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Neuroprotective factors in schizophrenia: BDNF, NGF, NT3, GDNF and their connection to the pathogenesis of schizophrenia. A narrative review

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Abstract

Introduction: There are several hypotheses of schizophrenia pathogenesis, including the neurodegenerative theory, which is supported by evidence for the decrease of neuroprotective factors' serum levels. The proteins, that exert a protective effect on neurons and are researched concerning schizophrenia pathogenesis, include the brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 (NT3), and glial cell line-derived neurotrophic factor (GDNF). This review aims to discuss the role of neuroprotective factors in the development of schizophrenia and their relevance in clinical trials.

Material and methods: This review was performed by search of the PubMed, Google Scholar, and Science Direct databases from December 25th, 2022, through January 31st, 2023, using keywords: 'schizophrenia', 'schizophrenia pathogenesis', 'neuroprotection', 'neurodegeneration', 'BDNF', 'NGF', 'NT3', and 'GDNF'. We considered original research papers and systematic reviews published in English or Polish. Additionally, clinical trials, which included the assessment of neuroprotective factors' levels in schizophrenia as outcome measures, were searched for on clinicaltrials.gov.

Results: Lower levels of serum BDNF have been linked to cognitive impairment in schizophrenia. In clinical trials, the assessment of serum BDNF is used as a clinical outcome measure for novel schizophrenia therapies. Schizophrenia has also been associated with reduced peripheral NGF levels. During remission, lower NGF levels correlate with higher severity of negative symptoms. Decreased NT3 and GDNF levels can also be seen, but literature reports are inconsistent.

Conclusions: Neuroprotective factors are most likely related to the pathogenesis of schizophrenia. Assessing the serum level of these proteins may prove to be an invaluable element of schizophrenia management.

Keywords: schizophrenia, brain-derived neurotrophic factor, nerve growth factor,neurotrophin 3, glial cell line-derived neurotrophic factor

Streszczenie

Wstęp: Istnieje kilka hipotez dotyczących patogenezy schizofrenii, między innymi teoria neurodegeneracyjna, która jest poparta dowodami na obniżenie stężenia czynników neuroprotekcyjnych w surowicy pacjentów z rozpoznaną schizofrenią. Białka, które wywierają ochronny wpływ na neurony oraz są badane w kontekście patogenezy schizofrenii to: neurotroficzny czynnik pochodzenia mózgowego (BDNF), czynnik wzrostu nerwów (NGF), neurotrofina 3 (NT3) i neurotroficzny czynnik pochodzenia glejowego (GDNF). Niniejszy przegląd literatury ma na celu omówienie roli czynników neuroprotekcyjnych w rozwoju schizofrenii oraz ich znaczenia w badaniach klinicznych.

Materiał i metoda: Dokonano przeglądu następujących baz danych: PubMed, Google Scholar i Science Direct. Przegląd został przeprowadzony w okresie od 25 grudnia 2022 r. do 31 stycznia 2023 r. przy użyciu słów kluczowych: „schizofrenia", „patogeneza schizofrenii", „neuroprotekcja", „neurodegeneracja", „BDNF", „NGF", „NT3" i „GDNF". Uwzględniono jedynie prace oryginalne oraz

przeglądy systematyczne opublikowane w języku angielskim lub polskim. Dodatkowo na stronie clinicaltrials.gov wyszukano badania kliniczne, które obejmowały ocenę stężenia czynników neuroprotekcyjnych w przebiegu schizofrenii.

Wyniki: Niższe stężenie BDNF w surowicy zostało powiązane z zaburzeniami funkcji poznawczych w przebiegu schizofrenii. W badaniach klinicznych ocena stężenia BDNF w surowicy była stosowana do oceny skuteczności nowych metod terapii. Schizofrenia została również powiązana z obniżonym stężeniem obwodowego NGF. W okresie remisji niższe stężenie NGF koreluje z większym nasileniem objawów negatywnych. Zaobserwowano też obniżone stężenie NT3 i GDNF, choć doniesienia literaturowe są niejednoznaczne.

Wnioski: Czynniki neuroprotekcyjne są najprawdopodobniej związane z patogenezą schizofrenii. Ocena stężenia tych białek w surowicy może okazać się nieocenionym elementem postępowania w diagnostyce i leczeniu schizofrenii.

