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SUPLEMENTAÇÃO DA VITAMINA D NA MELHORA DOS SINTOMAS DA ESQUIZOFRENIA: UMA REVISÃO DE ESCOPO

VITAMIN D SUPPLEMENTATION IN IMPROVING SCHIZOPHRENIA SYMPTOMS: A SCOPING REVIEW

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RESUMO

INTRODUÇÃO: Estudos prévios mostram que pacientes com esquizofrenia apresentam níveis mais baixos de vitamina D em comparação com indivíduos saudáveis, com maior incidência de sintomas negativos entre esses pacientes. Considerando este cenário, infere-se que a vitamina D desempenha um papel potencial nesse transtorno. Este estudo avaliou a eficácia da administração de vitamina D na melhora dos sintomas de pacientes com esquizofrenia, identificando as principais tendências e lacunas no conhecimento atual. **METODOLOGIA**: Esta revisão de escopo seguiu o checklist PRISMA-ScR e foi conduzida em cinco etapas: 1). Formulação da pergunta de pesquisa utilizando o método PCC; 2). Seleção das bases de dados e delineamento das estratégias de busca; 3). Exportação dos estudos recuperados e estabelecimento dos critérios de elegibilidade; 4). Seleção dos artigos por dois revisores independentes/cegos; 5). Construção da tabela de evidências. **RESULTADO**: Foram analisadas 6 áreas pertinentes à eficácia da suplementação de vitamina D na esquizofrenia: 1). métodos empregados para avaliar a severidade dos sintomas da esquizofrenia; 2). tratamentos principais adotados para a esquizofrenia; 3). doses de suplementação de vitamina D; 4). duração da suplementação; 5). concentrações séricas de vitamina D antes e após a intervenção; 6). eficácia da suplementação nos ensaios clínicos randomizados. **DISCUSSÃO**: Os achados sugerem que a correção da hipovitaminose D pode ser um mecanismo-chave para benefícios adjuvantes, especialmente em sintomas negativos e parâmetros metabólicos. A heterogeneidade nos protocolos (dose, via de administração, duração) e populações (gravidade basal, tratamentos concomitantes) pode ter causado disparidades nos resultados. **CONCLUSÃO**: Durante a pesquisa, foi identificada uma tendência de melhora nos sintomas esquizofrênicos com a suplementação de vitamina D. Contudo, nem todos os estudos corroboraram essa associação, com alguns não observando impactos significativos. Destacando assim, a necessidade de novas pesquisas acerca do tema para ampliar a base de dados que comprova essa relação.

PALAVRAS-CHAVE: *Vitamina D; Esquizofrenia; Suplementação Nutricional; Cognição; Drogas antipsicóticas .*

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ABSTRACT

INTRODUCTION: Previous studies have shown that patients with schizophrenia present lower levels of vitamin D compared to healthy individuals, with a higher incidence of negative symptoms among these patients. Considering this scenario, it is inferred that vitamin D plays a potential role in this disorder. This study evaluated the efficacy of vitamin D administration in improving the symptoms of schizophrenic patients, identifying the main trends and gaps in current knowledge. **METHODOLOGY:** The elaboration of this scoping review followed the PRISMA-ScR checklist and was conducted in five steps: 1) Formulation of the research question using the PCC method; 2) Selection of databases and design of search strategies; 3) Exportation of retrieved studies to Rayyan and establishment of eligibility criteria; 4) Selection of articles by two independent and blinded reviewers; 5) Construction of an evidence table, following the JBI model. **RESULTS:** Six areas relevant to the effectiveness of vitamin D supplementation in schizophrenia were analyzed: 1) methods used to assess the severity of schizophrenia symptoms; 2) primary treatments adopted for schizophrenia; 3) doses of vitamin D supplementation; 4) duration of supplementation; 5) serum vitamin D concentrations before and after the intervention; 6) effectiveness of supplementation in randomized clinical trials. **DISCUSSION:** The findings indicate that the correction of hypovitaminosis D could be a pivotal mechanism for achieving adjuvant benefits, particularly in relation to negative symptoms and metabolic parameters. Disparities in results may have arisen from the heterogeneity observed in protocols (dose, route, duration) and populations (baseline severity, concomitant treatments). **CONCLUSION:** During the research, a trend of improvement in schizophrenic symptoms with vitamin D supplementation was identified. However, not all studies corroborated this association, with some reporting no significant impacts. This highlights the need for further research on the topic to expand the evidence base supporting this relationship.

KEYWORDS: *Vitamin D; Schizophrenia; Nutritional Supplementation; Cognition; Antipsychotic Drugs.*

INTRODUÇÃO

Schizophrenia is a chronic psychiatric disorder characterized by a broad range of impairments in affective, behavioral, cognitive and perceptual domains, directly impacting individuals' quality of life and their ability to establish interpersonal relationships and maintain occupational functioning. With an estimated prevalence ranges from 0.2% to 2% in the general population, its etiology is considered complex and multifactorial, involving interactions among genetic, epigenetic, and environmental factors[1,2].

Mollon and Reichenberg (2018)[3], observed that deficits in domains such as working memory, attention, and executive function often precede the onset of psychotic symptoms. These findings suggest that cognitive functions are a core feature of the disorder. Complementarily, Barch and Sheffield (2014)[4], in a study involving high-risk individuals and first-degree relatives of patients, identified similar cognitive patterns, reinforcing the hypothesis of a shared neurobiological basis.

Regarding vitamin D, Ruscalleda (2023)[5] examined its neurobiological effects and highlighted its role in maintaining cognitive function and preventing neurodegenerative diseases. Chai et al. (2019)[6] demonstrated that vitamin D deficiency is associated with an increased risk of developing dementia and Alzheimer's disease. Wang et al. (2023)[7] explored the mechanisms underlying this association, emphasizing the regulation of neurotrophic factors, modulation of oxidative stress and neuroinflammation, and its involvement in neurotransmission.

In the context of schizophrenia, McGrath et al. (2010)[8] conducted a population-based study showing that low neonatal vitamin D levels are associated with an increased risk of developing the disorder. Furthermore, Doğan Bulut et al. (2016)[9], in their investigation of biochemical markers in patients with schizophrenia, found a correlation between reduced serum vitamin D levels and the exacerbation of negative symptoms such as apathy, anhedonia, and affective flattening.

