert back into adrenaline. Hoffer (1981) discussed the influence of stress on changes in the neurotransmitter system: „Stress is harmful for two reasons. The increase in the production of noradrenaline and adrenaline will lead to an increase in adrenochrome," and genetically predisposed individuals might experience an„increase in adrenolutin", a toxic metabolite of adrenochrome [32]. Many authors have studied the hypothesis that early life stress is associated with the development of schizophrenia later in life. This is linked to changes in the hippocampus during stressful situations, leading to neuroinflammation, microglial activation, the expression of proinflammatory mediators (IL-1β, TNF-α, IL-6), the loss of hippocampal neurons, and schizophrenia-like behavior. NAD therapy reverses these changes. It is believed that NAD has neuroprotective activity and could be used during puberty to prevent neuronal loss and improve hippocampal function in people exposed to early life stress [30-33]. The biological importance of NAD metabolites extends beyond participation in carbohydrate metabolism. They also play a role in oxidative stress processes and are involved in many metabolic pathways. NAD+ supports various processes, including the conversion of glucose and other nutrients into energy, energy metabolism and modulation, repair of damaged DNA and gene expression, support of cell defense systems and immunological functions, calcium homeostasis, regulation of the sleep-wake cycle, and antioxidant activity. Additionally, it participates in apoptosis, the aging process, and carcinogenesis [30]. Taking the tablet form of NADH helps increase wakefulness, attention, daily performance, and vitality [31]. Indications for prescribing NADH include the prevention of fatigue and maladjustment when changing time zones, as well as improving memory, attention, and other aspects of cognitive functioning of various causes. These causes include stress-related maladjustment, aging, and metabolic syndrome. Improvement is observed in cases of asthenia of any origin, chronic fatigue syndrome, Parkinson's and Alzheimer's diseases, depression, and the normalization of mood swings [31].

The Redox Ratio as an index for oxidative stress

According to Ryszard Sitarz et al. (2023), the niacin skin test is a simple and inexpensive method "used to assess the fatty acid content of cell membranes" and is "a possible indicator in the diagnosis of mental disorders" [4]. The niacin skin patch test is characterized by a decrease in skin hyperemia in patients with schizophrenia, manifesting as an abnormal response to niacin (niacin response abnormality - NRA). This serves as an endophenotype for schizophrenia, compared with the control group, where redness is pronounced [7, 34, 35]. The practical significance of this test involves the rapid screening of patients at risk for schizophrenia at the onset of the disease, even before clinical symptoms appear, allowing for timely intervention [7]. The NAD+/NADH ratio plays a crucial role in maintaining redox homeostasis. Sang-Young Kim et al. (2017) describe redox balance as the ratio of NAD+ to NADH concentrations, expressed as the Redox Ratio (RR) = [NAD+]/[NADH]. According to authors, the Redox Ratio serves as an index for determining oxidative stress levels in the brains of individuals with schizophrenia, as measured by magnetic resonance spectroscopy [30].

Interaction of the GPR109A receptor and phospholipase A2 in individuals with schizophrenia

Oxenkrug G. and Forester B. (2024) report the interaction between the GPR109A receptor and phospholipase A2 in individuals with schizophrenia. The GPR109A receptor exhibits anti-inflammatory and neuroprotective activities. In the brains of individuals with schizophrenia and those at high risk of developing psychosis, phospholipase A2 levels are elevated. Phospholipase A2 regulates the conversion of arachidonic acid to prostaglandins, contributing to pathological activity in schizophrenia by producing excess prostaglandins and depleting arachidonic acid levels. This enzyme can destroy the myelin layer of axons, thereby reducing neuroprotective functions and disrupting nerve conduction. The authors found correlations between the upregulation of the GPR109A receptor and the inhibition of phospholipase A2. One of the mechanisms influencing the niacin test result, as noted by the authors, is attributed to a genetic mutation in GPR109A. This mutation leads to a decreased blood flow response to niacin exposure, which is a characteristic of individuals with schizophrenia [34]. Tavares et al. (2003) conducted a study involving 38 individuals

with schizophrenia and 28 individuals in a control group. They found that phospholipase A2 levels were significantly increased in the schizophrenia group compared to the control group (344±115 pmol/ml/min vs. 290±71 pmol/ml/min; p=0.03). Over 8 weeks of antipsychotic treatment, phospholipase A2 levels were reduced to approximately 267±39 pmol/ml/min (p=0.001). Additionally, 4 out of 13 individuals who previously showed no response to the niacin test exhibited a positive response after treatment [36].