Słowa kluczowe: schizofrenia, czynnik neurotroficzny pochodzenia mózgowego, czynnik wzrostu nerwów, neurotrofina 3, czynnik neurotroficzny pochodzenia glejowego

Introduction

According to the diagnostic criteria introduced in the latest version of the International Classification of Diseases 11th Revision (ICD-11), schizophrenia is a chronic disease characterized by positive symptoms (hallucinations, delusions, disorganized speech, and behavior), negative symptoms (avolition, flattened affect), and maniac or depressive symptoms. Some patients may also experience cognitive impairment and psychomotor dysfunction [1, 2]. The main hypothesis for explaining schizophrenia pathophysiology includes the dysregulation of brain dopamine levels. The increase in dopamine concentration in the mesolimbic pathway is mainly connected to psychotic symptoms. The negative symptoms of schizophrenia are presumed to result from decreased dopamine activity in the prefrontal cortex and the nucleus caudatus. Standard treatment of schizophrenia with dopamine antagonists is not sufficient for relieving all the symptoms, thus, new hypotheses and therapies are searched for [3]. Further research into other neurotransmitters revealed the dysfunctions in glutamate [4], gamma-aminobutyric acid (GABA) [5] and serotonin systems [6] in the course of schizophrenia, which contributed to the development of the glutamatergic and serotonin hypotheses of disease development. Further theories of schizophrenia pathophysiology link it with chronic low-grade inflammation. It has been proven that patients with schizophrenia have an increased pro-inflammatory cytokine concentration within the blood and cerebrospinal fluid. Some studies even found anti-inflammatory drugs useful in the treatment of schizophrenia [7]. The inflammatory theory has been linked to the metabolic disturbances associated with the disease – researchers suggest a causal relationship between pro-inflammatory cytokines and altered glucose and lipid metabolism and metabolic syndrome in the development of schizophrenia [8].

According to the altered neurodevelopment hypothesis, schizophrenia has a diachronic course of development. The biological vulnerability acquired prenatally, perinatally, or postnatally in combination with specific environmental characteristics, precludes the brain's normal development. Later in life, the patient becomes affected by some internal or external factors that cause the condition to manifest [9, 10]. Nowadays, several findings support the neurodegenerative hypothesis in the pathogenesis of schizophrenia [11, 12]. Studies showed that patients diagnosed with schizophrenia have a reduced volume of the temporal and frontal lobes, and larger ventricles [13]. The alterations are seen during follow-ups, suggesting a chronic degenerative process [14, 15]. Symptoms of schizophrenia, such as cognitive dysfunction and a higher incidence of dementia among patients, may provide evidence for a neurodegenerative process. No proof of gliosis or β-amyloid deposits has been found; however, the neurodegenerative theory of schizophrenia explains the neuronal loss by graded cell apoptosis caused by glutamate toxicity [16, 17]. The theories of pathological neurodevelopment and neurodegeneration are intertwined [18, 19] and some researchers propose the progressive neurodevelopmental model of schizophrenia, which summarizes the claims of both these theories [10, 17, 20].

Due to evidence of neurodegenerative processes' involvement in schizophrenia pathomechanisms, the role of neuroprotective factors in the course of the disease is researched. Those are proteins, whose role includes promoting neuronal survival and regulating synaptic plasticity [21]. Dysregulation of the level of neuroprotective factors is seen in the course of schizophrenia and other psychiatric and neurological diseases [22]. Various substances are being examined for their neuroprotective effect and potential use as add-on therapies for schizophrenia. These substances include, among others, curcumin, raloxifene, celecoxib, erythropoietin, modafinil, memantine, glycine,

n-acetylcysteine, and D-serine [23-26].

This review aims to discuss the role of neuroprotective factors in the development of schizophrenia and their relevance in clinical trials. We present the current knowledge and advances in preclinical and clinical research on the role of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 (NT3), and glial cell line-derived neurotrophic factor (GDNF) in the pathogenesis of schizophrenia. These four neuroprotective proteins were chosen due to sufficient evidence present in scientific literature linking them to disease development.