Based on a literature review, Mayne and Burne (2019)[10] suggests that vitamin D supplementation may have beneficial effects on neuroplasticity and cognitive functioning in individuals with psychiatric disorders. Despite these advances, systematic reviews that consolidate the available evidence on the effects of vitamin D supplementation in the clinical management of schizophrenia—particularly in relation to cognitive and negative symptoms—remain scarce. In this context, the present scoping review aims to investigate the relationship between vitamin D supplementation and its effectiveness in managing schizophrenia

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symptoms, contributing to a better understanding of the role of this nutrient in mental health and its potential clinical applications

METODOLOGIA

This manuscript is a scoping review, developed according to the PRISMA-ScR checklist[11] and enhanced following the methodological framework proposed by Mattos; Cestari, and Moreira (2023)[12]. The choice of scoping review as a research method is justified by its role in identifying, analyzing, and investigating scientific evidence and gaps, while also enabling a deeper understanding of the characteristics, concepts, and theoretical definitions of the proposed field of study[12].

DATA SOURCE AND RESEARCH

The review followed five stages: 1). formulation of the research question, following the Patient (P), Concept (C), Context (C) - PCC method; 2). selection of databases and definition of search strategies; 3). exportation of the retrieved studies to the Rayyan reference manager and establishing inclusion and exclusion criteria; 4). selection of retrieved articles by two blinded/independent reviewers, with any discrepancies resolved by a third researcher; 5) preparation of a table summarizing the evidence found, according to the JBI Manual for Evidence Synthesis.

The research question, formulated based on the PCC method, was defined as follows: "What is the efficacy of vitamin D supplementation in improving the symptoms of patients with schizophrenia?" P (Population) - patients with schizophrenia; C (Concept) - efficacy of vitamin D supplementation; C (Context) - in the last ten years.

The following databases were selected to identify potentially relevant research: Web of Science, SCOPUS, EMBASE, PubMed, and BVS. Then, keywords were established based on the Health Sciences Descriptors (DeCS)[13] and the National Library of Medicine (NIH) catalog. These terms, combined with Boolean operators, formed the following search strategy: ("Vitamin D") AND ("Therapeutic" OR "Therapy" OR "Therapies" OR "Treatment" OR "Treatments" OR "Supplementation" OR "Dietary Supplement" OR "Supplements, Dietary" OR "Dietary Supplementations" OR "Supplementations, Dietary" OR "supplementation, vitamin" OR "vitamin supplementation" OR "support, nutritional" OR "nutritional support" OR "supplement") AND ("Schizophrenia" OR "Schizophrenias" OR "Dementia Praecox" OR "Schizophrenic Disorders" OR "Disorder, Schizophrenic" OR "Disorders, Schizophrenic" OR "Schizophrenic Disorder" OR "schizophrenic syndrome").

Schizophrenia-related symptoms such as delusions, hallucinations, and other terms were not included among the keywords, as their mention could lead to the retrieval of articles related to other diseases and disorders, thus making it more difficult to filter studies specifically focused on the topic. In addition, the search strategy prioritized terms more directly associated with the scope of the review (schizophrenia, symptoms, vitamin D, deficiency) to facilitate article selection. For this reason, terms such as cognition and cognitive were also excluded from the keywords. The term cholecalciferol was not included either, since according to MeSH terms, cholecalciferol is not classified as a synonym of vitamin D.

STUDY SELECTION AND ELIGIBILITY CRITERIA

The studies retrieved from the five databases were uploaded to the Rayyan reference manager, a tool used to facilitate article screening. Additionally, the researchers decided the eligibility criteria for this review, which are: Primary studies published between 2014 and 2024, in any language, investigating the efficacy of vitamin D supplementation for improving symptoms in patients diagnosed with schizophrenia were included. Duplicate manuscripts and studies that did not directly address the topic were excluded, as well as articles associating vitamin D with other types of supplements, such as probiotics. Theoretical studies, editorials, abstracts, opinion articles, and case studies were also excluded due to their low level of scientific evidence. Furthermore, reviews of any nature were excluded.

To ensure consistency in the review, two blinded/independent reviewers followed a three-step process to analyze the retrieved publications: 1 - first, duplicates were removed across the databases to avoid analysis errors; 2 - next, the titles and abstracts of the remaining research were analyzed, excluding those that did not meet the established criteria; 3 - finally, manuscripts whose titles and abstracts were inconclusive regarding the eligibility criteria were fully read, including those aligned with the review's objectives. Any discrepancies between the two reviewers were resolved by a third researcher, arriving at the set of articles comprising this study. These selection steps and the respective article counts were organized into a flowchart (Figure 1).

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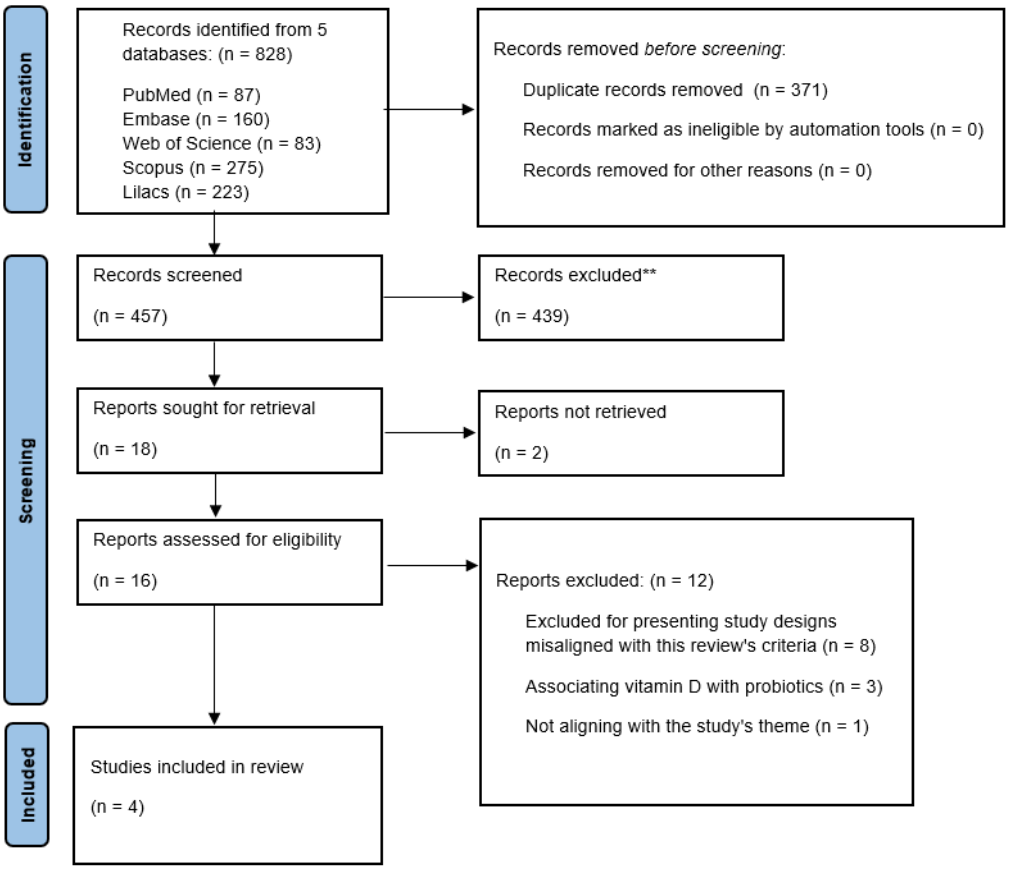
FIGURA 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



**Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).*
***If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.*
Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
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DATA EXTRACTION AND ANALYSIS

After selection, independent reviewers prepared a data-mapping form to record variables extracted from the reviewed studies. In an iterative process of recording and updating this form, information regarding the efficacy of vitamin D supplementation in improving symptoms in patients diagnosed with schizophrenia was organized into a Mycrosoft Word table. The variables recorded followed the JBI Manual for Evidence Synthesis guidelines[14], covering aspects such as authorship, year of publication, country of origin, objectives, study design, sample size, and main outcomes, which were included in the evidence table of this study.

TABLE 1. Summary and characteristics of the included manuscripts

Author, year and country.	Sample size. Study design Objective.	Outcomes	Value used to identify vitamin D deficiency. Antipsychotics used. Supplementation, follow-up period, and attained levels. Used medication Supplementation, follow-up period, and attained levels.

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Krivoy et al., 2017. Israel and United Kingdom	45, 23 allocated to placebo and 24 to vitamin D. 42 individuals remained until completing the 8-week experimental period. (18–65 years old). A randomized, double-blind, placebo-controlled clinical trial. Explore the effects of vitamin D supplementation in patients with chronic schizophrenia undergoing clozapine treatment.	No advantage of vitamin D over placebo was found in psychotic, metabolic, or depressive aspects. However, a slight positive effect was observed in cognitive performance. According to regression analysis, vitamin D supplementation was a factor that increased the total score on the MoCA. Therefore, vitamin D is correlated with an improvement in cognitive performance in this population of schizophrenic patients treated with clozapine. Therefore, the study did not find a significant improvement in positive or negative symptoms or in the general picture of psychopathology with vitamin D supplementation. In the article *"Vitamin D Supplementation in Chronic Schizophrenia Patients Treated with Clozapine: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial"* (Krivoy et al., 2017), the outcomes of interest (e.g., PANSS, MoCA, metabolic parameters) are continuous variables assessed through the difference in means. This implies that: The study does not present: Official percentages of improvement (percentage increase or decrease) relative to the baseline value. Odds Ratios (OR), Risk Ratios (RR), Hazard Ratios (HR), or their confidence intervals. These indicators (OR, RR, HR) are appropriate when the outcome is dichotomous (e.g., “occurred vs. did not occur” or “improved vs. did not improve”) or when analyzing time-to-event data (survival analysis). In the study in question, there is no "binary" outcome or "time to relapse" measure that would allow for the calculation of OR, RR, or HR.	The study measured low levels of vitamin D as values lower than 30 ng/ml. Values lower than 25 nmol/l were considered as vitamin deficiency. Clozapine. patients received supplement vitamin D (14,000IU weekly) or placebo for eight weeks. In the drug group, the levels of the vitamin increased (from 37.2 to 68.6 nmol/l). In the placebo group there weren’t significant changes.
Sheikhmoonesi et al., 2016. Iran.	120 (18–65 years). 60 in the control group and 60 in the vitamin D group. Randomized controlled clinical trial. To determine whether adding vitamin D to the standard treatment of male schizophrenic patients with inadequate vitamin D status could improve aspects of their symptomatic condition.	A negative, but non-significant, correlation was found between changes in serum vitamin D levels and negative subscale scores of the PANSS in the intervention group. No relationship was found between changes in serum vitamin D levels and improvement in negative and positive symptoms in patients. In the study by Sheikhmoonesi et al. (2016) – Effectiveness of Vitamin D Supplement Therapy in Chronic Stable Schizophrenic Male Patients: A Randomized Controlled Trial – measures such as OR (odds ratio), RR (relative risk), or HR (hazard ratio), as well as their confidence intervals, were not reported. This is because the outcome was assessed through the difference in means on continuous scales (positive and negative PANSS subscales), without involving dichotomous occurrences (yes/no) or time-to-event data that would justify the calculation of OR, RR, or HR. Additionally, the article does not directly present improvement percentages in the format of “percentage reduction” for each group.	vitamin D deficiency and insufficiency have been defined by the study as 25(OH) D of less than 20 ng/mL and 21–29 ng/mL, respectively. Chlorpromazine. In the study, it was prescribed a total dose of 600,000 IU for patients in a period of four months. Serum vitamin D was measured twice: first at the baseline and again on the fourth month. After four months: 50,5 ± 9,0 ng/mL in the intervention group and 14,0 ± 6,8 ng/mL in the control group.