Inflammatory imbalance, phospholipid dysregulation, and the „Two hit hypothesis of schizophrenia"

In schizophrenia, there is an imbalance between pro-inflammatory and anti-inflammatory metabolites. Levels of polyunsaturated fatty acids, anti-inflammatory prostaglandins PGE1 and 15d-PGJ2 are reduced, while the level of the pro-inflammatory prostaglandin PGE2 is increased. According to the "two-hit hypothesis," changes in membrane phospholipids can contribute to the pro-inflammatory pathogenesis of schizophrenia and act as a vulnerability factor [37]. Jeffrey K. Yao (2016) discussed mechanisms underlying the abnormal niacin response in individuals with schizophrenia, focusing on signaling pathways involving cell membrane phospholipids, arachidonic acid, and eicosanoids. G protein-coupled receptors, such as GPR109A or HM74A, located on dermal macrophages and adipocytes, activate phospholipase A2, releasing arachidonic acid from cell membranes. This arachidonic acid is then converted into prostaglandins PGD2 and PGE2, which have vasodilatory effects [35]. Proinflammatory responses in patients with schizophrenia activate microglia, leading to neuronal apoptosis. According to Fillman, S.G., et al. (2014), "excessive activation leads to increased synthesis of cyclooxygenases, causing inflammatory reactions". Microglia synthesize various cytokines and respond to stimuli, which also occurs in patients with schizophrenia, but with a shift towards pro-inflammatory activity [38]. Keith A. Feigenson also reports the "Two-Hit Hypothesis of Schizophrenia," which posits that "early immune activation of microglia may sensitize them to later activation." This hypothesis suggests that prenatal risk factors, stress, and early infections lead to the formation of pathological microglia that are easily "activated" in the long term, for example, at puberty in response to a new trigger [37].

The Niacin Test and High Risk for Psychosis. Correlation between PUFA and Phospholipase A2

Oxenkrug G. and Forester B. (2024) also highlight the antipsychotic effect of nicotinic acid in clinical studies [34]. Similar conclusions are drawn by Nadalin S. et al. (2010), who establish the niacin test as a potential marker in schizophrenia. They assert that it "may be useful for further research into the genetics and pathophysiology of schizophrenia," considering it "an indicator of vulnerability to the development of psychosis" and a "simple, non-invasive, and easily reproducible method for the study of schizophrenia" [7]. The practical relevance of the niacin skin test is emphasized by Sabrina H. Ansarey (2021), who states that "the niacin skin flush test is useful in identifying patients with ultra-high-risk schizophrenia," and "may offer effective treatment". The author also notes that reducing the skin redness reaction depends on the interaction of neurons and microglia [39]. As mentioned previously, the niacin test has been proposed as a biomarker for schizophrenia or as a "potential factor" for screening for schizophrenia [7, 24, 40]. However, according to Berger, G. E., et al. (2016), an atypical "significantly increased response in patients" with ultra-high risk for schizophrenia is also possible [40]. They found that "sensitivity was inversely correlated with the levels of omega-3 and -6 fatty acids, but positively correlated with phospholipase A2 (PLA2)," leading the authors to associate the cause of psychosis with a "pro-inflammatory state" [40]. Ryszard Sitarz et al. (2023) propose the hypothesis that "the reduction of skin reaction in patients with schizophrenia can be caused by the deficiency of arachidonic acid in the cell membrane" [4]. It has been established that the most important omega-3 polyunsaturated fatty acids are alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid [41]. Arachidonic acid refers to omega-6 polyunsaturated fatty acids. Its adequate level in the body is very important, as the omega-3/omega-6 ratio should ideally be 1:1. However, in reality, omega-6 usually prevails in these ratios, and a lower omega-3 ratio increases the risks of somatic and mental diseases. Both omega-3 and omega-6 play an important role, as they are part of the phospholipids of cell membranes. They can change the fluidity of membranes and the activity of ion channels, membrane receptors, and neurohormones [7]. Deficiency of both polyunsaturated fatty acids can lead to phospholipase A2 activation, excessive release of these polyunsaturated fatty acids from cell membranes, cyclooxygenase-2 activity and prostaglandin synthesis, accumulation of oxidative stress products, free radicals, lipid peroxidation, synthesis of pro-inflammatory mediators of arachidonic acid, and pathological activity of desaturases. These processes have been related in other publications concerning patients with schizophrenia [7, 13, 35]. One meta-analysis found that levels of the omega-3 fatty acids docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), and the omega-6 fatty acid arachidonic acid (AA) were reduced in the red blood cells of patients with schizophrenia, "especially DHA and AA" [42]. Yu Y-H et al. (2022) related that the abnormal response to niacin in patients with schizophrenia may "reflect dysfunctional signaling" due to low AA levels [13]. Additionally, they concluded that, with a probability of $p < 0.05$ compared with the control group "adjusted for age, sex, and smoking," patients with schizophrenia had higher delta-5 desaturase (D5D) and delta-6 desaturase (D6D) activity [13]. Furthermore, D5D and D6D, encoded by the FADS1 and FADS2 genes, are rate-limiting enzymes for the conversion of polyunsaturated fatty acids [43]. This indicates a connection between the niacin skin test and omega fatty acids.