Material and methods

This review was prepared based on the current knowledge gathered in the PubMed, Google Scholar, and Science Direct databases. Search of the previously mentioned databases was performed from December 25th, 2022, through January 31st, 2023. The keywords used to search the libraries were: schizophrenia, schizophrenia pathogenesis, neuroprotection, neurodegeneration, BDNF, NGF, NT3, and GDNF. We considered original research papers and systematic reviews published in English or Polish in peer-reviewed journals. Relevant articles with novel findings, which assessed the role of BDNF, NGF, NT3, and GDNF in the course of schizophrenia were included in the review. Clinical trials, which included the assessment of neuroprotective factors' levels as outcome measures, were searched for on clinicaltrials.gov. Published results of those trials were searched for within the PubMed, Google Scholar, and Science Direct databases by their clinicaltrials.gov identifying number.

1. BDNF in schizophrenia

BDNF is a key regulator of synaptic plasticity in the hippocampus and cortex. This process was linked to the development of cognitive function and is associated with schizophrenia pathogenesis [21, 27-29]. Patients with the first episode of schizophrenia have been shown to exhibit lower serum levels of BDNF [30, 31]. A meta-analysis from 2019 proved that lower levels of BDNF are related to the reduction of cognitive function in patients with chronic schizophrenia [32]. Moreover, BDNF levels are higher in patients with non-deficit schizophrenia, which can be related to its neuroprotective effects [33]. It was reported that higher BDNF expression correlates with better problem-solving abilities among patients [34]. BDNF has also been shown to modulate dopaminergic neurotransmission within the brain tissue [35].

BDNF has been the subject of many studies on the genetic background of schizophrenia. Initially, research focused on the Val66Met polymorphism of the BDNF gene (substitution of valine to methionine within the 66th codon), which is associated with the disruption of BDNF levels. This polymorphism may account for the disturbance of the intracellular protein transport leading to a reduction of activity-dependent BDNF secretion, while constitutive secretion remains unaffected. It was reported that this genetic factor is associated with the age of schizophrenia onset, response to therapeutics, neural morphology, and cognitive function [36]. The Val66Met polymorphism was also related to the patient's response to treatment with antipsychotic drugs [35]. Other genetic variations of the BDNF gene were studied including the rs10835210 polymorphism, which was associated with higher schizophrenia prevalence and severity of positive symptoms [37]. In the genome-wide association studies (GWAS) of schizophrenia, the BDNF gene locus did not reach the genome-wide statistical threshold; however, it was associated with the disease (P-value < 10 -4) [38].

The failure of genetic studies on the pathogenesis of schizophrenia is related to the heterogeneity of the disease. Additionally, the impact of epigenetic factors affecting gene expression, which may additionally interact with numerous environmental factors, should be taken into consideration. DNA methylation is one of the well-studied epigenetic mechanisms, and BDNF expression can also be regulated via gene methylation. A relationship between BDNF gene methylation and symptoms of schizophrenia has not been proven; however, the status of methylation has been linked to fear, stress, and learning among schizophrenia patients [39, 40].

The level of BDNF can be regulated by various external factors. In a preclinical study on a murine schizophrenia model, it has been shown that housing BDNF haploinsufficient mice (BDNF+/-) in an enriched environment (with running wheels, etc.) prevents the development of behavioral phenotypes of schizophrenia observed in mice housed in poorer conditions. BDNF+/- mice from the enriched environment had similar BDNF levels in the brain tissue to those of proper BDNF expression (BDNF+/+), which was higher than among BDNF+/- mice housed in poorer conditions [41]. BDNF levels can also be influenced by antipsychotic drugs. Risperidone and haloperidol have been shown to decrease the level of BDNF in the hippocampus and frontal and occipital cortex in animal model [42]. Similarly, in patients, neurofeedback training and physical rehabilitation can increase BDNF serum levels, which correlates with improvement in positive and negative symptoms of the disease [43]. However, the administration of atypical antipsychotics, for example, olanzapine, in human causes an increase in the level of BDNF [44, 45].

More research is needed to understand the relationship between BDNF levels and schizophrenia. Some researchers proposed using serum BDNF level

as a biomarker of the course and management of the disease. The majority of studies suggested that lower levels of BDNF relate to more severe symptoms [33, 46, 47]. It was reported that repeated BDNF serum level assessment can be useful in monitoring the effectiveness of neurorehabilitation, which improves social functioning among patients [48], whereas baseline values of BDNF can be valuable to assess the severity of negative schizophrenia symptoms; however, they are not associated with the risk of relapse [49, 50].