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Kalejahi et al., 2022. Iran.	42 (18-65 years old), 21 in the placebo group and 21 in the vitamin D group. Single-center, randomized, double-blind, placebo-controlled study. To evaluate the impact of vitamin D supplementation on symptom severity in schizophrenic patients and cardiometabolic parameters.	There was a correlation between the decrease in LDL and an improvement in PANSS scale scores, suggesting that vitamin D supplementation may be effective in cardiometabolic indices and in the treatment of patients with SZ. Vitamin D supplementation showed benefits especially on the negative symptoms of schizophrenia and on the overall severity of symptoms. Positive symptoms did not show a statistically significant difference compared to placebo, and there was no specific measurement of cognitive symptoms. These studies do not present OR (odds ratio), RR (relative risk), or HR (hazard ratio) for schizophrenia symptom improvement outcomes following vitamin D supplementation. This is because the variables of interest (symptom scale scores) are continuous (e.g., PANSS) rather than incidence events or time-to-event data. Therefore, effect measures are reported as differences in means with confidence intervals rather than OR, RR, or HR.	The study considered that hypovitaminosis is measured by levels of vitamin D lower than 25 nmol/l. Typical antipsychotics, atypical antipsychotics and combined antipsychotics. The intervention was the administration of 2000 IU of vitamin D daily for 8 weeks for the intervention group. At the end of the study, there was a significant decrease in PANSS-GPSS and PANSS-TS in the intervention group compared with placebo (P=0.036 and P=0.049, respectively).Besides that, all subscales of PANSS significantly decreased in both groups.
Kalejahi et al., 2023. Iran.	Forty-eight chronic schizophrenia patients with vitamin D deficiency were supplemented for an 8-week period with vitamin D (2000 IU/day) or a placebo. A randomized controlled trial (RCT). To examine the effect of vitamin D supplementation on serum vitamin D levels, metabolic factors related to insulin resistance (IR), and the severity of the disorder in patients with schizophrenia.	A beneficial effect of vitamin D supplementation was found in reducing serum levels of GSK-3β and the severity of psychotic symptoms in hospitalized patients with vitamin D deficiency and schizophrenia. However, further studies are needed to confirm these findings. That way, is an improvement in negative symptoms, while positive symptoms generally do not show a statistically significant change. The randomized controlled trial conducted by Kalejahi, Kheirouri, and Noorazar investigated the effects of vitamin D supplementation in Iranian patients with schizophrenia, focusing on serum levels of glycogen synthase kinase-3β (GSK-3β) and symptom severity. Although the results showed statistically significant differences in various measures, such as reductions in waist circumference, total scores on the Positive and Negative Syndrome Scale (PANSS-TS), and GSK-3β levels in the vitamin D group, the available abstract does not provide specific statistical values, such as percentages, odds ratios (OR), relative risks (RR), or hazard ratios (HR). To obtain these specific statistical details, it would be necessary to access the full text of the article.	The study considered that vitamin D deficiency is determined by levels lower than 20 ng/ml. Not found due to inability to access full article. Subjects were supplemented for 8 weeks with vitamin D (2000 IU/day) or placebo. Within-group comparison revealed that the vitamin D group had a significant reduction in waist circumference, Positive and Negative Syndrome Scale - total score (PANSS-TS), and glycogen synthase kinase 3 beta (GSK-3β) levels (*P* = .022, *P* = <.001 and *P* = .013, respectively). On the other hand, the placebo group showed a significant increase in the level of fasting serum insulin and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (*P* = .003 and *P* = .003).

Source: authors, 2025.

DEFINITION OF VITAMIN D DEFICIENCY

Serum levels of the inactive form of vitamin D, calcidiol, below a threshold of 20 to 25 ng/mL, characterize what is known as vitamin D deficiency—a condition with multifactorial causes, including low sun exposure, poor dietary intake of vitamin D-rich foods, ethnicity, place of residence, among others[15].

RESULTADOS

During the identification phase of the publications, a total of 828 manuscripts were retrieved from various renowned databases. These sources included 87 from PubMed, 160 from Embase, 83 from Web of Science, 275 from Scopus, and 223 from Lilacs. Using the filters available in Rayyan Reference Manager, 371 duplicate studies were excluded, resulting in 457 citations. Of

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these, 439 manuscripts were removed after analyzing the titles and abstracts, leaving 18 articles. From this remaining total, 6 articles were excluded for presenting study designs misaligned with this review's criteria, 3 for associating vitamin D with probiotics, 1 for not aligning with the study's theme, and 2 due to data retrieval issues. In the end, 4 articles were considered eligible for this review.

In preparing this scoping review, Iran stood out as the primary origin of the selected studies, representing 75% (n=3)[16,17,18]. Additionally, there was one binational study conducted in the United Kingdom and Israel[19], representing 25%.

All of the analyzed articles consist of randomized and controlled clinical trials (n=4), accounting for 100% of the total manuscripts[16,17,18,19]. Among these trials, 50% (n=2) were double-blind[17,19], and the other 50% (n=2) evaluated exclusively the effects of vitamin D supplementation on metabolic and psychotic outcomes[16,18].

Thus, the selected studies reported mixed outcomes regarding the impact of vitamin D supplementation on schizophrenia symptoms. Two of the four clinical trials demonstrated significant improvements in either psychotic symptom severity or cardiometabolic markers following vitamin D intervention[17,18]. The other two studies did not observe statistically significant effects on core symptoms, although one suggested a trend toward cognitive improvement[19] and another reinforced the need for additional research[16]. To synthesize the findings, the included studies were categorized according to key clinical and methodological variables, such as the assessment tools used, treatment regimens, supplementation protocols, and measured outcomes.

Methods Used to Assess the Severity of Schizophrenia Symptoms

The methods used to assess the severity of schizophrenia symptoms were consistent across all articles. The Positive and Negative Syndrome Scale (PANSS) was the most frequently used instrument, appearing in 100% (n=4) of the manuscripts[16,17,18,19].

In addition to the PANSS, Krivoy et al. (2017)[19] also used the Montreal Cognitive Assessment (MoCA) to evaluate cognitive function and the Calgary Depression Scale (CDS) to assess depressive symptoms.

Furthermore, Kalejahi et al. (2023)[18] incorporated GSK-3β (glycogen synthase kinase-3 beta) as a biochemical biomarker, measured in serum, to explore its association with psychotic symptom severity. The study highlighted the role of vitamin D in modulating this enzyme via the PI3K/AKT pathway, suggesting a possible molecular mechanism linked to symptom improvement[18].

Main Treatments for Schizophrenia Used in the Studies

Regarding the main treatments for schizophrenia in the evaluated studies, 100% (n=4) reported the use of atypical antipsychotics[16,17,18,19]. However, only 50% (n=2) of the manuscripts exclusively addressed atypical antipsychotics[16,19]. In the article by Krivoy et al. (2017)[19] clozapine is highlighted as the main treatment, while Sheikhmoonesi (2016)[16] addressed the use of risperidone, olanzapine, and fluphenazine decanoate.

In the study of Sheikhmoonesi et al. (2016)[16], it was observed that in the intervention group of 40 patients, 65% (n=26) used risperidone, 7.5% (n=3) used only olanzapine, and fluphenazine decanoate was not used. Additionally, the combination of olanzapine and decanoate was used by 7.5% (n=3), while risperidone and decanoate were used by 20% (n=8).