Kynurenine pathway in schizophrenia

An important component in the pathophysiology of schizophrenia is the kynurenine pathway. Tryptophan, an essential amino acid, is vital for the development of the serotonin and kynurenine pathways. The World Health Organization recommends a daily intake of tryptophan of

about 3.5–6.0 mg/kg of body weight [44]. In the serotonin pathway, metabolism ends with the production of serotonin and melatonin. In the kynurenine pathway, the production of nicotinic acid occurs, followed by nicotinamide, and finally NAD+[45]. Plitman et al. (2017) attribute about 90% of tryptophan metabolism to the kynurenine pathway [46]. Increased levels of kynurenic acid and cytokines in the brain have been reported post-mortem in patients with schizophrenia [47]. The kynurenine pathway influences behavior, the immune system, energy metabolism, and serotonin balance. Dysregulation of this pathway is also associated with gut and brain inflammation [45].

In Table 2, the most common mechanisms underlying the abnormal response to the niacin test in schizophrenia are highlighted:

Table 2. Mechanisms of abnormal niacin response in patients with schizophrenia

Mechanism	Description	References
Endophenotype of skin reactions	Reduction of skin hyperemia and decreased vasodilation response in patients at risk for schizophrenia	[4, 5, 7, 8, 12, 14, 15, 32, 33]
Prostaglandin levels	Reduced levels of anti-inflammatory prostaglandins (PGE1 and 15d-PGJ2) and increased level of pro-inflammatory PGE2	[33, 35]
Immune activation and inflammation	Excessive immune activation of microglia, expression of pro-inflammatory mediators (IL-1β, TNF-α, IL-6), loss of hippocampal neurons, and schizophrenia-like behavior	[28. 30, 31]
Fatty scid levels	Reduced levels of docosahexaenoic acid (DHA) and the omega-6 fatty acid arachidonic acid (AA) in red blood cells	[4, 12, 13]
Kynurenine pathway dysregulation	Dysregulation of the kynurenine pathway, affecting serotonin balance and immune response	[43-45]
Omega-3/omega-6 imbalance	Imbalance in the omega-3/omega-6 ratio, affecting cell membrane fluidity and signaling pathways	[11, 14]
Phospholipase A2 (PLA2) activity	Increased activity of the enzyme phospholipase A2 (PLA2), leading to excessive release of polyunsaturated fatty acids from cell membranes	[34]
GPR109A receptor and phospholipase A2 correlation	Correlations between the upregulation of the GPR109A receptor and the inhibition of phospholipase A2 (PLA2)	[34]
NAD+/NADH Ratio Reduction	Significant reduction in the NAD+/NADH ratio in chronically ill schizophrenia patients compared to healthy controls; Redox Ratio (RR) = [NAD+]/[NADH] serves as an index for determining oxidative stress levels	[2, 27, 28]
Delta-5 Desaturase (D5D) and Delta-6 Desaturase (D6D) activity	Higher activity of delta-5 desaturase (D5D) and delta-6 desaturase (D6D), enzymes involved in polyunsaturated fatty acid conversion	[41]

Note: *IL-interleukin, NAD+ - Nicotinamide adenine dinucleotide oxidized form, NADH - Nicotinamide adenine dinucleotide reduced form*

There are publications describing oral niacin reactions in schizophrenia. Francisco Carena et al. (2023) state that even with this route of niacin administration, patients with schizophrenia have an abnormal response to niacin compared to controls and individuals with other mental illnesses. The prevalence of abnormal niacin response is higher in patients with schizophrenia. According to the authors' studies, the prevalence of this abnormal response in patients with schizophrenia is 90.5%, while in the control group it is 0%. Additionally, the abnormal response to oral niacin in these patients is dose-dependent [27].