Because of low BDNF levels in schizophrenic patients, treatment of the disease with BDNF application is researched in preclinical trials. In a murine model of schizophrenia, it has been shown that a two-dose intranasal BDNF administration improved the animals' behavior [51]. Drugs that influence BDNF secretion, like vinpocetine, have also been shown to alleviate symptoms of schizophrenia by upregulating BDNF expression in an animal model [52].

The knowledge of the role of BDNF in schizophrenia is applied to designing clinical trials. Serum/plasma levels of BDNF are assessed as clinical outcome measures for various new treatments and therapies. As of January 2023, there are 40 registered trials at clinicaltrials.gov, which include the evaluation of BDNF as an outcome measure for treatment among patients diagnosed with schizophrenia. Out of the 40 registered trials, 7 have published results regarding the role of BDNF in the study and have been summarized in Table 1.

Table 1. Summary of clinical trials with published results regarding BDNF levels, which include the evaluation of BDNF as an outcome measure for treatment among patients diagnosed with schizophrenia (clinicaltrials.gov, last search January 31st 2023).

Group of patients	Clinicaltrials.gov identifying number	Title of the clinical trial	Main objective of the study	Role of BDNF in study design	Actual study duration time	Trial phase	Results regarding BDNF levels	References
treatment-naïve, first-episode SCZ	NCT03304457	"Effect of Lurasidone Vs Olanzapine on Neurotrophic Biomarkers and Cardiometabolic Parameters in First Episode Untreated Schizophrenia: A Randomized, Open Label, Active Controlled Study"	to assess the influence of olanzapine and lurasidone on the levels of neurotrophic biomarkers of SCZ (BDNF, NGF, NT3, and more)	assessment of serum BDNF levels before and after treatment of SCZ with olanzapine and lurasidone	August 2017 – March 2018	phase 4	after 6 weeks of treatment, serum levels of BDNF increased in both groups, but the increase was higher after olanzapine than lurasidone treatment	[53, 54]
SCZ treated with antipsychotic medication	NCT02104752	"Curcumin as a Novel Treatment to Improve Cognitive Dysfunction in Schizophrenia"	to assess the efficacy of adding curcumin to the antipsychotic treatment of SCZ in improving cognitive function	assessment of serum BDNF level as a biomarker of neurogenesis	July 2014 – October 2017	phase 1, phase 2	patients treated with curcumin had higher BDNF levels than at baseline	[55]
first episode SCZ, schizophreniform disorder, or schizoaffective disorder (depressed type)	NCT02267070	"Enhancing Cognitive Training Through Exercise After a First Schizophrenia Episode"	to assess the efficacy of combining cognitive training with aerobic exercise in the treatment of SCZ	assessment of serum BDNF levels in patients before and after therapy with cognitive training, or cognitive training combined with exercise	November 2013 – July 2017	NA	no significant differences or correlations between therapy types and BDNF levels	[56]
treated SCZ with cognitive impairment	NCT02341131	"BDNF as a Potential Biomarker for Cognitive Remediation Therapy in Schizophrenia"	to assess the role of BDNF as a marker of CRT efficacy in SCZ	(1) assessment of BDNF as a biomarker of CRT treatment (2) assessment of the association between Val66Met BDNF gene polymorphism and outcome measures	January 2012 – March 2016	NA	(1) no difference in BDNF levels between groups (2) serum BDNF level after CRT was higher in Val/Val group than in other genotypes groups	[57]

SCZ	NCT01503359	"Effect of Sarcosine on Symptomatology, Quality of Life, Cognitive and Sexual Functioning, Blood Levels of Sarcosine, Glycine, BDNF and MMP-9, Oculomotor, Brain Metabolism and Oxidative Stress Parameters in Schizophrenia."	to assess the effect of sarcosine supplementation to standard treatment methods	assessment of the relationship between sarcosine add-on treatment and serum BDNF levels	January 2012 – January 2016	phase 2	serum levels of BDNF are not related to the effects of sarcosine treatment and its NMDA receptor-mediated action	[58]
SCZ with obsessive-compulsive symptoms	NCT02105064	"Repetitive Transcranial Magnetic Stimulation (rTMS) as an add-on Treatment for Resistant Obsessive-compulsive Symptoms in Patients With Schizophrenia"	to assess the efficacy of rTMS in treating obsessive-compulsive symptoms in SCZ	assessment of plasma BDNF levels as markers of treatment	July 2011 – February 2016	NA	changes in plasma BDNF levels were not observed among patients treated with rTMS	[59]
pharmaco-resistant SCZ, resistant depression	NCT02652832	"Effects of Noninvasive Brain Stimulation Techniques on BDNF Levels"	to assess the relationship between non-invasive brain stimulation and BDNF serum levels	assessment of serum BDNF as a marker of treatment efficacy and clinical improvement	December 2010 – unknown	NA	higher serum levels of the mature isoform of BDNF (mBDNF) are associated with future remissions after electroconvulsive therapy	[60]