Meanwhile, the research of Krivoy et al. (2017)[19] recruited 47 patients with schizophrenia who had been on clozapine treatment for at least 18 weeks, with no gender restrictions. In the intervention group of 24 participants, 75% were men (n=18).

In the remaining 50% (n=2) of the articles, both typical and atypical antipsychotics or their combinations were explored in managing schizophrenia[17,18].

In the manuscript by Kalejahi et al. (2023)[17], 42.3% (n=9) of participants in the intervention group (n=21) used typical antipsychotics, 38.1% (n=8) used atypical antipsychotics, and 19% (n=4) used a combination of antipsychotics.

In another article by Kalejahi et al. (2023)[18], 42 patients completed the trial, with an even division across both groups (n=21). In the intervention group, 42.1% (n=9) used typical antipsychotics, 38.1% (n=8) used atypical antipsychotics, and 19% (n=4) used both.

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Dose of Vitamin D Supplementation

Vitamin D supplementation was addressed in various ways in the analyzed articles, with variations in both the route of administration and the dosage. The study by Krivoy et al. (2017)[19] (25%) adopted weekly supplementation through oral drops, totaling 14,000 IU. In contrast, the research by Sheikhmoonesi et al. (2016)[16] used monthly intramuscular injections of vitamin D3, administering 2 mL per ampoule (300,000 IU/mL), resulting in a total dose of 600,000 IU.

On the other hand, two manuscripts opted for oral supplementation with different regimens[17,18]. The articles by Kalejahi et al. (2023)[17] and Kalejahi et al. (2023)[18] employed daily capsules of 2,000 IU of vitamin D and D3 (cholecalciferol), respectively.

Duration of Vitamin D Supplementation

Regarding the duration of vitamin D supplementation, the 8-week period was the most frequently reported, being mentioned in 75% (n=3) of the studies[17,18,19]. The 3-month period was cited only in the article of Sheikhmoonesi et al. (2016)[16], corresponding to 25% (n=1) of the manuscripts.

Serum Vitamin D Concentration Before and After Supplementation

All four studies included in this review reported hypovitaminosis D among participants prior to supplementation[16,17,18,19]. In two of these studies, Sheikhmoonesi et al. (2016)[16] and Krivoy et al. (2017)[19], patients presented serum levels below 75 nmol/L (30 ng/mL), **thus** encompassing both deficiency and insufficiency. The other two studies, by Kalejahi et al. (2023)[17] and Kalejahi et al. (2023)[18], included only participants with vitamin D deficiency.

The serum vitamin D concentration before and after supplementation was analyzed across several studies, yielding varying results. After the intervention, 75% (n=3) of the studies observed a statistically significant increase in serum vitamin D concentrations in the intervention groups compared to the placebo groups[16,18,19]. Specifically, Krivoy et al. (2017)[19] reported an average increase of 12.56 ng/mL, Sheikhmoonesi et al. (2016)[16] observed a gain of 35.8 ng/mL, and Kalejahi et al. (2023)[18] reported a rise of 32.18 ng/mL in the intervention group.

Meanwhile, the manuscript by Kalejahi et al. (2023)[17] did not observe a significant increase in serum levels in the intervention group compared to placebo. It is important to note that this particular study did not provide **detailed** post-supplementation concentration values, which limits a more precise analysis of the effectiveness of the intervention in restoring adequate vitamin D status.

Efficacy of Vitamin D Supplementation in Clinical Trials

When evaluating the efficacy of vitamin D supplementation on schizophrenia symptoms, it is relevant to highlight that 100% (n=4) of the analyzed studies were clinical trial[16,17,18,19]. The analyzed studies presented mixed results, with 50% (n=2) identifying a positive relationship with significant improvement in symptoms or associated markers[17,18]. Conversely, 50% (n=2) of the trials also indicated a neutral relationship, with no significant impact[16,19]. None of the clinical trials reported negative effects of vitamin D supplementation.

Specifically, the article by Kalejahi et al. (2023)[17] found positive results, it included 42 patients with schizophrenia randomized into two groups: an intervention group (n=21) and a placebo group (n=21) with a PANSS score ≥ 70. This study observed a significant improvement in both the negative subscale scores (PANSS-NSS) and the total score (PANSS-TS). It also reported that vitamin D supplementation led to a significant reduction in low-density lipoprotein cholesterol (LDL-C) levels, suggesting potential benefits in mitigating cardiometabolic complications in schizophrenia patients, contributing to the reduction of disorder-related symptoms[17].

Additionally, the article by Kalejahi et al. (2023)[18], involving 42 men aged 18 to 65 years with no history of nutritional supplementation in the last six months, reported a significant reduction in serum GSK-3β (glycogen synthase kinase-3 beta) levels and a reduction in the severity of psychotic symptoms in hospitalized patients with vitamin D deficiency who received supplementation[18].

According to data from the research by Krivoy et al. (2017)[19], which included 24 participants in the intervention group and 23 in the placebo group, no significant advantages of vitamin D were found compared to the placebo in psychotic, depressive, or

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metabolic parameters. However, a trend toward cognitive improvement was observed, suggesting that the benefits of vitamin D may be limited to cognitive function in this population of schizophrenia patients treated with clozapine.

Finally, the trial by Sheikhmoonesi et al. (2016)[16], which included 80 male patients equally distributed across both groups, found a negative but non-significant correlation between changes in serum vitamin D levels and the negative subscale scores of PANSS in the intervention group. The study emphasized the need for further randomized clinical trials to confirm these findings.

DISCUSSÃO

Methods Used to Assess the Severity of Schizophrenia Symptoms

The use of validated clinical instruments is fundamental for assessing the various symptom dimensions of schizophrenia[20]. According to Medeiros et al. (2015)[20], the combination of clinical scales and complementary tools provides a more complete and multidimensional understanding of the disorder, enabling more accurate monitoring of treatment outcomes and progression.

Although The Positive and Negative Syndrome Scale (PANSS) was the main method used to assess the severity of schizophrenia symptoms in all included articles, other complementary tools were also employed to capture the multifaceted nature of the disorder across cognitive, behavioral, and emotional domains[18,19]. The Positive and Negative Syndrome Scale (PANSS) is one of the most widely used instruments to evaluate psychotic symptoms[21]. It is composed of 30 items divided into three subscales – Positive Symptoms, Negative Symptoms, and General Psychopathology – developed to assess the severity of symptoms and measure general psychopathology and drug-related changes[21].