A genome linkage scan of niacin skin flush response

A study conducted by Yin-Ju Lien et al. (2011) on 115 families, including 226 affected individuals, 137 unaffected individuals, and 94 healthy controls (HCs), established that both affected and unaffected individuals had lower niacin flush scores compared to HCs for moderate (0.01 M) and high (0.1 M) concentrations of niacin in skin patches. The authors revealed a linkage region with a significant signal (3.39 at 14q32.12). They identified two genes located in the 14q32.12 region that could be related to schizophrenia: ataxin 3 (AT3) and chromogranin A (CGA). Both genes are not related to phospholipase A2, which is encoded by the PLA2G6 gene located in the 22q13.1 region. The authors concluded that the 14q32.12 region could be responsible for the response to niacin in schizophrenia [48].

Conclusions

1. The abnormal niacin response in schizophrenia is linked to metabolic disturbances such as imbalances in the omega-3/omega-6 and NAD+/NADH ratios, along with low levels of vitamin B3. These imbalances contribute to a pro-inflammatory state, oxidative stress, and phospholipid dysregulation.
2. Vitamin B3 (niacin) and its derivatives, along with omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), show potential as adjunctive therapies for schizophrenia by reducing oxidative stress, inflammatory responses, and improving membrane fluidity.
3. Genetic factors, including mutations in the GPR109A receptor and dysregulation of the kynurenine pathway, play a significant role in the pathophysiology of schizophrenia. These genetic influences contribute to the observed metabolic imbalances and inflammatory responses.
4. The niacin test has a high degree of sensitivity and specificity, making it an easy and cost-effective screening tool for identifying clinical high-risk (CHR) individuals, patients with schizophrenia, or those at risk for developing schizophrenia. Assessing additional parameters could enhance preventive or adjunctive interventions.

Competing interests

None declared.

Authors' contribution

LB conceived the original draft preparation and was responsible for the conception and design of the review. LB and IN were responsible for the data acquisition, collection and assembly of the articles/published data, as well as their inclusion and interpretation in this review. Both authors reviewed the manuscript and approved the final version.

Informed consent for publication

Not needed for this article.

Ethics approval

No approval was required for this study.

Funding

None.