BDNF – brain-derived neurotrophic factor; NGF – nerve growth factor; NT3 – neurotrophin 3; SCZ – schizophrenia; CRT - Cognitive Remediation Therapy; NMDA - N-methyl-D-aspartate; rTMS – repetitive Transcranial Magnetic Stimulation; NA – not applicable

2. NGF in schizophrenia

NGF is a neuropeptide that controls the proliferation and survival of neurons within the central and peripheral nervous systems. It is a crucial element in many diseases that cause cell death and neurodegeneration, especially in the brain [61]. NGF plays a major role in the development, proliferation, and survival of neurons of the sensory and sympathetic tracts, preventing apoptosis. By regulating synaptic plasticity, tissue development, and loss in significant limbic system regions, NGF also influences the processes of learning and memory [22, 62]. This neuroprotective protein has been shown to play a role in the pathogenesis of schizophrenia. Multiple meta-analyses showed that schizophrenia is associated with reduced peripheral NGF levels [63-66]. During the remission of the disease, lower NGF levels correlated with higher severity of negative symptoms [49]. NGF has also been associated with gray matter volume in specific regions of the brain of patients with schizophrenia [67]. More research is needed to fully understand and confirm these relationships.

Polymorphisms of the NGF and NGF receptor (NGFR) genes were researched to assess their possible influence on schizophrenia susceptibility. The rs6330 and rs4839435 NGF gene polymorphisms and the rs734194, rs11466155, rs2072446 NGFR gene polymorphisms were associated with reduced NGF blood levels, which was previously linked to disturbances of the synaptic plasticity. The contribution of these genetic findings to the development of schizophrenia needs further consideration [62].

Due to abundant evidence showing the relationship between NGF levels and schizophrenia, NGF could be evaluated as a potential biomarker, especially for first-episode, drug-naïve schizophrenia [68]. The baseline NGF level may also be an important marker of long-term disease severity, especially in terms of negative symptoms. However, measuring NGF levels is not helpful while assessing the risk of relapses [49]. Treatment of schizophrenia with NGF has not been pursued. Lazar et al. showed that postnatal NGF injections into the frontal cortex of rat pups led to dopaminergic hyperactivity in adulthood, which caused a change in behavior consistent with human schizophrenia symptoms [69].

As of January 2023, there is only one clinical trial registered at clinicaltrials.gov that includes NGF in the study design. In a trial that compared the effect of olanzapine and lurasidone on neurotrophic biomarkers, the serum level of NGF (as well as BDNF, NT3, and others) was assessed at baseline and 6 weeks after treatment of drug-naïve schizophrenia to conclude whether these drugs positively influence the serum levels of neuroprotective factors. However, no difference between groups in the serum level of NGF was observed [53, 54].

3. NT3 in schizophrenia

NT3 belongs to the neurotrophins family along with BDNF, NGF, and neurotrophin 4/5 (NT4/5) with which it shares a similar structure and function. NT3 plays an important role in the development of neurons, neuron growth, and survival, as well as in modulating synaptic formation, transmission, and plasticity [70]. The role of NT3 is implied in the pathogenesis of many neuropsychiatric disorders, including schizophrenia [71]. It was reported that in drug-naïve, first-episode schizophrenia, the NT3 serum level was reduced [45, 72]. Additionally, research revealed that, probably due to the influence of antipsychotic medication on the expression of neurotrophins, patients with chronic schizophrenia had higher NT3 serum concentrations [73]. For example, risperidone treatment leads to a significant increase in NT3 blood levels, which made Chenniappan et al. suggest a potential use of NT3 as a biomarker in predicting the response to risperidone treatment [74]. Some authors do not report significant differences in NT3 levels between patients and healthy controls but note that schizophrenia with concomitant depressive symptoms is associated with higher NT3 levels, than the control group [75, 76].