In Krivoy et al. (2017)[19], two additional instruments were applied: the Montreal Cognitive Assessment (MoCA), used to evaluate cognitive functioning, and the Calgary Depression Scale for Schizophrenia (CDSS), which provides a reliable measure of depressive symptoms in patients with schizophrenia. The MoCA has been validated as a sensitive screening tool for cognitive impairment in schizophrenia, covering domains such as attention, memory, and executive functions[22], while the CDSS is considered a gold standard for distinguishing depressive symptoms from negative or extrapyramidal features in these populations[23].

Furthermore, Kalejahi et al. (2023)[18] incorporated the biochemical marker GSK-3β (glycogen synthase kinase-3 beta), measured in serum, to explore its association with psychotic symptom severity. GSK-3β is a serine-threonine kinase involved in neuronal plasticity and cellular signaling pathways, and its dysregulation has been implicated in the pathophysiology of schizophrenias[24]. The study suggested that vitamin D supplementation may modulate GSK-3β activity via the PI3K/AKT pathway, contributing to symptom improvement[18].

Main Treatments for Schizophrenia Used in the Studies

The choice of a baseline treatment for patients with schizophrenia is essential, considering the complexity of the disease and the variability of responses to medications[25]. Establishing an appropriate therapeutic regimen promotes symptom stability and reduces the risk of relapses, ensuring greater treatment adherence[20,25]. In addition, combining typical and atypical options, as observed in some studies, allows for greater personalization of the therapeutic approach, adjusting to the individual needs and responses of each patient[25].

The treatment of schizophrenia with typical and atypical antipsychotics shows differences in efficacy, tolerability, and side effects[25]. Typical antipsychotics, such as haloperidol and fluphenazine decanoate, are effective for positive symptoms but are often associated with extrapyramidal adverse effects[25]. Atypical antipsychotics, such as risperidone, olanzapine, and clozapine, are preferred due to the lower risk of extrapyramidal effects and better management of negative and cognitive symptoms[25]. Clozapine is considered the gold standard for treatment-refractory cases, showing superior efficacy in randomized controlled trials[19,25], as described in one of the articles[19], although its use is limited by severe side effects, including agranulocytosis and the need for constant hematological monitoring[25].

The literature indicates that fixed doses in therapeutic regimens can influence treatment outcomes[16,25]. Antipsychotics like risperidone and olanzapine, when administered in fixed doses, showed positive results in reducing psychotic symptoms compared to flexible regimens[16]. However, metabolic side effects, such as weight gain and dyslipidemia, remain a concern[17]. The combination of antipsychotics, addressed in some texts[17,18], is a strategy adopted in certain cases. While some studies suggest benefits, the efficacy and safety of this approach remain uncertain, with individual responses being unpredictable[17,18].

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Further research is necessary to validate its use as an effective long-term therapeutic strategy, highlighting the importance of rigorous patient monitoring[25].

Treatments with both typical and atypical antipsychotics are also discussed in the context of treatment adherence and their impact on quality of life[25]. According to Barnes (2020)[25], second-generation antipsychotics are associated with higher treatment adherence due to the reduced intensity of motor side effects, whereas typical antipsychotics continue to be primarily used in contexts where costs or limited resources restrict access to newer options.

Dose of Vitamin D Supplementation

The included studies used different vitamin D supplementation protocols, both in route of administration and dosage, which may have influenced clinical outcomes. Although all protocols increased serum vitamin D concentrations to some extent, only the daily supplementation reported by Kalejahi et al. (2023)[18] and the high-dose intramuscular regimen by Sheikhmoonesi et al. (2016)[16] were associated with significant improvements in symptom severity. In contrast, the study focused on cardiometabolic outcomes by Kalejahi et al. (2023)[17] and the trial by Krivoy et al. (2017)[19] did not observe meaningful symptom changes, even with increased serum levels. This divergence suggests that vitamin D's clinical effect may be dose-dependent and influenced by both frequency and administration route, especially in chronic or treatment-resistant patients.

Furthermore, existing evidence highlights that achieving and maintaining optimal 25(OH)D concentrations depends not only on the total dose but also on consistent supplementation patterns, especially in populations with low adherence or altered vitamin D metabolism[15,16,26].

Duration of Vitamin D Supplementation

This review aligns with the findings of Pludowski et al. (2022)[26], as a duration of 8 weeks of supplementation with higher doses (6,000 IU/day or 50,000 IU/week) is frequently recommended by various guidelines[15,27]. This approach aims to rapidly correct severe vitamin D deficiency and achieve serum levels of 25(OH)D in the desired range (typically between 30-50 ng/mL). This period is considered sufficient to achieve steady-state serum levels, which can be assessed after 6-12 weeks[15,26]. The protocol is based on evidence of efficacy and safety within this timeframe to normalize levels and avoid toxicity[26].

On the other hand, supplementation for 3 months (12 weeks) is also cited in some guidelines[28,29] reviewed by Pludowski et al. (2022)[26]. This duration is used to correct moderate deficiencies or when vitamin D levels are in an intermediate range (insufficiency, not necessarily severe deficiency). This period ensures a continuous and sustained response in individuals with specific needs, such as obesity or conditions that impair absorption[26,28,29].

Serum Vitamin D Concentration Before and After Supplementation

Although all studies confirmed the presence of hypovitaminosis D prior to supplementation, the variation in biochemical outcomes suggests that dosage, baseline deficiency severity, and regimen consistency may play key roles in treatment efficacy[16,17,18,19]. Studies that achieved substantial increases in serum 25(OH)D, such as Sheikhmoonesi et al. (2016)[16] and Kalejahi et al. (2023)[18], also reported improvements in clinical or biochemical outcomes, indicating that reaching sufficient serum levels may be necessary for therapeutic benefits.

In contrast, studies with more modest biochemical responses[19] or lacking post-intervention concentration data[17] did not demonstrate clinical improvement, suggesting that vitamin D efficacy may not rely solely on supplementation itself, but on the degree of correction achieved. Moreover, while the correction of hypovitaminosis D was evident in most cases, only one study[18] linked it to a biological marker of schizophrenia (GSK-3β), indicating a gap in understanding how biochemical improvement translates to symptom modulation.