References

1. Morris G, Walder KR, Berk M, et al. The interplay between oxidative stress and bioenergetic failure in neuropsychiatric illnesses: can we explain it and can we treat it? Mol Biol Rep. 2020;47(7):5587-5620. doi: 10.1007/s11033-020-05590-5.
2. Zapata-Pérez R, Wanders RJA, van Karnebeek CDM, Houtkooper RH. NAD(+) homeostasis in human health and disease. EMBO Mol Med. 2021;13(7):e13943. doi: 10.15252/emmm.202113943.
3. Santander Ballestín S, Giménez Campos MI, Ballestín Ballestín J, Luesma Bartolomé MJ. Is supplementation with micronutrients still necessary during pregnancy? A Review. Nutrients. 2021;13(9). doi: 10.3390/nu13093134.
4. Sitarz R, Juchnowicz D, Karakuła K, et al. Niacin skin flush backs - from the roots of the test to nowadays hope. J Clin Med. 2023;12(5). doi: 10.3390/jcm12051879.
5. Periyasamy S, John S, Padmavati R, et al. Association of schizophrenia risk with disordered niacin metabolism in an Indian genome-wide association study. JAMA Psychiatry. 2019;76(10):1026-1034. doi: 10.1001/jamapsychiatry.2019.1335.
6. Firth J, Teasdale SB, Allott K, et al. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. World Psychiatry. 2019;18(3):308-324. doi: 10.1002/wps.20672.
7. Nadalin S, Buretić-Tomljanović A, Rubesa G, Tomljanović D, Gudelj L. Niacin skin flush test: a research tool for studying schizophrenia. Psychiatr Danub. 2010;22(1):14-27.
8. Messamore E, Hoffman WF, Yao JK. Niacin sensitivity and the arachidonic acid pathway in schizophrenia. Schizophr Res. 2010;122(1-3):248-256. doi: 10.1016/j.schres.2010.03.025.
9. Horrobin DF. Schizophrenia as a prostaglandin deficiency disease. Lancet (London, England). 1977;1(8018):936-937. doi: 10.1016/s0140-6736(77)92228-0.
10. Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med (Baltim). 2004;39(1):212-220. doi: 10.1016/j.ypmed.2004.02.030.
11. Antao HS, Sacadura-Leite E, Bandarra NM, Figueira ML. Omega-3 index as risk factor in psychiatric diseases: a narrative review. Front Psychiatry. 2023;14:1200403. doi: 10.3389/fpsyt.2023.1200403.
12. Horrobin DF, Glen AIM, Vaddadi K. The membrane hypothesis of schizophrenia. Schizophr Res. 1994;13(3):195-207. https://doi.org/10.1016/0920-9964(94)90043-4.
13. Yu YH, Su HM, Lin SH, et al. Niacin skin flush and membrane polyunsaturated fatty acids in schizophrenia from the acute state to partial remission: a dynamic relationship. Schizophrenia. 2022;8(1):38. doi: 10.1038/s41537-022-00252-w.
14. Gan R, Wei Y, Wu G, et al. Attenuated niacin-induced skin flush response in individuals with clinical high risk for psychosis. Gen Psychiatr. 2022;35(2):e100748. doi: 10.1136/gpsych-2022-100748.
15. Zhang T, Gan R, Zeng J, et al. Attenuated niacin response is associated with a subtype of first-episode drug-naïve psychosis characterized as serious negative symptoms. Eur Arch Psychiatry Clin Neurosci. 2023;273(8):1725-1736. doi: 10.1007/s00406-023-01556-3.
16. Xu XJ, Jiang GS. Niacin-respondent subset of schizophrenia – a therapeutic review. Eur Rev Med Pharmacol Sci. 2015;19(6):988-997.
17. Hoffer A. Vitamin B3 and schizophrenia: discovery, recovery, controversy. Kingston: Quarry Health Books; 1998. 165 p.
18. Mousa TY, Mousa OY. Nicotinic acid deficiency (Archived). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557749/
19. Naicin. Medscape [Internet]. Newark: Medscape; 2024 [cited 2024 May 12]. Available from: https://reference.medscape.com/drug/vitamin-b3-niacor-niacin-344422#0
20. Glen AI, Cooper SJ, Rybakowski J, Vaddadi K, Brayshaw N, Horrobin DF. Membrane fatty acids, niacin flushing and clinical parameters. Prostaglandins Leukot Essent Fatty Acids. 1996;55(1-2):9-15. doi: 10.1016/s0952-3278(96)90139-8.
21. Fukuwatari T, Shibata K. Nutritional aspect of tryptophan metabolism. Int J Tryptophan Res. 2013;6(Suppl 1):3-8. doi: 10.4137/IJTR.S11588.
22. Puri BK, Hirsch SR, Easton T, Richardson AJ. A volumetric biochemical niacin flush-based index that noninvasively detects fatty acid deficiency in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2002;26(1):49-52. doi: 10.1016/s0278-5846(01)00220-2.
23. Nilsson BM, Hultman CM, Wiesel FA. Niacin skin-flush response and electrodermal activity in patients with schizophrenia and healthy controls. Prostaglandins Leukot Essent Fatty Acids. 2006;74(5):339-346. doi: 10.1016/j.plefa.2006.02.002.
24. Karakula-Juchnowicz H, Rog J, Wolszczak P, Jonak K, Stelmach E, Krukow P. SKINREMS-A new method for assessment of the niacin skin flush test response in schizophre-