NT3 gene polymorphisms had been researched at the end of the 20th century as a possible vulnerability factor for schizophrenia; however, results were ambiguous, with some authors denying any association [77]. The A3/147-bp allele was detected more frequently among patients who suffered from schizophrenia and it was described as having an association with the earlier age of disease onset [78-80]. A missense mutation, Gly-63 to Glu-63, was linked to a higher risk of severe schizophrenia symptoms in the course of the disease [81].

Like NGF, NT3 is only a part of a single clinical trial that includes NT3 level assessment as a clinical outcome measure (registered at clinicaltrials.gov as of January 2023), where the influence of olanzapine and lurasidone on neuroprotective factors' serum levels was assessed. A statistically significant difference between NT3 serum levels of patients before and after treatment with olanzapine was observed [53, 54].

4. GDNF in schizophrenia

GDNF is a protein important in the process of promoting neuronal survival and differentiation, guiding axons to form synapses, and maintaining connections with other tissues. GDNF also plays a role in modulating the pain response via sensitization of the sensory fibers and is hypothesized to promote the differentiation of dopaminergic neurons. The role of GDNF is best characterized in the pathology of the dopamine signaling within the nigrostriatal pathway of the midbrain, making it the point of interest for Parkinson's disease treatment [82-84]. As dopaminergic transmission dysregulation also underlies many neuropsychiatric disorders, the role of GDNF is also researched in the pathophysiology of schizophrenia. GDNF levels are lower in the blood serum and cerebrospinal fluid in patients diagnosed with schizophrenia [85, 86]. Lower protein levels are correlated with more severe symptoms of the disease [87], especially cognitive deficiency impairment [85, 88]. There is a positive association between the GNDF level and better cognitive functioning among patients with deficit symptoms of schizophrenia [89]. Longer duration of disease relates to lower GDNF serum levels [90]. The level of GDNF has also been shown to be lower among patients with tardive dyskinesia appearing as a side effect of antipsychotic medication. Ye et al. presented a study, where all schizophrenic patients had significantly lower GDNF serum levels than healthy controls and among patients suffering from schizophrenia, those with symptoms of tardive dyskinesia had reduced GDNF levels in comparison to those without the symptoms [91]. Atypical antipsychotic drug therapy has been shown to gradually increase serum levels of GDNF, along with the psychotic symptoms' reduction [92]. However, some authors do not confirm that GDNF levels are significantly reduced in schizophrenia, leaving the topic up for further discussion [93]. On the other hand, Mätlik et al. showed, that an increase in GDNF levels in the striatum and cerebrospinal fluid is related to increased dopamine signaling, suggesting that the interplay between GDNF and the A2A receptor may play a role in the schizophrenia pathomechanisms [94].

Genome scans have identified the GDNF gene as a possible locus for schizophrenia predisposition. The predilection of specific GDNF gene polymorphisms to schizophrenia development has not been proven [84, 95-97]. However, specific polymorphisms of GDNF receptor genes – the GDNF family receptor alpha (GFRA) seem to be of importance. The gene variants GFRA3 rs11242417 and GFRA1 rs11197557 are more commonly found among patients with schizophrenia diagnosis [98].

Until January 2023, GDNF has not been included in any clinical trial registered at clinicaltrials.gov.

Conclusions

Based on multiple evidence, neuroprotective factors are most likely related to the pathogenesis of schizophrenia, which supports the neurodegenerative theory of disease development. The levels of BDNF, NGF, NT3, and GDNF vary depending on the severity of symptoms, disease relapse or remission, or treatment methods. Assessing the level of these proteins in the serum of patients may prove to be an invaluable element of schizophrenia diagnosis, management, and prognosis

in the next years. This can become useful not only for psychiatrists but also for other physicians because routine assessment of serum biomarkers of schizophrenia would be an objective and relatively easy diagnostic method to help recognize schizophrenia. A screening diagnostic test would have to be later confirmed by a detailed psychiatric examination, which is essential to make a diagnosis.

Ethical considerations

The process of preparing this review did not involve any use of human or animal subjects.

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Conflict of interest

The authors have declared no conflict of interest.

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