These findings emphasize that evaluating vitamin D supplementation in schizophrenia requires more than measuring serum levels; it involves assessing clinical response, biomarker modulation, and tailoring intervention protocols to individual patient profiles. Future research should explore how achieving sufficiency, defined as ≥30 ng/mL[15], correlates with symptom relief and functional recovery in this population.

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Efficacy of Vitamin D Supplementation in Clinical Trials

According to Bhide, Shah, and Acharya (2018)[30], a randomized clinical trial is a prospective, comparative, and quantitative study conducted under controlled conditions, with interventions randomly allocated to comparison groups. It is, therefore, the most rigorous and robust research method to determine whether there is a cause-and-effect relationship between an intervention and an outcome.

Studies on the relationship between vitamin D and schizophrenia presented mixed results, with a division between those that indicated benefits and those that found no significant impact. According to the analysis, 50% (n=2) of the clinical trials[17,18] reported a positive association, with improvements in symptoms or markers related to schizophrenia following vitamin D supplementation. Kalejahi et al. (2023)[17] observed a reduction in negative symptoms of schizophrenia and an improvement in lipid profiles. Meanwhile, Kalejahi et al. (2023)[18] suggested a reduction in psychotic symptoms in patients with vitamin D deficiency. Importantly, no clinical trial found negative effects of supplementation. On the other hand, 50% (n=2) of the trials suggested a neutral relationship[16,19]. The manuscript by Krivoy et al. (2017)[19] reported no significant association between supplementation and improvements in psychotic symptoms or other evaluated parameters. Another study, by Sheikhmoonesi et al. (2016)[16], stated that there was no relationship between changes in serum vitamin D levels and improvements in both negative and positive symptoms in patients with schizophrenia.

Among the articles that found a positive association, Kalejahi et al. (2023)[17] highlighted that the high prevalence of metabolic abnormalities, including obesity, hyperlipidemia, hypertension, and glucose intolerance, in schizophrenia patients contributes to an increased incidence of cardiovascular diseases (CVD) and other chronic diseases, leading to premature death and reduced life expectancy. Atypical antipsychotics (AAPs) in particular, can cause a wide range of side effects, likely resulting in cardiometabolic and endocrine disturbances[17,25].

Meanwhile, Kalejahi et al. (2023)[18] aimed to evaluate the effect of vitamin D supplementation on serum 25-hydroxyvitamin D levels, factors related to insulin resistance (IR), and symptom severity in schizophrenia patients with vitamin D deficiency. It also assessed glycogen synthase kinase 3 (GSK-3), a serine-threonine kinase expressed in all tissues, due to its relevance to brain processes regulated by the PI3K/AKT pathway, such as gene expression and cell proliferation, as well as its association with mental disorders, including schizophrenia[24]. Dysregulated GSK-3β activity has been linked to the severity of the disorder[24]. Thus, the analysis aimed to explore how vitamin D supplementation could modulate these mechanisms, positively influencing insulin resistance and schizophrenia symptoms[24].

CONCLUSÃO

This study has limitations that should be acknowledged. First, the selection of only four articles restricts the breadth of the analysis, potentially limiting the generalizability of the findings[13]. Additionally, many of the included studies have small sample sizes, which may reduce the statistical power and reliability of the results[16,19]. Furthermore, as a scoping review, this study has an exploratory nature, making it less suitable for determining intervention efficacy[31]. A systematic review, which follows a more rigorous methodology for assessing efficacy, would be more appropriate in this context[31]. Despite these limitations, the findings provide valuable insights that can contribute to future research[16,17,18,19].

In several analyzed articles, there is a consensus regarding the need for further studies to confirm the findings related to the effects of vitamin D supplementation[8,10,13]. These studies emphasize the necessity of research with larger sample sizes, longer durations, and higher or adjusted doses of vitamin D based on serum levels. Additionally, some manuscripts highlight the importance of randomized clinical trials and placebo-controlled designs to better assess the clinical impact of vitamin D in the treatment of schizophrenia[16,19].

This scoping review mapped the scientific literature on the effectiveness of vitamin D supplementation in patients with schizophrenia, emphasizing methodological designs, assessment tools, and supplementation protocols. The findings suggest a potential adjunctive benefit of vitamin D, with reported improvements in negative symptoms, metabolic parameters, and neurobiological biomarkers such as GSK-3β. In half of the clinical trials included, significant improvements were observed, reinforcing its therapeutic potential. Nevertheless, the heterogeneity of study designs and the limited number of available trials currently hinder the formulation of robust clinical recommendations. Further well-designed, randomized controlled trials are needed to strengthen and consolidate the existing evidence.

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CONFLITOS DE INTERESSE

Os pesquisadores afirmam que não há conflitos de interesse nesta pesquisa.