nia. J Clin Med. 2020;9(6):1848. doi: 10.3390/jcm9061848.
25. Arzanlou M, Armanikian A, Saed O, Dobakhti F, Motamed N, Ahmadiafshar A. Accuracy of niacin skin flush test for diagnosing schizophrenia. Iran J Psychiatry Clin Psychol. 2021;27(1). doi: 10.32598/ijpcp.27.1.3144.1.
26. Wang DD, Hu XW, Jiang J, et al. Attenuated and delayed niacin skin flushing in schizophrenia and affective disorders: a potential clinical auxiliary diagnostic marker. Schizophr Res. 2021;230:53-60. doi: 10.1016/J.SCHRES.2021.02.009.
27. Carena F, Martino P, Vera CF, Bonet J. [Test for abnormal niacin response syndrome in schizophrenia: reclaiming the oral route]. Vertex. 2023;34(161):24-31. doi: 10.53680/vertex.v34i161.483. Spanish.
28. Zhang T, Xiao X, Wu H, et al. Association of attenuated niacin response with inflammatory imbalance and prediction of conversion to psychosis from clinical high-risk stage. J Clin Psychiatry. 2023;84(5):22m14731. doi: 10.4088/JCP.22m14731.
29. Hoffer A, Osmond H. Nicotinamide adenine dinucleotide (NAD) as a treatment for schizophrenia. J Psychopharmacol. 1966;1(3):79-95.
30. Kim SY, Cohen BM, Chen X, et al. Redox dysregulation in schizophrenia revealed by in vivo NAD+/NADH measurement. Schizophr Bull. 2017;43(1):197-204. doi: 10.1093/schbul/sbw129.
31. Ramachandran P, Thirunavakarasu P. Vitamins in schizophrenia: a literature review. Arch Ment Heal. 2012;13(2):74-79.
32. Hoffer A. The adrenochrome hypothesis of schizophrenia revisited. J Orthomol Med. 2009;24:160-182.
33. Vallée A. Neuroinflammation in schizophrenia: the key role of the WNT/β-Catenin pathway. Int J Mol Sci. 2022;23(5). doi: 10.3390/ijms23052810.
34. Oxenkrug G, Forester B. Anthranilic acid, a GPR109A agonist, and schizophrenia. Int J Tryptophan Res. 2024; 17:11786469241239124. doi: 10.1177/11786469241239125.
35. Yao JK, Dougherty GGJ, Gautier CH, et al. Prevalence and specificity of the abnormal niacin response: a potential endophenotype marker in schizophrenia. Schizophr Bull. 2016;42(2):369-376. doi: 10.1093/schbul/sbv130.
36. Tavares H, Yacubian J, Talib LL, Barbosa NR, Gattaz WF. Increased phospholipase A2 activity in schizophrenia with absent response to niacin. Schizophr Res. 2003;61(1):1-6. doi: 10.1016/s0920-9964(02)00281-5.
37. Feigenson KA, Kusnecov AW, Silverstein SM. Inflammation and the two-hit hypothesis of schizophrenia. Neurosci Biobehav Rev. 2014;38:72-93. doi: 10.1016/j.neubiorev.2013.11.006.
38. Fillman SG, Sinclair D, Fung SJ, Webster MJ, Shannon Weickert C. Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. Transl Psychiatry. 2014;4(2):e365. doi: 10.1038/tp.2014.8.
39. Ansarey SH. Inflammation and JNK's role in Niacin-GPR109A diminished flushed effect in microglial and neuronal cells with relevance to schizophrenia. Front Psychiatry. 2021;12:771144. doi: 10.3389/fpsyt.2021.771144.
40. Berger GE, Smesny S, Schäfer MR, et al. Niacin skin sensitivity is increased in adolescents at ultra-high risk for psychosis. PLoS One. 2016;11(2):e0148429. doi: 10.1371/journal.pone.0148429.
41. Krupa KN, Fritz K, Parmar M. Omega-3 fatty acids. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564314/
42. van der Kemp WJM, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE. A meta-analysis of the polyunsaturated fatty acid composition of erythrocyte membranes in schizophrenia. Schizophr Res. 2012;141(2-3):153-161. doi: 10.1016/j.schres.2012.08.014.
43. Tosi F, Sartori F, Guarini P, Olivieri O, Martinelli N. Delta-5 and delta-6 desaturases: crucial enzymes in polyunsaturated fatty acid-related pathways with pleiotropic influences in health and disease. Adv Exp Med Biol. 2014;824:61-81. doi: 10.1007/978-3-319-07320-0_7.
44. Comai S, Bertazzo A, Brughera M, Crotti S. Tryptophan in health and disease. Adv Clin Chem. 2020;95:165-218. doi: 10.1016/bs.acc.2019.08.005.
45. Campanale A, Inserra A, Comai S. Therapeutic modulation of the kynurenine pathway in severe mental illness and comorbidities: a potential role for serotonergic psychedelics. Prog Neuropsychopharmacol Biol Psychiatry. 2024;134:111058. doi: 10.1016/j.pnpbp.2024.111058.
46. Plitman E, Iwata Y, Caravaggio F, et al. Kynurenic acid in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2017;43(4):764-777. doi: 10.1093/schbul/sbw221.
47. Kindler J, Lim CK, Weickert CS, et al. Dysregulation of kynurenine metabolism is related to proinflammatory cytokines, attention, and prefrontal cortex volume in schizophrenia. Mol Psychiatry. 2020;25(11):2860-2872. doi: 10.1038/s41380-019-0401-9.
48. Lien YJ, Huang SS, Liu CM, et al. A genome-wide quantitative linkage scan of niacin skin flush response in families with schizophrenia. Schizophr Bull. 2013;39(1):68-76. doi: 10.1093/schbul/sbr054. https://doi.org/10.52645/MJHS.2024.4.11