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REFERÊNCIAS

1. Lima AB, Espindola CR. Esquizofrenia: funções cognitivas, análise do comportamento e propostas de reabilitação. Rev Subjetividades. 2015;15(1):105-112.
2. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016;388(10039):86–97. doi:10.1016/S0140-6736(15)01121-6.
3. Mollon J, Reichenberg A. Cognitive development prior to onset of psychosis. Psychol Med. 2018 Feb;48(3):392-403. doi: 10.1017/S0033291717001970. Epub 2017 Jul 24. PMID: 28735586.
4. Barch DM, Sheffield JM. Cognitive impairments in psychotic disorders: common mechanisms and measurement. World Psychiatry. 2014 Oct;13(3):224-32. doi: 10.1002/wps.20145. PMID: 25273286; PMCID: PMC4219054.
5. Ruscalleda RMI. Vitamina D - Aspectos Fisiológicos, Nutricionais, Imunológicos, Genéticos. Ações em doenças autoimunes, tumorais, infecciosas. Funções musculoesqueléticas e cognitivas. Rev Med. 2023; 102(3) :e-210547. doi:10.11606/issn.1679-9836.v102i3e-210547.
6. Chai B, Gao F, Wu R, Dong T, Gu C, Lin Q, Zhang Y. Vitamin D deficiency as a risk factor for dementia and Alzheimer's disease: an updated meta-analysis. BMC Neurol. 2019 Nov 13;19(1):284. doi: 10.1186/s12883-019-1500-6. PMID: 31722673; PMCID: PMC6854782.
7. Wang W, Li Y, Meng X. Vitamin D and neurodegenerative diseases. Heliyon. 2023 Jan 12;9(1):e12877. doi: 10.1016/j.heliyon.2023.e12877. PMID: 36820164; PMCID: PMC9938420.
8. McGrath JJ, Eyles DW, Pedersen CB, Anderson C, Ko P, Burne TH, et al. Neonatal Vitamin D Status and Risk of Schizophrenia: A Population-Based Case-Control Study. Arch Gen Psychiatry. 2010; 67(9) :889–894. doi: 10.1001/archgenpsychiatry.2010.110.
9. Doğan Bulut S, Bulut S, Görkem Atalan D, Berkol T, Gürçay E, Türker T, Aydemir Ç. The Relationship between Symptom Severity and Low Vitamin D Levels in Patients with Schizophrenia. PLoS One. 2016 Oct 27;11(10):e0165284. doi: 10.1371/journal.pone.0165284. PMID: 27788194; PMCID: PMC5082915.
10. Mayne PE, Burne THJ. Vitamin D in Synaptic Plasticity, Cognitive Function, and Neuropsychiatric Illness. Trends Neurosci. 2019 Apr;42(4):293-306. doi: 10.1016/j.tins.2019.01.003. Epub 2019 Feb 19. PMID: 30795846.
11. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018; 169(7):467-473. doi:10.7326/M18-0850.
12. Mattos SM, Cestari VRF, Moreira TMM. Scoping protocol review: PRISMA-ScR guide refinement. Rev Enferm UFPI. 2023; 12(1). doi: 10.26694/reufpi.v12i1.3062
13. Health Sciences Descriptors: DeCS [Internet]. 2023 ed. São Paulo (SP): BIREME / PAHO / WHO. 2023 [updated 2023 December 04; cited 2024, March, 20]. Available from: https://decs.bvsalud.org/en/.
14. Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI. Published online 2020.
15. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 2011; 96: 1911–1930. doi: 10.1210/jc.2011-0385.
16. Sheikhmoonesi F, Zarghami M, Mamashli S, Charati J Y, Hamzehpour R, Fattahi S, et al. Effectiveness of vitamin D supplement therapy in chronic stable schizophrenic male patients: a randomized controlled trial. Iranian Journal of Pharmaceutical Research 2016; 15: 941-950. PMID: 28243293.
17. Kalejahi P, Kheirouri S, Noorazar SG. Effect of vitamin D supplementation on cardio-metabolic indices and the severity of symptoms in male patients with chronic schizophrenia. Crescent Journal of Medical & Biological Sciences 2023; 10. doi: 10.34172/cjmb.2023.21.
18. Kalejahi P, Kheirouri S, Noorazar S G. A randomized controlled trial of vitamin D supplementation in Iranian patients with schizophrenia: effects on serum levels of glycogen synthase kinase-3β and symptom severity. The International Journal of Psychiatry in Medicine 2023; 58: 559-575. doi: 10.1177/00912174231193303.

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DOI: 10.53843/bms.v10i14.1123

19. Krivoy A, Onn R, Vilner Y, Hochman E, Weizman S, Paz A, et al. Vitamin D supplementation in chronic schizophrenia patients treated with clozapine: a randomized, double-blind, placebo-controlled clinical trial. EBioMedicine 2017; 26: 138-145. doi: 10.1016/j.ebiom.2017.11.027.
20. Medeiros WR, Silva Filho JF, Soares RCN, Conceição NR, Oliveira IR. Escalas de avaliação de sintomas na esquizofrenia validadas para uso no Brasil: uma revisão sistemática. Revista de Psicologia da IMED 2015; 7(1): 101–110. Disponível em: https://revistardp.org.br/revista/article/view/78. Acesso em: 23 mar. 2025.
21. Higuchi CH, Ortiz B, Berberian AA, Noto C, Cordeiro Q, Belangero SI, et al. Factor structure of the Positive and Negative Scale (PANSS) in Brazil: convergent validation of the Brazilian version. *Brazilian Journal of Psychiatry* 2014; 36: 336–339. doi: 10.1590/1516-4446-2013-1330.
22. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment (MoCA): a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005; 53(4): 695–699. doi: 10.1111/j.1532-5415.2005.53221.x.
23. Addington D, Addington J, Maticka-Tyndale E. The Calgary Depression Scale for Schizophrenia: development and validation of a depression rating scale for schizophrenia. Schizophrenia Research 1993; 11(3): 239–244. doi: 10.1016/0920-9964(93)90005-R.
24. Lovestone S, Killick R, Di Forti M, Murray R. Schizophrenia as a GSK-3 dysregulation disorder. Trends Neurosci. 2007 Apr;30(4):142-9. doi: 10.1016/j.tins.2007.02.002. Epub 2007 Feb 26. PMID: 17324475.
25. Barnes TR, Drake R, Paton C, Cooper SJ, Deakin B, Ferrier IN, et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: updated recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2020; 34: 3-78. doi: 10.1177/0269881119889296.
26. Pludowski P, Takacs I, Boyanov M, Belaya Z, Diaconu CC, Mokhort T, et al. Clinical practice in the prevention, diagnosis and treatment of vitamin D deficiency: A Central and Eastern European expert consensus statement. Nutrients 2022; 14: 1483. doi: 10.3390/nu14071483.
27. Cesareo R, Attanasio R, Caputo M, Castello R, Chiodini I, Falchetti A, et al. Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults. Nutrients 2018, 10, 546. doi: 10.3390/nu10050546.
28. Pigarova EA, Rozhinskaya LY, Belaya JE, Dzeranova LK, Karonova TL, Ilyin AV, et al. Russian Association of Endocrinologists recommendations for diagnosis, treatment and prevention of vitamin D deficiency in adults. Probl. Endocrinol. 2016, 62, 60–84. doi: 10.14341/probl201662460-84.
29. Takacs I, Benko I, Toldy E, Wikonkal N, Szekeres L, Bodolay E, et al. Hungarian consensus regarding the role of vitamin D in the prevention and treatment of diseases. Orv. Hetil. 2012, 153 (Suppl. 2), 5–26. doi: 10.1556/oh.2012.29410.
30. Bhide A, Shah PS, Acharya G. A simplified guide to randomized controlled trials. Acta Obstetricia et Gynecologica Scandinavica 2018; 97: 380–387. doi: 10.1111/aogs.13309.
31. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Medical Research Methodology 2018; 18: 143. doi: 10.1186/s12874-018-0611-x.

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